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# Postoperative pain assessment, and opioid utilisation after hospital discharge following colectomy

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by

**Reham M. Baamer, PharmD, MSc**

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degree of Doctor of Philosophy

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## **Abstract**

### **Background and aims**

Opioids have an established role in the management of postoperative pain; however, inappropriate opioid utilisation is evident, influenced by several factors including the overreliance on unidimensional pain assessment tools to guide opioid dosing. This thesis aims to advance the understanding of the management of postoperative pain, including pain assessment, opioid utilisation trends and persistent postoperative opioid use (PPOU) following colectomy.

### **Methods**

Three interrelated studies were performed: 1) a systematic review to assess the measurement properties of unidimensional and functional pain assessment tools in adult postoperative patients. Two pharmacoepidemiological studies were conducted using linked primary and secondary care data sources from England. 2): a retrospective cohort study to determine the prevalence and predictors of PPOU after colectomy. 3) A repeated cross-sectional analysis to describe the temporal trends in opioid prescriptions following discharge after colectomy.

### **Results**

After a systematic search of four databases, 31 studies involving 12,498 participants were included. The quality of evidence for the measurement properties of all identified unidimensional pain assessment tools was suboptimal. Studies on functional assessment tools were scarce, with only one study including an 'objective pain score'. However, it had suboptimal quality, with a very low quality of evidence.

Amongst the 93,262 patients undergoing colectomy between 2010 and 2019, 15,081 (16.2%) were issued at least one opioid prescription within 90 days of discharge. From the whole cohort, 7540 (8.1%) developed PPOU. The odds of developing persistent opioid use were highest [OR 3.41 (95%CI 3.07–3.77)] for individuals who used long-acting opioid formulations in the 180 days before colectomy. Predictors of PPOU included previous opioid exposure; high deprivation index; multiple comorbidities; use of long-acting opioids; white race; and open surgery. Minimally invasive surgical approaches were associated with lower odds of PPOU.

There was a downward trend in the proportion of opioid naïve patients who had post-discharge opioid prescriptions, from 11.4% in 2010 to 6.7% in 2019 (-41.3%,  $p < 0.001$ ). However, the proportions prescribed opioids prior to surgery remained stable [57.5% in 2010 to 58.3% in 2019 ( $p = 0.637$ )]. Codeine represented 44.5% of all prescriptions and prescribing increased by 14.5%. Prescriptions for morphine and oxycodone rose significantly by 76.6% and 31.0% respectively, while tramadol prescribing dropped by 48.0%.

## **Conclusion**

This thesis contributes to a deeper understanding of postoperative pain assessment and challenges the validity and reliability of unidimensional tools to quantify postoperative pain, and shows limited evidence for the use of functional pain assessment tools. There have been changes in the prescription of opioids following colectomy over the last decade and PPOU does occur after colectomy in England.

## **Dedication**

This thesis is dedicated to:

My great parents, Sameera and Mohammed. Nothing would have been possible without the unconditional love and support you showered upon me. Thanks for always encouraging me to chase my dreams and to only compare myself to the better version of me.

My beloved husband, Lutfi, your unwavering love and encouragement have been my guiding lights when the path seemed daunting. Thanks for always believing in me and for being my rock, and my greatest supporter. This achievement is as much yours as it is mine.

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I would like to thank Dr. Nicholas Levy for his expertise and collaborative spirit, which significantly enriched the systematic review study. Additionally, I thank Dr. Douglas Grindlay for his guidance in building the search strategy for the systematic review. I am also indebted to Mr. David Humes, who was generous with his time and attention and supported me immensely during electronic health records data research. His clinical and practical expertise provided a unique lens for examining CPRD and HES data. Collaborating with him has been both enjoyable and rewarding.

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## **Impact of COVID 19 on the research process, and literature review development**

This PhD project started in October 2019; within a few months, some research questions were identified, and initial research plans were developed. These were to conduct a systematic review to evaluate the validity and reliability of several pain assessment tools and to undertake a clinical study to evaluate the measurement properties of (Functional Pain Activity score) compared with three unidimensional pain assessment tools used for post-operative adult patients. A descriptive correlational design was proposed to assess the agreement (validity, reliability) of scores obtained from different tools for pain assessment. However, due to the Coronavirus Disease 2019 (COVID-19) pandemic in March 2020, related lockdowns, and postponement of non-urgent clinical and research activity, the intended clinical study was cancelled. Accordingly, there was a shift in focus to pharmacoepidemiological study designs.

## List of publications

- Baamer RM, Iqbal A, Lobo DN, Knaggs RD, Levy NA, Toh LS. Utility of unidimensional and functional pain assessment tools in adult postoperative patients: a systematic review. *Br. J. Anaesth.* 2022; 128(5):874-888. doi: 10.1016/j.bja.2021.11.032.
- Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN. Predictors of persistent opioid use following colectomy: a population-based cohort study from England. *Anaesthesia* 2023; 78(9):1081-1092. doi: 10.1111/anae.16055.
- Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN. Temporal trends and patterns in initial opioid prescriptions after hospital discharge following colectomy in England over ten years. *BJS Open* 2023;7(6): zrad136. doi:10.1093/bjsopen/zrad136.

## Editorials by peers on publication arising from this thesis

- Simpson A, Keane E, Levy N. The prescribed opioid crisis as an impetus to improve postoperative pain management. *Anaesthesia* 2023; 78(9):1602-1066. doi: 10.1111/anae.16054.

## Published abstracts

- Baamer RM, Iqbal A, Lobo DN, Knaggs RD, Levy NA, Toh LS, O39 Unidimensional and functional pain assessment tools in postoperative

adult patients: a systematic review of their development and utility, *BJS* 2021, 108 (5): znab282.044. doi: org/10.1093/bjs/znab282.044.

- Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN, O39 Predictors of persistent opioid use after discharge following colectomy: a population-based cohort study from England, *BJS* 2023, 110(3): znad101.087. doi: 10.1093/bjs/znad101.087.
- Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN, O128 Time trends in opioid prescribing after discharge following colectomy in England: a cross-sectional study, *BJS* 2023, 110(3): znad101.128. doi: 10.1093/bjs/znad101.128.

### **Conference presentations**

- Unidimensional and functional pain assessment tools in postoperative adult patients: a systematic review of their development and utility. Oral presentation, Surgical Research Society Annual Scientific Meeting (virtual), March 2021.
- Predictors of persistent opioid use after discharge following colectomy: A population-based cohort study from England. Oral presentation, Surgical Research Society Annual Scientific Meeting, Nottingham, UK, March 2023.
- Time trends in opioid prescribing after discharge following colectomy in England: a cross-sectional study. Oral presentation, Surgical Research Society Annual Scientific Meeting, Nottingham, UK, March 2023.

- Temporal trends and prescribing patterns of initial opioid prescriptions following colectomy, 2010-2019: a cross-sectional study from England. Poster and oral presentation, The 56th Annual Scientific Meeting of the British Pain Society, Glasgow, UK, May 2023.

### **Presentations at Internal scientific meetings**

- Unidimensional and functional pain assessment tools in postoperative adult patients: a systematic review of their development and utility. Oral presentation, Pain Centre Versus Arthritis, 2021.
- Predictors of opioid prescribing following discharge from hospital after colectomy: A cohort study from England. Oral presentation, Pain Centre Versus Arthritis, 2021.
- Opioid prescriptions utilisation after discharge following abdominal surgery in England: A retrospective study using the Clinical Practice Research Datalink. Flash presentation, Allied Health Professionals PGR conference, 2021.
- Predictors of persistent opioid use after discharge following colectomy: A population-based cohort study from England. Oral presentation, Pain Centre Versus Arthritis, 2023.
- Postoperative pain assessment, and opioid utilisation after hospital discharge following colectomy. Oral presentation, Post graduate researchers seminar, School of Pharmacy, 2023.

- Temporal trends and patterns in initial opioid prescriptions following colectomy in England between 2010 and 2019. Flash presentation, School of Pharmacy research day, 2023.

## Prizes and awards

- University of Nottingham Graduate School Travel Prize - £300 towards attending the 56th Annual Scientific Meeting of the British Pain Society, Glasgow, UK, May 2023.
- The British Pain Society highly commended oral poster presentation award on the presentation titled “Temporal trends and prescribing patterns of initial opioid prescriptions following colectomy, 2010-2019: a cross-sectional study from England” The 56th Annual Scientific Meeting of the British Pain Society, Glasgow, UK, May 2023.



## **Declaration**

Except where acknowledged in the acknowledgements and text, I declare that this thesis is the result of my own work and is based on research undertaken by myself, under the guidance of my supervisors and advisors.

Chapters 3, 6, and 7 are expanded versions of published articles that have originated from this thesis, as indicated in the list of publications.

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## List of abbreviations

A&E	Accident and Emergency
aOR	adjusted Odds ratio
AMA	American Medical Association
AUC	Area Under the Curve
BNF	British National Formulary
BPI	Brief Pain Inventory
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
COX	Cyclooxygenase
COVID-19	Coronavirus Disease-2019
CPSP	Chronic Postoperative Pain
CPRD	Clinical Practice Research Datalink
CQUIN	Commissioning for Quality and Innovation
CYP450	Cytochrome P450
CYP2DK	Cytochrome P450 2DK
CYP3A4	Cytochrome P450 3A4
Dosageid	Dosage Identifier
DDD	Defined Daily Dose
DVA	Department of Veterans Affairs
EHRs	Electronic Health Records
ERAS	Enhanced Recovery After Surgery
ES	Effect Size
FAS	Functional Activity Score
FPS-R	Faces Pain Scale-Revised
GRADE	Grading of Recommendations Assessment, Development and Evaluation

GP	General Practitioner
HES	Hospital Episode Statistics
APC	Admitted Patient Care
HR	Hazard Ratio
IASP	International Association for the Study of Pain
ICD-10	International Classification of Diseases 10 <sup>th</sup> Revision
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
JCAHO	Joint Commission for Accreditation of Healthcare Organisations
LCD	Last Collection Date
LSOAs	Lower-Layer Super Output Areas
MAR	Missing at Random
MCAR	Missing Completely at Random
MCID	Minimal Clinically Important Difference
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum Inhibitory Concentration
MME	Morphine Milligram Equivalent
MNAR	Missing Not at Random
MPQ	McGill Pain Questionnaire
NHS	National Health Service
NMS	New Medicine Service
NNH	Number Needed to Harm
NRS	Numerical Rating Scale
NSAIDs	Non- Steroidal Anti-Inflammatory Drugs
OIH	Opioid Induced Hyperalgesia
OMEQ	Oral Morphine Equivalent
OPCS	Office of Population, Census Survey; Classification of Surgical Operations and Procedures
OR	Odd Ratio

OTC	Over the Counter
P5VS	Pain as the 5 <sup>th</sup> Vital Sign
PACU	Post- Anaesthesia Care Unit
PCA	Patient- Controlled Analgesia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	The International Prospective Register of Systematic Reviews
PROMs	Patient- Reported Outcome Measures
PPOU	Persistent Postoperative Opioid Use
PYs	Person-Years
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
RECORD-PE	Reporting of studies Conducted using Observational Routinely-collected Data statement for PharmacoEpidemiology
SD	Standard Deviation
SRM	Standardised Response Mean
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Text id	Text Identifier
TJC	The Joint Commission
VAS	Visual Analogue Scale
VDS	Verbal Descriptor Scale
VHA	Veterans Health Administration
VNRS	Verbal NRS



## **Chapter 1: Introduction**

## **1.1 Thesis outline**

This chapter provide an overview of the content of each of the remaining chapters presented in this thesis. Figure 1-1 illustrates the structure of this thesis.

### **Chapter 2: Literature review, aim and objectives**

This chapter provides an overview of pain, its assessment, and the tools used to assess postoperative pain. It considers strategies for managing postoperative pain, focusing on opioids and their associated benefits and risks. Additionally, this chapter provides a comprehensive summary of the existing literature concerning factors linked to inappropriate opioid utilisation following surgical procedures. The primary purpose of this chapter is to identify the gaps in the current literature to establish the rationale for the aims and objectives of the research program presented in this thesis and justify the selection of colectomy.

### **Chapter 3: Utility of unidimensional and functional pain assessment tools in adult postoperative patients**

This chapter provides a systematic review of the available pain assessment tools used to assess pain after surgery, and appraises the evidence relating to the utility of commonly used unidimensional pain assessment tools. Furthermore, it identifies the tools used to assess pain interference with functional recovery. The findings will help evaluate the current pain assessment practice for acute pain settings.

#### **Chapter 4: Data source and cohort identification**

This chapter discusses the strengths and limitations of using electronic health records (EHRs) for epidemiological research and justifies the selection of Clinical Practice Research Datalink (CPRD) Aurum and the Hospital Episode Statistics (HES) databases as data sources. It describes the identification of colectomy populations of interest and the processes used to reach the final cohort prescribed opioids after colectomy and to extract their opioid prescription records for analysis.

#### **Chapter 5: Preparing opioid prescription records for analysis**

This chapter describes the approach to handling opioid prescription records. Prescription records from CPRD are usually not complete, with common issues such as missing prescribing instructions, quantities and prescription end dates. Therefore, the methods for addressing these missing data, cleaning and formatting them to be ready for analysis are detailed.

#### **Chapter 6: Predictors of persistent postoperative opioid use following colectomy: a population-based cohort study from England**

Chapter 6 describes a retrospective cohort study on adults undergoing colectomy between 2010 to 2019 to determine the prevalence of persistent postoperative opioid use (PPOU) following colectomy, stratified by pre-admission opioid exposure. This study also applies logistic regression analysis to identify predictors associated with PPOU following colectomy.

**Chapter 7: Temporal trends and patterns in initial opioid prescriptions after hospital discharge following colectomy in England**

Chapter 7 includes a retrospective cohort study with repeat cross sectional analysis to investigate the changes in the proportion of people receiving initial opioid prescriptions after hospital discharge following colectomy. The analysis also identifies the type, formulation, and amount of opioid prescribed and describes trends and patterns in initial prescription characteristics.

**Chapter 8: General discussion**

This chapter summarises the key findings from the three studies presented in the thesis. Finally, the chapter discusses the implications for clinical practice, policy, and future research and closes with an overall conclusion.

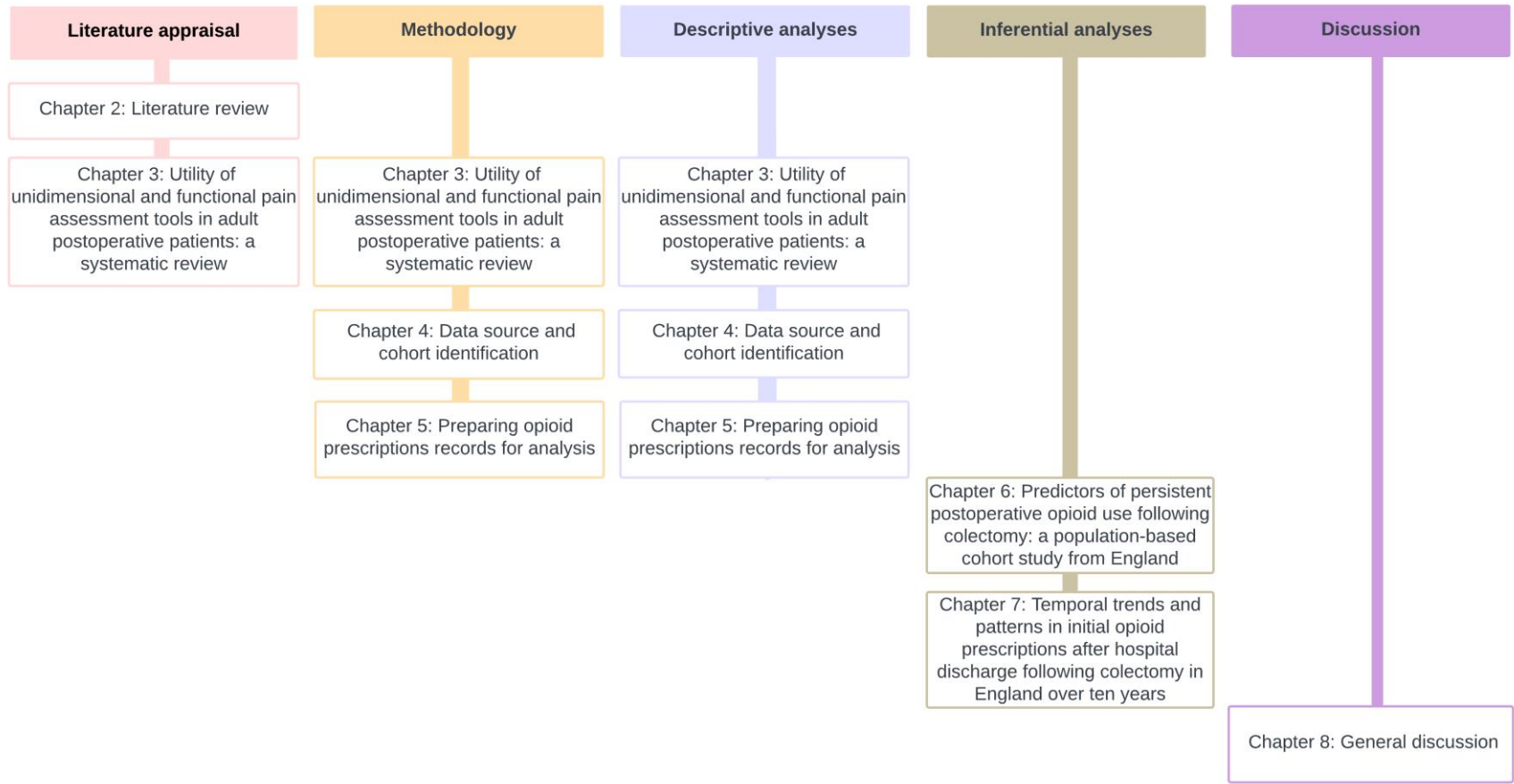


Figure 1-1. Thesis outline

## **Chapter 2: Literature review**

## **2.1 Introduction**

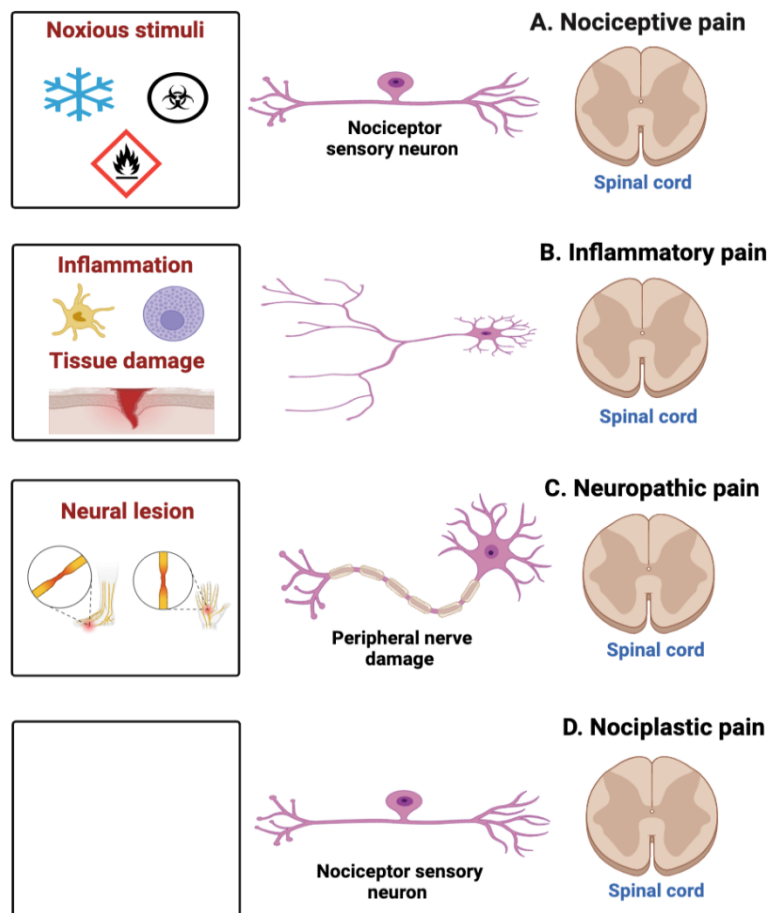
This chapter provides an overview of pain, its assessment, and the tools used to assess pain in postoperative settings. It delves into pain management, specifically focusing on opioids and their associated benefits and risks. Additionally, this chapter provides a comprehensive summary of the existing literature concerning factors linked to inappropriate opioid utilisation following surgery.

The primary purpose of this chapter was to identify the gaps in the current literature to establish the rationale for the aims and objectives of the research program presented in this thesis. An additional aim was to justify the selection of colectomy as a specific surgical procedure for in-depth analysis within the broader context of opioid utilisation.

## **2.2 Pain**

Pain was defined by the International Association for the Study of Pain (IASP) in 1979, as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”<sup>1</sup>. This definition has established the norms for how healthcare professionals should perceive pain. In recent years, it has been argued that this definition ignores that pain may occur without tissue damage; therefore, the definition warranted re-evaluation<sup>2, 3</sup>. Accordingly, In July 2020, IASP amended the definition of pain to “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”<sup>4</sup>. Pain is categorised as nociceptive, inflammatory, neuropathic or nociplastic in aetiology, and may present separately or in combination with variable levels of intensity. Nociceptive pain occurs

following the activation of nociceptors (i.e., pain receptors) by noxious stimuli. Inflammatory pain occurs because of tissue injury and inflammation which lead to the release of inflammatory mediators. Neuropathic pain results after injury to peripheral nerves or to sensory transmitting systems<sup>5</sup>. Nociceptive pain used to describe pain that arises from altered nociception without evidence of actual ongoing tissue damage or inflammation<sup>6</sup>. Figure 2-1



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**Figure 2-1. Classification of pain**

Pain can also be categorised based on its duration, as chronic or acute. Acute pain is defined as “the physiologic response to an experience of noxious stimuli that



can become pathologic, is normally sudden in onset, time limited, and motivates behaviours to avoid potential or actual tissue injury”<sup>7</sup>. Acute pain is short-lived and, in most cases, has a known cause, including surgery, trauma, or musculoskeletal. Surgical or postoperative pain occurs as a consequence of tissue damage, inflammation, nerve injury and nerve irritation at the operation site<sup>8</sup>. A meta-analysis estimated that the prevalence of moderate-to-severe postoperative pain ranged from 31% on the day after discharge to 58% between one- and two-weeks following discharge<sup>9</sup>.

Although recovery from acute pain is expected to occur within a few weeks, usually within the three months suggested for complete tissue healing, in a subset of patients, acute postoperative pain continues beyond the typical time of tissue healing and becomes chronic postsurgical pain (CPSP). The 11<sup>th</sup> revision of the International Classification of Diseases defines CPSP as “pain that intensifies or develops following surgery, remains in the surgical area for an extended period (at least 3 months), and cannot be attributed to other causes such as malignancy, or pre-existing pain conditions”<sup>10</sup>.

A notable characteristic of CPSP is that pain shifts from the localised site related to the surgical wound to a nearby or distant areas, and this pain can intensify over months following surgery<sup>11</sup>. The prevalence of CPSP can vary between different surgical procedures. The prevalence of CPSP, which is severe enough to limit functional ability, is around 10% following surgery, including knee arthroplasty<sup>12</sup>, and inguinal hernia repair<sup>13</sup>. According to a survey published in 1998, 1 in 4 patients who visited 10 pain clinics in the UK reported having CPSP<sup>14</sup>.

## **2.3 Pain assessment: pain as the 5<sup>th</sup> Vital Sign (P5VS) campaign**

In 1996, Dr. James Campbell addressed the American Pain Society and recommended that healthcare professionals should record pain along with vital signs to improve awareness of undertreated pain<sup>15</sup>. The concept of 'Pain as the 5<sup>th</sup> Vital Sign' (P5VS) then emerged, highlighting the essential need for improved pain care and patient wellbeing<sup>16</sup>. In 2000, the Veterans Health Administration (VHA) and other organisations, including the Joint Commission for Accreditation of Healthcare Organisations (JCAHO), now the Joint Commission (TJC), previously known as<sup>17</sup>, made pain assessment and management a priority in their national standards and accreditation process<sup>18, 19</sup>.

An essential part of the JCAHO recommendation was regular assessment of pain intensity using self-reported unidimensional pain assessment scales, with high pain intensity acting as a 'red flag' to promote action<sup>16</sup> for pain relief as a human right<sup>20</sup>. This practice was then adopted by healthcare organisations in different countries, including the UK<sup>21</sup>, to follow what was anticipated to improve standards of clinical care.

### **2.3.1 Unidimensional pain assessment tools**

The most frequently used unidimensional tools in adult postoperative clinical practice include the numerical rating scale (NRS), visual analogue scale (VAS), verbal descriptor scale (VDS). Pictorial pain scales can be used for adults but most commonly used for patients in children. These single-item measures rely on a score obtained from the patient to determine the perception of pain intensity<sup>22</sup>

and are widely used because they are quick to administer and do not encroach on the time required for usual care<sup>23</sup>. Table 2-1

**Table 2-1. Advantages and disadvantages of unidimensional pain assessment tools**

Scale	Advantages	Disadvantages
<b>Numerical rating scale</b>	<ul style="list-style-type: none"> <li>Simple to use in written form or verbally</li> <li>Minimal training is required</li> <li>Can be used in non-English speaking patients</li> <li>No need for clear vision, dexterity, paper, and pen</li> </ul>	<ul style="list-style-type: none"> <li>Measures pain intensity only</li> <li>Difficult for elderly and cognitively impaired patients and very young children who cannot differentiate words and numbers</li> </ul>
<b>Visual analogue scale</b>	<ul style="list-style-type: none"> <li>Simple to use and completed in &lt;1 minute</li> <li>The vocabulary level of the subject is not a consideration as there is no verbal description</li> </ul>	<ul style="list-style-type: none"> <li>Measures pain intensity only</li> <li>Difficult for some patients in converting the subjective sensation of pain to a straight line</li> <li>Cannot be used verbally</li> <li>Unsuitable for patients with severe visual impairment.</li> <li>People with little education and elderly find it difficult to use and tend to write on the line</li> </ul>
<b>Verbal rating scale</b>	<ul style="list-style-type: none"> <li>Short</li> <li>Easy for practitioner to score and analyses</li> <li>Used for adult and children more than 10 years old</li> </ul>	<ul style="list-style-type: none"> <li>Measures pain intensity only</li> <li>The selected words may not reflect the patient true sensation.</li> <li>It is subject to variations depending on how each patient understands "mild," "moderate," and "severe" pain</li> </ul>
<b>Faces pain scale- Revised</b>	<ul style="list-style-type: none"> <li>Easy to use</li> <li>Useful with individuals with communication barriers</li> <li>Useful for children</li> </ul>	<ul style="list-style-type: none"> <li>Measures pain intensity only</li> <li>Presented in printed form</li> <li>Difficult to determine whether pain or mood is being measured</li> </ul>

### 2.3.1.1 Numerical rating scale

The NRS is a segmented scale with numbers from 0 to 10 (or 0 to 5, 0 to 20). Patients select the number that best reflects their pain intensity, with 0 representing no pain and 10 (or 5, 20) representing the worst pain imaginable<sup>24</sup>

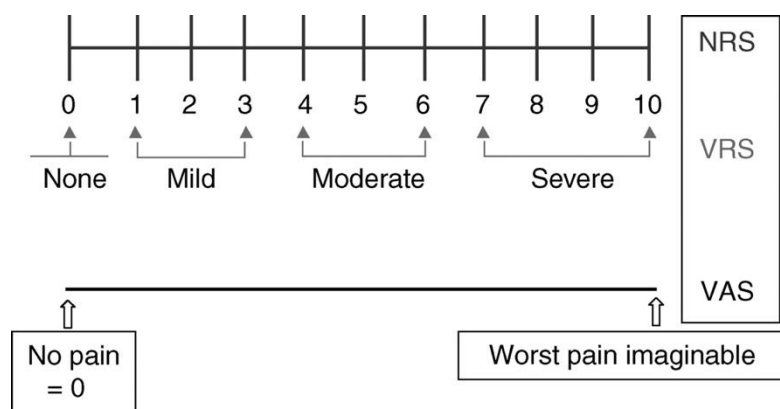
(Figure 2-2). The scale can be set up either on a vertical or horizontal line and has both written and verbal forms<sup>25</sup>. The verbal numerical rating scale (VNRS) uses a phrase such as ‘On a scale of zero to ten, with zero being no pain at all and ten being the worst pain you could imagine, where would you rate the pain you are experiencing right now?’<sup>26</sup>.

### 2.3.1.2 Verbal rating scale

The VRS uses words to describe the magnitude of pain. It normally uses four or five graded descriptors (e.g. none, mild, moderate, severe)<sup>26</sup> (Figure 2-2).

### 2.3.1.3 Visual analogue scale

The VAS consists of a 100 mm horizontal line with the words ‘no pain’ at the left end and ‘worst pain imaginable’ at the right and no tick marks. Patients are asked to mark the line, and the ‘score’ is obtained by measuring the distance from the left side of the scale to the mark<sup>26</sup>. VAS ratings of 0 to 4 mm are considered to indicate no pain, 5 to 44 mm represent mild pain, 45 to 74 mm imply moderate pain, and 75 to 100 mm signify severe pain<sup>27</sup>(Figure 2-2).



**Figure 2-2. NRS, VRS, and VAS**

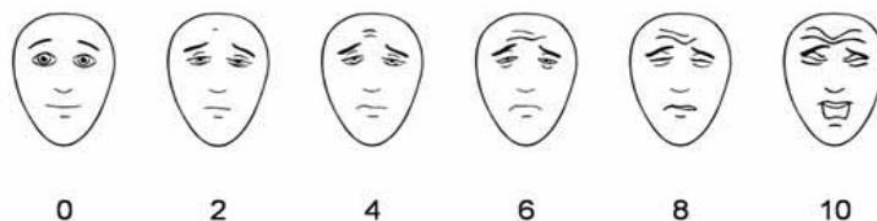
Reproduced from Breivik et al. (2008)<sup>22</sup>, with permission from Elsevier

### 2.3.1.4 Pictorial pain scales

Pictorial pain scales consist of a series of line diagrams of faces with expressions of increasing distress. Patients choose the face that represents the severity or intensity of their current pain<sup>28</sup>. The Wong-Baker Faces Pain Scale<sup>29</sup> and the Faces Pain Scale - Revised (FPS-R)<sup>30</sup> are commonly used pictorial scales (Figure 2-3 and Figure 2-4).



**Figure 2-3. Wong-Baker FACES Pain Rating Scale**



**Figure 2-4. Face pain scale revised (FPS-R)**

From Hicks et al. (2001)<sup>31</sup>, reproduced with permission from Wolters Kluwer Health, Inc

#### Different cut-off points for prescribing analgesics

Pain assessment should occur regularly during the immediate and early postoperative period<sup>32</sup>. To meet patient needs, pain is reassessed at suitable intervals after each analgesic intervention to determine if any additional

analgesics or modification are required. Healthcare organisations should have policies for prescribing analgesics, and often the opioid dose prescribed is based on assessment of pain known as 'Dosing to Numbers'<sup>33, 34</sup>. Some guidelines suggested an NRS >4 as a cut-off for prescribing simple analgesics like paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs)<sup>16, 35, 36</sup>, whereas other guidelines suggest an NRS >3 as a cut-off<sup>35</sup>. Severe pain as indicated by any scale requires the prescription of opioids. More details about opioids and NSAIDs are discussed in a later section (2.4 pain management).

### **2.3.2 Consequences of the Pain as the 5<sup>th</sup> Vital Sign (P5VS) campaign**

After implementing the TJC pain standards, pain clinicians and critics challenged the safety of ignoring the complexity of the pain experience and focusing on pain intensity as the sole element of pain assessment<sup>37-40</sup>. A considerable body of literature suggested that the P5VS campaign has not improved pain outcomes<sup>41,42</sup>. For instance, Frasco *et al.*<sup>41</sup> found that the use of opioid analgesics increased significantly in the post-anaesthesia care unit (PACU) in their hospital. The overuse of opioids has likewise resulted in life-threatening opioid-related adverse events<sup>43, 44</sup>. Vila *et al.*<sup>44</sup> reported that even though patient satisfaction with pain services was increased following the implementation of the P5VS initiative, opioid-related adverse drug reactions, including oversedation or respiratory depression, increased from 11.0 to 24.5 per 100,000 inpatient hospital days in one US hospital<sup>44</sup>. This finding highlights the risk of allowing patient satisfaction surveys to influence pain management decisions<sup>15</sup>.

The reliance on unidimensional tools as the sole approach to measure pain is now being discouraged because cut-off values commonly used by healthcare providers do not reflect a patient's desire for additional analgesics<sup>34, 35</sup>. Furthermore, patients have reported difficulties in describing the complexity of their pain experience through a single numerical value, descriptive words or as a line on a scale<sup>23</sup>. Some patients have refused to take pain medicines for fear of side effects even when NRS cut-off points signify treatment according to the institutional pain protocol<sup>35</sup>. Studies have also showed that patients' lack of knowledge on the use of pain assessment scales can result in errors, which lead to a possible risk of overtreatment when healthcare providers strictly follow the score-based algorithm for prescribing analgesics without looking at the multiple aspects of pain other than intensity<sup>35</sup>. A further complicating factor is that some patients and pain professionals interpret pain scores differently<sup>45</sup>. As a consequence of these inconsistencies in pain assessment, difficulties or even errors in treatment decisions may arise.

Despite positive intentions, the P5VS campaign has fallen short<sup>15</sup>, as it has not achieved the expected outcomes of improving pain outcomes for patients. American Medical Association (AMA) delegates and the Centres for Medicare and Medicaid Services have all voted to stop measuring P5VS, given that the campaign—along with other factors that will be discussed later in this review—contributed to the opioid epidemic<sup>15, 21</sup>. The opioid epidemic has emerged and caused widespread public health concerns in the US. In 2015, there were more than 33,000 deaths from opioid overdose, with half of these cases resulting from dispensed or diverted prescription opioids<sup>46-48</sup>. Similar trends have emerged in

Canada, where one-third of people who died between 2013 and 2016 as a result of drug-related overdose had been prescribed an opioid at their time of death<sup>49</sup>. Between 2010 and 2020, the number of opioid-related deaths in England increased by 54%, from 1384 to 2138 deaths annually<sup>50</sup>.

### **2.3.3 New recommendations for pain assessment and management**

#### **2.3.3.1 Multidimensional pain assessment tools**

A comprehensive multidimensional assessment that provides information about the characteristics of pain and its impact on the individuals has been recommended in evidence-based guidelines, expert consensus reports and position statements from health professional regulatory bodies to be incorporated as a fundamental component of appropriate pain management<sup>34, 51, 52</sup>.

Several multidimensional tools are available. The most frequently used multidimensional pain assessment tools developed for chronic pain include the McGill pain questionnaire (MPQ), which assesses the sensory, affective, location and evaluative dimensions of pain<sup>53</sup>, and Brief Pain Inventory (BPI), which assesses pain intensity and associated disability<sup>54</sup>. Some efforts have been made to incorporate these tools in the assessment of postoperative pain<sup>55</sup>. However, they involve detailed assessments that last anywhere from 5 minutes to 30 minutes for each patient, a length of time that may hinder their routine use for frequent assessment when employed in acute care practice<sup>21</sup>.



### 2.3.3.2 Functional pain assessment tools

A convenient alternative to multidimensional tools could be the assessment of the functional impact of pain, including the objective assessment by a healthcare provider who evaluates if the pain prevents the patient from performing necessary activities to promote recovery<sup>56</sup>. Hence, treatment options for pain will be used to maximise functional capacity rather than striving to reduce the postoperative pain intensity for patients to a certain numerical value<sup>21, 22</sup>. As suggested by Kehlet *et al.*<sup>57</sup>, the restoration of function by enabling the patient to breathe, cough, ambulate and turn in the bed is one of the important aims of postoperative pain relief. Furthermore, in the current opioid epidemic in the US, where opioid prescriptions and related misuse are increasing<sup>58</sup>, implementing measures that focus on the functional impact of pain may have a role in educating patients about various pain interventions other than opioid that can be indicated as a treatment option<sup>59</sup>.

The Functional Activity Score (FAS) is a simple three-level ranked categorical score designed to be applied at the point of care<sup>26</sup>. Its primary purpose is to assess the ability of the patient to perform an appropriate activity at their current level of experienced pain. The patient is asked to complete the activity with nurse-assisted care (e.g. walking, turning in bed, coughing, deep breathing, etc.)<sup>17</sup>. Scott and McDonald suggested assessing the ability of a patient to perform an activity by using FAS<sup>26</sup> as follows:

A — no limitation; the patient can undertake the activity without limitation due to pain (pain intensity score is typically 0 to 3).

B — a mild limitation; the patient can undertake the activity but experiences moderate to severe pain (pain intensity score is typically 4 to 10).

C — a significant limitation; the patient is unable to complete the activity due to pain or pain treatment-related adverse effects (independent of pain intensity scores).

The obtained score can then be used to monitor the effectiveness of analgesia on function and modify the interventions as required.

The implementation of FAS into the healthcare system may improve the assessment and management of pain. However, FAS has not been independently validated<sup>21</sup>. Therefore, an evaluation of its measurement properties compared to those of the most frequently used unidimensional pain assessment tools is necessary to assess the correlation and consistency between the scores obtained by the tools for a single patient.

## **2.4 Pain management**

Effective postoperative pain management is important for ensuring patient comfort, facilitating recovery and mobility, ensuring patient satisfaction, and reducing healthcare costs<sup>60</sup>. On the converse, failure to control postoperative pain adequately can delay patient mobilisation and impair respiratory effort which are contributing risk factor for venous thromboembolism, atelectasis and respiratory infection. Consequently, prolongation of hospital stay and transition of acute to chronic pain can occur, which may lead to a referral to outpatient chronic pain management services<sup>26</sup>.

Owing to the complex and subjective nature of pain, the appropriate management of postoperative pain can be difficult to achieve despite available interventions, such as epidural analgesia and patient-controlled analgesia, and the availability of acute pain teams<sup>56, 61, 62</sup>. Various types of analgesics can be used to manage postoperative pain and a multimodal approach is often adopted, which involves using different classes of drugs to target multiple parts of the pain processing pathway. A brief overview of some of these analgesics will be provided in the following section, with a specific focus on opioid analgesics.

### **2.4.1 Non-steroidal anti-inflammatory drugs and paracetamol**

NSAIDs are commonly used to manage mild to moderate pain and are usually administered orally or intravenously. They inhibit the cyclooxygenase (COX) enzyme which is responsible for production of prostaglandins in response to pain, fever, and trauma. Therefore, NSAIDs decrease the tissue inflammation due to surgical trauma along with decreasing pain perception and peripheral nociception<sup>63</sup>. When used as a component of a multimodal approach, NSAIDs produce superior analgesia and are associated with a decrease in some opioid related adverse events, including nausea, vomiting and postoperative sedation<sup>64</sup>. While NSAIDs have been shown to be effective in managing postoperative pain<sup>65</sup>, they can be associated with platelet dysfunction, cardiovascular risks<sup>66</sup>, gastrointestinal tract irritation or bleeding, anastomotic leak, and some (e.g., diclofenac) can induce acute kidney injury<sup>67</sup>.

Like NSAIDs, paracetamol (acetaminophen) can be administered orally, intravenously or rectally. It is an antipyretic and has a modest anti-inflammatory

action. Despite being commonly used as an analgesic, its mechanism of action remains unclear<sup>68</sup>. When administered as a part of multimodal approach, paracetamol resulted in an additive synergistic analgesic effect<sup>64</sup>. As paracetamol is cleared by the liver, its use is contraindicated for people with liver failure<sup>69</sup>.

### **2.4.2 Gabapentinoids**

Gabapentinoids (gabapentin and pregabalin) are antiepileptic medicines that have been shown to be effective for managing chronic neuropathic pain. Meta-analysis showed that preoperative administration of a single dose of gabapentin or pregabalin is associated with reduced postoperative pain within 24 hours, but it is also linked to increased postoperative dizziness, sedation and visual disturbances<sup>70</sup>. Current evidence varies on whether gabapentinoids should be administered before or after surgery, complicating the decision-making process regarding their usage<sup>71</sup>. Both drugs are limited by central nervous system side-effects and need careful up and down titration. In April 2019, they were recategorised as controlled medicines in the UK to minimise deaths related to their misuse<sup>72</sup>.

### **2.4.3 Opioids**

Opioids have been the mainstay treatment for acute pain for many years. Opioids can be categorised based on their synthetic process, the receptors they interact with, and their pharmacological effects<sup>73</sup>. Natural opioids or 'opiates' (e.g., codeine, morphine) are extracted from the opium poppy plant, semi-synthetic opioids (e.g., buprenorphine, oxycodone) are derived from chemical modifications of these natural compounds, whereas synthetic opioids like fentanyl and

tapentadol are entirely artificially produced to replicate the effects of natural opioids<sup>73</sup>.

Opioids produce their analgesic effects by interacting with four opioid receptors: the classical mu ( $\mu$ ), delta ( $\delta$ ), and kappa ( $\kappa$ ) receptors, and the nonclassical nociceptin receptor<sup>74</sup>. The interaction with these receptors leads to a wide range of effects, including analgesia (all receptor types), euphoric effect (primary throughout  $\mu$ ), respiratory depression (involving  $\mu$  and  $\delta$ ), and dysphoria ( $\kappa$ )<sup>75</sup>. Opioids can also be classified in potency based on their affinity for the  $\mu$  receptor and efficacy. Opioids are classified as controlled drugs in the UK, and their use is legal when prescribed by licensed practitioners and taken by the person for whom the prescription was intended. However, some low-strength weak opioids are available over the counter (OTC) combined with other analgesics; these include co-codamol (paracetamol and codeine) and co-dydramol (paracetamol and dihydrocodeine).

Prescription opioids come in various formulations, such as solutions, tablets, capsules, syrups, injectable liquids, skin patches, and transdermal preparations. These opioid formulations can be classified into one of two categories: short-acting (immediate release) or long-acting (modified release). Short-acting opioids typically provide relief for about three to six hours, whereas long-acting opioids can extend their effects for 12 to 24 hours or longer in case of skin patches, reducing the need for frequent dosing to maintain their effectiveness.

While opioids have an established role in managing moderate to severe acute pain and form an integral component of balanced multimodal analgesic strategies,

their use is not without risks and potential side effects as they interact with endogenous receptors located in the central nervous system, gastrointestinal tract, respiratory and peripheral tissues. Side effects of opioids include constipation, postoperative ileus, sedation, nausea, vomiting, urinary retention, and shivering<sup>76</sup>. Hypoventilation can also result from opioid administration, characterised by a reduction in respiratory rate and a decrease in airflow<sup>77</sup>. In higher doses or when strong opioids are used, they can induce severe ventilatory impairment and sleep-disordered breathing<sup>78</sup>.

Opioid induced hyperalgesia (OIH) can result from opioid use and is manifest by a increase in pain intensity; as diffuse pain (or pain disseminating to other locations); or as an exacerbation in pain sensation to normal external stimuli<sup>79</sup>. OIH has been observed with various opioids either in experimental<sup>80</sup> or clinical trials<sup>81</sup>. Closely linked to OIH is the concept of opioid tolerance. This occurs when the administration of an opioid medicine leads to adaptations that cause a decrease in effectiveness over time with higher doses being needed to achieve a given analgesic effect<sup>82</sup>. Tolerance develops not only to the pain-relieving properties of opioids but also to side effects such as nausea and sedation. Acute withdrawal syndrome is a set of clinical signs of symptoms including anxiety, restlessness, muscle aches that develops from opioid cessation.

Opioids are mainly metabolised by the liver, using the cytochrome P450 (CYP450) family of enzymes, particularly cytochrome P450 2D6 (CYP2D6) and cytochrome P3A4 (CYP3A4)<sup>83</sup>. Genetic variations in these metabolising enzymes can lead to individuals being categorised as poor metabolisers, extensive metabolisers, or

ultra-rapid metabolisers. Some opioids are prodrugs requiring activation by CYP2D6 to produce analgesic activity. Examples of opioid prodrugs include codeine, which undergoes metabolism to morphine, and tramadol, which is transformed into its active metabolite<sup>84</sup>. Poor metabolisers of CYP2D6 may experience reduced efficacy with opioids like codeine and tramadol and increased side effects. Therefore, understanding these metabolic pathways and genetic variations is crucial to ensure opioid effectiveness and minimising adverse effects in clinical practice.

#### **2.4.4 Racial disparities in pain assessment and management**

Racial and ethnic disparities within the context of pain assessment and analgesic prescribing have been previously reported in different healthcare settings, raising concerns that minority patients, particularly patients of black race, are more likely to receive inadequate pain assessment and management compared to their white counterparts<sup>85-88</sup>. It is possible for a healthcare provider to give lower ratings of a patient's pain compared to the patient's self-assessment of pain, but this discrepancy was reported to be larger for minority ethnic populations<sup>89,90</sup>. Staton *et al.* found that observed physicians underestimated the pain scores of patients of black race by more than 2 points on an 11-point numeric pain rating scale 47% of the time, versus 33.5% for patients of white race ( $p < 0.0005$ )<sup>85</sup>.

The variation in pain assessment could result from implicit or explicit bias about different races (e.g., that individuals of some racial groups are more tolerant of pain, people of black race have thick skin, are less pain-sensitive and possess super strength)<sup>91, 92</sup>. Studies have also shown that racial discrepancy extends to opioid

prescribing practices, with some studies showing that white patients being more likely to be prescribed opioids than black patients<sup>87,88,93</sup>. It remains important that the mechanisms behind disparities in pain assessment and management are complex and should be examined from perspectives of hospital, healthcare providers and patients.

## **2.5 Postoperative opioid utilisation**

There is a widespread practice of prescribing opioids to alleviate postoperative pain because of their established role in managing acute pain<sup>94</sup>. However, there are variable opioid utilisation patterns which may be influenced by the advertising of some types and formulations of opioids over other types leading to variation in choice and amount of opioid prescribed for each patient and between different countries. Moreover, excessive opioid prescribing leads to a high number of unused tablets which might be available for misuse. These issues will be explored in detail in the following section.

### **2.5.1 Variation in postoperative opioid prescribing**

There is international variation in opioid prescribing patterns for patients undergoing similar procedures. Comparative studies illustrate cross-cultural variations in the role of opioids and provide some hypotheses regarding drivers of inappropriate prescribing<sup>95</sup>. Some studies have highlighted discrepancies between the US and other countries in opioid prescribing<sup>95</sup>. However, there remains an absence of data comparing prescribing patterns in the US or Canada with the UK.

The US has usually been used as a comparator as it has the highest opioid consumption per capita in the world<sup>96</sup>. For example, based on physician surveys,



the dependence on opioids for the management of acute pain was found to be higher in the US compared with Japan, France and the Dominican Republic<sup>97-99</sup>. In the same way, researchers found that 77% of people who underwent surgery for hip fracture in a US hospital were prescribed an opioid, while none were prescribed for patients who underwent the same procedure in the Netherlands<sup>100</sup>.

Recently, significant findings have been reported from a large-scale cohort study compared the frequency, amount and type of opioid prescribed after four minor surgical procedures across the US, Canada, and Sweden<sup>95</sup>. Ladha *et al.* found that the rate of filled opioid prescriptions in the US and Canada during the first week after discharge was 7-times greater than in Sweden. Although the frequency of filled prescription was similar between Canada and the US, patients treated in the US hospitals received higher quantities of opioids compared with the other two countries. Moreover, codeine and tramadol together accounted for around 50% of prescribed opioids in Canada and Sweden compared with only 7% in the US. A multicentre study conducted in England found that 52% of patients were discharged with an opioid prescription following major abdominal surgery<sup>101</sup>.

### **2.5.2 Excess prescribing following surgery**

Data from several studies showed variable and excessive postoperative opioid prescribing patterns after different surgical procedures<sup>102, 103-105</sup>, which might be a contributing factor to the current opioid epidemic in the US and Canada<sup>106</sup>.

A considerable amount of literature reported that surgeons tend to prescribe opioid tablets in a quantity that exceeds patients' consumption<sup>102, 107-109</sup>. For instance, Table 2-2 shows that surgeons usually prescribe a high number of tablets

(e.g. 60 tablets) while ignoring any patient comorbidities and factors that might either exacerbate or decrease pain<sup>110, 111</sup>. Other authors reported a lower mean number of prescribed tablets that ranged from 16.8 to 40 tablets per patient, the number of unused tablets was still high and ranged from 11.2 to 31.9 per patient, accounting for 62% of unused tablets prescribed by surgeons<sup>112, 113</sup>. This one-size-fits all approach, which ignores the need for variable quantities based on individual opioid doses and the frequency of their use, can lead to significant waste and potentially result in diversion or misuse.

In addition, one systematic review identified six prospective cohort and cross-sectional studies of intermediate quality that looked at oversupply of opioids following several surgical procedures<sup>109</sup>. Bicket *et al.* found that all included studies showed a high proportion of patients, ranging from 67% to 92%, reported unused opioid tablets and the number of leftovers ranged from 42% to 71% of the total dispensed tablets<sup>109</sup>. Despite the importance of these results, these findings cannot be extrapolated to other patients since two of the included studies in the review have a small sample size; only 30 patients are included<sup>115</sup>. Moreover, the lack of reporting crucial information like missing data and non-respondent rates in the conducted surveys can limit the reliance on the findings.

Another systematic review identified 11 patient survey studies evaluating opioid use in 3525 patients after discharge from various inpatient and outpatient procedures<sup>118</sup>. The sample size in included studies ranged from 50 to 1416 (median 223) participants, and the proportion of prescribed and used opioids

ranged from 11% to 90.1%, and opioid consumption ranged from 5 to 22 tablets<sup>102</sup>,

107, 114 .

**Table 2-2. Results of studies evaluating post-operative opioid prescribing and utilisation**

<b>Study</b>	<b>Country / year of publication</b>	<b>Method of data collection</b>	<b>Procedures</b>	<b>Number of patients</b>	<b>Mean number of prescribed tablets</b>	<b>% of unused opioid tablets</b>
Rodgers <i>et al.</i> <sup>102</sup>	US/ 2012	Telephone survey	Outpatient upper extremity surgery	287	30	77%
Kim <i>et al.</i> <sup>114</sup>	US/ 2016	interview at first postoperative visit	Orthopaedics, hand, wrist, elbow, forearm, or shoulder surgery	1416	24	66%
Bartels <i>et al.</i> <sup>115</sup>	US/ 2016	Survey via email or postal mail	Caesarean delivery and thoracic surgery	30 31	53	57%
Bates <i>et al.</i> <sup>107</sup>	US/ 2016	Telephone survey or mail-out survey	Urologic procedures	275	23	42%
Hill <i>et al.</i> <sup>105</sup>	US/ 2016	Telephone survey	Outpatient general surgery procedures	642	26	71%
Harris <i>et al.</i> <sup>116</sup>	US/2013	Telephone survey	Dermatology	72	9	68%
Maughan <i>et al.</i> <sup>117</sup>	US/ 2016	Text message and telephone survey	Elective surgical extraction of impacted teeth	79	28	54%
Kumar <i>et al.</i> <sup>104</sup>	US/ 2017	Telephone or email survey	Outpatient shoulder surgery	81	55	37%

Work by Sabatino *et al.*, in a telephone survey of 198 patients treated in a US hospital indicated that around 29% of prescribed opioids were unused after hip replacement surgery, and 18% were unconsumed by patients who underwent knee replacement<sup>119</sup>. Therefore, it is important to consider the possibility of recall bias as patients may forget the actual number of used tablets.

The studies reviewed so far cannot provide a complete picture of global opioid oversupply following surgical procedures because of the small sample size used, and lack of studies evaluating prescribing patterns outside North America. This gap in current understanding provides an opportunity for research around opioid prescribing patterns after surgery in the UK and other countries.

### 2.5.3 Unused opioids after prescribing

Multiple studies have reported a lack of proper disposal of unused tablets. The findings from various surveys after several surgical procedures found that only between 4% and 59% of patients planned proper disposal<sup>117, 120</sup>. Furthermore, at least 70% of patients kept excess opioids in unlocked storage at home<sup>105, 107, 115</sup> ignoring the fact that this can be a common source for diversion, misuse or non-medical use in adolescents<sup>121, 122</sup>. Table 2-3 defines terms describing opioid misuse.

**Table 2-3. Terms describing opioid misuse**

<b>Opioid misuse</b>	The use of opioid medicines in a manner or dose other than directed by a physician <sup>123</sup>
<b>Opioid diversion</b>	The inappropriate use of a medication by current patients as well as use by individuals to whom it was not prescribed <sup>124</sup>
<b>Opioid abuse</b>	The use of opioids to feel euphoria <sup>123</sup>

Khan *et al.* found that the odds ratio (OR) of opioid overdose for family members of patients who were prescribed opioids was between 2.71 [95% confidence interval (CI) 2.42– 3.03 ] and 15.1 [95% CI, 8.66–26.27], the higher odds were associated with stronger prescriptions including  $\geq 90$  morphine milligram equivalents (MME) per day<sup>125</sup>.

The non-medical use of opioids, defined as using opioid without a prescription or specific indications, or using opioids for the feeling or the experience caused by them, can lead to serious harms<sup>126</sup>. One study found that the non-medical consumption of various opioids was linked to transitioning to heroin administration<sup>127</sup>. Likewise, Muhuri *et al.* reported that patients using prescription opioids for non-medical purposes had a 19-times higher incidence of heroin use compared with individuals who reported no previous non-medical use of opioids<sup>128</sup>. More than 80% of heroin users had a history of use or misuse of opioid analgesics<sup>129</sup>. Notably, studies that have included people from different economic backgrounds and geographical areas have shown comparable associations as well<sup>130-132</sup>.

## **2.5.4 Persistent postoperative opioid use (PPOU)**

### **2.5.4.1 Definitions**

PPOU refers to the extended opioid use beyond the initial prescription provided by the healthcare provider for the management of acute pain. However, an increasing body of literature has indicated that a proportion of individuals prescribed opioids for acute pain do not discontinue usage within the expected

period. Instead, they continue to receive opioid prescriptions beyond the three-month period from the onset of the acute pain event. In this context, long-term opioid use is often referred to as PPOU, and it is typically unintentional when the initial prescription is issued.

The definition of PPOU includes essential information to measure opioid use, the timeframe to measure opioid use and the quantity of opioid that required to assign the patient as a persistent user<sup>133, 134</sup>. A systematic review identified observational studies evaluating several definitions of PPOU. The review found 29 different definitions used to define PPOU<sup>134</sup> and summarised in Table 2-4.

The most common definition that was reported in 22 studies was filling one or more prescriptions, or self-reported consuming opioids based on a questionnaire, at a distinct time point after surgery<sup>134</sup>. Twelve studies used this definition focusing on the period from 90 days to 1 year after surgery<sup>110, 141, 144, 151, 161, 164, 165</sup>. The second most frequent used definition was the duration of filled or written opioid prescriptions (15 studies). The least used definition (six studies) relied on the number of written or filled prescriptions, or their associated duration or dose<sup>134</sup>.

**Table 2-4. Definitions of persistent postoperative opioid use**

Definition	Source
<b>Prescriptions filled, or opioid consumed at a distinct time point. Filled more than 30 days postoperatively</b>	
Opioid prescription beyond 30 days after date of surgery	Stafford <i>et al.</i> <sup>135</sup>
Opioid consumed 6 weeks postoperatively	Grace <i>et al.</i> <sup>136</sup>
Filled 90–180 days postoperatively	Cancienne <i>et al.</i> <sup>137</sup>
Filled at least one opioid prescription between 90 and 180 days after surgery	Qureshi <i>et al.</i> <sup>138</sup>
Continuation of prescription opiates greater than 12 weeks postoperatively	Ladha <i>et al.</i> <sup>139</sup>
Filled prescription within 1 to 90 days after discharge; and filled at least one additional opioid prescription between 91 and 180 days after surgery	Holman <i>et al.</i> <sup>140</sup>
Filled prescription within 30 days before surgery and 14 days after discharge	Clarke <i>et al.</i> <sup>141</sup>
Filled at least one additional opioid prescription between 90 and 180 days after surgery	Johnson <i>et al.</i> <sup>142</sup>
Filled at least one opioid prescription overlapping 90 or 180 days	Lee <i>et al.</i> <sup>143</sup>
Filled at least one opioid prescription overlapping 90 or 180 days	Brummett <i>et al.</i> <sup>144</sup>
Opioid consumption at time of interview (180 days postoperatively)	Lindestrand <i>et al.</i> <sup>145</sup>
<b>Filled 90–120 days postoperatively</b>	Goesling <i>et al.</i> <sup>127</sup>
Opioid use, based on questionnaire, between 90 and 120 days after surgery	Kim <i>et al.</i> <sup>146</sup>
	Stark <i>et al.</i> <sup>147</sup>
	Marcusa <i>et al.</i> <sup>148</sup>



Definition	Source
(1) Filled prescription within 30 days before surgery and 30 days after discharge; (2) filled at least one additional opioid prescription between 90 and 120 days after surgery	
<b>Filled 90–365 days postoperatively</b>	Mueller <i>et al.</i> <sup>149</sup>
Filled at least one opioid prescription between 90 and 365 days after surgery	Pang <i>et al.</i> <sup>150</sup>
Filled more than 1 opioid prescription more than 90 days after surgery	Alam <i>et al.</i> <sup>151</sup>
Filled within 60 days of the 1-yr anniversary date (e.g., 305–425 days after the index date)	
Opioid use at 12 months (365 days) postoperatively	Pugely <i>et al.</i> <sup>152</sup>
Filled more than 3 years postoperatively	
Filled at 795 days postoperatively	Yang <i>et al.</i> <sup>153</sup>
<b>Opioids filled at multiple time points</b>	
Filled at three distinct time points: (1) 28–56 days, (2) 90–180 days, and (3) 300–365 days after surgery (or first two time intervals if the patient had an event death and/or graft loss between 3 and 12 months)	Kulshrestha <i>et al.</i> <sup>154</sup>
<b>60 days of noncontinuous use</b>	
60 days of noncontinuous prescriptions filled (within 275 days, excluding the first 90 days)	Kent <i>et al.</i> <sup>133</sup>
90 days of continuous use or 120 days of noncontinuous use	Hansen <i>et al.</i> <sup>155</sup>
90 days of continuous use or at least 120 days of noncontinuous use (within 275 days, excluding the first 90 days)	Inacio <i>et al.</i> <sup>156</sup>
<b>150–180 days of continuous use</b>	
Prescribed opioids for more than 6 contiguous months after surgery (followed for 24 months postoperatively)	Politzer <i>et al.</i> <sup>157</sup>

Definition	Source
Patient reported continuous consumption of opioid (with no gaps greater than 5 days) in the 150 days after discharge	<i>Carroll et al.</i> <sup>158</sup>
Opioids prescribed uninterrupted for greater than 3 months after surgery	<i>Rozet et al.</i> <sup>159</sup>
<b>365 days of continuous or noncontinuous use</b>	
365 days of filled opioid prescriptions (within 24 months after surgery)	<i>Connolly et al.</i> <sup>160</sup>
Continuously filled prescriptions (with no gaps greater than 14 days) in the 12 months after discharge	<i>Hadlandsmyth et al.</i> <sup>161</sup>
<b>Time to discontinuation</b>	
Combination of days supplied and number of prescriptions	<i>Sun et al.</i> <sup>110</sup>
1) 10 or more prescriptions; or (2) more than 120 days' supply within the first year of surgery (excluding the first 90 postoperative days)	<i>O'Connell et al.</i> <sup>162</sup>
(1) 10 or greater opioid prescriptions (over 90 or more days); or (2) 120 or more total days' supply dispensed (within 330 days, excluding the first 30 days)	<i>Raebel et al.</i> <sup>163</sup>
<b>Model derivation approaches</b>	
Having any use of opioid prescriptions in each of the 12 months continuously based on a group-based trajectory modelling	<i>Kim et al.</i> <sup>146</sup>

Reproduced from Jivraj *et al.* (2020)<sup>134</sup>, with permission from Wolters Kluwer Health, Inc]

Jivraj *et al.* then performed a population-based cohort study to evaluate the agreement between several definitions for estimating the incidence of PPOU when applied to the same cohort of Canadian patients. The authors found that more restricted definitions of opioid use following procedures such as '90 days of continuous prescribing or 120 non-consecutive filled prescriptions or 10 more prescriptions in 90 to 365 days postoperatively' had a high level of agreement to identify the same patient as a persistent users, (Cohen's Kappa ( $\kappa$ ) = 0.84; 95% CI, 0.82 - 0.87)<sup>134</sup>.

To provide an accurate definition, Kent *et al.* suggested that the quantity of opioid used to define a patient as a persistent user should vary between opioid-naïve and non-opioid naïve patients as opioid-tolerant patients may be predicted to consume more opioids after surgery<sup>133</sup>. Therefore, the American Society for Enhanced Recovery published a consensus statement to provide a standardised definition for persistent opioid use. They proposed that for patients not taking opioids prior to surgery, using opioids for at least 60 days in the 90-365 days following surgery should be considered long-term use<sup>133</sup>. However, in opioid tolerant patients, persistent use is defined as an increase in opioid use in the 90-365 days after surgery when compared with their use in the 90 days before surgery<sup>133</sup>. Unlike the other definitions that were extensively adopted in US and Canadian studies to define PPOU, the proposed definition has not been widely used.

The evidence around the continuous use of postoperative opioids has considerable methodological inconsistencies. The most apparent one is the wide

variability between different studies in defining persistent use of opioids as an outcome measure, which hinders the comparison between studies<sup>133, 134</sup>. Since no previous studies have examined persistent opioid use in the UK, it is essential to adopt one of the frequently used definitions for this outcome to compare with data from other countries.

#### **2.5.4.2 Outcomes of PPOU**

It is expected that acute pain will resolve before 3 months postoperatively, and any pain after that may not benefit from the use of opioids needs further assessment. The use of opioids to manage chronic pain might be appropriate for some patients despite the limited evidence regarding its effectiveness in providing relief and improving function. Current guidelines for the use of opioids in the treatment of chronic non-cancer pain highlight that physicians should prioritise non-opioid therapies as the preferred method for managing chronic pain<sup>166, 167</sup>. In 2022, a report from the Agency for Healthcare Research and Quality found that opioids might offer limited benefits in managing chronic non-malignant pain conditions. They are not superior to non-opioid therapy and are linked to an increased risk of short-term and long-term adverse effects<sup>168</sup>.

A systematic review of randomised clinical trials published in 2018 found that opioids were associated with small but statistically significant improvements in pain and physical functioning and an increased risk of vomiting compared with a placebo. Comparisons of opioids with non-opioid analgesics, including NSAIDs, anticonvulsants, and tricyclic antidepressants, showed that the benefits for pain

and function were similar<sup>169</sup>. When opioids are initiated to manage chronic pain, it is recommended to establish treatment goals and assessment of harms and benefits should be carried out regularly<sup>167</sup>.

Long-term opioid use after surgery, may have a negative impact on both patients and society<sup>170, 171</sup>. In a systematic review conducted regarding the adverse effects linked to the use of opioids for chronic pain, patients using opioids for longer than 90 days over a 12-month period were 14.9 times more likely to experience opioid abuse or dependence compared with those using non-opioid analgesics<sup>168</sup>.

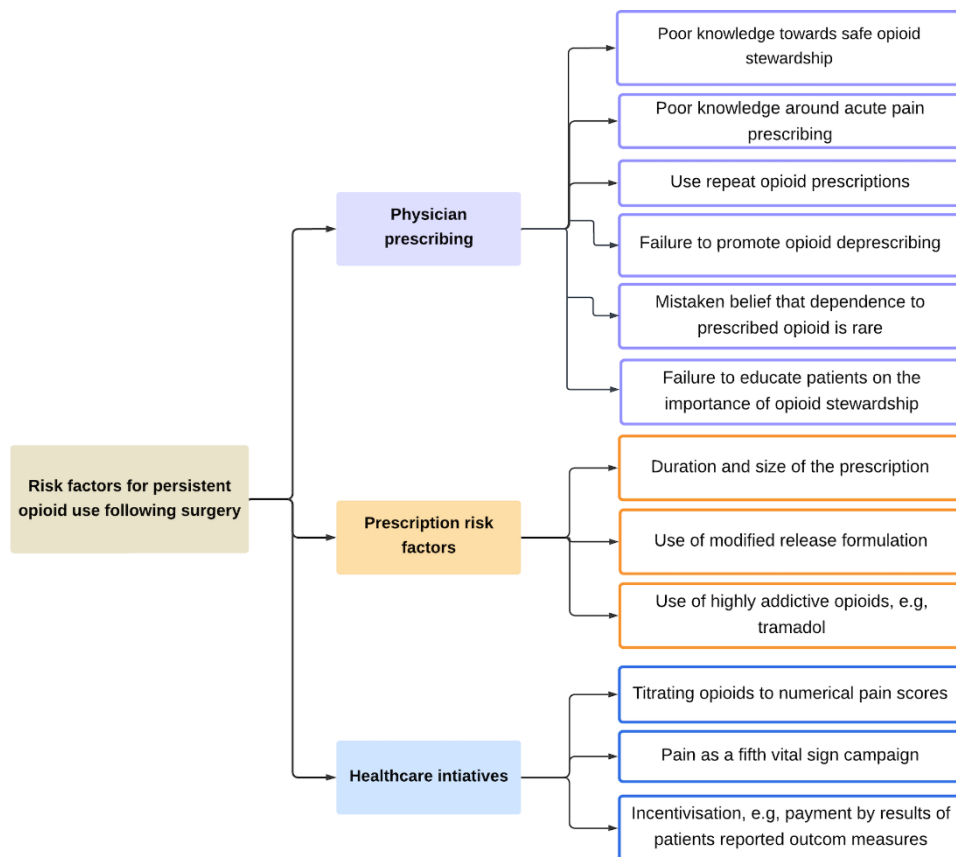
The risk of hospitalisation due to opioid-related harms was higher in opioid-naïve patients who continued to use opioids for one year following initiation compared with those with short-term opioid use<sup>172</sup>. Patients using long-term opioids had a 1.3 times higher risk for fractures<sup>173, 174</sup>, and a three-fold higher risk of myocardial infarction compared with non-users<sup>175</sup>. A US study has indicated that extended opioid use may lead to increased healthcare expenses compared with shorter-term usage<sup>176</sup>.

An extensive body of research has shown that numerous patient-related factors might predispose individuals to persistent opioid use<sup>110, 144, 164, 177</sup>. These include:

- Age<sup>110</sup> (50 years or older)
- Sex (male)<sup>110, 141</sup>
- Sex (female)<sup>156, 178, 179</sup>
- Lower household income, deprivation<sup>141</sup>
- Specific comorbidities (diabetes mellitus, heart failure, pulmonary disease)<sup>110, 141</sup>
- Mood disorders (depression, anxiety)<sup>177, 180</sup>
- Preoperative opioid use<sup>110</sup>
- Early postoperative opioid use<sup>151</sup>
- Specific preoperative medications (benzodiazepine, antidepressants, angiotensin converting enzyme inhibitors)<sup>110, 141, 164</sup>
- Preoperative history of drug misuse<sup>144, 164</sup>
- Preoperative tobacco use<sup>144, 164</sup>
- Preoperative pain disorders (back pain, neck pain, arthritis and centralised pain disorders)<sup>110</sup>

Considering these patient risk factors might assist healthcare providers to tailor postoperative pain management plans to avoid PPOU. Figure 2-5 Illustrates identified risk factors for PPOU.

Numerous studies have shown that the use of opioids prior to surgery is the most important factor for prolonged opioid use<sup>141, 144</sup>, albeit the exact definition of preoperative opioid use varies between studies. One systematic review that synthesised results of studies around the risk factors of persistent opioid use after



**Figure 2-5. Risk factors associated with PPOU**

Redrawn from Quinlan *et al.* (2019)<sup>181</sup>

surgery found that 12 articles defined it as opioid use for more than 90 days prior to surgery. While six studies considered it as use for only 3 months before surgery, and some studies did not clearly provide a definition<sup>171</sup>.

Kent *et al.* reported that the rate of persistent use following orthopaedic and abdominopelvic surgery was 10 times higher in non-opioid naïve patients<sup>133</sup>. This was attributed to the development of tolerance or hyperalgesia which may make the control of immediate postoperative pain more challenging and require higher opioid doses and result in persistent use (59% opioid demand vs. 26% in the opioid naïve population)<sup>171</sup>. These findings of Kent *et al.*<sup>133</sup> are comparable to those of Mohammadi *et al.*<sup>182</sup> who conducted a meta-analysis to report the pooled effect of risk factors that predispose patients to prolonged opioids use. Mohammadi *et al.*<sup>182</sup> found that prior use of opioids (number needed to harm (NNH) = 3; OR= 11.04 [95% Confidence Interval (CI) = 9.39 to 12.97]; p < 0.001), depression (NNH = 40; OR = 1.62 [95% CI = 1.49 to 1.77]; p < 0.001), longer hospital stay (NNH = 25; OR = 2.03 [95% CI = 1.03 to 4.02]; p = 0.042), and history of back pain (NNH = 23, OR = 2.10 [95% CI = 2.00 to 2.20]; p < 0.001) were among the most significant predictors of persistent opioid use. When considering sex difference as a risk factor for persistent use, males usually have a lower risk<sup>155, 171, 178, 179</sup> despite some studies showing opposite findings<sup>110, 141</sup>.

Because of the retrospective, observational design of studies included in these previous systematic reviews and meta-analysis, there is a possibility of confounding even after risk adjustment. Therefore, the association described in these studies cannot be interpreted as causation<sup>183</sup>. For instance, data from health administrative claims do not provide sufficient information about differences in severity of pain before and after surgery which can have a greater probability of developing chronic pain<sup>151, 184</sup>.



### 2.5.4.3 Incidence and risk of PPOU

Both minor and major surgical procedures are associated with an increased risk of persistent opioid use<sup>141, 151, 182</sup>. Brummett *et al.*<sup>144</sup> suggested that the complexity of surgery plays a minor role in predicting the risk of persistent opioid use; they found a similar incidence of chronic postoperative opioid use between major and minor surgical procedures (6.5% and 5.9%, respectively). Even opioids prescribed for ambulatory surgery or short-stay surgical procedures have been found to increase the risk of persistent opioid use, with the reported risk in several studies ranging 5% to 7.7%<sup>102, 151, 185</sup>.

In contrast to these findings, a meta-analysis that reported the pooled hazard ratio of risk factors for PPOU showed that exposure to invasive procedures augmented the possibility of long-term opioid use (Hazard ratio (HR) = 1.14, 95% CI = 1.09–1.19)<sup>182</sup>. However, this finding must be approached with some caution as the heterogeneity of the included observational studies and variable definitions of PPOU, may have affected the findings.

Retrospective studies looking at the persistent use of opioids after surgery have been conducted in several countries (e.g. the US, Canada and Australia). Most published works in this area conclude that opioids prescribed during and after surgery might trigger long-term opioid use<sup>186</sup>. However, the rates, prevalence and risk factors associated with this outcome vary according to the population studied, methodologies used, surgical procedures. Other causes leading to variable rates will be discussed below within the text.

Considering three retrospective cohort studies conducted in Canada, there is a discrepancy in the reported risk of persistent use (Table 2-5). The reported risk ranged from 0.4% to 7.7% for opioid-naïve patients; however, these studies restricted inclusion to patients older than 66 years<sup>141, 177, 187</sup>. This variation in risk may be attributed to the different approaches used to obtain the results and the types of surgeries included. Moreover, these three studies focused on major abdominal surgical procedures and excluded orthopaedic procedures, which might have resulted in different results if included in the analysis.

There is extensive variation in the reported percentages of patients persistently using opioids after surgery in the US. Some surgical procedures resulted in a low rate of persistent use. For instance, Bateman *et al.*<sup>164</sup> found that only 1 in 300 (0.23%) opioid-naïve women become persistent opioid users in the first year following a Caesarean delivery. Sun *et al.*<sup>110</sup> reported nearly identical rates of persistent use after Caesarean delivery, even though they used a different definition for persistent use (Table 2-5). Likewise, a relatively low risk of 0.5% was reported for opioid-naïve women following a hysterectomy<sup>188</sup>. However, Brummett *et al.*<sup>144</sup>, looking at several types of surgical procedures, including hysterectomy, reported a higher incidence (5%) of new persistent opioid use, which is ten times greater than the incidence rate reported by Swenson *et al.*<sup>188</sup>. Brummett *et al.*<sup>144</sup>, also noted that colectomy appeared to have greater risk of persistent opioid use compared with other procedures included in their study. Table 2-5 shows the characteristics of some retrospective cohort (population

based) studies which examined PPOU the persistent use of opioid after surgeries  
the time of identifying the gap for this PhD project.

**Table 2-5. Characteristics of some retrospective cohort (population based) studies examined the persistent use of opioid after surgeries the time of identifying the gap for this PhD project**

Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Brummett <i>et al.</i> , 2017 <sup>144</sup> 18 to 64 years US	Minor: Varicose vein removal Laparoscopic Cholecystectomy Laparoscopic appendectomy Haemorrhoidectomy Thyroidectomy Prostate surgery Parathyroidectomy Carpal tunnel Major: Hernia repair Colectomy Bariatric surgery Hysterectomy	Clinformatics Data Mart	Total 36,177  Minor surgeries 29 068 (80.3%)  Major surgeries 7109 (19.7%)	Opioid prescription fulfilment between 90 and 180 days after the surgical procedure	No prescription 11 months prior to index date (365 days – 31 days)	Not specified	Laparoscopic cholecystectomy 6% Laparoscopic appendicctomy 4-5% Hernia repair 8% Colectomy 10% Anti-reflux surgery 7% Bariatric surgery 8% Hysterectomy 5-6%
Zaveri <i>et al.</i> , 2019 <sup>185</sup> ≥ 18 Years US	Ambulatory surgery or outpatient surgery	The Institutional Data Warehouse	17,325	Receipt of a new opioid prescription 90 days to 365 days after the surgery	Not receive opioid 30 days prior to 30 days after surgery	Not specified	5%

Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Alam <i>et al.</i> , 2012 <sup>151</sup> ≥ 66 years Canada	Minor surgery Cataract surgery Laparoscopic cholecystectomy Transurethral resection of the prostate Varicose vein stripping	Ontario drug benefit database and The Canadian institute for health information discharge abstract database	391,139	Filled prescription for an opioid within 60 days of the 1-year anniversary date (e,g 305-425 days after the index date)	Did not fill a prescription for an opioid in the 12 months prior to their surgery	Not specified	Opioid naïve 7.7%
Clarke <i>et al.</i> , (2014) <sup>141</sup> ≥ 66 years Canada	One of nine elective major surgeries Open thoracotomy Lung resection surgery Thoracoscopic surgery Open colon resection Minimally invasive (laparoscopic) colon resection Open radical prostatectomy Minimally invasive (laparoscopic or robot assisted) Open total or radical hysterectomy.	The discharge abstracts database of the Canadian Institute for Health Information and the Ontario Health Insurance Plan database and the registered persons database and the Ontario Drug Benefit database	39,140	Filling one or more opioid prescriptions within 1 to 90 days after surgery along with filling one or more prescriptions for opioids within 91 to 180 days after surgery. (6 month)	No prescription for opioids (or analgesic drugs) within 90 of index date.	Codeine, morphine, Oxycodone, hydromorphone, Meperidine, oxymorphone, Methadone, transdermal fentanyl	3.1%

Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Soneji <i>et al.</i> , (2016) <sup>187</sup> ≥ 66 years Canada	Similar to Clarke <i>et al.</i> (2014) <sup>141</sup>	Several linked populations based administrative databases similar to Clarke <i>et al.</i> (2014) <sup>141</sup>	39,140	Cessation for any individual receiving an opioid prescription within 90 days after surgery, with the date of cessation defined by the absence of any opioid prescription within the preceding 90 days	No prescription in prior year	Not specified	0.4% continued to receive prescription at 1 year
Bateman <i>et al.</i> (2016) <sup>164</sup> 12 to 55 years old US	Caesarean delivery	Clinformatics Data Mart	80,127	Based on trajectory of opioid use in 12 months after surgery: defined the group of patients with the highest probability of filling over time as persistent users	Opioid naïve in the year prior to delivery	Hydrocodone, oxycodone, codeine, meperidine, hydromorphone, morphine, fentanyl, methadone, and oxymorphone	Overall 0.36% persistent use rate at 1 year overall  Opioid naïve 0.23% persistent use rate at 1 year

Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Sun <i>et al.</i> (2016) <sup>110</sup> 18 to 64years old US	11 surgical procedures: Total knee or hip arthroplasty, Laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, caesarean delivery, cataract surgery, TURP, or simple mastectomy.	MarketScan (Truven Health Analytics)	641,941	1)filled 10 or more Prescriptions or 2) more than 120 days' supply within the first year of surgery (excluding the first 90 postoperative days)	Patients who did not fill a prescription for an opioid in the 12 months prior to procedure	Fentanyl (patch or oral form), hydrocodone hydromorphone (oral form) methadone, morphine oxymorphone, oxycodone	Opioid Naïve 1.41% TKA 0.59% THA 0.119% caesarean delivery
Swenson <i>et al.</i> (2018) <sup>188</sup> < 63 years US	Hysterectomy	OPTUM national database	28,279	1) Filled prescription within 15 to 90 days after discharge and filled at least one additional opioid prescription between 91 and 180 days after surgery; and 2) either A) 1150 oral morphine equivalent total dose OR B) 39 days supplied and 2 filled prescriptions	Women with any opioid fills from 243 days to 31 days prior to hysterectomy	Not specified; either opioid agonist or opioid partial agonist.	Opioid naïve 0.5%.

Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Hadlandsmyth <i>et al</i> (2018) <sup>161</sup> Veterans US	TKA	VHA datasets	6,653	Continuously filled prescriptions (with no gaps greater than 14 days) in the 12 months after discharge	No opioid use in the year prior to surgery	Preoperative opioid use was defined as any outpatient prescription of noninjectable butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine or tramadol	Opioid naïve 4% received opioids for at least 6 months and  2% for at least 12 months after TKA.
Politzer <i>et al.</i> , 2018 <sup>157</sup> US	TKA	Medication racking database of the large private payer Humana Health Insurance	66,950	Opioid prescriptions over 6 months (followed for 24 months after surgery)	No opioid use within one year before total knee arthroplasty	Morphine extended release, hydromorphone, fentanyl, oxycodone ER, morphine, oxycodone, tramadol."	Opioid naïve 2.2% incidence  Opioid tolerant 34.8% incidence
Hansen <i>et al.</i> (2017) <sup>155</sup> ≥ 18 Years Australia	TKA	DVA	15,020	1) 90 days of continuous opioid use or 2) at least 120 days of non-continuous use (within 275 days, excluding the first 90 days)	No opioid use in the year prior to surgery	Weak (Codeine, dextropropoxyphene, tramadol) Strong (Buprenorphine, fentanyl, hydromorphone, hydrocodone, morphine, oxycodone, oxycodone naloxone, pethidine hydrochloride).	Opioid naïve 0.7%  Non opioid naïve 66.5



Reference Population Location	Procedure	Data source	Sample size	Definition of persistent use	Definition of opioid naïve	Opioid used	Results
Inacio, 2016 <sup>156</sup> ≥ 18 years Australia	Elective unilateral THA	DVA	9,525	1) 90 days of continuous opioid use or 2) at least 120 days of non-continuous use (within 275 days, excluding the first 90 days)	No opioid use in the year prior to surgery	Opioids	Overall 5.2%  Opioid naïve 2.1% Non opioid naïve 50.9%

TURP, Transurethral Resection of the Prostate; TKA, Total Knee Arthroplasty; THA; Total Hip Arthroplasty; VHA, Veterans Health Administration; DVA; Australian Department of Veterans affairs

Several systematic reviews have provided a pooled estimate for PPOU <sup>133, 171</sup> The systematic review by Kent *et al.*<sup>133</sup>, reported that PPOU can range from 0.6% to 12% in opioid naïve patients following abdominopelvic surgery and can have higher ranges for those with previous opioid exposure. Table 2-6 shows the reported incidence of PPOU based on Kent *et al.*<sup>133</sup>. Hinthner *et al.*<sup>171</sup>, reported that within the opioid-naïve population, the prevalence of postoperative opioid use following several orthopaedic and abdominal surgical procedures at 3, 6, and 12 months postoperatively was 10.4% (95% CI 3.1–17/7%), 7.7% (95% CI 0.3–15.2%), and 9.1% (95% CI 3.0–15.2), respectively. The pooled PPOU prevalence rate in total joint arthroplasty was reported similarly by 2 systematic reviews (12%; 95% CI: 10.0%, 14.0%)<sup>189</sup> (12.1%; 95% CI: 9.7%, 14.9%)<sup>190</sup>.

**Table 2-6. Reported incidences of PPOU across surgical subgroups**

Surgery	Overall sample	Opioid naïve sample	Preoperative opioid sample
<b>Arthroplasty</b>			
All studies	5.5% - 32%	0.6% - 8%	14% - 68%
Moderate level	5.5% - 32%	0.6% - 4%	35% - 68%
<b>Abdominopelvic</b>			
All studies	0.36% - 77%	0.09% - 12%	8.1% - 77%
Moderate level	0.36% - 14%	0.119% - 6%	59% - 77%
<b>Spine</b>			
All studies	18% - 85%	0.02% - 26%	59%
Moderate level	18% - 59%	26%	59%
<b>Mastectomy</b>			
All studies	Not applicable	10% - 11%	Not applicable
Moderate level	Not applicable	10% - 11%	Not applicable
<b>Thoracic</b>			
All studies	22%	<2% - 14%	Not applicable
Moderate level	Not applicable	14%	Not applicable

Adapted from Kent *et al.*<sup>133</sup> with permission from Wolters Kluwer Health, Inc.

Moderate level refers to studies of moderate quality based on GRADE assessment

A study conducted in Australia to investigate opioid use before and after TKA showed a much lower rate of persistent opioid use (0.7%) compared with the previously mentioned US studies<sup>155</sup>. This lower rate may be due to the practice of prescribing larger opioid quantities in the US but not in Australia and variations in the accuracy of data obtained from different health administrative claims<sup>157</sup>. However, another Australian retrospective analysis<sup>156</sup> recruiting patients undergoing Total Hip Arthroplasty (THA) using the same time frame and administrative health claims used by Hansen *et al.*<sup>155</sup> found that 5% of the total cohort became chronic opioid users after the surgery, of whom 61% were already persistent chronic users and 39% became chronic users after surgery. Although both studies used a similar population, time frame, administrative health claim database and definition of persistent use, the different rates were reported may arise from variations in the surgical procedures conducted within the broader categories of knee and hip arthroplasties. Moreover, both studies failed to describe which patients underwent the procedure to eliminate the pain that had caused the preoperative opioid use. To provide a pooled estimate on persistent opioid use in Australia a recent systematic review reported that persistent opioid use among opioid naïve surgical patients generally ranged from 3.9% to 10.5% at between 3 and 4 months after discharge<sup>191</sup>.

### **2.5.5 Marketing of opioids by pharmaceutical companies**

Pharmaceutical companies encouraged healthcare providers in the US and Canada to prescribe more opioids by underplaying their risk of abuse and harm and inflating their benefits for the management of acute pain<sup>98, 192, 193</sup>. This is evident in the case of Purdue Pharma, the manufacturer of OxyContin<sup>®</sup> and MS Contin<sup>®</sup>, which sponsored numerous campaigns and pain management educational programmes to promote OxyContin, a new 'controlled-release oxycodone' was more efficient and less addictive than other marketed opioids<sup>192-194</sup>.

Purdue Pharma with the support of its sister companies Mundipharma and Napp Pharmaceuticals claimed that OxyContin should be an essential analgesic for patients enrolled in Enhanced Recovery After Surgery (ERAS) Programmes, which designed to help people to recover rapidly after major surgical procedures<sup>195</sup>. These pharmaceutical companies stated that OxyContin could manage acute pain and enhance patients' function, enabling them to be discharged earlier<sup>196</sup>. They supported their claims by the finding from studies showing OxyContin was superior to patient-controlled analgesia (PCA) or epidural analgesia for the restoration of mobility following orthopaedic surgery<sup>17, 197</sup>. However, they ignored the evidence showing that oxycodone is as addictive as other opioids and more likeable by patients with a higher possibility of opioid misuse<sup>198</sup>.

The aggressive advertising of modified-release opioid preparations as a more efficient and less addictive opioid formulations can be considered a pseudo-axiom; 'a false principle or rule handed down from generation to generation of medical

providers and accepted without serious challenge or investigation',<sup>196</sup> which played an integral role for the continuous use of opioids after surgery. However, in 2020, because of several criminal charges linked to the false marketing of OxyContin, Purdue Pharma were found guilty in the federal court and ordered to pay penalties of more than \$8 billion<sup>199</sup>.

## **2.6 Opioid stewardship**

The concept of opioid stewardship is based on the success of the antibiotic stewardship program, which emphasises appropriate drug use for the right patient at the right time<sup>200</sup>. Opioid stewardship emerged as part of a broader efforts to mitigate the consequences of the opioid epidemic by ensuring that opioids are used sensibly and safely in medical practice.

Currently, there is a lack of an established definition and scope of opioid stewardship<sup>201, 202</sup>. Two definitions within the context of postoperative pain management include: "Perioperative opioid stewardship is the judicious use of opioids to treat surgical pain and optimise pre- and postoperative patient outcomes"<sup>203</sup>, and "Opioid stewardship includes appropriate opioid prescription, precision pain management and ensuring that patients are not taking opioids unnecessarily"<sup>204</sup>. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued recommendations related to opioid stewardship principles<sup>205</sup>. Before prescribing opioids, clinicians must discuss the risks and features of tolerance, dependence, and addiction with patients and jointly agree a treatment strategy and plan for the end of treatment<sup>205</sup>.

## **2.7 Rationale for choosing colectomy as a specific surgical procedure for in depth analysis within the context of post operative opioid utilisation**

Colectomy is a common abdominal surgical procedure, with 300,000 performed annually in the US<sup>206</sup> and approximately 33,000 in England<sup>207</sup>. People undergoing colectomy might have diseases that may be associated with pain, such as inflammatory bowel disease, diverticulitis and cancer<sup>208</sup>. Additionally, the procedure itself can lead to significant postoperative pain<sup>208</sup> and opioid analgesia may be indicated. Following major abdominal surgical procedures, including colectomy in England 52% of patients were discharged with an opioid prescription<sup>101</sup>.

Colectomy is not expected to have treatment pathways that require extended recovery periods and patients may be more likely to discontinue opioids if surgery treated their chronic pain. However, as seen from literature from other countries some patients continue to use opioids after initial exposure following colectomy. Furthermore, some patients who used opioids before surgery may persist with their use after surgery, which might be associated with opioid-related harms or side effects. It is important to note that the population undergoing colectomy may predominantly consist of older adults, who, due to factors like decreased drug metabolism, comorbidities, polypharmacy, and decreased cognitive function might be at a higher risk of experiencing opioid-related side effects and harms<sup>209</sup>. Despite the growing body of literature on this subject from other countries, the

study of opioid utilisation and persistent use within the colectomy population in England is very limited.

## **2.8 Summary of literature review**

The careful assessment of pain by a valid and reliable tool is essential for effective care following surgery<sup>29</sup>. However, the previously mentioned issues on unidimensional pain assessment tools raise significant concerns regarding the available evidence supporting their validity and reliability for use with postoperative patients. Furthermore, looking at studies that involve assessment of the functional impact of pain is also essential to appraise the measurement properties of these tools to find the best available assessment tool to be used in acute care practice. (Figure 2-6). provides summary for the identified area of research and proposed methodologies to fill these gaps.

The study of opioid utilisation and persistent use within the surgical population in England remains lacking despite the growing body of literature from the other countries on this subject. Currently, there are no studies evaluating at the trends and patterns of opioid prescribing over the years following surgical discharge within England. Having such studies is fundamentally important, first for regional comparisons (estimating the risk locally will allow decision makers to determine how prevalent the problem is and how to compare it with the global coverage) of prescribing practices and then for global insight.

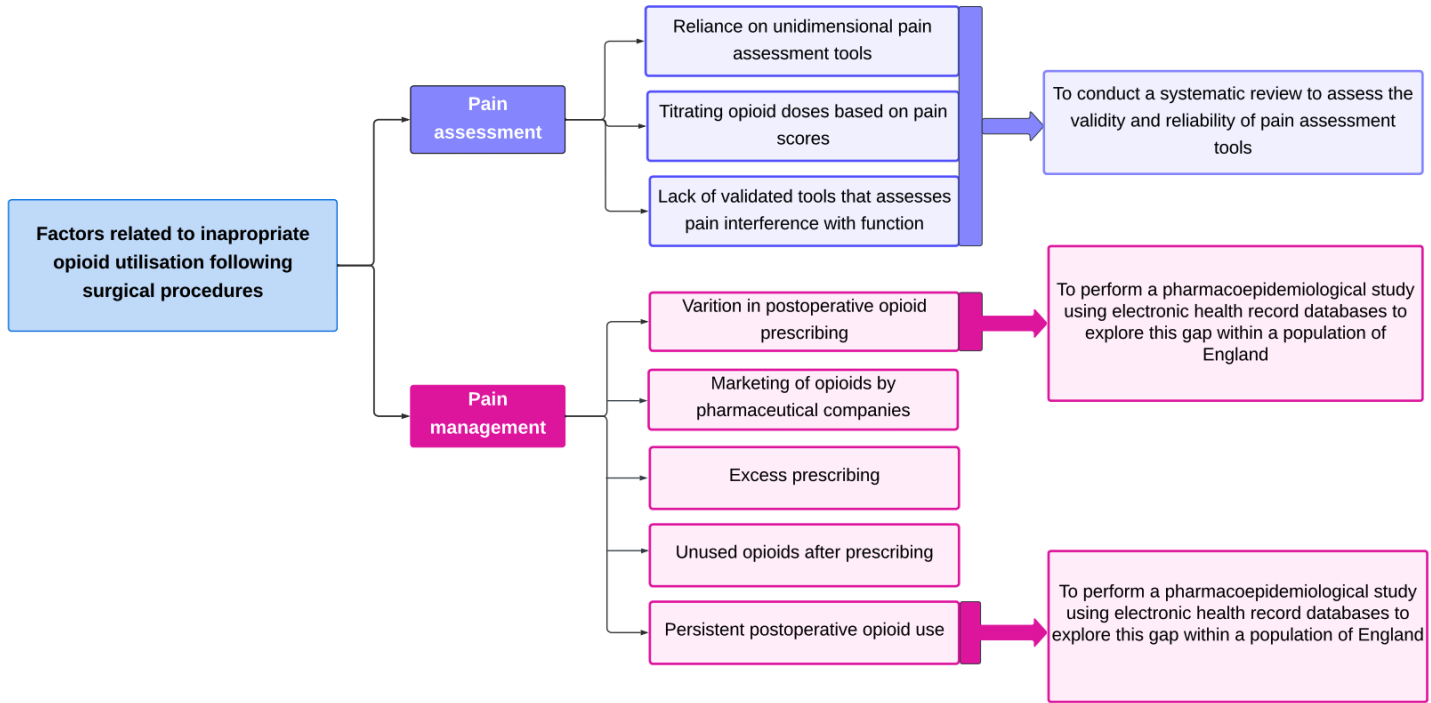


Figure 2-6. Summary of identified research gap



A substantial amount of literature has described the incidence and risk of PPOU using population-based data from various countries and different type of surgical procedures. The majority of published work in this area concludes that opioids prescribed during and after major or minor surgery might trigger long-term opioid use. However, no previous studies have investigated the rate and associated risk factors for persistent opioid use following surgery in a UK population. Therefore, there is a need for population-based studies for more investigation. As justified in the earlier section, colectomy was chosen as a specific surgical procedure for in depth analysis within the context of postoperative opioid utilisation.

## **2.9 Thesis aims and objectives**

This thesis centres on enhancing the understanding of postoperative pain management starting from pain assessment to opioid use patterns and development of persistent opioid use with a focus on colectomy as a specific surgical procedure for in-depth analysis within the context of postoperative opioid utilisation. The objectives are:

1. To evaluate the validity and reliability of pain assessment tools used to assess acute postoperative pain by identifying, summarising, and appraising studies that reported the use of assessment tools following surgical procedures.
2. To determine the prevalence of PPOU following colectomy, stratified by pre-admission type and opioid exposure.
3. To identify predictors associated with PPOU.

4. To describe prescribing patterns and trends for patients receiving their first opioid prescription from primary care following colectomy.

### **Chapter 3: Utility of unidimensional and functional pain assessment tools in adult postoperative patients: a systematic review**

This chapter is an expanded version of published article: Baamer RM, Iqbal A, Lobo DN, Knaggs RD, Levy NA, Toh LS. Utility of unidimensional and functional pain assessment tools in adult postoperative patients: a systematic review. *Br. J. Anaesth.* 2022; 128(5):874-888. doi: 10.1016/j.bja.2021.11.032.

### **3.1 Abstract**

#### **Background**

In this systematic review we aimed to appraise the evidence relating to the measurement properties of unidimensional tools to quantify pain after surgery. Furthermore, we wished to identify tools used to assess interference of pain with functional recovery.

#### **Methods**

Four electronic sources (MEDLINE, EMBASE, CINAHL, PsycINFO) were searched until August 2020. Two reviewers independently screened articles and assessed risk of bias using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.

#### **Results**

Thirty-one studies with a total of 12498 participants were included. Most of the studies failed to meet the methodological quality standards required by COSMIN. Studies of unidimensional assessment tools were underpinned by low quality evidence for reliability (5 studies), and responsiveness (7 studies). Convergent validity was the most studied property (13 studies) with moderate to high correlation ranging from 0.5 to 0.9 between unidimensional tools. Interpretability results were available only for the visual analogue scale (7 studies) and numerical rating scale (4 studies). Studies on functional assessment tools were scarce in which only one study included an 'Objective Pain Score,' a tool assessing pain interference with respiratory function and had low-quality for convergent validity.

## Conclusions

This systematic review challenges the validity and reliability of unidimensional tools in patients after surgery. We found no evidence that any one unidimensional tool has superior measurement properties in assessing postoperative pain. In addition, because promoting function is a crucial perioperative goal, psychometric validation studies of functional pain assessment tools are needed to improve pain assessment and management.

## 3.2 Introduction

Patients experience acute pain after surgery due to tissue damage and inflammation at the operation site<sup>8, 210, 211</sup>. Careful assessment of pain by a valid and reliable tool<sup>22</sup> is the first step towards a rational choice of analgesic therapy<sup>212</sup> which is essential for ensuring patient comfort, mobility, satisfaction and reducing healthcare costs<sup>60</sup>. Most commonly used tools for the assessment of postoperative pain are unidimensional and assess only pain intensity<sup>22</sup>. These include VAS<sup>213</sup>, NRS<sup>214</sup>, VRS<sup>215</sup>, sometimes referred as VDS<sup>216</sup>, and FPS<sup>29</sup>. They are quick to administer and do not encroach on the time required for usual care<sup>23</sup>.

Despite their extensive use, the reliance on these unidimensional tools as the sole approach to measuring pain is currently insufficient as the cut-off points commonly used by healthcare providers do not reflect the patient's desire for additional analgesics<sup>34, 35</sup>. Furthermore, patients have reported difficulties in describing the complexity of their pain experience by a single numerical value, descriptive words or as a mark on a line<sup>23</sup>. Striving to lower pain intensity scores

to zero as suggested by the P5VS campaign has not improved pain outcomes<sup>41, 42, 217</sup>, and resulted in increased opioid analgesic use in the post-anaesthesia care unit<sup>41</sup>. Furthermore, Vila *et al.*<sup>44</sup> highlighted the potential hazards associated with a pain score-based treatment algorithm in increasing the prevalence of sedation-related side effects by more than twofold. Treating pain as the 5<sup>th</sup> vital sign has been abandoned now as it may have contributed to the current US opioid epidemic<sup>21, 218</sup>.

Restoration of function by allowing the patient to breathe, cough, ambulate and turn in bed is important for postoperative pain relief<sup>17, 57</sup>. Therefore, assessing the functional impact of pain, which includes patient-centred objective assessment by a healthcare provider who judges if the pain prevents the patient from performing activities that help accelerate recovery, could be an appropriate alternative to achieve better pain assessment<sup>56</sup>. Hence, options to treat pain will be used to maximise functional capacity, rather than striving to reduce the patient's postoperative pain score to below a specified numerical value<sup>21, 22</sup>.

Despite being used widely, the validity, reliability, and utility of unidimensional pain assessment tools for postoperative patients have not been reviewed systematically. Furthermore, it is important to include studies that identified tools which assess pain interference with functional recovery and to appraise the measurement properties of these tools. In recent years, the COSMIN initiative developed tools that allow researchers to conduct high-quality systematic reviews on the measurement properties of patient-reported outcome measures

(PROMs)<sup>219</sup>. This type of systematic review allows the researchers to choose the best available tool for practice and future research.

### **3.3 Aims and objectives**

The aim of this systematic review was to appraise the available evidence concerning the measurement properties of different unidimensional and functional pain assessment tools when used to assess postoperative pain in hospitalised adults. Specific objectives include:

1. To identify unidimensional pain assessment tools for acute postoperative pain for hospitalised adults.
2. To summarise and critically appraise the available evidence on the measurement properties of unidimensional pain assessment tools when used to assess acute pain.
3. To identify functional pain assessment tools available for assessment of acute postoperative pain in adult patients and to summarise their measurement properties.
4. To summarise the evidence around tools feasibility, interpretability, and ability to detect patient desire for analgesia.

### **3.4 Methods**

The systematic review was performed according to COSMIN (<http://www.cosmin.nl/>) guidelines, and was reported according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines<sup>220</sup>.

### **3.4.1 Protocol registration**

The protocol was registered (No. CRD42020213495) with the International prospective register of systematic reviews (PROSPERO) database and can be accessed at

[https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=213495](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=213495).

(Appendix S 1).

### **3.4.2 Search strategy**

A systematic search of the MEDLINE, EMBASE, PsycINFO (all via OVID) and CINAHL (via EBSCOhost) databases was performed from their inception to August 2020. Our search strategy consisted of four search concepts: 1) measurement properties or outcome terms, 2) pain assessment tool terms, 3) acute postoperative pain and 4) limits (English language or English translation, human adults  $\geq 18$  years old). The first three concepts were combined using the Boolean operator AND, which works as a conjunction to narrow the search to include our specific three search concepts resulting in more focused results. This was then combined with the result string of the fourth concept to limit the results. These steps were performed separately for each pain assessment tool. The search was restricted to studies available in the English language or that had an English translation, as translation to other languages was not feasible. Backward citation tracking was also carried out by

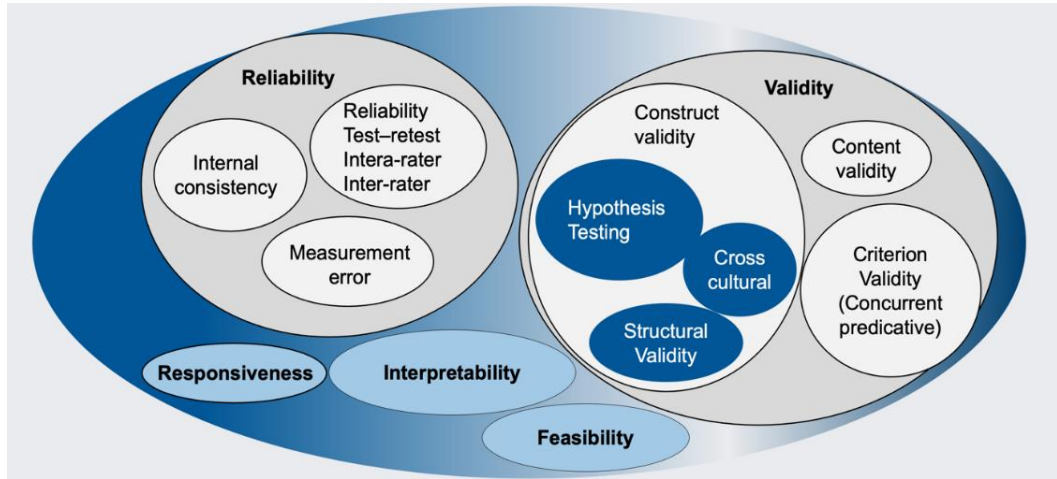


checking the reference lists from eligible studies. The comprehensive search strategy used is provided in (Appendix S 2).

### **3.4.3 Inclusion criteria**

1. Any of the following pain measurement tools to assess acute pain in hospitalised adult patients from all surgical specialties were included: unidimensional pain assessment tools [including the numerical pain rating scale, verbal rating scale, visual analogue scale, faces scales (Wong-Baker FACES, FPS-R)].
2. Functional pain assessment tools included any tool that helps assess acute pain based on its interference with functional activity, including walking, breathing, turning in bed and coughing. Included functional pain assessment tools could be used objectively by the clinician or when self-reported by patients.
3. Instrument validation or instrument evaluation types of studies were included.
4. Any studies that included at least one or more of the instruments to evaluate postoperative pain and assessed at least one of the nine measurement properties identified by COSMIN taxonomy. Figure 3-1 : internal consistency, test-retest reliability, measurement error, content validity, structural validity, construct validity, hypothesis testing, cross-cultural validity, criterion validity and responsiveness were considered. Table 3-1 provides definitions for measurement properties included in the main domains of the COSMIN taxonomy.

5. Any study that evaluated any of the specified additional outcomes of the tools, including feasibility, interpretability, and desire for analgesia.



**Figure 3-1 COSMIN taxonomy**

Redrawn from Mokkink *et al* (2010)<sup>221</sup>, with permission from Elsevier

**Table 3-1 Measurement properties included in the main domains of the COSMIN taxonomy**

Domain	Psychometric property	Definition
Reliability		The extent that the measurement is free from measurement error such that scores for patients who have not changed are the same under repeated measurements
	Internal consistency	The extent that items are inter-related
	Measurement error	Error in a participant's score that is not attributed to the construct being measured
Validity		The extent that an assessment measures what it aims to measure
	Content validity	The extent that an assessment's content reflects the construct being measured
	Face validity	The extent that an assessment looks like it reflects the construct being measured
	Construct validity	The extent that an assessment's scores are consistent with hypotheses based on the assumption that the tool measures what it purports to measure
	Structural validity	The extent that an assessment's scores reflect the dimensionality of the construct being measured
	Hypothesis testing	Construct validity for the items of an assessment
	Cross-cultural validity	The extent that items on a translated or culturally modified assessment reflect the original items
Criterion validity	The extent that an assessment's scores represent the 'gold standard'	
Responsiveness		An assessment and/or its items' ability to detect change over time in the construct being measured
Interpretability*		The extent that clinical or everyday understanding can be applied to an assessment's scores
Feasibility*		How easily a pain measure can be scored and interpreted

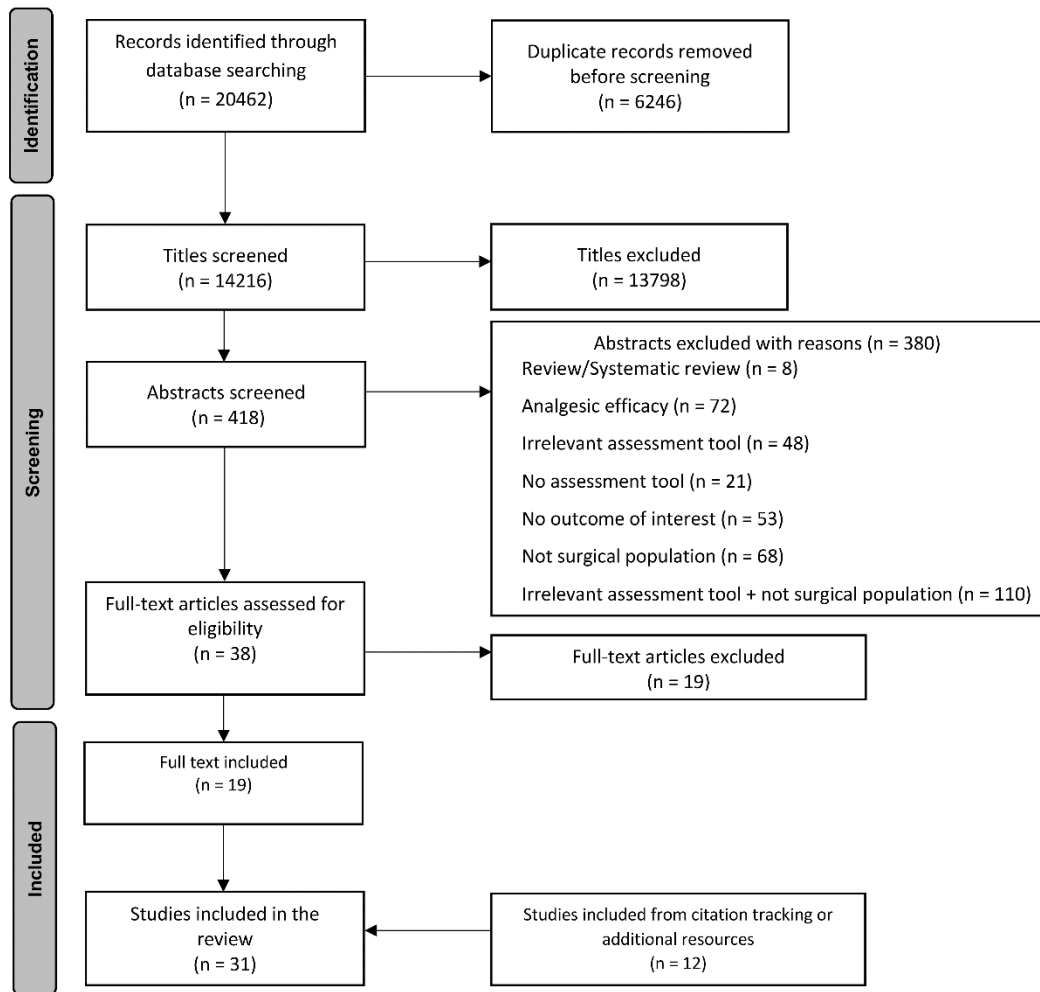
COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments. \*Interpretability and \*feasibility are not considered measurement properties, but important characteristics of a measurement instrument. [Adopted from Mokkink *et al.* (2010)<sup>221</sup>, with permission from Elsevier]

#### **3.4.4 Exclusion criteria**

Abstracts, editorials, reviews and studies that included paediatric or adolescent populations, or sedated, mechanically ventilated and critically ill patients were excluded.

#### **3.4.5 Selection of articles**

Following the database search, all identified citations were collated and uploaded to EndNote X9 (Clarivate Analytics, Philadelphia, PA, US) and duplicates were removed. The identified studies were uploaded to Rayyan QCRI online software<sup>222</sup>, a web and mobile app for systematic review screening that facilitates collaboration between different reviewers for study inclusion and exclusion. The application of the inclusion criteria to the titles, then to relevant abstracts was independently applied by two reviewers (R Baamer and A Iqbal). Afterwards, potentially eligible full texts were thoroughly examined for inclusion. The full search results were documented in the PRISMA flow diagram (Figure 3-2). Excluded studies and the reasons for their exclusion are provided in Appendix S 3.



**Figure 3-2 PRISMA flow diagram**

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

### 3.4.6 Data extraction

One reviewer (R Baamer) extracted data from the included full-text articles, with the extraction verified by a second reviewer (A Iqbal). The two reviewers resolved any disagreements through discussion, or consultation with other reviewers (R Knaggs, L Toh or D Lobo) when necessary. The data extracted included specific details about the assessment tool used, country, language of scale administration, study design, patient characteristics, surgical procedure, the specific

measurement properties assessed, outcomes related to the review question and objectives, and the main statistical analysis.

### **3.4.7 Assessment of methodology**

Two independent reviewers (R Baamer and A Iqbal) critically appraised the methodological quality of studies looking at feasibility and interpretability using a modified version of the Newcastle Ottawa Scale<sup>223</sup> (Appendix S 4).

For validation studies, the quality was assessed using the COSMIN criteria for methodological quality<sup>219, 224, 225</sup>. The following sections describe quality assessment phases in more detail:

#### **3.4.7.1 Assessing risk of bias**

Risk of bias pertains to the methodological quality of a study. The COSMIN risk of bias checklist is a standardized modular tool that includes 10 boxes designed to assess several measurement properties<sup>225</sup>. It is not mandatory to fill in all boxes; as such, the box related to each study's measurement properties to score their quality was filled. Each item in the box was rated based on a four-point scale ranging from very good to adequate, doubtful or inadequate. Then, the overall scores per box were obtained based on the "worst score counts" principle in which the lowest rating across all box items determined the methodological quality of the study.

### 3.4.7.2 Assessing measurement properties

We rated the psychometric property of each pain assessment tool as sufficient, insufficient or inconsistent using the updated criteria for good measurement properties<sup>224</sup> (Appendix S 5).

As recommended by the COSMIN initiative, some hypotheses were developed to guide the quality assessment of the measurement properties.

A set of a priori hypotheses were formulated to evaluate the results in terms of construct validity and responsiveness. It was anticipated that correlations would be high if the correlation coefficient  $\geq 0.7$ , Between  $< 0.60$  and  $\geq 0.30$  moderate correlation and  $< 0.30$  low correlation. For responsiveness, a threshold of  $\geq 0.70$  was set for the area under the curve (AUC) to distinguish between patients who experienced improvement and those who did not. However, defining hypotheses to assess responsiveness based on the standardized response mean (SRM) or effect size (ES) was not possible, because these are context-specific indices that depend on several factors, including the interventions used in the studies. It was anticipated that authors would provide clear hypothesis defining the magnitude of expected change in their respective studies when these responsiveness indices were present. Similarly, in the case of measurement error, determination of the minimum inhibitory concentration (MIC) for VAS or NRS was precluded, given the variability of these values depending on the baseline pain score and anchor used in each study.

### **3.4.7.3 Summarising and grading the quality of evidence**

This step focused on the quality of each pain assessment tool as a whole. Accordingly, extracted data was reviewed to determine whether the results of all studies of the pain assessment tool were consistent.

### **3.4.7.4 Assessing certainty in the findings**

According to COSMIN guidelines, the certainty of the quality of evidence for each pain assessment tool's psychometric properties was evaluated using modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach<sup>226, 227</sup> (Appendix S 6 and Appendix S 7). Certainty was also assessed by considering the risk of bias, inconsistency, imprecision and indirectness. In this context, risk of bias referred to limitations in the methodological quality of the eligible studies; imprecision referred to a low number of patients included in the studies; inconsistency referred to unexplained heterogeneity in the results of the studies; and indirectness referred to the extent to which the study characteristics met the review inclusion criteria.

For the measurement properties, one risk of bias level was downgraded if there was only one adequate quality study and two levels if there were only doubtful or inadequate studies. Imprecision of one level was noted if the total patient sample was < 100 and two levels if < 50, as well as inconsistency of one level if ≥ 75% of the studies' results were not all sufficient (+), insufficient (-) or inconsistent (?). No downgrading was performed for indirectness, as all the included studies used pain assessment tools for the postoperative adult population.



### **3.4.8 Data synthesis**

Data synthesis was conducted to compare the measurement properties of unidimensional and functional postoperative pain assessment tools, and to provide recommendations on the most valid research and clinical tool. All eligible studies were included in the narrative summary regardless of their overall judgement in the quality assessment. It was not possible to statistically pool the psychometric evidence for the included studies due to their different outcome measures; therefore, the data synthesis took the form of a narrative review of the postoperative pain tools' measurement properties.

## **3.5 Results**

### **3.5.1 Selection of studies**

The search identified 14,216 potential studies following removal of duplicates. After reviewing the titles, 13,798 studies were excluded for irrelevance and another 380 were excluded after abstract screening. Of the 38 remaining studies, 19 were excluded after examination of the full texts against the inclusion criteria (Appendix S 3). An additional 12 studies were identified through searching the bibliography of eligible studies, so a total of 31 studies<sup>27, 35, 60, 210, 211, 228-253</sup> (Figure 3-2) with 12498 participants were included. The number of participants in individual studies ranged from 35<sup>228</sup> to 3045<sup>229</sup>.

### **3.5.2 Study population**

The distribution of male and female participants in the studies varied, with some studies including only female participants<sup>228</sup> or only male participants<sup>238</sup> and

others not reporting sex distribution<sup>236 , 247, 249, 250</sup>. Studies aligned with the inclusion criteria were published between 1982<sup>249</sup> and 2018<sup>235</sup>, and assessed postoperative pain following different types of surgical procedures (Table 3-2). Nine studies included only cognitively intact participants<sup>60, 230, 233, 236 , 244, 246, 248, 251, 252</sup> while two studies included participants with mild cognitive impairment<sup>243, 253</sup>. The remaining 20 studies did not report on cognitive function<sup>27, 35, 210, 211, 228, 230-234, 237-242, 245, 247, 249, 250</sup>.

Seven studies were performed in the US<sup>27, 211, 234-236, 242, 249</sup>, three in China<sup>243 , 244, 253</sup>, three in Australia<sup>245-247</sup>, and two each in the UK<sup>233, 241</sup>, Netherlands<sup>35, 251</sup>, Ghana<sup>231, 240</sup>, France<sup>230</sup> and Canada<sup>60, 238</sup>. One study each was performed in Finland<sup>248</sup>, Spain<sup>232</sup>, Nigeria<sup>228</sup>, Iran<sup>237</sup>, India<sup>250</sup>, Vietnam<sup>252</sup>, Israel<sup>210</sup>, and Germany<sup>239</sup>. Although all the included studies were reported in English, some of the tools were administered in other languages: Chinese<sup>243, 244, 253</sup>, Twi<sup>231, 240</sup>, Vietnamese<sup>252</sup>, Finnish<sup>248</sup>, and both English and Yoruba<sup>228</sup>.

**Table 3-2 Characteristics of included studies**

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Van Dijk 2015 <sup>35</sup> Netherlands	NRS	Cross-sectional design	Orthopaedic, ENT, gynaecological, cardiothoracic, Others	Ability to detect desire for analgesics	Worst pain imaginable	ICU patients, not proficient in Dutch or English, ambulatory surgery	1,084 (48)	53 (18–90)
Banos 1989 <sup>232</sup> Spain	VAS VRS-5	Descriptive correlational design	Abdominal, orthopaedic, gynaecological	Convergent validity	10 Unbearable pain	NR	212 (50)	<30 = 43 31-50 = 69 >50 = 107
Akinpelu 2002 <sup>228</sup> Nigeria	VAS M-VRS BNS	Cross-sectional design	Caesarean section	Convergent validity	Worst pain Worst imaginable Worst pain	Complications, Illness Unconscious	35 (100)	31 $\pm$ 5
Briggs 1999 <sup>233</sup> UK	VAS VRS**	Secondary analysis of RCT	Orthopaedic	Convergent validity Feasibility	Number 100 Severe pain at rest and movement	NR	417 (45)	47 $\pm$ 20* 64 $\pm$ 17
Fadaizadeh 2009 <sup>237</sup> Iran	VAS FPS	Cross-sectional design	General, gynaecological	Convergent validity	10 Agonized	History of substance abuse, Unconscious	82 (72) 34 GS 48 GYN	32 $\pm$ 14 GYN 27 $\pm$ 7 GS 38 $\pm$ 18

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
DeLoach 1998 <sup>236</sup> US	VAS VPS	Descriptive correlational design	Various type of surgeries	Convergent validity	Worst imaginable Horrible pain	NR	NR	NR
Pesonen 2008 <sup>248</sup> Finland	VAS VRS-5 RWS FPS-7	Descriptive correlational design	Cardiac surgery: elective CABG, valvular repair	Feasibility	Worst possible pain Unbearable pain Worst possible pain Worst possible pain	Dementia, Cognitive impairment	160 FPS 80 (36) RWS 80(44)	73 $\pm$ 5
Aubrun 2003 <sup>230</sup> France	VAS NRS VRS Behavioural scale	Prospective observational design	Orthopaedic, abdominal, gynaecological, others	Feasibility	Worst imaginable pain Worst imaginable pain Severe NR	NR	600 (47)	51 $\pm$ 17
Myles 1999 <sup>246</sup> Australia	VAS	Clinical study	General, orthopaedic, ENT, faciomaxillary, cardiothoracic	Interpretability	100 worst pain ever	Severe pain, inability to complete the VAS	52 (40)	42 $\pm$ 15

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Myles 2005 <sup>247</sup> Australia	VAS	Clinical study	General, orthopaedic, ENT, faciomaxillary, cardiothoracic	Interpretability	100 worst pain ever	Postoperative delirium Frailty, visual impairment	22 (NR)	33 $\pm$ 17
Jensen 2003 <sup>27</sup> US	VAS VRS-4 VRS-P	Secondary analysis of RCT	Total knee replacement, hysterectomy, laparotomy	Interpretability	Worst pain Severe pain Complete relief	NR	123 (66)	65 $\pm$ 10
Gerbershage 2011 <sup>239</sup> Germany	NRS	Comparative study design	Cholecystectomy, thyroidectomy, gastrointestinal, inguinal hernia repair, others	Interpretability	Worst imaginable pain	Repeated surgical, procedures, mechanical ventilation	444 (44)	18–20 = 38 21–30 = 75 31–40 = 88 41–50 = 96 51–60 = 87 61–70 = 49 71–80 = 2
Cepeda 2003 <sup>234</sup> US	NRS VRS	Clinical study	Head and neck, thoracic, spinal abdominal, orthopaedic	Interpretability	Worst imaginable Severe pain	NR	700 (62)	50 $\pm$ 15

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Jensen 2002 <sup>242</sup> US	VAS VRS Pain relief	Secondary analysis of RCT	Total knee replacement, abdominal hysterectomy, laparotomy	Responsiveness	Worst pain Severe pain Complete relief	NR	246 (66)	Knee 65 $\pm$ 10 Laparotomy 41 $\pm$ 7.5
Jenkinson 1995 <sup>241</sup> UK	VAS CPI McGill	RCT	Orthopaedic	Responsiveness	Severe pain	NR	75 (64)	Male: 41 $\pm$ 13 Female: 43 $\pm$ 12
Aubrun 2003 <sup>229</sup> France	VAS	Clinical study	Orthopaedic, urological, abdominal gynaecological, vascular, thoracic	Interpretability	100	Minor pain, delirium, dementia, non- French speaking	3045 (54)	50 $\pm$ 18
Sriwatanakul 1982 <sup>249</sup> US	VAS	Secondary analysis of RCT	NR	Interpretability	Pain as bad as it could be	NR	NR	NR
Van Giang 2015 <sup>252</sup> Vietnam	FPS NRS	Validation study	Orthopaedic	Concurrent validity Responsiveness	The worst possible pain	Hearing impairment Altered mental status	144 (45)	37 $\pm$ 13

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Van Dijk 2012 <sup>251</sup> Netherlands	NRS VRS	Cross-sectional design	General, ENT, orthopaedic, neurosurgical, urological, gynaecological, plastic, vascular, cardiothoracic	Interpretability	10 Worst pain imaginable	ICU patients Non-Dutch speaking Cognitive or hearing impairment, inability to use self-report	2674 (51)	73 $\pm$ 6
Li 2007 <sup>244</sup> China	VAS NRS-11 VDS FPS	Prospective clinical study	NR	Convergent validity Scale reliability Responsiveness Feasibility	10 Worst pain 10 worst pain 10 worst pain Worst pain	NR	173 (45)	45.3 $\pm$ 15
Li 2009 <sup>243</sup> China	FPS NRS IPT	Descriptive correlational design	Gastrointestinal, orthopaedic, abdominal	Convergent validity Scale reliability Responsiveness Feasibility	10 10 The most intense imaginable pain	Did not speak Chinese More than one surgery ASA score of 4 Chronic pain	180 (68)	72 $\pm$ 6

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Zhou 2011 <sup>253</sup> China	VDS NRS FPS CAS	Descriptive comparative design	NR	Criterion validity Convergent validity Test–retest reliability Feasibility	Worst pain	Severe cognitive impairment	200 (46)	56 $\pm$ 16
Gagliese 2005 <sup>60</sup> Canada	VAS-H VAS-V NRS VDS MPQ	Validation study	NR	Feasibility Convergent validity Criterion validity	10 Worst possible pain 10 Worst pain imaginable Excruciating	On epidural or regional analgesia, ASA score of >3 Chronic pain, Cognitive impairment, Opioid or substance abuse	504 (58)	53 $\pm$ 15
Tandon 2016 <sup>250</sup> India	OPS NRS	Descriptive correlational design	Abdominal surgery	Convergent validity	Worst possible pain Inadequate pain relief/pain at rest	Haemodynamic instability Unable to use a PCA pump	93	NR



First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Aziato 2015 <sup>231</sup> Ghana	NRS FPS CCPS	Two phases: qualitative and psychometric testing	Caesarean section, leg amputation, laminectomy, laparotomy, others	Convergent validity Inter-rater reliability Responsiveness Feasibility	Worst possible pain Hurts worst	NR	150 (77)	<30 = 44.7 30–39 = 35 40+ = 21
Hamzat 2009 <sup>240</sup> Ghana	VAS	Validation study	Various gynaecological procedures	Cross-cultural validity	Worst possible pain	History of psychological or psychiatric disorders	60 (100)	NR
Gagliese 2003 <sup>238</sup> Canada	MPQ PPI VAS-R VAS-M	Descriptive correlation design	Radical prostatectomy	Convergent validity Responsiveness	Worst possible pain 5 Excruciating 10 Worst possible 10 Worst possible pain	Non–English speaker ASA >3 Chronic pain Chronic use of opioids	200	Younger patients: 56 $\pm$ 6 Older patients: 67 $\pm$ 3

First author Year Country	PROM/s	Study Design	Surgical procedure	Outcome/s	High anchor*	Main exclusion criteria	Patient characteristics	
							n (Female%)	Age Years, Mean $\pm$ SD (range)
Myles 2017 <sup>245</sup> Australia	VAS	Observational design	General, orthopaedic, gynaecological, urological, major vascular, cardiac faciomaxillary, others	Test–retest reliability Interpretability	Very severe pain	Poor English comprehension Drug or alcohol dependence Psychiatric disorder Uncontrolled pain	219 (68)	53 $\pm$ 17
Danoff 2018 <sup>235</sup> US	VAS	Prospective observational design	THA TKA	Measurement error	Worst possible pain	Preoperative pain Catastrophising Scale score greater than 30 points	304 THA (21) TKA (30)	THA: 60 (20–81) TKA; 63 (46–88)
Sloman 2006 <sup>210</sup> Israel	NRS	One group pretest–post-test design	Abdominal, orthopaedic, others	Interpretability	10 Excruciating	NR	150 (47)	47 (14–89)
Bodian 2001 <sup>211</sup> US	VAS McGill	Clinical study	Intraabdominal Surgery	Interpretability Desire for analgesics	Worst pain imaginable	NR	150 (48)	49 (37–61)

PROM/s, patient-reported outcome measures; NRS, numerical rating scale; ENT, ear, nose and throat; ICU, intensive care unit; VRS-5, 5-point verbal rating scale; VAS, visual analogue scale; NR, not reported; M-VRS, modified verbal rating scale with 11 description of pain intensity; BNS, box numerical rating scale; RCT, randomized controlled trial, VRS\*\*, four-point verbal rating scale; FPS, face pain scale; VPS, 11-point verbal scale; RWS, red wedge scale; VRS-P; verbal rating scale for pain relief; CCPS, colour circle pain scale; MPQ, McGill pain questionnaire ;VDS; verbal descriptor scale; CAS, coloured analogue scale; ASA; American Society of Anesthesiologists class; PPI, present pain intensity; OPS, objective pain score; PCA, patient controlled analgesia; VAS-R , visual analogue scale at rest, VAS-M; visual analogue scale at movement; THA, total hip arthroplasty; TKA, total knee arthroplasty. \*The low anchor was "no pain".

### 3.5.3 Quality assessment

Using the modified Newcastle Ottawa Score, the majority of studies looking at feasibility were of medium<sup>210, 228, 230, 231, 235, 237, 246, 251</sup> or high quality<sup>35, 60, 211, 233, 234, 239, 243-245, 247, 248</sup>. The methodological quality of three secondary analysis studies that looked at VAS interpretability could not be assessed<sup>27, 242, 249</sup>. The methodological quality for other measurement properties is described under each measurement property section.

### 3.5.4 Measurement properties

The following measurement properties were assessed: measurement error (n=1)<sup>235</sup>, cross-cultural validity (n=1)<sup>240</sup>, reliability (n=5)<sup>231, 243-245, 253</sup>, responsiveness (n=7)<sup>231, 238, 241-244, 252</sup> and hypothesis testing for construct validity (namely convergent validity; n=13)<sup>60, 228, 231-233, 236-238, 243, 244, 251-253</sup> and criterion validity (n=2)<sup>60, 253</sup>. No studies assessed structural validity, internal consistency, or content validity of any pain assessment tool. Interpretability was measured in eleven studies<sup>27, 210, 211, 229, 234, 239, 245-247, 249, 251</sup>. Two studies included the desire for analgesics as an outcome<sup>35, 211</sup>. The feasibility of pain assessment tools as an outcome measure was examined in eight studies<sup>60, 230, 231, 233, 243, 244, 248, 253</sup>.

### 3.5.5 Outcomes for measurement properties

#### 3.5.5.1 Unidimensional pain assessment tools

##### Convergent validity

Eight studies<sup>60, 228, 232, 233, 236-238, 244</sup> reported the convergent validity of the VAS with moderate-to-high correlations between several self-report scales that also

measured pain intensity. Similarly, seven studies reported good convergent validity results for VRS<sup>60, 232, 233, 242, 244, 251, 253</sup>, and six studies each reported good convergent validity results for NRS<sup>60, 231, 243, 244, 251, 253</sup> and FPS<sup>231, 237, 243, 244, 252, 253</sup> scores (Table 3-3). The correlations between scores obtained from several unidimensional tools were moderate to high, ranging from 0.5 to 0.9.

### **Cross-cultural validity**

One study<sup>240</sup> established the validity of a Twi (Ghanaian) version of the VAS. The pain scores reported by patients using the new instrument correlated significantly with those reported by patients using the original (English) version of the VAS, with the highest correlation on the fifth postoperative day. Because of inadequate quality due to an extremely serious risk of bias and imprecision, very low-quality evidence was reported for cross-cultural validity of the VAS.

**Table 3-3. Summary of methodological quality of studies using COSMIN risk of bias and measurement properties**

First Author	Content Validity	Structural Validity	Internal Consistency	Cross Cultural Validity	Reliability	Measurement Error	Criterion Validity	Construct Validity/ Convergent	Responsiveness	
VAS	Methodological quality assessment (COSMIN risk of bias)									
Banos <sup>232</sup>								Adequate		
Akinpelu <sup>228</sup>								Doubtful		
Briggs <sup>233</sup>								Adequate		
Fadaizadeh <sup>237</sup>								Adequate		
DeLoach <sup>236</sup>								Doubtful		
Li <sup>244</sup>					Inadequate			Adequate	Inadequate	
Gagliese <sup>60</sup>								Inadequate	Inadequate	
Gagliese <sup>238</sup>								inadequate	Inadequate	
Myles <sup>245</sup>					Inadequate					
Jensen <sup>242</sup>										Inadequate
Danoff <sup>235</sup>								Adequate		
Hamzat <sup>240</sup>				Inadequate						
Rating				?	+	?	?	+	?	
LoE				Very low	Low	Moderate	Very low	High	Low	
NRS	Methodological quality assessment (COSMIN risk of bias)									
Van Dijk <sup>251</sup>								Adequate		
Li <sup>244</sup>					Inadequate			Adequate	Inadequate	
Li <sup>243</sup>					Inadequate			Adequate	Inadequate	
Zhou <sup>253</sup>					Inadequate			Adequate	Adequate	
Gagliese <sup>60</sup>								Inadequate	Inadequate	
Aziato <sup>231</sup>					Inadequate			Doubtful	Inadequate	
Rating					+			±	+	?
LoE					Low			low	High	Low

First Author	Content Validity	Structural Validity	Internal Consistency	Cross Cultural Validity	Reliability	Measurement Error	Criterion Validity	Construct Validity/ Convergent	Responsiveness
VDS	Methodological quality assessment (COSMIN risk of bias)								
Banos <sup>232</sup>								Adequate	
Briggs <sup>233</sup>								Adequate	
Van Dijk <sup>251</sup>								Adequate	
Li <sup>244</sup>					Inadequate			Adequate	
Zhou <sup>253</sup>					Inadequate			Adequate	
Gagliese <sup>60</sup>							Inadequate	Inadequate	
Jensen <sup>242</sup>									Inadequate
Rating					+			±	±
LoE					Low			low	High
FPS	Methodological quality assessment (COSMIN risk of bias)								
Fadaizadeh <sup>237</sup>								Adequate	
Van Giang <sup>252</sup>								Adequate	Doubtful
Li <sup>244</sup>					Inadequate			Adequate	Inadequate
Li <sup>243</sup>					Inadequate			Adequate	Inadequate
Zhou <sup>253</sup>					Inadequate			Adequate	
Aziato <sup>231</sup>									Inadequate
Rating					+			+	+
LoE					Low			Moderate	High
OPS	Methodological quality assessment (COSMIN risk of bias)								
Tandon <sup>250</sup>								Doubtful	

VAS, visual analogue scale; NRS, numerical rating scale; VDS, verbal descriptor scale; FPS, faces pain scale; OBS, objective pain score; LoE, Level of evidence using GRADE approach reported as: High, Moderate, Low, or Very low; Ratings for overall quality reported as sufficient (+), insufficient (-), inconsistent (±), indeterminate (?). Empty cells indicate no available results for measurement properties.

**Reliability**

The VAS showed high scale<sup>243, 244</sup>, and test-retest reliability<sup>245</sup> with an intraclass correlation coefficient of 0.79 (95% CI: 0.49 to 0.91)<sup>245</sup>. The NRS demonstrated high test-retest<sup>253</sup>, inter-rater<sup>231</sup> and scale reliability<sup>231, 243, 244, 253</sup>. VDS demonstrated high scale<sup>244</sup> and test-retest reliability<sup>253</sup>. Similarly, FPS demonstrated high inter-rater<sup>231</sup> and test-retest reliability<sup>253</sup> (**Table 3-4**). All four scales showed low-quality evidence due to very serious risk of bias.

**Measurement error**

Only one study assessed measurement error of VAS by determining the minimal detectable change (MDC)<sup>235</sup>, which describes the smallest change outside of inherent measurement error that the VAS can detect. The study showed that the MDC on a 100 mm VAS was 15 mm for total hip arthroplasty and 16 mm for total knee arthroplasty<sup>235</sup>. The evidence regarding VAS measurement error was evaluated as moderate-quality due to inability to determine the minimal important change for VAS in acute pain to compare with MDC and the risk of bias.

**Responsiveness**

Seven studies<sup>231, 238, 241-244, 252</sup> reported responsiveness results for the four unidimensional pain assessment tools and provided low-quality evidence due to a very serious risk of bias (Table 3-5). The identified risk of bias was mainly related to the use of inappropriate measures of responsiveness like effect size and statistical tests used.

**Table 3-4. Reliability of unidimensional pain assessment tools in surgical patients**

First Author Year	PROM/s	Pain construct	Reliability Type	n	Time interval	Interclass correlation coefficient
Li 2007 <sup>244</sup>	VAS NRS VDS FPS	Current, worst, least, average pain on 7 postoperative days	Scale reliability	173	Every 24 hours	*0.66 *0.76 *0.72 *0.72
Li 2009 <sup>243</sup>	FPS NRS Iowa Pain Thermometer	Current pain and daily retrospective ratings of worst and least pain	Scale reliability	180	Every 24 hours	0.95 to 0.97 ‡
Zhou 2011 <sup>253</sup>	VDS NRS FPS Numeric Box-21 Scale Coloured Analogue Scale	Recalled pain and postoperative pain	Test–retest reliability	153	24 hours	0.96, 0.88, 0.93, 0.84¶ 0.94, 0.90, 0.91, 0.80¶ 0.93, 0.91, 0.84, 0.80¶ 0.92, 0.91, 0.78, 0.76¶ 0.93, 0.90, 0.88, 0.77¶
Aziato 2015 <sup>231</sup>	NRS FPS Colour Circle Pain Scale	No pain – worst possible pain No pain – worst possible pain No pain – unbearable	Inter-rater reliability	150	5 to 10 minutes	0.92 0.93 0.93
Myles 2017 <sup>245</sup>	VAS	Pain unchanged or almost the same	Test–retest reliability	22	Not reported	0.79 (0.49–0.91)**

PROM/s, patient-reported outcome measures; n, number of patients; VAS, visual analogue scale; NRS, numerical rating scale; VDS, verbal descriptor scale; FPS, faces pain scale; \* average interclass correlation coefficient calculated for 7 days, ‡ no separate result for each scale; ¶ results categorised in 20–44 years (n = 43), 45–59 years (n = 39), 60 years without cognitive impairment (n = 40), ≥60 years with mild cognitive impairment (n = 31); \*\* 95% CI.



**Table 3-5. Responsiveness results of unidimensional tools**

First author Year	PROM/s	Time interval	n	Better, same, worse %	Mean difference pre and post treatment (95% CI)	Effect size SRM (95% CI)	OR	Correlation with changes in Other Instruments
Jensen 2002 <sup>242</sup>	VAS VDS Relief rating	Baseline then several times	123 125		10.37€, 20.71¶ 7.17€, 15.09¶ 7.59€, 26,61¶			
Jenkinson 1995 <sup>241</sup>	VAS CPI MPQ	Baseline then 120 minutes	75	Moderate 2.23 <sup>^</sup> , 1.83 <sup>#</sup> Good 1.91 <sup>^</sup> ; 3.13 <sup>#</sup> Complete 1.89 <sup>^</sup> , 5 <sup>#</sup>		G1;0.99 <sup>^</sup> , 1.93 <sup>#</sup> G2;1.23 <sup>^</sup> , 1.82 <sup>#</sup> G3; 2 <sup>^</sup> , 3.29 <sup>#</sup> G4;1.48 <sup>^</sup> , 1.48 <sup>#</sup>		CPI 0.67 to VAS
Van Giang 2015 <sup>252</sup>	FPS NRS	Every 30 minutes for 2 hours	144		-1.17* -1.59+ -1.66† -1.82\$	-0.70* -1.05+ -1.20† -1.31\$		0.78
Li 2007 <sup>244</sup>	VAS NRS VDS FPS	NR	28		4.3 ± 2.4† 4.2 ± 2.3† 4.5 ± 2.1† 4.3 ± 1.9†			
Li 2009 <sup>243</sup>	FPS NRS IPT	NR	180		14.095 †*			
Aziato 2015 <sup>231</sup>	NRS FPS CCPS	NR	150		2.3 (2.1–2.5)† 1.5 (1.4–1.6)† 1.4 (1.3–1.5)†			

First author Year	PROM/s	Time interval	n	Better, same, worse %	Mean difference pre and post treatment (95% CI)	Effect size SRM (95% CI)	OR	Correlation with changes in Other Instruments
Gagliese 2003 <sup>238</sup>	MPQ PPI VAS-R VAS-M	NR	200			0.31 <sup>¥</sup> , 0.39 0.25 <sup>¥</sup> , 0.26 0.23 <sup>¥</sup> , 0.32 Not reported		

**PROM/s** , patient-reported outcome measures; SRM, standardized response mean; VAS, visual analogue scale; VDS, verbal descriptor scale; €, knee surgery; ¶, laparotomy; ^, VAS score; #, CPI score; CPI, categorical verbal pain rating scale; MPQ, McGill pain questionnaire; G, group; FPS, face pain scale; VDS, verbal descriptor scale; FPS, face pain scale; CCPS, colour circle pain scale; PPI, present pain intensity; VAS-R, visual analogue scale at rest; VAS-M, visual analogue scale at movement; Effect size, calculated by taking a mean change of variable and dividing it by standard deviation of that variable; \*, time 2 versus time 1; +, time 3 versus time 1; †, time 4 versus time 1; \$, time 5 versus time 1; †, p-value is statistically significant at <0.0001; ¥, results for younger patient split of the sample at the median age of 62 years. Note: Empty cells indicate data not available or not assessed.

### 3.5.5.2 Functional pain assessment tool

Only one study examined the 'Objective Pain Score' which assesses the interference of pain with respiratory function<sup>250</sup>. The study evaluated the correlation between scores obtained from Objective Pain Score and NRS. While patients rated their pain using a printed NRS, the clinician rated pain using the Objective Pain Score. A linear regression model determined the relationship between NRS and Objective Pain Score and showed that for every unit increase in the NRS, the Objective Pain Score decreased by 0.334. The study reported sufficient convergent validity with the NRS, although with low-quality evidence due to risk of bias and imprecision. A summary of finding on all assessed measurement properties is provided in (Table 3-6).

Table 3-6. Summary of methodological quality of studies using COSMIN risk of bias and measurement properties

First author	Content Validity	Structural Validity	Internal Consistency	Cross cultural Validity	Reliability	Measurement Error	Criterion Validity	Construct Validity/ Convergent	Responsiveness
<b>VAS Methodological quality assessment (COSMIN risk of bias)</b>									
Banos <sup>232</sup>								Adequate	
Akinpelu <sup>228</sup>								Doubtful	
Briggs <sup>233</sup>								Adequate	
Fadaizadeh <sup>237</sup>								Adequate	
DeLoach <sup>236</sup>								Doubtful	
Li <sup>244</sup>						Inadequate		Adequate	Inadequate
Gagliese <sup>60</sup>							Inadequate	Inadequate	
Gagliese <sup>238</sup>								inadequate	Inadequate
Myles <sup>245</sup>						Inadequate			
Jensen <sup>242</sup>									Inadequate
Danoff <sup>235</sup>							Adequate		
Hamzat <sup>240</sup>						Inadequate			
<b>Rating</b>					?	+	?	?	+
<b>LoE</b>					Very low	Low	Moderate	Very low	High
<b>NRS</b>	<b>Methodological quality assessment (COSMIN risk of bias)</b>								
Van Dijk <sup>251</sup>								Adequate	
Li <sup>244</sup>						Inadequate		Adequate	Inadequate
Li <sup>243</sup>						Inadequate		Adequate	Inadequate
Zhou <sup>253</sup>						Inadequate		Adequate	Adequate
Gagliese <sup>60</sup>							Inadequate	Inadequate	
Aziato <sup>231</sup>						Inadequate		Doubtful	Inadequate
<b>Rating</b>						+		±	+
<b>LoE</b>						Low		low	High
<b>VDS</b>	<b>Methodological quality assessment (COSMIN risk of bias)</b>								
Banos <sup>232</sup>								Adequate	
Briggs <sup>233</sup>								Adequate	
Van Dijk <sup>251</sup>								Adequate	

First author	Content Validity	Structural Validity	Internal Consistency	Cross cultural Validity	Reliability	Measurement Error	Criterion Validity	Construct Validity/ Convergent	Responsiveness
Li <sup>244</sup>					Inadequate			Adequate	
Zhou <sup>253</sup>					Inadequate		Adequate	Adequate	
Gagliese <sup>60</sup>							Inadequate	Inadequate	
Jensen <sup>242</sup>									Inadequate
<b>Rating</b>					+		±	±	?
<b>LoE</b>					Low		low	High	Low
<b>FPS</b>	<b>Methodological quality assessment (COSMIN risk of bias)</b>								
Fadaizadeh <sup>237</sup>								Adequate	
Van Giang <sup>252</sup>								Adequate	Doubtful
Li <sup>244</sup>					Inadequate			Adequate	Inadequate
Li <sup>243</sup>					Inadequate			Adequate	Inadequate
Zhou <sup>253</sup>					Inadequate		Adequate	Adequate	
Aziato <sup>231</sup>					Inadequate			Doubtful	Inadequate
<b>Rating</b>					+		+	+	?
<b>LoE</b>					Low		Moderate	High	Low
<b>OPS</b>	<b>Methodological quality assessment (COSMIN risk of bias)</b>								
Tandon <sup>250</sup>								Doubtful	
<b>Rating</b>								+	
<b>LoE</b>								Very low	

VAS, visual analogue scale; NRS, numerical rating scale; VDS, verbal descriptor scale; FPS, faces pain scale; OBS, objective pain score; LoE, Level of evidence using GRADE approach reported as: High, Moderate, Low, or Very low; Ratings for overall quality reported as sufficient (+), insufficient (-), inconsistent (±), indeterminate (?). Empty cells indicate no available results for measurement properties

### 3.5.6 Other outcomes

#### 3.5.6.1 Interpretability and desire for analgesics

##### Visual analogue scale

Seven studies<sup>27, 229, 235, 245-247, 249</sup> looked at the interpretability of VAS, and one study<sup>211</sup> included the desire for analgesics as an outcome. Several studies<sup>27, 229, 249</sup> reported nearly similar cut-off points for VAS, indicating that VAS ratings of 0-5 mm were very likely to be rated as no pain by patients, 6-44 mm were considered mild pain, 45-69 mm were considered moderate pain, and VAS ratings  $\geq 70$  mm were suggestive of severe pain.

Two studies<sup>235, 245</sup> determined the interpretability of VAS by identifying the minimal clinically-important difference (MCID) defined as the minimal change in score indicating a meaningful change in pain status<sup>254</sup>. The use of a combination of distribution- and anchor-based methods resulted in an MCID of 9.9 mm for VAS in assessing several types of surgical procedures<sup>245</sup>. In contrast, Danoff *et al.*<sup>235</sup> reported higher MCID values for pain improvement in patients undergoing total hip or knee arthroplasty. Pain was improving clinically when the VAS decreased by 19 and 23 mm, respectively.

Bodian *et al.*<sup>211</sup> found that the proportion of patients requesting additional analgesia following abdominal surgery increased as VAS increased (4%, 43%, and 80% with VAS scores of 30 mm or less, 31-70 mm, and greater than 70 mm, respectively).

**Numerical rating scale (NRS)**

Four studies<sup>210, 234, 239, 251</sup> looked at interpretability of the NRS, one study include desire for analgesics as an outcome<sup>35</sup>. Sloman *et al.*<sup>210</sup> determined the meaning of changes in NRS in relation to perceived pain relief before and after treatment. Patients who rated their pain relief as 'minimal' had, on average, a 35% reduction in NRS. NRS was less sensitive to detect changes from 'moderate' to 'much' as there was a 67% reduction for those who rated their reduction as 'moderate', a 70% decrease for those who rated it is as 'much', and a 94% reduction for those assessed their pain reduction as 'complete'<sup>210</sup>.

Inconsistent cut-off points between moderate to severe pain were identified for NRS. For example, Gerbershagen *et al.*<sup>239</sup> determined NRS  $\geq 4$  as a cut-point for moderate pain, while 'pain interfering with function' resulted in a lower cut-off point of NRS  $\geq 3$ . While using receiver operating characteristic analysis in another study, Van Dijk *et al.*<sup>251</sup> found that the sensitivity of NRS to differentiate bearable pain (VRS  $< 2$ ) from unbearable pain (VRS  $> 2$ ) reached higher values (94%) for high cut-off point of NRS  $> 5$  compared with lower cut-off points of 3 and 4 (sensitivity 72%, 83%) respectively.

In another study, Van Dijk *et al.*<sup>35</sup> showed that 19% of patients with NRS scores ranging from 5-10 had no desire for additional opioids; 62% reported that they did not want additional opioids because their pain was tolerable. When patients were asked at which score, they would request opioids, both the median and the modal pain scores were an NRS of 8.

**Feasibility**

Eight studies included feasibility of pain assessment tools as an outcome measure<sup>60, 230, 231, 233, 243, 244, 248, 253</sup>. Error rates were reported as an inability to understand the tool, responses that could not be scored reliably, and lack of responses<sup>60, 233, 244, 248</sup>. Some studies reported the most preferred scale or the easiest to complete ones<sup>60, 231, 243, 253</sup>. There was a lack of studies that assessed the time required to complete the tool or time taken to train patients or nurses.

For multiple types of surgical procedures and in different populations VDS or VRS were more successful when compared with other tools. Using VRS in patients aged  $\geq 75$  years after cardiac surgery showed a higher success rate (81%) compared with VAS (60%) and the FPS (44%). These rates varied significantly on all postoperative days ( $p < 0.02$ )<sup>248</sup>. The reported reasons for the failure rate, which was identified as failure to understand or express level of pain using the assessment tool, were postoperative confusion, delirium, exhaustion, and an inability to differentiate between facial expressions<sup>248</sup>. In a similar way, VRS was more suited for compliance and ease of use following orthopaedic surgery compared with VAS in which 56% of patients included in the study did not understand how to complete VAS and one-third could not perform the assessment using VAS due to visual or hearing impairment<sup>233</sup>. Moreover, VAS showed the highest error rate of 12.3% when used in Chinese populations, whereas VRS reported the lowest error rate (0.8%), which was statistically significant ( $p < 0.05$ )<sup>244</sup>. Interestingly, 40% of the patients rated NRS as the easiest, most preferred tool for assessment; on the contrary, VAS was reported the least preferred<sup>60</sup>.



From the nurses' perspectives in post-anaesthesia care units, NRS was the most preferred tool in 60% of the included sample<sup>230</sup>. Even though the VAS was the recommended tool to be used in the institution where the study was conducted, 50% of the nurses preferred to use either NRS or VRS due its complexities making it difficult for patients to understand VAS<sup>230</sup>. Three studies reported FPS as the preferred tool among a Chinese population<sup>244</sup>, for women<sup>243</sup>, middle-aged adults, and elderly patients without and with mild cognitive impairment, followed by VRS and NRS<sup>253</sup>. Likewise, FPS (55%) was preferred to NRS (33%) among a Ghanaian population<sup>231</sup>.

### **3.6 Discussion**

This systematic review presents a comprehensive examination of the measurement properties of unidimensional and functional assessment tools used for adult postoperative patients. The quality of evidence for the measurement properties and utility of the VAS, VDS, NRS, and FPS was suboptimal. Overall, construct validity (convergent validity) was most commonly assessed across measures. Content validity, internal consistency and structural validity were not assessed as these measures are not designed for single-item scales. The VAS had the greatest number of studies assessing its measurement properties in the postoperative setting, followed by the NRS. Studies on functional pain assessment tools were scarce. Most of the reviewed studies failed to meet the COSMIN methodological standards required. Good-quality studies were found for interpretability and feasibility as assessed by the Newcastle Ottawa Scale<sup>223</sup>.

Most of the studies reported sufficient convergent validity of several unidimensional pain assessment tools, indicating that the scales tended to measure score variations in the same direction<sup>255</sup>. Similar positive findings of good convergent validity results were reported when these tools were used to assess pain associated with rheumatoid arthritis<sup>256</sup> and osteoarthritis<sup>257</sup>, and low back pain<sup>258</sup>. However, the methodology used to measure convergent validity was limited. Because no gold standard tool exists for assessing pain, most studies assessed the correlation of scores obtained from one unidimensional tool with another, measuring only pain intensity. However, when a multidimensional tool such as the MPQ was used as a comparator, studies reported lower correlation scores<sup>60, 238, 259</sup>. This variation may be related to assessor and patient fatigue during the detailed pain assessment.

There was good reliability of pain assessment for all the unidimensional tools. However, the quality of evidence was low for all four scales because of serious risk of bias due to unreported intervals for repeated measures or the use of inappropriate reliability measures by treating ranked NRS, VDS or FPS scores as a continuous value. Measurement error was only available for VAS; however, the study outcome was indeterminate as it was not possible to determine for VAS in acute pain to compare it with the MDC. When the MDC is smaller than the minimal important change, significant change can be distinguished from measurement error<sup>260</sup>.

Small, albeit statistically significant changes in VAS do not necessarily indicate clinically important changes to guide the interpretation of studies evaluating analgesic therapies<sup>235</sup>. Therefore, obtaining an accurate MCID (the minimal change in VAS score to indicate a real change in pain intensity) is crucial<sup>261</sup>. Previous studies have shown that the MCID differs by patient population and diagnosis. The current systematic review identified two studies reporting inconsistent MCID values for the postoperative population<sup>235, 245</sup>. The MCID tended to be higher in patients who underwent joint arthroplasties than other procedures<sup>245</sup>. One explanation might be that patients reporting severe, acute pain need a larger reduction in pain to be clinically meaningful<sup>262</sup>. another possibility for the variable results could be the use of different anchored arbitrary Likert scales to relate VAS scores. The findings of these two studies cannot be generalised to other postoperative populations.

Measures of responsiveness are an important psychometric property to assess the sensitivity of change in pain over time<sup>55</sup>. Measures of responsiveness used included effect size, standardized response mean and scores pre- and post-intervention<sup>27, 231, 238, 241, 243, 244, 252</sup>. According to COSMIN methodology, effect size and standardized response mean are inappropriate to assess responsiveness because they measure the size of the change scores rather than their validity. Moreover, the p value of statistical tests only measures the statistical significance of the change in scores rather than their validity<sup>260</sup>.

Pain assessment tools help diagnose surgical catastrophes, allow communication between health care providers, and are used to assess efficacy of analgesic

treatments and allow comparison between therapies. As no agreement exists on how to identify the optimal cut-off point of a unidimensional pain assessment tool, various arbitrarily chosen values are used<sup>239</sup>. Generally, VAS cut-off points of 30, 70, 100 mm indicate the upper boundaries of mild, moderate and severe pain. However, a recent study conducted found a higher cut-off point between mild and moderate pain of around 55 mm on the VAS, which is greater than the values reported by most earlier studies and physicians' consensus<sup>27, 263-265</sup>.

NRS cut-off points used by healthcare professionals do not necessarily reflect patients' desire for additional analgesics<sup>35</sup>. Previous studies have also found that a high proportion of patients with pain scores  $>4$  did not demand analgesics (28% of patients visiting an emergency department<sup>266</sup> and 42% of children after surgery<sup>267</sup>). Cho *et al.*<sup>259</sup> showed that postoperative patients requested an analgesic when their pain was VAS  $\geq 5.5$ , NRS  $\geq 6$ , FPS-R  $\geq 6$  or VRS  $\geq 2$  (moderate or severe pain). This might be influenced by a general refusal for analgesic medicines, or fear of side effects or addiction, especially with opioids<sup>35, 268, 269</sup>. Cut-off points, although important are not validated to guide analgesic interventions.

Previously, postoperative pain assessment and management was focused on providing humanitarian pain relief, which constitutes only one objective to tackle a complex experience, and that was achieved by using unidimensional scores. However, health care providers should address pain by several approaches to determine if the pain is tolerable, is hindering recovery or requires intervention<sup>259</sup>.

Efforts have been made to encourage use of multidimensional tools to assess postoperative pain. A recent systematic review indicated that the Brief Pain Inventory and the American Pain Society Pain Outcomes Questionnaire – Revised were the two commonly used and studied multidimensional pain assessment tools for patients after surgery, followed by the MPQ. These multidimensional tools showed good ratings for some psychometric properties like internal consistency. However, this recommendation was based on low- to moderate-quality evidence<sup>55</sup>. Moreover, these tools involve a detailed assessment that can range from 5 to 30 minutes<sup>270</sup>, hindering routine use for frequent assessment in a busy surgical ward<sup>21</sup>. Alternatively, functional pain assessment has been recommended<sup>34, 271</sup>.

Since no gold standard objective measures exist for pain-related functional capacity in postoperative patients<sup>272</sup>, objective tools assessing the impact of pain on function was included. Only one study reported sufficient convergent validity of functional assessment based on pain interference with normal breathing and NRS score<sup>250</sup>. The low methodological quality of the study limits the generalisability of the result. Other researchers have tried to incorporate a non-formally validated three-level FAS<sup>21</sup> into clinical practice. One study in a Chinese population combining the Functional Activity Score and dynamic NRS found that this allowed nurses to guide and educate patients to better use patient-controlled analgesia to facilitate functional recovery<sup>273</sup>. In addition, a pilot study in hospitalised patients validated a four-level scale (no interference, interference with some or most activities, or inability to do any activity)<sup>59</sup>. It established the

convergent validity of this tool compared with NRS and VAS in cognitively intact patients. Patients aged  $\geq 40$  years also preferred a functional assessment scale<sup>59</sup>, possibly because functional assessment considered the impact of pain on activity.

The heterogeneity of study designs, including the assessment scales used, surgical procedures, sample sizes, countries in which the studies were conducted, and the languages used, make determining the most feasible assessment tool difficult. However, the VAS showed the highest error rate and was the least preferred in several studies, whereas the VRS showed the lowest error rate. Difficulties comprehending the VAS and linearly quantifying pain resulted in a higher frequency of incomplete responses, especially for older patients<sup>23, 35</sup>. Therefore, older adults and children who have less abstract thinking ability might prefer a categorical scale like the VRS for easier use<sup>34</sup>. Interestingly, although the FPS is commonly used in paediatric populations, it was also the most preferred tool in the Ghanaian and Chinese adult populations. This might be because of the simplicity of facial expressions, which can quickly reflect pain. Alternatively, cultural aspects may explain why the FPS was preferred<sup>274</sup>.

### **3.6.1 Strengths and limitations**

The main strength of this review is that it includes the most frequently used unidimensional and functional pain assessment tools. In addition, no limits were applied on publication date, facilitating the obtaining of information on early studies of these tools. To our knowledge, this is the first review to evaluate the

validity of these tools focusing solely on postsurgical populations and applying COSMIN methodology.

Potential limitations include the fact that the search strategy may have excluded grey literature and studies published in languages other than English. However, to limit the effect of language and publication biases, references of included studies were searched. In addition, the clinical diversity and limitations in the methodologies and quality of the included studies, may have reduced the strength of the conclusions.

### **3.7 Conclusion**

This systematic review challenges the validity and reliability of unidimensional tools to quantify pain in adult patients after surgery. Despite their extensive use, no evidence clearly suggests that one tool has superior measurement properties in assessing postoperative pain. Therefore, future studies should be prioritized to assess their validity, reliability, measurement error, and responsiveness using COSMIN methodology. Moreover, adequate quality head-to-head comparison studies are required to assess several unidimensional pain assessment tools alongside other tools covering multiple dimensions of the pain experience. In addition, because promoting function is a crucial perioperative goal, psychometric validation studies of functional pain assessment tools are needed to identify patients who need additional interventions to promote recovery and improve postoperative pain assessment and management.

## **Chapter 4: Data source and cohort identification**



## **4.1 Introduction**

The availability of reliable and appropriate data sources plays a pivotal role in identifying a cohort of adults undergoing colectomy and providing details about their hospital admission, demographics, and opioid utilisation. These data sources need to contain research-quality records for enough individuals to effectively represent the population of interest and ensure the validity and generalisability of the study findings. This chapter focuses on data source selection and cohort identification, which form the foundation for any pharmacoepidemiology study.

## **4.2 Aims and objectives**

This chapter provides an overview of the rationale for selecting the data source, identifying the study cohort, and extracting relevant study variables for the current research. The objectives were:

1. To describe the data sources used in this research and outline their strengths and limitations.
2. To identify a cohort of adult people having colectomy
3. To define and extract study variables that relate to the demographic and clinical characteristics of the study cohort.
4. To define and extract study variables related to opioid prescription records for the study cohort.

### 4.3 Data sources

Data were obtained from CPRD and HES databases for this research. These EHR databases report characteristics and clinical information about a sample of the UK population. The following sections provide an overview of EHR databases in general and their strengths and limitations. Furthermore, it will describe CPRD and HES and the other databases used in this thesis, with their respective strength and limitations.

An EHR is a digital version of the real-world patient's medical history that healthcare providers use. It includes all the essential administrative and clinical data related to patient's care under a specific provider, such as demographics, diagnosis, medicines, past medical histories, immunisations, laboratory information, and radiology reports. These anonymised records can be transferred and collected in large databases to be used for research purposes. Various databases worldwide cover different elements of the healthcare pathway and vary in the details provided and the representativeness of the included patient populations.

In the UK, EHR data are stored in various databases that can be utilised for research purposes and health improvement. It also, provides a rich and comprehensive source of data that captures real-time clinical information from diverse healthcare settings. This information includes and is not limited to patient demographics, diagnoses, prescribed drugs, and test results. The availability of these data allow researchers to identify their population of interest. Accordingly,

they may examine medicines use, adverse events, and treatment results, offering insightful information that can influence clinical practice and guide prescribing decisions. Table 4-1 lists EHR databases available in the UK.

**Table 4-1. EHR databases available in the UK**

<b>Data Source</b>	<b>Country</b>	<b>Type of care</b>	<b>Start date</b>
<b>The electronic Data Research and Innovation Service</b>	Scotland	Mixed	1981
<b>Clinical Practice Research Datalink (CPRD)</b>			
<b>CPRD Gold</b>	UK	Primary care	1987
<b>CPRD Aurum</b>	UK	Primary care	2017
<b>QResearch</b>	UK	Primary care	1989
<b>Medicines Monitoring Unit Scotland</b>	Scotland	Mixed	1990
<b>The Health Improvement Network (THIN)</b>	UK	Primary care	2002
<b>Secure Anonymised Information Linkage (SAIL)</b>	Wales	Mixed	2007
<b>Hospital Treatment Insights</b>	UK	Secondary care	2010
<b>Research One</b>	UK	Primary care	2012
<b>OpenSAFELY</b>	UK	Primary care	2020

### 4.3.1 Strengths and limitations of the EHR databases

To effectively utilise EHR databases for research purposes, it is crucial to understand their strengths and limitations.

#### Strength of EHR databases

EHR databases provide data collected during the routine delivery of health care and presented in electronic format to capture information over a prolonged period. This longitudinal information enables researchers to examine the long-term effects of certain diseases or medicines and assess outcomes over time. EHR

databases provide real-world data representing how drugs are prescribed in everyday clinical practice. Accordingly, the findings from EHR research can complement results from randomised controlled clinical trials that can often be limited by restricted inclusion and exclusion criteria. Thus, they allow researchers to assess medicine effectiveness, safety, and utilisation patterns in real-world settings.

The availability of extensive patient data from diverse populations allows researchers to study the effects of medicines on a broad range of individuals, including those with different demographics, comorbidities, and treatment histories, thus providing a representative sample and increasing statistical power and allowing the detection of rare adverse events or medicines effects. Additionally, because data are collected as a part of the usual patient care process, the collected recordings did not require agreement from the patient to participate in a research study or memorising specific facts about a disease or medicines. Thus, the risks of recall bias or patient non-response are minimised.

Some EHR databases expand research opportunities and provide more robust and meaningful research studies by allowing linkage to other data sources to offer a broader range of information not captured in a single database or cross-referencing information across multiple databases to validate data and identify errors.

EHR can potentially reduce the time, resources and costs required to answer research questions compared to conducting new studies or clinical trials. In

addition, remotely accessing EHR makes it an invaluable data source for continuous research, especially during unforeseen constraints or restrictions, such as those imposed during the COVID-19 pandemic or other unexpected limitations affecting clinical research. Thus, HER provides timely access to patient data, allowing researchers to analyse recent medicines exposures and outcomes. This can be particularly useful in studying emerging drug safety issues or monitoring the impact of new medicines in real-time.

### **Limitations of EHR databases**

Because EHRs are collected during routine delivery of health care, they vary in completeness and consistency based on the provider's accuracy in data documentation which excessive or busy workloads can largely influence. Biases also may be introduced at several steps while delivering patient care, which cannot be captured.

Since EHR data include records only for people seeking healthcare in organisations that agreed to share their patient data for research purposes, selection bias could be introduced in some cases. Accordingly, results may only represent part of the population. Also, because people might not seek care for mild or transient diseases, only conditions that are regularly recorded in electronic health records can be studied.

Some research questions need to be complemented by data from detailed clinical contexts, such as patient-reported outcomes, medicines adherence or quality of

life which are lacking. In some cases, this can limit research questions that can be answered, the depth of analysis and interpretation of findings.

Studies using empirical data and EHR can have a loss of follow-up, which may result in attrition bias, which can be a problem in longitudinal research. In the case of traditional cohort studies, loss of follow-up can result from a long study period, loss of people's interest in the study, or moving to a different location. While in EHR, attrition can arise because of patients' disenrollment with the participating practice. However, because EHR still captures details for many patients, a sufficient sample size can be easily maintained.

Accurately extracting relevant data relies on identifying the code lists for diagnosis, medicines or outcomes of interest. This step requires time to develop and validate these codes. as missing a single code related to the events of interest might result in misclassification bias and underrepresentation of the events of interest. Therefore, familiarity with the standardised coding system is crucial to ensure accurate data extraction and analysis.

### **4.3.2 Overview of Clinical Practice Research Datalink**

CPRD is a UK government research service that has supplied anonymised electronic health records data from general practices for over 30 years. General practitioners (GP) are the first point of contact for most people seeking non-emergency healthcare services within the National Health Service (NHS). Over 89.1% of the population is registered at one of approximately 7300 GP practices in England as of January 2022<sup>275</sup>.

CPRD collects anonymised patient electronic health records from GP practices that utilise either the Vision® or EMIS® software IT systems. The EMIS WebVR software is used in 56% of English practices and offers the most extensive coverage in the database<sup>276</sup>. CPRD also collects data from practices using Vision GP software that contributes to the CPRD GOLD database has been used in epidemiological research for three decades<sup>277</sup>. CPRD Aurum is an alternative version of the CPRD database, which was launched in October 2017 and collected data from practices using EMIS software. Aurum offers improved data quality and coverage by including data from a larger number of general practices compared with CPRD GOLD. Aurum has significantly increased its capture of current UK patients, now accounting for almost 20% of the population, compared with only around 4% for GOLD. In addition to differences in clinical coverage, these databases also vary in structure and clinical coding.

In recent years, there has been a trend for general practices to transition from the Vision practice system to EMIS, resulting in a more significant market share for EMIS and 20% more practices contributing data than CPRD GOLD. Accordingly, CPRD Aurum is selected as the data source for this thesis. Table 4-2 provides key details about CPRD Aurum dataset used in this research. The following section will provide a detailed description of its structure.

**Table 4-2. Key details about CPRD Aurum dataset used in this research**

Percentage UK population coverage (current patients only)	13,299,826 of 66,796,800 (19.91%)
<b>Total number of research acceptable patients:</b>	39,555,354
<b>Median (25th and 75th percentile) follow-up time in years</b>	8.96 (3.4 – 20.1)
<b>for currently registered patients:</b>	
<b>Patients eligible for linkage</b>	35,444,484
<b>Total number of GP practices</b>	1,489
<b>Percentage coverage of UK general practices (Currently contributing practices only)</b>	1,375 of 8,961 (15.3%)

#### 4.3.2.1 CPRD Aurum

Data about patients obtained from CPRD Aurum are structured in eight files in text format, Table 4-3 provides an overview on data files in the CPRD. Patient-identifiable information, such as names and addresses, along with any free text notes, are removed from the data to protect privacy. In cases where primary care practices are part of the CPRD linkage scheme, patient-level data are connected to additional health-related information, including secondary healthcare records, the national death registry, and socioeconomic status data.

Observations are coded within Aurum using SNOMED CT (UK edition) a clinical coding system that is increasingly used internationally and has also recently become a requirement for NHS providers<sup>275</sup>. CPRD Aurum offers data dictionaries and code browsers that aid in identifying relevant codes. These resources enable researchers to find the appropriate codes within the database. The Medical Dictionary within CPRD Aurum contains comprehensive information about all recorded medical history observations.



**Table 4-3. An overview of data files in the CPRD Aurum**

<b>CPRD files</b>	<b>Description</b>
<b>Patient</b>	Contains basic patient demographics and patient registration details for the patients
<b>Practice</b>	Contains details of each practice, including region and collection information
<b>Staff</b>	Contains practice staff details, with one record per member of staff
<b>Consultation</b>	Contains information relating to the type of consultation as entered by the GP (e.g. telephone, home visit, practice visit)
<b>Observation</b>	Contains the medical history data entered on the GP system including symptoms, clinical measurements, laboratory test results, and diagnoses, as well as demographic information recorded as a clinical code (e.g. patient ethnicity)
<b>Referral</b>	Contains referral details recorded on the GP system. Data in the referral file are linked to the observation file and contain 'add-on' data for referral-type observations
<b>Problem</b>	Contains details of the patient's medical history that have been defined by the GP as a 'problem'. Data in the problem file are linked to the observation file and contain 'add-on' data for problem-type observations
<b>Drug issue</b>	Contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP

### 4.3.3 Hospital Episode Statistics

HES is a comprehensive database that contains patient care data related to all admissions to NHS hospitals in England or care delivered in the independent sector but commissioned by the NHS. The NHS funds approximately 98% of hospital activity in England, with information dating back to 1989<sup>276</sup>. HES Admitted Patient Care (HES APC) data includes hospitalisation, episodes and events. Hospitalisation is the overall duration of a patient's stay in the hospital from admission to

discharge. A patient can have more than one hospitalisation recorded in HES data as the patient may have multiple instances of being admitted and discharged from a hospital. A hospitalisation is made up of one or more episodes; each episode represents a period of patient care provided by healthcare providers within the NHS. Each episode is made up of events and a final diagnosis with or without procedures. More than 17 million episodes are added each year. The data are recorded for episodes ending from April 1<sup>st</sup> to the following March 31<sup>st</sup> each year, corresponding to NHS fiscal years<sup>278</sup>. HES admitted patient care does not include accident and emergency (A&E) attendances or outpatient clinic appointments; these data are detained in separate HES databases called HES A&E data and HES Outpatient data. Linkage to these data was deemed unnecessary for this research because the focus was on surgical admissions and discharges related to colectomy. Within HES data, diagnosis records are coded using International Classification of Disease, 10th revision (ICD-10), while procedures are coded using Office of Population, Census Survey; Classification of Surgical Operations and Procedures (OPCS).

These data obtained from HES are structured in different files including patient file, hospitalisation, episodes, diagnoses, procedures, critical care, maternity, and health resource group. For this thesis, data from critical care, maternity, and health resource group were not required because the focus was not on these areas. A description of the data files used in this research is described in Table 4-4. For this study, set-19 which covers the period from 1st April 1997 to March 2020, was linked to CPRD Aurum data using the same unique patient identifier.

**Table 4-4. Description of HES data files used in this research**

HES file	Description
<b>Patient data</b>	Contains one line of data per patient including patient's year of birth, sex, ethnicity, start/end dates of HES data collection and encrypted unique practice identifier
<b>Hospitalisation data</b>	Contains information on every hospitalisation a patient has, include date of admission, date of discharge, method of admission (day case, elective or emergency) and a unique number identifying each hospitalisation
<b>Episode data</b>	Contains all information on every episode a patient has, including date of admission, date of discharge, date of start of episode, date of end of episode, a unique number identifying the hospitalisation the episode is associated with, and a unique number identifying the episode.
<b>Diagnosis data</b>	Contains information on every diagnosis a patient has, including date of start of episode, date of end episode, a unique number identifying the episode the diagnosis associated with, an ICD-10 code and a binary variable stating whether the diagnosis is a primary one or not.
<b>Procedure data</b>	Contains information on every procedure a patient has, including date of admission, date of discharge and unique number identifying each hospitalisation, date of start of episode, date of end episode, a unique number identifying the episode the procedure was associated with, an OPCS code and a date of procedure.

ICD-10, International Classification of Diseases 10th Revision; OPCS, Office of Population, Census Survey; Classification of Surgical Operations and Procedures

#### 4.3.4 Index of Multiple Deprivation

The Index of Multiple Deprivation (IMD) is the official measure of the relative deprivation level of different residential areas or neighbourhoods in England<sup>279</sup>. It considers various measures across multiple deprivation indicators, including employment, health, income, education, crime, housing, and living situation. These indicators are combined using a weighted formula to calculate an overall deprivation score for each area ranked into Quintiles. Quintiles are determined by ranking the 32,844 small areas in England from most to least deprived and dividing them into five equal groups. These small areas, also called lower-layer super

output areas (LSOAs), maintain fixed boundaries over time, enabling the examination of temporal patterns and changes<sup>279</sup>. IMD scores undergo periodic updates every few years. For this thesis, the dataset utilised relied on the 2015 version of the IMD scores and was selected to indicate the socioeconomic status of people having colectomy within the study period.

#### **4.3.5 Office for National Statistics (ONS) death registration data**

The ONS data comprises the national death registry data from registered death certificates in England since 1998. This comprehensive dataset offers insights into the underlying cause of death, the date of death, and additional contributing causes of death. Notably, this dataset encompasses all deceased patients as it is not limited to those who were hospitalised. The completion of death certificates follows WHO guidelines and adheres to internationally agreed rules and uses ICD-10 for standardised coding. Consequently, these data enable international comparisons and facilitates valuable research and analysis.

#### **4.4 Databases used in this research**

The linkage between HES and CPRD data was essential for this research. Identifying patients having colectomy and their hospitalisation details was required to define the cohort of interest using secondary care HES data. Linkage to primary care CPRD data was essential to gain details of opioid prescriptions and medicines prescribed from primary care after hospital discharge. IMD data was crucial so the socio-economic status can be assigned to each patient and its effect adjusted for, as a covariate, when assessing study outcomes of this thesis. Linkage

to ONS data will help to identify the accurate death date and validate the date of death obtained from CPRD and HES.

#### **4.4.1 Strengths and limitations of databases used in this research**

The CPRD database offers a notable advantage when compared with other UK databases due to the extensive nature of patients' medical records, sourced from a diverse primary care population across different regions in the UK. Patients included in CPRD exhibit a broad representation of age, sex, and ethnicity, mirroring the demographics of the UK population<sup>280</sup>. Moreover, the CPRD encompasses longitudinal data, allowing to study long-term trends in prescribing patterns and healthcare utilisation.

The CPRD and HES are among the most extensive databases providing longitudinal medical records from primary and secondary care worldwide. The CPRD Aurum holds data from 1,356 practices, and for individual patients, there is a long follow-up period with a mean of 8 years<sup>281</sup>. This extended follow-up period enables studying diseases with long latency and long-term outcomes.

The large number of practices contributing data to CPRD [1,356 of 8,178 (16.6%)] allows for conducting studies with higher statistical precision than studies using smaller data sources or other data collection methods. However, since the linkage to HES is only available for English practices (65% of CPRD practices), the power of linked studies is lower than studies using HES or CPRD alone.

The validity of data obtained from CPRD Aurum has been confirmed previously<sup>282</sup>, and the accuracy of primary diagnoses in HES data was also previously validated<sup>283</sup>. The prescription records obtained from CPRD lack details on counselling provided, whether the prescription was dispensed and the level of patient adherence to medicines. Additionally, prescription records have missing prescription details like quantity dispensed and durations. Therefore, appropriate data cleaning and assumptions based on current literature and clinical practice should be applied for reliable and accurate findings (further explained in Chapter 5).

The reliability of HES data depends on the completeness of data provided by healthcare providers, which can vary between hospitals. Additionally, the use of financial incentives to improve coding in hospitals, with variation between conditions, in which some have a higher remuneration than others, could make some hospitals incentivise healthcare providers to code multiple and specific comorbidities compared to other diagnoses. Also, clinical coders use discharge summaries to enter data; therefore, the accuracy of recorded data accuracy might be impacted on some occasions if the discharge summaries lack necessary details or contain errors.

HES data may lack comprehensive hospital clinical details, including specific treatment protocols, patients reported outcomes measures. These may limit its ability to provide a holistic understanding of the broad interventions given to the patient during the hospital stay.

## **4.5 Study design, population and data extraction**

### **4.5.1 Independent Scientific Advisory Committee (ISAC) approval**

The research presented in the following chapters of this thesis was started after approval of the study protocol by CPRD ISAC (Protocol 21\_000668) on 29<sup>th</sup> November 2021. Approval notification is provided in Appendix S 8.

### **4.5.2 Study design**

A retrospective open cohort of adults undergoing colectomy from 2010 to 2019 were identified using HES data and linked to CPRD data to obtain opioid prescriptions prescribed after colectomy. This period was selected to assess the changing trends for opioid utilisation following colectomy and based on data availability at the start of the PhD study. This chapter aims to outline the procedure of selecting the study cohort, extracting the relevant variables, and characterising the cohort. The following chapters in this thesis will provide detailed explanations of the specific cohorts and methods employed for each analysis.

#### **4.5.2.1 Data extraction and study variables**

HES data files were provided in a text tab delimited files format and were downloaded into secure server at the University of Nottingham. Then CPRD data files were downloaded and saved on the same sever. Saved files were then imported into STATA® version 17 (StataCorp, College Station, TX, US) and linked via encrypted patient key (patid) to undertake data management and analyses. Data cleaning was performed prior to any analyses and involved data inspection

for missing information or outliers. (Further details on data management is provided in Chapters 5 and 6)

#### **4.5.2.2 Defining study time-periods**

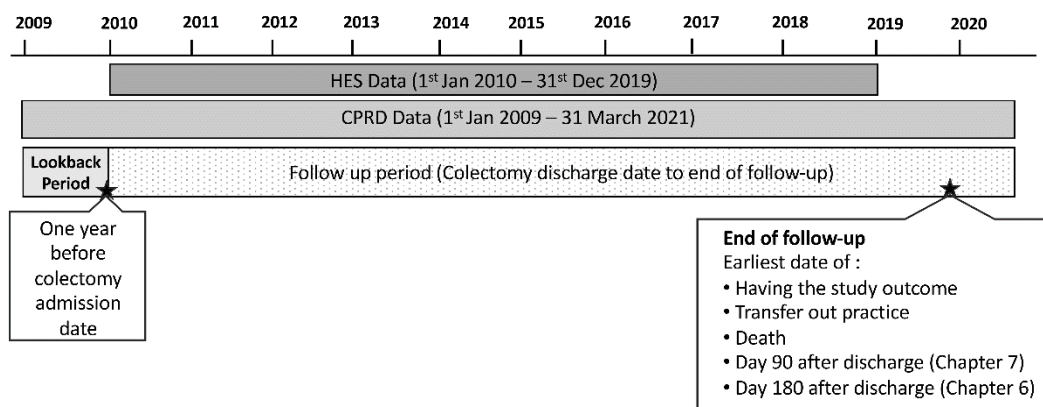
##### **Time period for data obtained from HES**

The colectomy cohort was selected based on their (event date) which was the date when colectomy was performed. Any adult patient having colectomy performed between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2019 was included. This period was selected based on the available HES data release at the start of the PhD study. Figure 4-1 illustrates time periods relevant to the study design.

##### **Time period for CPRD data to identify opioid prescriptions**

The last included admission date for the colectomy cohort was December 2019. However, some patients had their discharge date later in 2020. To account for one year after discharge date, prescription records were included until March 2021 (The end of CPRD dataset coverage). Opioid prescription data covering the period from 1<sup>st</sup> January 2009 and 31<sup>st</sup> March 2021 were obtained. This period was chosen to allow for sufficient data for the look-up period (detailed in the section below) and the follow-up period after colectomy discharge date (vary based on the outcomes in Chapters 5, 6 and 7).





**Figure 4-1. Time periods relevant to the study design**

### Lookback period

In pharmacoepidemiological studies, a lookback period refers to a specific time period that is retrospectively examined to collect information about a patient's previous diagnosis and exposure to medicines. While there has yet to be an agreement on the optimal duration of a lookback period, it is generally recognised that a more extended one can reduce the likelihood of misclassifying individuals as new users of a medicines<sup>284</sup>. A one-year opioid lookback period before the colectomy admission date was selected to allow for categorising the study cohort based on varying degrees of opioid exposure and recency before colectomy (further details will be explained in Chapter 6).

### Time period for follow up

The discharge date was chosen as the starting point for follow-up because it follows the event date (surgery date), which confirms that the colectomy was completed. Possibly, some opioids might be prescribed for patients during

their hospital stay, and these opioids are not recorded within HES data. Only prescriptions received from the GP after surgical discharge are recorded in CPRD data. Therefore, the discharge date represents the closest date to receiving a prescription from a GP following colectomy and allows for identifying prescriptions given by the GP after the patient leaves the hospital. Patients were followed up starting from their colectomy discharge date up to 90 days later; this was referred to as the early post-discharge period (used in Chapters 6 and 7). Another follow-up period started from day 91 to day 180 of surgery discharge day and was referred to as the late post discharge period (used in Chapter 7). A follow-up period of one-year opioid prescription data following discharge date (used only in Chapter 5 for cleaning opioid prescription records). People were censored from the cohort at the earliest of the following dates:

1. The date the patient stopped their registration with their GP, indicated by the 'transfer out date' (tod) variable from the Patient file in the CPRD Aurum.
2. The date the patient's GP ceased to contribute data to the CPRD, indicated by the 'last collection date' (lcd) variable from the Practice file in the CPRD Aurum.
3. The date the person died, if this was during the study period, indicated by the 'death date' (deathdate) variable from the Patient file in the CPRD Aurum, HES and ONS.
4. Day 90 after colectomy discharge (Chapter 7).
5. Day 180 after colectomy discharge (Chapter 6).

### **4.5.2.3 Study cohort selection**

Patients were included in the colectomy cohort if they met all the following inclusion criteria:

1. Having their admission date for colectomy between 1st January 2010 to 31st December 2019.
2. Age  $\geq 18$  years on their surgery date.
3. Admission date is after the 'first registration to CPRD practice' date.
4. Surgery date before recorded death date in HES, CPRD, and ONS.
5. Surgery date recorded before the date of discharge.
6. Acceptable standard data – determined by the CPRD 'accept' indicator within the CPRD Patient file.
7. Patients have at least 12 months of Aurum data before the admission date for surgery to ensure sufficient data on pre-operative opioid exposure is available for each patient.
8. Patients who survived the first 90 days following discharge (early post-discharge period).
9. Have admission-type recorded in HES data, as this will be used as a study variable.

#### **4.5.2.4 Study medicines**

CPRD Aurum provides (a product code look-up file) which can be searched to identify codes for opioids of interest. Therefore, the CPRD Aurum product code look-up file was searched using the drug substance and term field to identify opioid-containing products for inclusion in the study.

The search followed a similar sequence as outlined in the British National Formulary (BNF) (edition-79). Each opioid included was searched for and matched against the product codes (Appendix S 10). Additionally, the product names, drug substance fields, and formulations of the obtained list were manually reviewed to ensure adherence to the predefined inclusion criteria. (list of opioids included are provided in Chapter 5).

Products were included in the opioid code list if they met all the following criteria:

1. They contained an opioid drug.
2. The 'product' field within the CPRD product code look-up file detailed the drug substance and strength or, for branded products, if this information could be found in the BNF.

Products were excluded from the opioid code list if they met the following criteria:

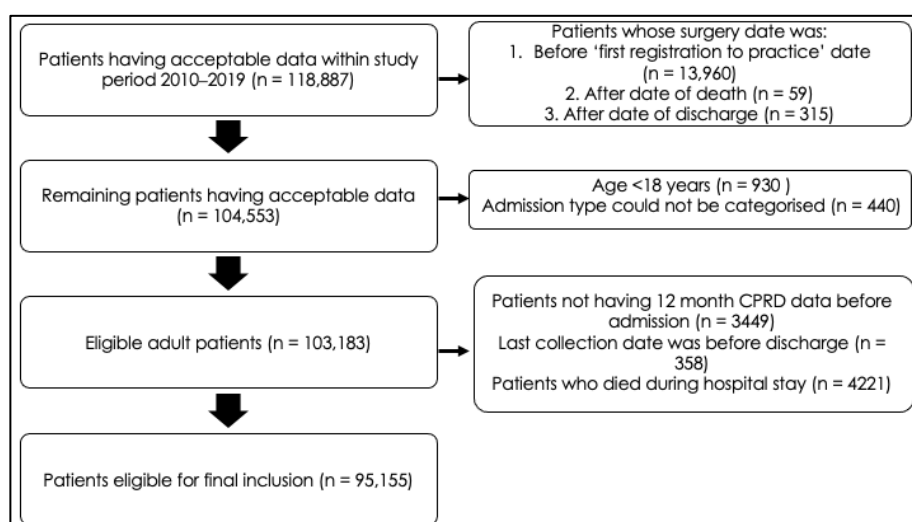
1. Injectable formulation as these formulations are typically administered by healthcare professionals.

2. Generic or branded version of higher-strength buprenorphine sublingual tablets (2, 4 and 8 mg) as these are primarily prescribed as an opioid addiction treatment in the UK.

3. Generic or branded version of methadone oral solution as these are primarily prescribed as an opioid addiction treatment in the UK.

#### 4.5.2.5 Process of selecting colectomy cohort from HES

The selection of an eligible cohort of adult patients having colectomy started by searching for procedure codes for colectomy surgeries performed between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2019. Operations that were limited to or included the anal canal and rectum were excluded (Appendix S 9) Patients aged  $\geq 18$  years were identified from HES. All steps included in cohort selection are illustrated in the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) diagram (Figure 4-2).



**Figure 4-2. Selection of study cohort**

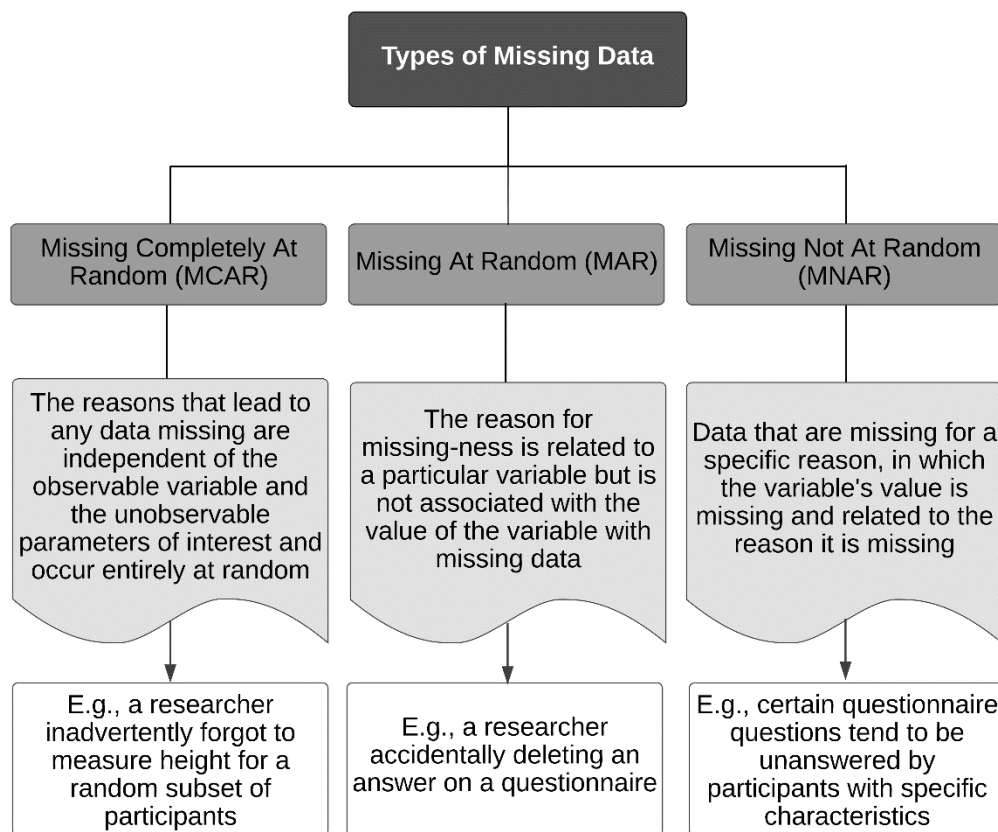
#### **4.5.2.6 Identifying opioid prescriptions from CPRD**

The CPRD drug issue file was searched for opioid prescriptions using selected opioid codes (Appendix S 9). The obtained prescription records were then combined with the colectomy patients identified from HES using patient IDs. Eligible patients who underwent colectomy were assessed for the presence of an opioid prescription during their lookback period or one year of colectomy discharge date. Two datasets were generated. One dataset contained all colectomy patients having colectomy admissions between 2010 and 2019, whether they had opioid prescriptions or not. Along with the opioid prescription records for one year before and after colectomy for patients having opioid prescriptions (used in Chapter 6). The second dataset included only the colectomy patients who had records of opioid prescription for one-year before admission and one-year after colectomy discharge (used in Chapter 5). In each analysis chapter more variables specific to each analysis were generated; these are described in the methods sections of the relevant chapters.

#### **4.6 Data analysis**

The number of patients at each stage of cohort identification were quantified and reported in the STROBE diagram (Figure 4-2). Additionally, missing data regarding variables associated with opioid prescription records were represented as a total count and a proportion relative to the overall number of opioid prescription records. The study in Chapter 7 primarily relies on opioid prescription records known to have missing information that needs to be addressed using a suitable

approach. Therefore, it is essential to understand the nature of this missing information and determine whether it is missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Figure 4-3 provides description of these terms. Accordingly, a subsample of opioid prescription records was manually inspected to understand the nature of missing data better. Missing data regarding variables associated with opioid prescription records were represented as a total count and a proportion relative to the overall number of opioid prescription records.



**Figure 4-3. Types and description of missing data**

## **4.7 Results**

### **4.7.1 Selection of study cohort**

A total of 246,240 patients with colectomy procedures code and linked to CPRD data covering the period between 1997 and March 2020 were identified. Of these, 146,466 people had colectomy codes eligible for the study period. Of these, 27,579 people were excluded for not having sufficient CPRD data. Inclusion criteria were applied to the remaining 118,887 patients. A full description of the results is presented in Figure 4-2. The demographics of the identified cohort will be discussed under subsequent chapters (Chapters 6 and 7).

### **4.7.2 Opioid prescription records**

Opioid product codes were merged with CPRD drug issue file to obtain opioid prescriptions. Opioid prescription records only contain variables for the issue date of the prescription and the drug prescribed. Therefore, these prescriptions were merged with a supplementary common dosage look-up file that contains text identifier (text id) which list prescription instruction and daily doses. In total 3,575,765 records of opioid prescriptions were identified until 2021. After combining these prescription records into the cohort, 251,782 prescriptions for the overall cohort were identified. After applying further restrictions to prescriptions related to colectomy who had them one year before and after colectomy date, prescription records for 29,617 patients (used in Chapter 5) were identified. A subsample of 30,000 prescription records of 3,676 patients was used to understand the nature of missing data. 634 unique dosage\_text instructions



were manually checked and categorised as ambiguous, unambiguous, unknown or missing. (See Table 4-5 for definitions) All data were available for the prescription issue date and the type of prescribed opioid. However, a high proportion of missing daily doses variable, duration and text id was noted.

**Table 4-5. Inspection of dose instructions in a sample of opioid prescription records (n=30000)**

Category	Definition	Example	Proportion of records	
			(n)	(%)
<b>Ambiguous</b>	Assume $\frac{3}{4}$ the maximum dose translated into ndd	1-2 Four times daily (ndd=6)	4,772	15.9
<b>Unambiguous</b>	The dose is correctly translated into an ndd	One capsule four times a day (ndd=4)	5,847	19.5
<b>Unknown</b>	Cannot be translated into an ndd	As directed (ndd=0)	290	0.97
<b>Missing</b>	Text identifier is not recorded as a typical dose and cannot be translated as text instruction	Missing (ndd=0)	19,084	63.6

ndd - numeric daily dose

## 4.8 Discussion

This chapter highlights the significant role of EHR databases in pharmacoepidemiology research. Despite some limitations, these databases offer numerous advantages over alternative methods for data collection to conduct research. The data collected in EHR databases are routinely recorded by healthcare providers and represent actual prescribing practices in everyday healthcare settings.

The number of patients in the colectomy cohort identified is comparable to previous studies using HES data to look at other outcomes. By using colectomy OPCS, validated previously in studies using HES data<sup>285</sup>, the accuracy of the identified cases of colectomy was ensured. This accurate identification allows for more reliable and meaningful comparisons of studies using the cohort but looking at other outcomes.

The selection of study period of patients having colectomy between 1<sup>st</sup> January 2010 to 31<sup>st</sup> December 2019, with 180 days of follow up after surgery allow to examine trends and changes in the study outcomes over time and identifies patterns of opioid utilisation. The one-year lookback period before the admission date allows for a sufficient period to look at different trajectories of opioid utilisation before colectomy and permits categorisation the cohort into three distinct groups based on prior opioid exposure (Details presented in Chapters 6 and 7).

When EHR data are used to answer questions about opioid utilisation, the presence of an opioid prescription during the follow-up or lookback period indicates opioid use. However, it is not possible to confirm whether opioids in prescriptions were dispensed or taken by the patients according to the dose instructions on the prescription.

Prescription records obtained from CPRD may not represent all opioid utilisation. For instance, some opioid preparations like codeine and dihydrocodeine can be obtained without a prescription over the counter or by using opioids that were

originally prescribed for their friends or family members. This might result in exposure misclassification in some instances.

## **4.9 Conclusions**

Using linked CPRD and HES data provides an appropriate data source for this thesis. A sizeable cohort of adults undergoing colectomy and their opioid prescription records were identified with a sufficient duration of lookback and follow-up periods. The study cohort identified in this chapter serves as the main group for all the cohorts investigated in the subsequent chapters of this thesis. Each chapter comprehensively describes how the specific cohort was selected from the main study cohort and the outcomes related to opioid utilisation studied.

The study variables related to colectomy were obtained from HES database, while the opioid prescription data were extracted from CPRD. There was a significant amount of missing data for the daily dose and duration of opioid prescriptions, which were MNAR. Chapter 5 outlines the methodology to address these missing data and effectively prepare the opioid prescription records for subsequent analyses.

## **Chapter 5: Preparing opioid prescription records for analysis**

## 5.1 Introduction

Prescription data obtained from EHR are becoming an essential source for pharmacoepidemiology studies. However, despite their extensive use, they also have some intrinsic limitations, as they are collected to support the provision of clinical care and are not collected primarily for research purposes. Therefore, the precision of data entry is potentially a lower priority than administering care. Accordingly, researchers using these data must prepare and clean the data to be ready for analysis.

Data preparation is the process of converting raw data into a cleaned dataset ready to be used for analysis<sup>286</sup>. It involves generating variables, identifying errors, duplicate records, and dealing with missing data. Generally, in prospective studies, avoiding missing data can be achieved by careful data collection and follow-up. However, avoiding missing data in EHR research is usually impossible as the gathered data are not always of research quality. It is important to use appropriate statistical techniques to address missing data. Table 5-1 shows some strategies for handling missing data.

**Table 5-1. Strategies for dealing with missing data**

Method	Description	Consideration
<b>Complete-case analysis/deletion</b>	Commonly used and straightforward approach for dealing with missing data by complete exclusion of incomplete observations from the analysis Example: excluding observations that have missing details of a primary predictor variable in a study	This approach will not bias the result if the data is MCAR, as the analysed sample is a subset of the complete sample. However, complete-case analysis might diminish statistical power and precision due to the loss of sample size
<b>Single imputation methods</b>	Single imputation techniques substitute missing values with a reasonable assumption Example: a male participant has missing data on weight, mean weight for all men in the sample can be calculated and used to substitute the missing value	When a variable has a large number of missing values, single imputation can reduce the standard deviation for the imputed variable, resulting in low standard errors and p values. Therefore, single imputation can be suitable when missing data are relatively scarce
<b>Multiple imputation methods</b>	Multiple values for the missing variable are generated and held in multiple datasets. Final analyses are performed on each dataset separately, and then the results are integrated into single estimates of effect	May be challenging to decide which variable to include in the imputation model to predict the missing values, or how many imputed datasets should be included. It might be optimal for most common missing data scenarios and provides unbiased and valid estimates of associations based on information from the available data <sup>287</sup>
<b>Last observation carried forward</b>	Using the previously recorded value to impute the missing value	The previous value might not reflect the actual missing value. Not applicable when participant is having single value for missing variable
<b>The dummy variable method</b>	A new variable is created to keep missing data, no imputation will be performed Example: a new indicator variable is created to keep missing data as "1" and non-missing data as "0"	This approach allows the use of all available information about missing observations and retains the entire dataset <sup>288</sup> . However, it can lead to biased associations of the original variables and outcome due to residual confounding effects. The magnitude and direction of bias are difficult to be predicted
<b>Statistical procedures for all available data</b>	Applying statistical algorithms to include incomplete observations rather than excluding them Examples: Maximum likelihood method Cox regression Generalised estimation equation	There is a potential for some errors when specifying models

The preliminary analysis conducted in the previous chapter showed that there are several possible sources for prescription duration within CPRD data, but their complete details are rarely specified. Along with a high proportion of missing quantity and daily doses. The nature of the missingness of these data was MNAR.

In published drug utilisation research studies, the steps of drug preparation are rarely transparent in terms of describing all the steps followed and influence of the decisions made on the results of the study. Transparency in reporting drug preparation steps is crucial to allow appropriate interpretation of study results and enable comparisons between studies<sup>289</sup>. These reasons were sufficient to motivate Pye *et al.*<sup>286</sup> to develop and publish their 'DrugPrep' algorithm for preparing CPRD prescription records for analysis, aiming to facilitate systematic decision-making and reporting of this process. The algorithm is made up of ten sequential decision nodes, that start with handling implausible or missing data, calculating duration, and managing concurrent prescriptions (Figure 5-1). Each decision node has different assumption that can be followed, assumptions made in each stage can have considerable implications on the final produced dataset.

The DrugPrep algorithm has been increasingly used in pharmacoepidemiological research looking at opioid use in different contexts using CPRD data<sup>173, 290</sup>. However, the DrugPrep algorithm does not include the preparation of a total current dose variable, combined drugs name, or formulation variable when several prescriptions are given to a patient on the date. These variables are crucial to describe the characteristics of opioid prescriptions and to form the main

variables for the analyses presented in Chapter 7. Therefore, an extension to the DrugPrep algorithm was required to produce a daily Oral Morphine Equivalent (OMEQ) dose variable and several other variables to retain details about the opioid prescribed, formulation, and combination of opioid medicines.

## **5.2 Aims and objectives**

The chapter aimed to use the DrugPrep algorithm to prepare the opioid prescription records for the research cohort, expand the algorithm to produce a daily OMEQ dose variable, and generate variables that retain information about prescribed opioids and formulations when multiple prescriptions were prescribed on the same day. The specific objectives were:

1. To use the DrugPrep algorithm to clean opioid prescription records and obtain the duration value for each prescription.
2. To extend the DrugPrep algorithm and generate a daily OMEQ dose for the study cohort.
3. To extend the DrugPrep algorithm to produce variables that retain information about prescribed opioids and formulations when multiple prescriptions were prescribed on the same day.
4. To create a dataset containing opioid prescriptions prescribed within 90 days of colectomy discharge and ready for analysis for Chapter 7.



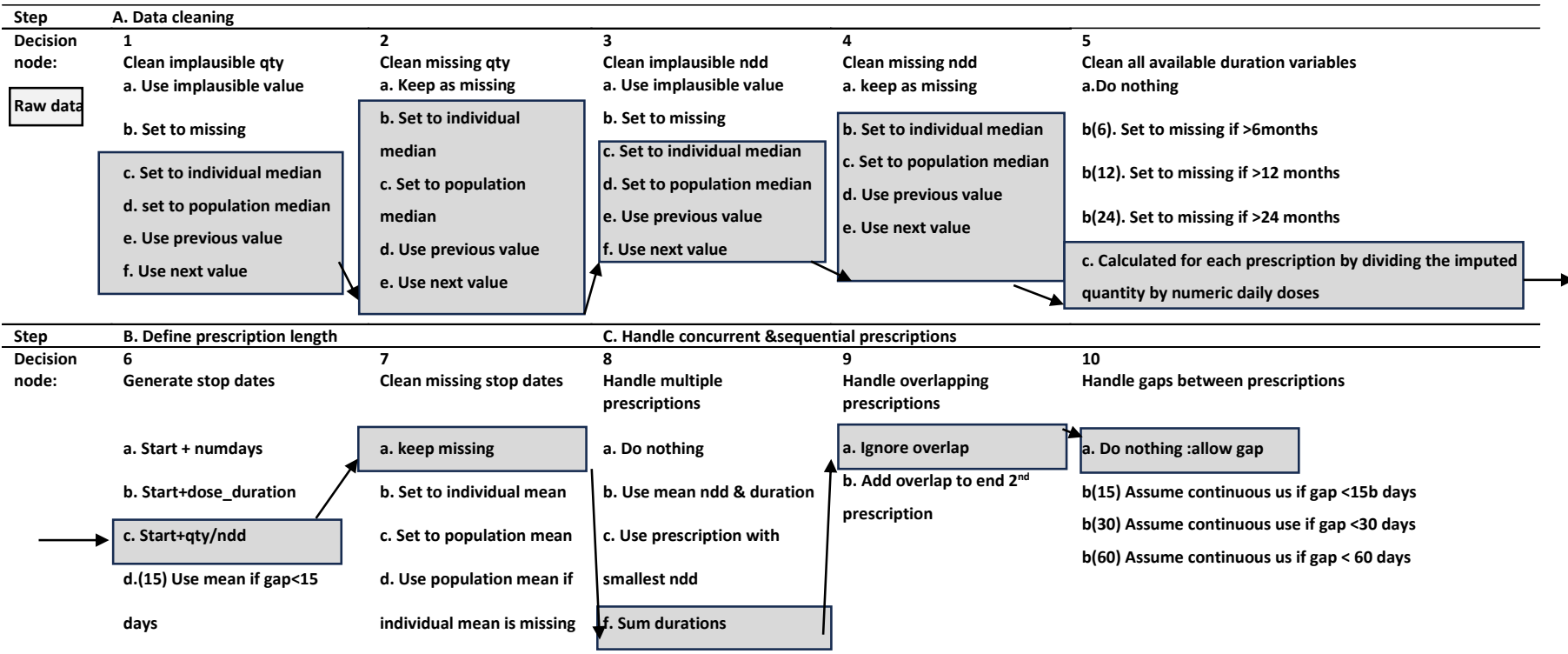


Figure 5-1. DrugPrep algorithm decision nodes

Adapted from Pye *et al.*<sup>286</sup>

## 5.3 Methods

For the eligible colectomy population, all opioid prescriptions records issued within one year before colectomy admission date and one year after colectomy discharge date were extracted from CPRD Aurum, as explained in Chapter 4. The inclusion of one-year opioid prescription data before colectomy admission is consistent for all studies in this thesis. However, rather than being limited to 90 or 180 days of follow-up of opioid prescriptions after colectomy discharge, a one-year follow-up of prescription data was only necessary in the early steps of opioid prescription cleaning process described in this chapter. This approach was chosen because previous and subsequent prescriptions may contain important information for accurately summarising the prescribed quantities and daily doses of each opioid drug and formulation, providing sufficient values for guiding further imputation of missing or implausible data.

Before applying the DrugPrep algorithm, an 'opioid product look-up file' was created to facilitate categorising prescribed opioid medicines during the prescription preparation stage.

### 5.3.1 Developing opioid product look-up file

The development of an opioid product look-up file helped organise drug names, strengths, and formulations into columns representing variables ready for prescription records preparation and cleaning. For the included opioid product code list (Appendix S 10), product name, strength, formulation and route of administration were extracted from CPRD supplementary product look-up files.

These details were then manually screened and classified to generate variables specific to our analysis. Variables included in the opioid product look-up file are listed in Table 5-2. The created opioid product look-up file included 17 different opioid medicines and eight pharmaceutical formulations, retained in a category called 'form' to allow differentiation from the final formulation category (Table 5-3). These were then categorised into three final formulation categories (Table 5-4), and the OMEQ dose per unit prescribed was assigned for each opioid based on the oral morphine equivalent dose for each opioid, as listed in Table 5-2. The created opioid product look-up file included 17 different opioid medicines and eight pharmaceutical formulations. These were then categorised into three final formulation categories (Table 5-4), and the OMEQ dose per unit prescribed was assigned for each opioid based on the oral morphine equivalent dose for each opioid, as listed in Table 5-5.

**Table 5-2. Variables included in opioid product look-up file**

Variable	Description	Categories
<b>Opioid</b>	The name of opioid drug	1=Oxycodone 2=Tramadol 3=Morphine 4=Fentanyl 5=Buprenorphine 6=Codeine/paracetamol 7=Tapentadol 8=Hydromorphone 9=Dihydrocodeine 10=Dihydrocodeine/paracetamol 11=Codeine 12=Naloxone/Oxycodone 13=Pentazocine 14=Pethidine 15=Meptazinol 16=Codeine/Ibuprofen 17=Cyclizine/ Dipipanone
<b>Product code</b>	The code that corresponds to the opioid product supplied	
<b>Formulation *</b>	Formulation of the opioid as categorised in Table 5-3	
<b>Form **</b>	Formulation of the product as categorised in Table 5-4	1= Immediate release (short-acting) 2= Modified release (long-acting) 3= Transdermal patches
<b>Strength/unit</b>	The strength in milligrams (mg) of the product per unit prescribed. Except for patches strength is mcg/hr, and sublingual tablets mcg***	
<b>Days per patch</b>	The number of days a transdermal patch is required to be worn, based on the manufacturer's instruction	
<b>Equianalgesic ratio</b>	An equianalgesic ratio was assigned to each combination of opioid and formulation (Table 5-4)	
<b>OMEQ/unit <math>\phi</math></b>	It is calculated by multiplying the strength/unit by the equianalgesic ratio for each opioid	

\*This category was created to allow the calculation of OMEQ dose for each drug formulation combination;

\*\*This category was created because modified-release oral and transdermal opioid formulations are not recommended to manage acute pain after surgery. By having this category, each of these formulations can be analysed separately; \*\*\*It was essential to consider the duration of delivery rate for transdermal patches to avoid underestimating daily OMEQ dose;  $\phi$ To standardise and compare different opioid medications based on their potency and dosage

**Table 5-3. Drug and formulation contained in each form category**

	<b>Form category</b>	<b>Formulation in opioid codes file</b>
<b>1</b>	Long-acting oral solids	Modified release capsule Modified release tablet Modified release granules
<b>2</b>	Short acting oral solids	Tablet Capsule
<b>3</b>	Transdermal patches	Transdermal patch Transdermal system
<b>4</b>	Oral solution	Oral solutions Oral drops Oral drops/oral solution
<b>5</b>	Solids/semi-solids for oral suspension	Oral suspension Effervescent powder Effervescent tablet Soluble tablet
<b>6</b>	Orodispersibles	Sublingual tablet Orodispersible tablet
<b>7</b>	Nasal sprays	Spray
<b>8</b>	Suppository	Suppository

**Table 5-4. Opioid products categorised into three final formulations**

	<b>Form category</b>	<b>Formulation in opioid codes file</b>
<b>1</b>	<b>Long-acting oral formulations</b>	Modified release capsule (Tramadol, morphine, hydromorphone, tapentadol)
Modified release tablet (oxycodone, tramadol, morphine, codeine+ibuprofen, naloxone+oxycodone, dihydrocodeine)		
Modified release granules (morphine)		
<b>2</b>	<b>Short acting oral formulations</b>	Tablet (Oxycodone, morphine, tapentadol, dihydrocodeine, codeine, pentazocine, pethidine, meptazinol, cyclizine+ dipipanone, dihydrocodeine+paracetamol, codeine+paracetamol)
		Capsule (Oxycodone, tramadol, hydromorphone, pentazocine, pethidine, codeine+paracetamol)
		Oral solutions (Morphine, tapentadol)
		Oral drops (Tramadol, morphine)
		Oral suspension (Dihydrocodeine, dihydrocodeine+paracetamol)
		Effervescent powder (Tramadol, codeine+paracetamol)
		Effervescent tablet (Codeine+paracetamol)
		Sublingual tablet (Buprenorphine)
		Spray (Fentanyl)
		Orodispersible tablet (Tramadol)

Form category	Formulation in opioid codes file
3	Suppository (Morphine, pentazocine)
	Oral solution (Morphine, oxycodone, tapentadol, dihydrocodeine, codeine, codeine+paracetamol, dihydrocodeine+paracetamol)
	Transdermal patch (fentanyl, buprenorphine)
Transdermal patches	Transdermal system (fentanyl)

Table 5-5. Equianalgesic ratios to OMEQ dose

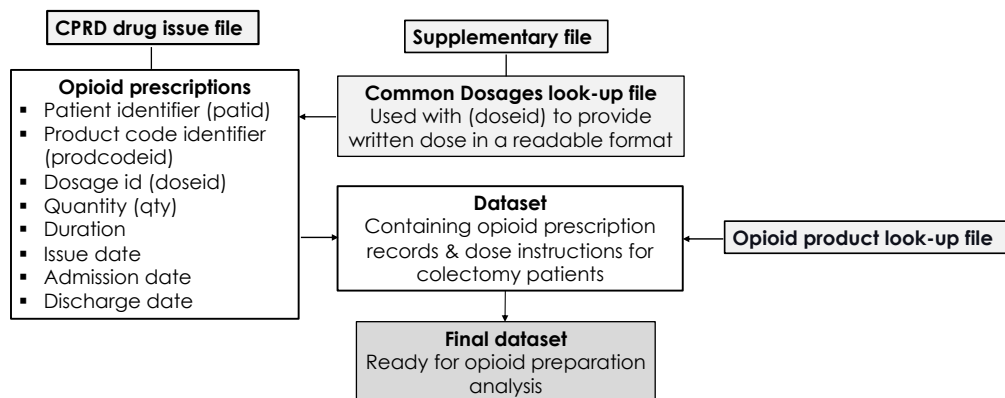
Opioid reference*	Form **	Equianalgesic ratio***
Buprenorphine <sup>291</sup>	Transdermal patch	1.8
	Sublingual tablets	10
Codeine <sup>292</sup>		0.15
Codeine/ Ibuprofen <sup>292</sup>		0.15
Codeine/ Paracetamol <sup>292</sup>		0.15
Dihydrocodeine <sup>291</sup>		0.25
Fentanyl <sup>291</sup>	Transdermal patch	2.4
	Sublingual tablets	0.13
	Nasal sprays	0.16
Hydromorphone <sup>292</sup>		4
Meptazinol <sup>293</sup>		0.03
Morphine Sulfate <sup>291</sup>		1
Naloxone/ Oxycodone		1.50
Oxycodone <sup>292</sup>		1.50
Pentazocine <sup>293</sup>		0.37
Pethidine <sup>291</sup>		0.10
Tapentadol <sup>292</sup>		0.40
Tramadol <sup>292</sup>		0.20
Cyclizine/ Dipipanone <sup>291</sup>		0.5

\*Opioid doses are in mg/day except for Buprenorphine and fentanyl transdermal (in mcg/hr), and sublingual tablets (mcg); \*\*form refers to an oral preparation unless otherwise stated; \*\*\*Equianalgesic ratio: the potency of respective opioid/opioid formulations compared with oral morphine

### 5.3.2 Obtaining text instructions for prescribed opioids

The prescription information obtained from the 'drug issue' file obtained from CPRD lacks details about text instructions for the medicine. However, CPRD provides a supplementary 'common dosage' file that provides these extra details for each prescription. Therefore, the 'common dosage' file was merged with the

dataset containing opioid prescriptions for the study cohort using the dosage identifier 'dosageid' variable. Following this step, the created dataset was merged with the developed opioid product look-up file to produce the final dataset, including variables ready for preparation using the DrugPrep algorithm (Figure 5-2).



**Figure 5-2. Process for obtaining datasets for opioid preparation analysis**

### 5.3.3 Preparing opioid prescription records for analysis

Applying the DrugPrep algorithm required several steps to prepare opioid prescription data for analysis. These steps, alongside the chosen decisions, are demonstrated in Figure 5-1. The subsequent section details the approach used to prepare opioid prescriptions in each step.

#### 5.3.3.1 Quantity and daily dose

##### Setting minimum and maximum values

The first step in preparing prescription records required defining plausible values for quantity and daily doses to detect aberrant values that might result from data

input or processing errors. This step was crucial since extreme values (outliers) may have a disproportionate impact on the overall analysis, resulting in outlier bias or misleading interpretations, which may ruin the further steps required to obtain variables necessary for the analysis.

As described in Table 5-4, there are multiple opioids with different formulations that can be prescribed in various doses and quantities. Therefore, to identify plausible quantities and daily doses, all opioid prescription records were grouped according to both opioid and formulations. Descriptive statistics were then obtained for each opioid drug and its formulation. The 1<sup>st</sup> and 99<sup>th</sup> percentiles were used to determine the minimum and maximum plausible values for daily dose and quantity. However, since some values were extreme outliers that could potentially skew the percentiles, adjustments were made to the plausible values based on opioids prescribing guidelines for acute pain, which was reported in the BNF, as well as the clinical experience of a specialist pain management pharmacist (R Knaggs).

### **Identifying implausible values**

An indicator variable (1=yes, 0=no) was created for each opioid drug-formulation combination to identify any anomalous quantities that exceeded the minimum or maximum plausible values. The same steps were applied to the numeric daily doses to identify any anomalous values.

### **Imputing implausible and missing values**

Records with values outside the plausible range for the quantity or daily dose variables were replaced with missing values. This was done to facilitate the



identification of implausible values during the data-cleaning process. These values were then treated and imputed in the same manner as the initially missing values. A sequence of imputation actions was then undertaken to address and fill in the missing values:

1. Missing value for (quantity or/ and daily dose) was substituted with value from the subsequent prescription of the same product for the same individual.
2. If the value of the next prescription was implausible or missing, the value was replaced with the value from the prior prescription of the same product and same individual.
3. If there was no prior prescription for the product or if the value from the previous prescription was missing or implausible, the value was replaced with the median value of all plausible values for the same product for each individual.
4. If there were no other prescriptions for the product, or if the values recorded for all other prescriptions were either implausible or missing, the value was replaced with the population-median value, calculated using all plausible values for all prescriptions of the same product across the entire study cohort. If the values recorded in other prescriptions were also implausible or if there were no other prescriptions for the product, records containing missing values for quantity or daily dose (following the imputation steps) were retained. These values could be further imputed using the calculated duration value whenever possible.

### **5.3.3.2 Durations and stop dates**

#### **Generating prescription duration**

Each opioid prescription record was assigned a new duration (in days) which was calculated by dividing prescriptions' quantity by the number of daily doses.

Following this step, the dataset contains three duration variables:

1. Dose duration: based on recorded daily doses and derived from the common dosages look-up file for CPRD Aurum.
2. Duration: the number of treatment days prescribed by the prescriber as recorded in the CPRD drug issue file.
3. Calculated duration: calculated for each prescription during prescription cleaning, by dividing the imputed quantity by numeric daily doses.

#### **Choosing a maximum duration**

To determine the maximum plausible duration, the median, 1<sup>st</sup> percentile, and 99<sup>th</sup> percentile of calculated duration values from all opioid prescription records were used. Clinical expertise in opioid prescribing and common prescription lengths were also taken into consideration.

#### **Identifying Implausible, missing, or multiple durations**

After setting the maximum duration, any duration values exceeding that threshold were considered implausible and replaced with missing values. In cases where multiple durations were present within a single prescription, an indicator variable was created to identify their presence. This allowed for assigning a single duration for those records, following the steps outlined in the subsequent section.

**Imputing multiple durations and missing durations**

For prescriptions with multiple durations that were  $\leq 30$  days apart, a new duration variable was created. The 'new duration' value was imputed using the mean duration values for that specific prescription. However, if the durations were not within the specified criteria, the 'new duration' was marked as missing. Missing durations were imputed in two sequential steps:

1. The median duration for all prescriptions of the same product and individual patient was used to replace the 'new duration' value.
2. The population-median duration, derived from all prescriptions of the same product across the entire study cohort, was used to substitute the 'new duration' value.

**Generating prescription stop date**

Generating a stop date was necessary to identify the end date for each prescription, and to compare stop dates calculated based on the three available durations within the dataset, allowing for further cleaning and imputation. Three stop dates were generated by adding a prescription issue date to each of the three durations available within the dataset. Then a final 'real stop date' variable was generated and replaced based on the 'new duration' assigned for each prescription. (Equation 5-1)

**Equation 5-1. Calculation of prescription stop date**

$$\text{stop date} = \text{prescription issue date} + \text{new duration (days)}$$

### **Handling sequential and concurrent prescriptions**

An indicator variable was generated to identify records for identical products with the same start date for each patient; these duplicate records were combined into one period of exposure. When prescriptions have overlapping exposure periods, which occurs when the start date of a period occurs before the end date of a previous prescription, a decision has been made to ignore this overlap. The following subsection describes these two steps in more detail.

### **Duplicates prescription records**

When two prescription records had the same start date, were for the same product and were prescribed for the same person, these prescriptions were marked as duplicates. The duration for these prescriptions was combined, and the original duration was replaced with the summed duration. Only one prescription record was kept. The remaining duplicates were removed from the dataset. A stop date for this period was recalculated using the summed duration. This final duration was used to calculate daily doses for records having missing daily doses following imputation steps detailed in section 5.3.3.1.

While if multiple prescriptions of different products had the same start date, that may indicate concurrent use, and some prescriptions will have a longer duration than others. Therefore, at this stage duration for multiple prescriptions for the same patient were retained, to be able to retain prescription details when two or more opioid products are prescribed on the same day and calculate the OMEQ dose.

### **Overlapping exposure periods**

Overlapping exposures occur when a prescription starts before the end of the previous prescription. Since the analysis in Chapter 7 focuses on the first prescription after colectomy discharge, any overlap between prescriptions will not impact the outcomes related to the type and doses of opioids prescribed. Therefore, a decision has been made to ignore the overlap.

### **Gaps between prescriptions**

Since the focus is on the characteristics of the first prescription after colectomy, any gaps between prescriptions have been disregarded.

### **5.3.4 Creating a dataset for Chapter 7**

The final aim of the opioid prescription preparation process was to create a dataset ready for analysis for Chapter 7. The analysis in Chapter 7 aimed to describe the characteristics of initial opioid prescription prescribed within 90 days of colectomy discharge (described in more detail in Chapter 7). Therefore, only prescription records prescribed within 90 days of colectomy discharge were retained, and patients not having opioids within 90 days of discharge and their records were removed from the dataset.

### **5.3.5 Steps for identifying prescriptions prescribed within 90 days of colectomy discharge**

A 90 day follow up period was created for each patient using Equation 5-2

#### **Equation 5-2. Calculation of 90 days follow up period**

$$90 \text{ days follow up} = \text{discharge date} + 90 \text{ days}$$

An indicator variable was created to identify prescriptions with issue dates within the 90-day follow-up period. Patients and their prescription details were kept. Any prescription records not prescribed in the 90-day follow-up period were removed from the dataset.

To identify the first opioid records within 90 days after the colectomy discharge. An indicator variable 'Days to prescription' was generated based on Equation 5-3 to create a serial number for prescription records based on the closest prescription issue date to each patient's discharge date. Records with the same and earliest day from discharge were retained, and any extra records were deleted.

**Equation 5-3. Calculation of number of days to prescription issue date**

$$\text{Days to prescription} = \text{issue date} - \text{discharge date}$$

### 5.3.6 Calculation of OMEQ dose

**Calculating OMEQ dose per day for a single prescription**

An OMEQ dose per day was assigned to each prescription to facilitate dose comparison across different opioids and opioid formulations. The OMEQ per unit was obtained from the previously generated opioid look-up file, which was then merged with the current dataset to calculate the OMEQ dose per day using Equation 5-4.

**Equation 5-4. Calculation of OMEQ dose per day**

$$\text{OMEQ dose/day} = \text{numeric daily dose} \times \text{OMEQ per unit}$$

### **5.3.7 Calculating the total OMEQ dose per day for overlapping prescriptions**

#### **Overlapping prescriptions of the same product**

As described previously an indicator variable was created to flag patients having multiple prescriptions of the same product at the exact start date, and then OMEQ dose for both prescriptions were combined to create a total OMEQ dose per day. Then, the extra records for that start date was removed.

#### **Overlapping prescriptions of different product**

Another indicator variable was created to account for concurrent use of differing opioid products at the same start date. Then OMEQ dose/day values for both products were summed to create a single value for one exposure period. Before dropping the surplus periods and records for that start date, an extra step was performed to retain the names of opioid drugs prescribed and formulation on the exact start date. This was done to ensure the availability of this information for opioid analysis in Chapter 7. More details are described in the section below.

#### **Retaining formulation details for overlapped prescriptions of different products**

A new variable was created to represent the formulation of different opioid products. This variable was categorised into the following categories: oral modified release, oral immediate release, transdermal patches, oral immediate & modified, oral immediate release & transdermal, oral modified release & transdermal, and other formulations.

### **Retaining opioid details for overlapped prescriptions of different products**

To retain the details of prescribed opioids for overlapping prescriptions of different products, a new variable called 'drug list' was created. This variable stores the information regarding the opioids that were prescribed. Furthermore, to address the potential complication of having multiple overlapping opioids and to facilitate the calculation of summary statistics, another variable was introduced. This variable categorised opioids based on their potency.

### **Generating new variables to retain opioid and formulation details**

Classes of opioids were divided into weak opioids (codeine, dihydrocodeine, meptazinol, pentazocine, tramadol) and strong opioids (morphine, oxycodone, fentanyl, buprenorphine, hydromorphone, pethidine, naloxone/oxycodone, cyclizine/dipipanone, hydromorphone, tapentadol), or combination of both<sup>294</sup>.

Tramadol has dual mechanisms of action as a centrally acting opioid and inhibits the reuptake of serotonin-and noradrenaline. Accordingly, it can be classified as a strong opioid<sup>295</sup>, and because of its low opioid potency, it can also be classified as a weak opioid<sup>294</sup>. In this context, to allow comparison with other UK studies<sup>290, 296</sup> tramadol was classified as a weak opioid.

Following this step, any concurrent prescriptions for the same patient were dropped, and only one record was kept, which included details of opioids prescribed in combination and their formulation. A dataset that was set aside at this stage to be used for the analysis in Chapter 7.



## 5.4 Data analysis

The number of prescription records and missing data in each stage of the prescription preparation process were presented as absolute numbers and proportions. The number of opioid prescription records was used as a denominator to calculate the proportion of each opioid drug prescribed. Also, the number of prescription records for each opioid drug formulation category was divided by the total number of prescription records within that opioid drug formulation category. The proportion of missing quantity or daily dose values for each opioid drug formulation category was similarly calculated by dividing the number of prescriptions with missing values within each opioid formulation category by the total number of prescription records within that category.

The spread of data was inspected using 1<sup>st</sup> and 99<sup>th</sup> percentile values to assess the plausibility of values and determine whether imputation was necessary if values lie outside this range. Initially, the distribution of values was examined to decide whether a mean (along with standard deviation (SD)) or median (along with interquartile range (IQR)) was a suitable statistic to guide decision-making.

## 5.5 Results

From CPRD drug issue file, 229,886 opioid prescription records were extracted for 27,561 patients. These prescriptions were issued any time within one year before colectomy admission date or one year after colectomy discharge date.

### 5.5.1 Quantity and daily doses

For each opioid drug-formulation category, the minimum and maximum plausible

quantity values ranged from 1 to 2,200 units. The proportion of missing daily dose values ranged from 0% to 100.0%, depending on the prescribed combination of opioid drug and formulation (Table 5-6).

Table 5-6. Minimum and maximum values for quantity, numeric daily dose, by opioid drug and formulations as recorded in CPRD

Drug	Number of prescriptions (%*)	Short-acting	Long-acting	Transdermal patch	Oral solution	Effervescent	Orodispersible	Prescription record		Numeric daily dose			Quantity		
								(n)	(%**)	Missing***	Min	Max	Min	Max	
Oxycodone	14,525 (6.3)	✓						3,408	23.6%	78.9%	1	6	7	224	
			✓					7,512	51.7%	69.3%	1	8	10	140	
						✓			3,607	24.9%	97.5%	2.5	40	100	1000
Tramadol	47,734 (20.8)	✓						42,279	88.5%	62.1%	1	9	20	224	
			✓					5,261	11.0%	58.4%	1	6	14	200	
							✓		122	0.26%	67.6%	2	8	20	200
								✓	72	0.15%	86.3%	2	8	60	224
Morphine	37,922 (16.5)	✓						1,098	2.9%	76.6%	1	16	8	224	
			✓					16,458	43.4%	69.8%	1	6	2	168	
						✓			20,366	53.9%	92.8%	3.8	45	45	1000
Fentanyl	8,092 (3.5)			✓				8,077	99.8%	76.5%	0.285	0.666	2	30	
								✓	15	0.19%	100%	-	-	10	30
Buprenorphine	8,866 (3.9)			✓				8,295	93.6%	78%	0.142	0.333	1	10	
								✓	571	6.5%	61.9%	1	8	7	150
Codeine/Paracetamol	68,641 (29.9)	✓						62,979	91.6%	59.7%	2	8	28	224	
							✓		5,662	8.3%	51.3%	2	8	30	300

Drug	Number of prescriptions (%*)	Short-acting	Long-acting	Transdermal patch	Oral solution	Effervescent	Orodispersible	Prescription record		Numeric daily dose			Quantity	
								(n)	(%**)	Missing***	Min	Max	Min	Max
Hydromorphone	23 (0.01)	✓						23	100%	100%	-	-	28	200
Tapentadol	346 (0.15)	✓						123	35.6%	99.2%	1	1	7	168
			✓					223	64.5%	81.2%	2	2	14	112
Dihydrocodeine	7,707 (3.4)	✓						6,772	87.8%	63.5%	1	8	21	300
			✓					917	11.9%	40.4%	1	4	7	112
						✓		18	0.23%	88.8%	60	60	150	600
Dihydrocodeine/Paracetamol	314 (0.14)	✓						314	100%	74.5%	2	8	56	448
Codeine	34,905 (15.2)	✓						34,409	98.6%	71.6%	1	9	10	224
						✓		496	1.42%	82.9%	5	60	100	2200
Naloxone/Oxycodone	314 (0.14)		✓					314	100%	69.3%	1	2	12	60
Pentazocine	56 (0.02)	✓						56	100%	0.00%	2	8	14	180
Pethidine	188 (0.08)	✓						188	100%	76.1%	1	8	6	336
Meptazinol	232 (0.10)	✓						232	100%	67.4%	1.5	6	7	224
Cyclizine/Dipipanone	19 (0.01)	✓						19	100%	100%	-	-	50	168

Notes: \*prescription records for each opioid, as a proportion of all opioid prescription records; \*\* as a proportion of the total prescription records within each opioid drug category; \*\*\*as a proportion of prescription records within each opioid drug-formulation category.

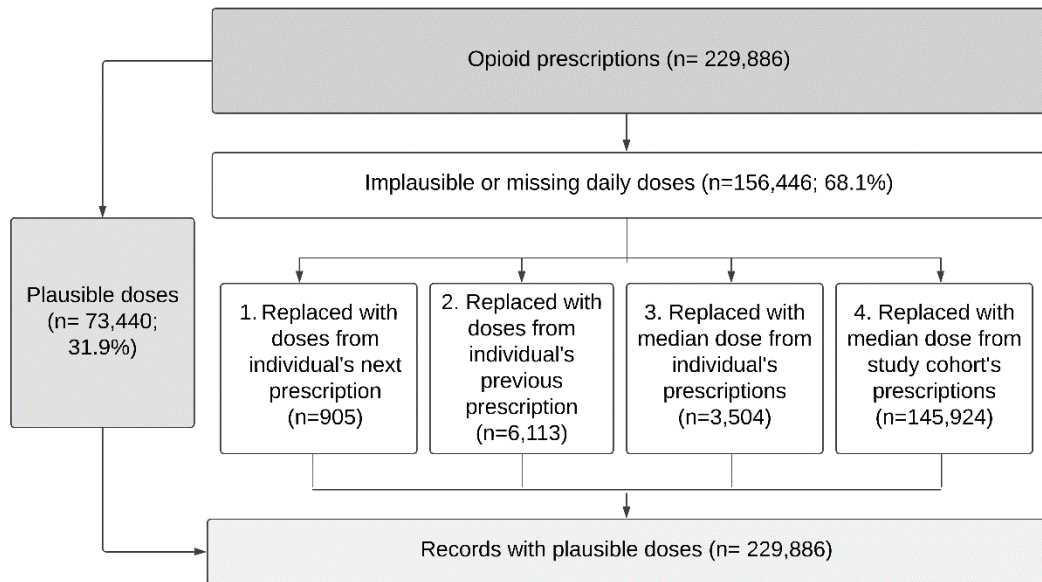
**Imputing missing or implausible quantities**

For each drug formulation combination, quantities were considered as implausible if they were smaller than the minimum plausible quantities or bigger than the maximum plausible quantity recorded in Table 5-7. In total, 2992 (1.30%) prescription records contained implausible quantities, and 42 (0.02%) records were missing quantity values. Following the imputation process outlined in section 5.3.3.1, 56 prescription records remained implausible or missing. Manual inspection for the records with remaining implausible values was performed. This showed that the implausible quantities were all for morphine modified release formulations, which had a recorded value for their duration. Therefore, a decision was made to calculate their implausible quantity by multiplying the minimum recorded quantity multiplied by duration, and then the implausible quantity value was replaced using the calculated value. The remaining 229,886 prescriptions, all had plausible quantity.

**Imputing missing or implausible doses**

For each drug formulation combination, daily doses were considered as implausible if they were less than the minimum plausible daily doses or more than the maximum plausible daily doses recorded in Table 5-7. In total, 5,589 (0.02%) prescription records contained implausible daily doses and 9,654,371 (35.4%) prescription records were missing daily doses. These implausible and missing daily doses were replaced using the imputing steps outlined in section 5.3.2.1. Following this process, all prescriptions had daily doses (Figure 5-3).

After setting min and maximum daily doses, 266 (0.11%) prescriptions still have implausible values, and 156186 (68%) had missing daily doses. These were combined as one missing category and imputations undertaken.



**Figure 5-3. Imputing implausible or missing doses**

**Table 5-7. Minimum and maximum values for quantity, numeric daily dose, by opioid drug and formulation used to replace implausible values**

Drug	Short-acting	Long-acting	Transdermal patch	Oral solution	Effervescent	Oro dispersible	Numeric daily dose		Quantity	
							Min	Max	Min	Max
Oxycodone	✓						1	6	6	224
		✓					1	8	10	140
				✓			2.5	80	100	1000
Tramadol	✓						1	9	14	224
		✓					1	6	14	200
					✓		2	8	20	200
						✓	2	8	60	224
Morphine	✓						1	16	8	224
		✓					1	6	2	168
				✓			3.8	45	45	1000
Fentanyl			✓				0.285	0.777	2	30
						✓	1	8	3	180
Buprenorphine			✓				0.142	0.333	1	10
						✓	1	8	7	150
Codeine / Paracetamol	✓						2	8	28	224
					✓		2	8	30	300
Tapentadol	✓						1	6	14	224
		✓					1	5	10	150
Hydromorphone	✓						2	6	14	200
Dihydrocodeine	✓						1	8	28	300
		✓					1	4	7	168
				✓			5	120	50	1350
Dihydrocodeine/ Paracetamol	✓						2	8	56	448
Codeine	✓						1	9	14	224
				✓			5	60	100	2200
Naloxone/ Oxycodone		✓					1	2	12	60
Pentazocine	✓						2	8	14	180
Pethidine	✓						1	8	10	336
Meptazinol	✓						1.5	6	7	224
Cyclizine/ Dipipanone	✓						4	10	50	168

## 5.5.2 Duration and stop dates

### Setting maximum duration values

The spread of the values of 'duration variable' and 'calculated duration variable' varied. Using summary statistics for the reported duration in the dataset (median=28 days; 1<sup>st</sup> percentile=4 days, 99<sup>th</sup> percentile=183 days). While summary statistics for calculated duration (median=16 days; 1<sup>st</sup> percentile=4 days, 99<sup>th</sup> percentile=60 days). To determine the maximum duration, a 60-day duration was chosen based on the spread of calculated duration and more feasible clinically based on clinical experience in opioid prescribing (R Knaggs).

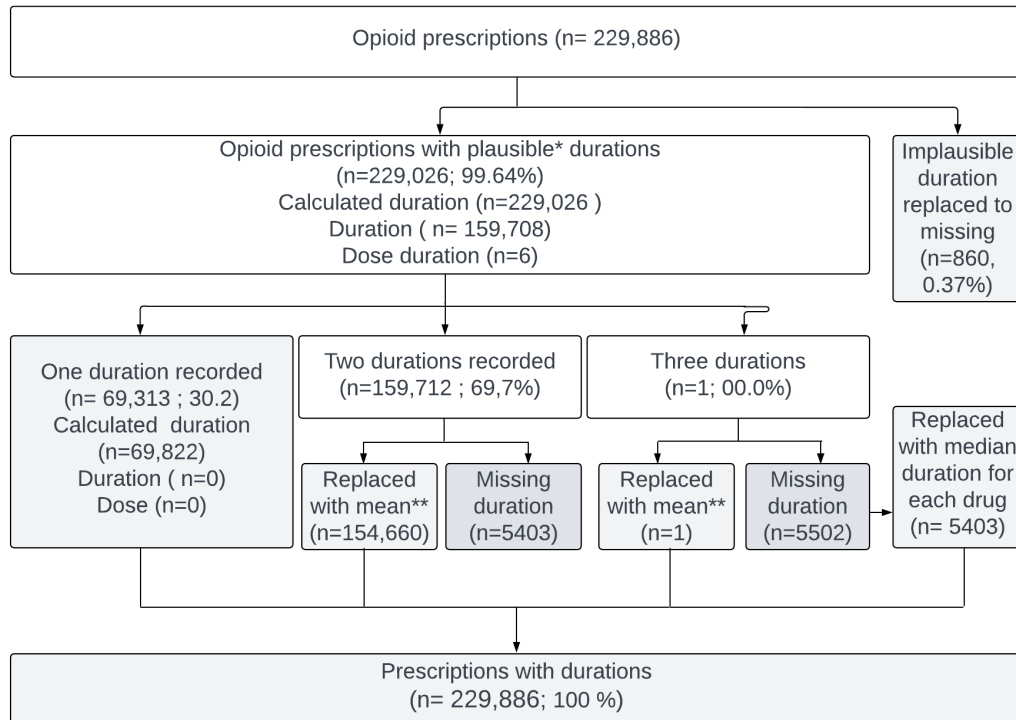
### Implausible durations

In total, 229,886 prescription calculated durations were identified. In which 860 (0.37%) duration values exceeded 60 days and were considered implausible and therefore replaced with missing.

### Prescriptions records with plausible duration values and multiple durations

In total, 229,026 prescription records (99.6%) included plausible durations, with (30.2%) having one recorded duration, (69.7%) having two, and 0.00% having three. In 159,712 prescriptions records, durations were replaced with the mean of the multiple durations if the duration values were  $\leq 30$  days apart. Following this step, 224,482 (97.78%) of records contained a single plausible duration, with 5373 (2.22%) records having missing duration values at this stage (Figure 5-4).





**Figure 5-4. Handling multiple duration values**

#### **Imputing missing durations and generating a stop date**

The missing values created for records exceeding maximum duration and missing values created following mean imputation for records with multiple durations were combined. Of the 5403 missing duration values, 2117 records had duration imputed using patient-median duration for their prescription for the same product. The remaining 3286 were replaced with the population median duration for the product, as patient median duration could not be calculated. Following these steps, all 229,886 prescription records had duration and stop date (Figure 5-4).

### **5.5.3 Identifying prescriptions within 90 days of discharge**

15,503 patients having prescriptions with 90 days of discharge were identified. 68,837 prescriptions were removed from the dataset as these were prescribed after 90 days. From the identified patients, 1157 patients had multiple prescriptions for first prescriptions after discharge (Table 5-8). The proportions of opioid prescriptions, categorised by opioid formulation, each opioid drug, and opioid potency, are detailed in Table 5-9,

Table 5-10, and Table 5-11).

**Table 5-8. Number of patients prescribed single or multiple prescriptions on the same date**

Number of prescriptions issued on the same day	Number of patients n=15,503 (100%)
1	14,346 (92.5)
2	1,011 (6.5)
3	111 (0.72)
4	22 (0.14)
5	3 (0.02)
6	4 (0.03)
7	2 (0.01)
8	1 (0.01)
12	3 (0.02)

**Table 5-9. Proportion of opioid prescriptions by opioid formulation**

Formulations prescribed on the same issue date	Number of prescriptions n=16,886 (100%)
Modified release only	973 (5.8)
Immediate release only	14,171 (83.9)
Transdermal release only	532 (3.2)
Modified and immediate	885 (5.2)
Modified and transdermal	12 (0.07)
Immediate and transdermal	306 (1.8)
Other	7 (0.04)

**Table 5-10. Proportion of opioid prescriptions for each opioid drug**

Opioid prescribed	Number of prescriptions n=16,886 (100%)	
Buprenorphine	339	(2.0)
Codeine	3,669	(21.7)
Codeine / Paracetamol	3,841	(22.8)
Dihydrocodeine	521	(3.1)
Dihydrocodeine/ Paracetamol	8	(0.05)
Fentanyl	379	(2.2)
Hydromorphone	1	(0.01)
Meptazinol	24	(0.14)
Morphine	2,062	(12.2)
Naloxone / Oxycodone	53	(0.31)
Oxycodone	918	(5.5)
Pentazocine	1	(0.01)
Pethidine	2	(0.01)
Tapentadol	12	(0.07)
Tramadol	5,056	(29.9)

**Table 5-11. Proportion of opioid prescriptions by opioid potency**

Opioid categorised by potency	Number of prescriptions n=16,886 (100%)	
Weak opioids only	12,747	(75.5)
Strong opioids only	3,357	(19.9)
Weak and strong opioids	782	(4.6)

#### 5.5.4 Daily OMEQ dose

The OMEQ dose variable was created for 16,886 prescriptions. When more than one prescription was issued on the same day (2,540 prescriptions), a total daily OMEQ dose was created for each patient.

## 5.6 Discussion

This chapter has outlined the steps used to prepare opioid prescription records of 27,000 patients from one year before their colectomy admission date to one year after their colectomy discharge. One dataset was generated that included

information on the duration, formulations, and daily total of all prescribed opioids (used for the analysis in Chapter 7).

This chapter highlights the importance of data preparation as a crucial step in generating a clean dataset suitable for analysis. In addition to addressing missing data for duration and quantity variables, various data entry errors have been identified, including typographical mistakes, incorrect quantity entries, and the use of different measurement units. Duplicate prescriptions issued on the same date were also occasionally found. Several reasons could explain these duplicate records, including patients requesting additional medicines supplies to cover a holiday period or when a public holiday leads to dispensing extra supplies to account for practice closure. In addition, to receive reimbursement from the NHS for the extra effort required in providing individuals with a weekly monitored dosage system, community pharmacies can be given multiple prescriptions with a 7-day duration on the same day.

The adopted drug preparation algorithm enables a systematic approach that involves a series of imputation steps based on different assumptions. These steps aim to clean the data by incorporating values from an individual's previous prescription, next prescription, and median values from records for the same opioid drug-formulation combination. It is important to note that the decisions made during the data preparation process may impact the findings of this study.

The impact of decision variations on the final study results was discussed previously. Pye *et al.*<sup>286</sup> showed that for oral hypoglycaemic drugs, changing one data preparation decision (using the clinician-reported duration rather than a

combination of sources to define prescription duration) increased the hazard ratio of having a cardiovascular event from 1.77 (95% CI: 1.56–2.00) to 2.83 (95% CI: 1.59–5.04). Osokugo *et al.*<sup>297</sup> compared childhood disease incidence rates using different definitions for disease episode duration. When the duration of the disease episode increased, incidence rate estimates decreased. The incidence rates of acute otitis media varied from 5.9/100 person-years (PYs) for a 90-day duration to 7.1/100 PYs for a 14-day duration. Therefore, providing transparent reporting of these steps will allow others to interpret the results or reproduce the findings appropriately.

To promote transparency and ensure comprehensive reporting of research conducted using routinely collected health data, the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) checklist<sup>289</sup> was developed explicitly for studies utilising EHR data as an extension to the STROBE checklist<sup>298</sup>. This checklist was designed to assist researchers using EHRs in reporting data preparation methodology and steps. However, it does not guide how these details might be achieved. In a study assessing research published in 2012 against the RECORD checklist, Hemkens *et al.*<sup>299</sup> found that only 20.5% of studies using EHRs adequately reported all the necessary details to define the study population, exposures, and outcomes.

### **5.6.1 Strength and limitations**

The current analysis made some assumptions regarding opioid quantity, daily doses, and duration, which were guided mainly by the usual doses prescribed for acute pain management. However, these assumptions might result in dose

misclassification or under- or over-estimation. For example, when a patient has concurrent prescriptions issued on the same day, the doses for both prescriptions were combined to produce the final daily doses; this might overestimate the OMEQ dose/day unless the patient took both doses together. However, given the limited occurrence of such cases, their impact on the analyses is expected to be negligible.

Another possible source of error is the assumption that patients collect their prescriptions on the exact recorded issue date. In reality, there might be delays in collecting prescriptions, which could be related to patients' reasons, leading to a discrepancy between the recorded issue date and the actual date of medicines use. This inconsistency could contribute to variations in the expected dosing timeline, potentially affecting the accuracy of our calculations of the prescription start or stop date.

Some studies examining opioid use based on CPRD data have used the DrugPrep algorithm, enabling their findings to be compared<sup>290, 300</sup>. However, it is important to note that the decisions made during the implementation of this algorithm and the cohort selection process can influence the extent of exposure misclassification and ultimately impact the final study findings.

During data preparation, OMEQ dose was used to convert the doses of different opioids into a standard unit based on their analgesic potency to provide more easily comparable data across a range of opioid medicines. It warrants consideration as a standard prescribing measure. Another opioid prescribing measure is the defined daily dose (DDD), which is defined as the “assumed average

maintenance dose per day for a drug used for its main indication in adults”<sup>301</sup>. The World Health Organization developed the DDD to standardise the measurement of drug prescribing across countries and regions. However, DDDs vary for each drug and between formulations of the same drug.

When comparing opioid prescribing patterns in four Nordic countries using OMEQ dose, notable differences were observed compared to DDDs<sup>291</sup>. “Weak” opioids like codeine had higher DDD values than “strong” opioids like morphine, causing countries with a higher prevalence of codeine prescribing to appear to have higher overall opioid consumption. However, this trend was reversed when OMEQ dose was used, and the contribution of “strong” opioids was considered. Therefore, OMEQ dose provided a more accurate assessment of opioid prescribing, highlighting the importance of considering the potency and equivalency of different opioid medicines when analysing prescribing patterns. Still the total OMEQ dose might not accurately represent the actual daily dose consumed by the patients. Patients may deviate from the prescribed daily dose due to the severity of their pain and variability in their symptoms.

## **5.7 Conclusion**

Applying the DrugPrep algorithm allowed a systematic approach to impute prescription data that was implausible or MNAR. The extension of the DrugPrep algorithm was used to generate a daily OMEQ dose to standardise the doses of various opioids based on their analgesic potency. This made data on variety of opioid medicines more easily compared. The dataset generated from the



prescription preparation process was used to describe trends and patterns in prescription characteristics following colectomy (Chapter 7).

## **Chapter 6: Predictors of persistent postoperative opioid use following colectomy: a population-based cohort study from England**

This chapter is an expanded version of published article: Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN. Predictors of persistent opioid use following colectomy: a population-based cohort study from England. *Anaesthesia* 2023; 78(9):1081-1092. doi: 10.1111/anae.16055.

## 6.1 Abstract

### Introduction

Little is known regarding whether opioid prescriptions following colectomy will lead to persistent use. This study aimed to determine the prevalence of persistent post-discharge opioid use following colectomy, stratified by preadmission opioid exposure, and identify associated predictors of PPOU.

### Methods

This retrospective cohort study on adults undergoing colectomy from 2010 to 2019 used linked primary CPRD, and secondary care HES data to determine the prevalence of PPOU following colectomy, stratified by pre-admission opioid exposure, and identify associated predictors. Based on pre-admission opioid exposure, patients were categorised as opioid-naïve, currently exposed (opioid prescription 0–6 months before admission) and previously exposed (opioid prescription 6–12 months before admission). PPOU was defined as requiring an opioid prescription within 90 days of discharge, along with one or more opioid prescriptions 91–180 days after hospital discharge. Multivariable logistic regression analyses were conducted to obtain odds ratios for predictors of PPOU.

### Results

Amongst the 93,262 patients, 15,081 (16.2%) were issued at least one opioid prescription within 90 days of discharge. Of these, 6791 (45.0%) were opioid-naïve, 7528 (49.9%) were currently exposed and 762 (5.0%) were previously exposed. From the whole cohort, 7540 (8.1%) developed PPOU. Patients with pre-operative opioid exposure had the highest persistent use: 5317 (40.4%) from the

currently exposed group and 305 (9.8%) from the previously exposed group, with 1918 (2.5%) from the opioid-naïve group. The odds of developing persistent opioid use were higher, OR 3.41 (95%CI 3.07–3.77), among individuals who used long-acting opioid formulations in the 180 days before colectomy than those who used short-acting formulations. Predictors of persistent opioid use included previous opioid exposure; high deprivation index; multiple comorbidities; use of long-acting opioids; white race; and open surgery. Minimally invasive surgical approaches were associated with lower odds of persistent opioid.

### **Conclusion**

After colectomy, more than 1:12 patients continued to receive opioids three months beyond discharge. Minimally invasive surgery was associated with lower risk of persistent opioid use and may represent a modifiable risk factor.

## **6.2 Introduction**

Colectomy is a common abdominal surgical procedure, with 300,000 performed annually in the US<sup>302</sup> and approximately 33,000 performed annually in England<sup>207</sup>. People undergoing colectomy might have diseases that may be associated with pain, such as inflammatory bowel disease, diverticulitis and cancer<sup>208</sup>. Additionally, the procedure itself can lead to significant postoperative pain<sup>208</sup> and opioid analgesia may be indicated.

While short-term opioid use has an established role in managing acute pain<sup>94</sup>, it has recently been identified as a risk factor for PPOU<sup>271, 290, 303</sup>, beyond the expected time frame for complete recovery<sup>304</sup>. PPOU is now widely acknowledged as a surgical complication<sup>134</sup>, which can be associated with harm, including

physical dependence, tolerance and opioid diversion<sup>303, 305, 306</sup>. Therefore, opioid prescriptions for surgical pain have been recognised as a public health concern and one of the factors implicated in the opioid epidemic in the US<sup>307</sup>. Accordingly, the UK's Medicines and Healthcare products Regulatory Agency has released recommendations to mitigate the risk of opioid addiction and recommended against extending opioid use for longer than three months in the management of acute pain<sup>205</sup>. Hence, it has become a significant focus for opioid-related policy and interventions<sup>151, 308, 309</sup>.

Minor and major surgical procedures are associated with development of PPOU<sup>133, 141, 151, 182</sup>; however, there is wide variability around its definition<sup>134</sup>. This variability in definition has prompted two systematic reviews to summarise the definitions of PPOU<sup>134, 182</sup>. The systematic search by Jivraj and colleagues<sup>134</sup> found 29 different definitions used to define PPOU, with 12 studies using definitions focusing on the presence of opioid prescription in the period from 90 postoperative days to 1 postoperative year. This definition was the most extensively used in other countries<sup>110, 141, 144, 151, 161, 164, 165, 310</sup>, and no studies have looked at PPOU in England. Other international studies have also used time-to-opioid cessation<sup>311</sup> or presence of repeat prescriptions<sup>312</sup> to define PPOU.

According to several studies from the US, which defined PPOU as having one opioid prescription within the early post-discharge period and another prescription 91–180 days after discharge, 11–17% of opioid naïve patients develop PPOU following colectomy<sup>144, 208</sup>. The prevalence of PPOU increases to > 30% for

patients previously exposed to opioids<sup>133, 134, 313</sup>, and this might be linked with poor surgical outcomes<sup>271, 314</sup> and higher healthcare costs<sup>176</sup>.

Despite the risk of PPOU following colectomy being quantified in the US and Canada, the external validity of these findings is limited and cannot be extrapolated to other populations due to significant variations in prescribing practices. Hence, the extent to which PPOU exists within a subset population from the UK has been hitherto unexplored.

### **6.3 Aims and objectives**

Given the evidence gap around whether opioid prescriptions following colectomy in England lead to persistent use, this chapter aimed to determine the prevalence of PPOU following colectomy and identify associated PPOU predictors using linked electronic healthcare data from England. The objectives of this chapter were to:

1. Describe the process for managing opioid prescription records to enable the generation of a stratified colectomy cohort based on pre-admission opioid exposure.
2. Describe the characteristics of all colectomy cohort identified within the study period between 2010 and 2019.
3. Determine the prevalence of PPOU following colectomy, stratified by pre-admission opioid exposure.
4. Identify predictors associated with PPOU after colectomy.

## 6.4 Methods

### 6.5 Study design

This was a retrospective cohort study on adults undergoing colectomy from 2010 to 2019 using linked primary (CPRD) and secondary (HES) care data and was reported in accordance with STROBE guidelines <sup>315</sup>.

#### 6.5.1 Data sources

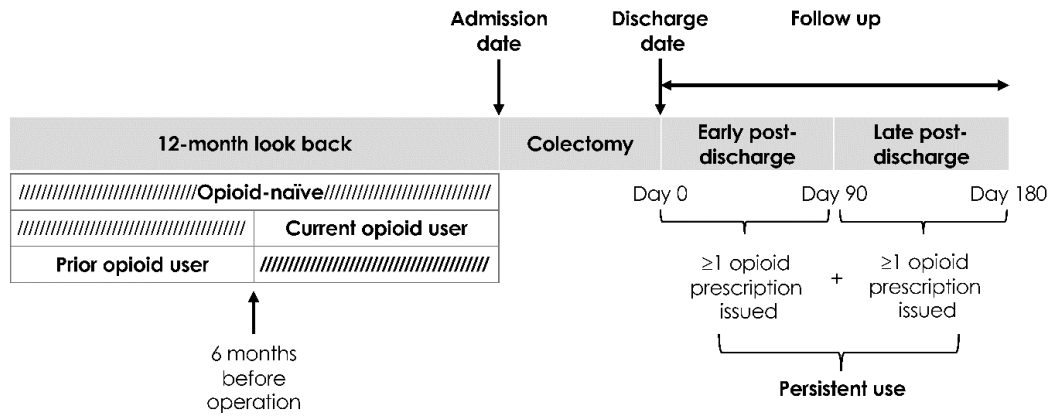
This study used linked primary and secondary care electronic databases previously described and validated<sup>277, 285</sup>. These have been described in detail in Chapter 4.

#### 6.5.2 Cohort identification

Patients aged  $\geq 18$  years were identified from HES data by searching for procedure codes for colectomy surgeries performed between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2019, as explained in Chapter 4. Operations that were limited to or included the anal canal and rectum were excluded. Patients who did not survive the first 90 days following discharge were excluded as they would be precluded from experiencing PPOU based on the study definition.

Eligible patients were followed up from the day of discharge to either having the study outcome of PPOU<sup>144</sup>, end of follow up (180 days), transfer out of participating practice or date of death, whichever came first (Figure 6-1).

To have sufficient data on pre-operative opioid exposure, patients were excluded if they did not have a minimum of 12 months of Aurum data before the admission date for surgery.



**Figure 6-1: Definitions used in the study**

Baseline characteristics, such as age, sex and race, were obtained from Aurum and HES data. Race was categorised as white, black, Asian, and others<sup>316</sup>. Comorbidities before admission were obtained from Aurum HES data and classified using the Charlson comorbidity index (CCI) based on the number of comorbidities into 0, 1 and  $\geq 2$ <sup>317</sup>. Index of Multiple Deprivation scores (IMD)<sup>318</sup> were categorised into quintiles from 1 to 5 (least to most deprived, respectively)<sup>277</sup>.

### 6.5.3 Stratification of colectomy cohort based on pre-operative opioid exposure

As justified in Chapter 4, a one-year lookback window before the date of admission was used to assess preoperative opioid exposure. In contrast to some studies that have categorised their cohorts based on the effects of varying degrees and patterns of opioid exposure<sup>312, 319</sup> or the continuity of opioid use<sup>320</sup>, the cohort in the current study was stratified based on the occurrence and recency of opioid exposure before colectomy, particularly to address the potential oversight of the



impact of naivety, remote and prior opioid exposure. Considering that no information is currently available regarding trajectories of postoperative opioid use based on recency of opioid exposure in a population of England, exploring this effect became crucial.

Patients were considered opioid-naïve if they did not have an opioid prescription issued in the year preceding their date of admission for surgery. They were considered 'currently exposed' if they were issued an opioid prescription within the 6 months before their admission date and 'previously exposed' if an opioid prescription was issued within 7–12 months before their date of admission, thus forming two mutually exclusive pre-operative opioid exposed groups<sup>321</sup> (Figure 6-1).

#### **6.5.4 Categorising preoperative opioid prescriptions by formulations**

The avoidance of initiating modified-release opioids in the peri-operative period was highlighted in the international consensus recommendations<sup>271</sup>. The concern stems from the belief that starting these opioid formulations during this time may increase the likelihood of long-term opioid use. This concern was supported by the findings of a US study, which demonstrated that the preoperative presence of a modified-release opioid prescription is associated with long-term opioid use following surgery<sup>311</sup>. Consequently, the effect of using long-acting opioid formulations for the currently exposed and previously exposed groups was aimed to be investigated. To examine the impact of preoperative opioid formulation in the current study, opioid prescriptions prescribed within the 180 days of opioid exposure before admission were categorised as either long-acting if they included

modified-release or transdermal formulations or short-acting if they contained immediate-release opioid formulations.

### **6.5.5 Predictors**

Baseline characteristics, such as age, sex and race, were obtained from Aurum and HES data. Race was categorised as white, black, Asian, and others<sup>316</sup>. Comorbidities before admission were obtained from Aurum and HES data and classified using the CCI based on the number of comorbidities into 0, 1 and  $\geq 2$ <sup>317</sup>. IMD scores<sup>318</sup> were categorised into quintiles from 1 to 5 (least to most deprived, respectively)<sup>277</sup>. Patients were recognised as having a diagnosis of cancer if a diagnosis of colorectal cancer was reported in HES data. Benign disease was assigned if the ICD-10 discharge codes related to the admission included diverticular disease or inflammatory bowel disease. Patients' admissions were categorised as either emergency or elective, based on the documented indications for their surgical procedures.

The choice of surgical approach has been associated with variations in postoperative pain levels and recovery trajectories. Since laparoscopic procedures are considered less invasive than open colectomy, this may impact the level of postoperative pain experienced and, subsequently, opioid use. Therefore, the surgical approaches were categorised as either open or minimally invasive, which included laparoscopic or robotic techniques using procedural codes (Y50.8, Y57.1 and Y75.2 for laparoscopic or Y75.3 for robotic, respectively).

### 6.5.6 Outcome measures

The primary outcome was PPOU after colectomy. To identify this, early post-discharge opioid use was defined first as having at least one opioid prescription issued within 90 days of hospital discharge. This 90-day period was selected to ensure that the opioid prescribed might be related to surgery, as the time from complete tissue healing may extend to 3 months<sup>304</sup>. PPOU was defined as one or more opioid prescriptions being issued within 90 days of surgical discharge along with one or more prescriptions for opioids within 91–180 days after hospital discharge (Figure 6-1)<sup>144</sup>. This commonly used definition was chosen to allow comparison with studies from other countries that have investigated PPOU following colectomy.

As explained in Chapter 4, opioid prescriptions were identified using opioid product codes identified from the Aurum product dictionary, which are listed in Appendix S 10. In the current study, the focus was on identifying cases of persistent opioid use resulting from prescriptions of opioids in primary care, where GPs serve as the main gatekeepers to healthcare in the UK. To achieve this, codes for all commonly prescribed opioids used for pain management in the UK, including transdermal buprenorphine patches, were included. However, unlike the US, high-strength sublingual buprenorphine tablets (2, 4, 8 mg) and methadone are exclusively used in the context of addiction treatment<sup>322</sup> and are not often prescribed by GPs. Therefore, prescriptions of these medications were not included as an exposure or in the follow-up period, as it is believed that this exclusion reflects the typical post-discharge opioid prescribing practice in the UK.

A similar approach for excluding these prescriptions was adopted in other UK studies<sup>290, 296, 323</sup>.

### **6.5.7 Data analysis**

Patient characteristics are presented as proportions and stratified based on pre-operative opioid exposure and persistent use. The proportion of patients being prescribed opioids within the early post-discharge period and persistent users were calculated for each stratum.

Because the study outcome (dependent variable) is a binary outcome (presence of persistent opioid use, yes) or (absence of persistent opioid use, no), univariable and multivariable logistic regression analyses were used to examine the association of different predictors with the odds of PPOU.

The analyses were stratified by pre-operative opioid exposure as opioid-naïve, currently exposed and previously exposed. This decision was made based on additional analysis investigating interactions between pre-operative opioid exposure and surgical approach. The likelihood ratio test was used to check for interaction and compare coefficients between the models. Further stratification of the opioid-naïve group by admission type was performed after detecting significant interaction between admission type and cancer-related surgery. However, when tested on the currently and previously opioid-exposed groups, this interaction was not significant; therefore, these two groups were not further stratified to preserve the statistical power, still the confounding effect of the type of admission was accounted for by including it as a predictor in the model.

Age was fitted as a continuous variable; this decision was made by conducting separate models with age fitted as either a continuous or categorical variable. Then the likelihood ratio test was used to compare model fit in both models, and the variable with the best fit was selected for the final model.

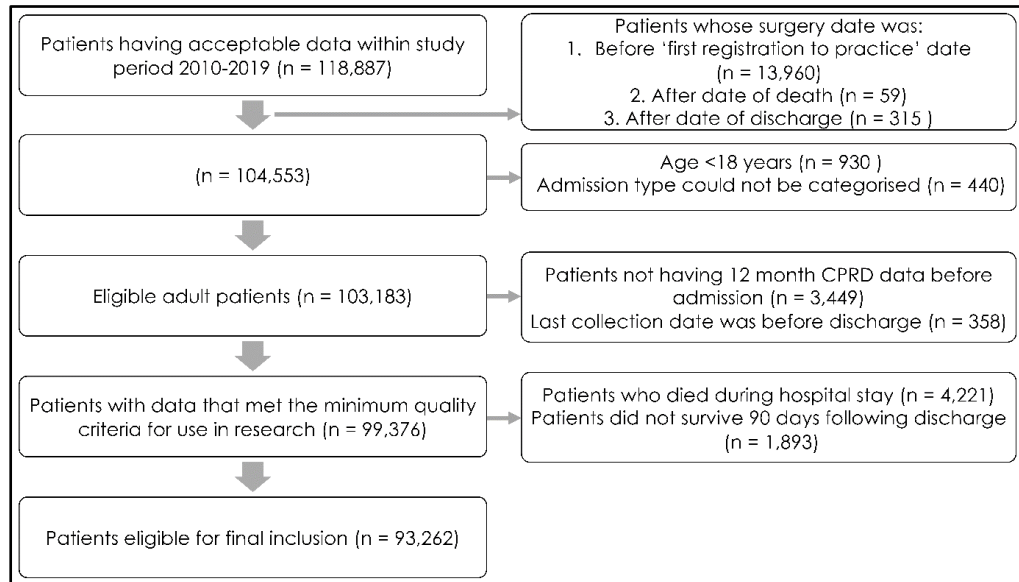
Potential predictor variables were also analysed and were identified based on previous literature, including sex; race; IMD; CCI; diagnosis of cancer; surgical approach; year of surgical admission; and the pre-operative use of long-acting opioid formulations. Unavailable IMD values were treated as a separate category. Length of hospital stay was not included as a predictor in the multivariable analysis because of collinearity with the surgical approach. Variables associated with the outcome in the univariable analyses ( $p < 0.05$ ) were included in a multivariable manual backward logistic regression model. The advantage of using a backward elimination approach is that the joint predictive ability of variables is assessed, leaving only the most important variables in the model. Also, this approach can help to reduce the dimensionality of the data and improve the interpretability of the model.

## **6.6 Results**

### **6.6.1 Cohort demographics**

Figure 6-2 demonstrates the identification of the study population. Demographics of the 93,262 eligible patients who had a colectomy within the study period are shown in Table 6-1. Overall, the median (IQR [range]) age was 65 (51–75 [36–81]) years. There were similar proportions of men and women; 76,981 (77.0%) patients were opioid-naïve in the year preceding their colectomy and 63,809 (68.4%) had

two or more significant comorbidities. Elective admission was predominant for 66,321 (71.1%), and the most common surgical approach was open for 55,413 (59.4%) patients.



**Figure 6-2: Study flow diagram**

The prevalence of people with high IMD of 5 was higher in the currently exposed group (21.1%) compared to the naïve (16.2%) and previously exposed groups (18.3%). The opioid naïve group saw an increase from 8.4% in 2010 to 12.4% in 2019. Short-acting opioid formulations were more prevalent in the groups with previous opioid exposure compared to long-acting formulations (Table 6-1).

Table 6-1: Characteristics of the colectomy cohort, stratified by exposure to opioids before surgery.

	Opioid naïve n = 76,981	Currently exposed n = 13,172	Previously exposed n = 3109	p value*
<b>Age</b>	64.6 (50.2-74.5[36.3-81.5])	68.3 (56.1-77.2 [42.5-83.2])	70.0 (57.1-78.2[40.9- 83.6])	< 0.001
<b>Sex</b>				
<b>Male</b>	39,521 (51.3%)	5519 (41.9%)	1366 (44.0%)	< 0.001
<b>Female</b>	37,460 (48.7%)	7653 (58.1%)	1743 (56.1%)	
<b>Race</b>				
<b>White</b>	70,043 (91.0%)	12,415 (94.3%)	2877 (92.5%)	< 0.001
<b>Black</b>	1717 (2.2%)	221 (1.7%)	63 (2.0%)	
<b>Asian</b>	2345 (3.0%)	275 (2.0%)	100 (3.2%)	
<b>Other</b>	2876 (3.7%)	261 (2.0%)	69 (2.2%)	
<b>IMD score</b>				
<b>1</b>	17,739 (23.0%)	2502 (19.0%)	643 (20.7%)	< 0.001
<b>2</b>	16,678 (21.7%)	2546 (19.3%)	671 (21.6%)	
<b>3</b>	15,552 (20.2%)	2672 (20.3%)	622 (20.0%)	
<b>4</b>	14,426 (18.7%)	2667 (20.3%)	603 (19.4%)	
<b>5</b>	12,479 (16.2%)	2778 (21.1%)	570 (18.3%)	
<b>Missing</b>	107 (0.14%)	7 (0.05%)	–	
<b>Charlson comorbidity index</b>				
<b>0</b>	20,077 (26.1%)	1954 (14.8%)	458 (14.7%)	< 0.001
<b>1</b>	5974 (7.8%)	805 (6.1%)	185 (6.0%)	
<b>≥ 2</b>	50,930 (66.2)	10,413 (79.1%)	2466 (79.3%)	
<b>Cancer diagnosis</b>				
<b>Yes</b>	43,879 (57.0%)	6412 (48.7%)	1679 (54.0%)	< 0.001
<b>No</b>	33,102 (43.0%)	6760 (51.3%)	1430 (46.0%)	

	Opioid naïve n = 76,981	Currently exposed n = 13,172	Previously exposed n = 3109	p value*
<b>Admission type</b>				
Emergency	21,802 (28.3%)	4386 (33.3%)	753 (24.2%)	< 0.001
Elective	55,179 (71.7%)	8786 (66.7%)	2356 (75.8%)	
<b>Length of stay; days†</b>				
≤ 3	8091 (10.5%)	873 (6.6%)	305 (9.8%)	< 0.001
4–7	27,908 (36.2%)	3841 (29.2%)	1063 (34.2%)	
≥ 7	40,982 (53.2%)	8458 (64.2%)	1741 (56.0%)	
<b>Surgical approach</b>				
Open	44,674 (58.0%)	8887 (67.5%)	1852 (59.6%)	< 0.001
Minimally invasive	32,307 (41.9%)	4285 (32.5%)	1257 (40.4%)	
<b>Year of surgery</b>				
2010	7017 (8.4%)	1392 (10.6%)	276 (8.9%)	< 0.001
2011	7208 (8.6%)	1355 (10.3%)	333 (10.7%)	
2012	7566 (9.1%)	1396 (10.6%)	309 (9.9%)	
2013	7718 (9.2%)	1342 (10.2%)	317 (10.2%)	
2014	7826 (9.4%)	1326 (10.1%)	312 (10.0%)	
2015	8346 (10.0%)	1343 (10.2%)	331 (10.7%)	
2016	8745 (10.5%)	1325 (10.1%)	327 (10.5%)	
2017	8980 (10.8%)	1341 (10.2%)	314 (10.1%)	
2018	9708 (11.6%)	1261 (9.6%)	308 (9.9%)	
2019	10,341 (12.4%)	1091 (8.3%)	282 (9.1%)	
<b>Practice region</b>				
North-east	2640 (3.4%)	743 (5.6%)	152 (4.9%)	< 0.001
North-west	12,061 (15.7%)	2624 (19.9%)	560 (18.1%)	
Yorkshire and the Humber	2843 (3.7%)	559 (4.2%)	121 (3.9%)	
East Midlands	1822 (2.4%)	313 (2.4%)	79 (2.5%)	



	Opioid naïve n = 76,981	Currently exposed n = 13,172	Previously exposed n = 3109	p value*
<b>West Midlands</b>	13,093 (17.0%)	2609 (19.8%)	593 (19.1%)	
<b>East of England</b>	3621 (4.7%)	516 (3.9%)	128 (4.1%)	
<b>South-west</b>	10,616 (13.8%)	1832 (13.9%)	420 (13.5%)	
<b>South central</b>	10,014 (13.1%)	1550 (11.8%)	379 (12.2%)	
<b>London</b>	12,878 (16.7%)	1325 (10.1%)	404 (12.9%)	
<b>South-east coast</b>	7375 (9.6%)	1101 (8.3%)	273 (8.8%)	
<b>Long-acting opioid</b>				
<b>Yes</b>	–	1972 (15%)	152 (4.9%)	< 0.001
<b>No</b>	–	11,200 (85%)	2956 (95.1%)	

Values are median (IQR [range]) or number (proportion)

IMD, Index of Multiple Deprivation

\* All p values were obtained using the chi-square test except for the median age for which the Kruskal-Wallis test was used

†Length of hospital stay calculated as the number of days from the first day of admission to the day of discharge

### 6.6.2 Early post discharge opioid use

At least one opioid prescription was issued to 15,081 (16.2%) patients within 90 days of surgical discharge. Of these, 6791 (45.0%) patients were opioid-naïve, 7528 (49.9%) were currently exposed and 762 (5.0%) were previously exposed. Among each category of pre-operative opioid exposure in the overall colectomy cohort, 6791 (8.8%) of opioid-naïve, 7528 (57.2%) of those currently exposed and 762 (24.5%) of previously exposed received opioid prescriptions after discharge (Table 6-2).

### 6.6.3 Persistent opioid use after hospital discharge

In this cohort of patients who underwent colectomy, 7540 (8.1%) developed PPOU. Patients with pre-operative opioid exposure had the highest persistent use ( $p < 0.001$ ): 5317 (40.4%) in the currently exposed group; 305 (9.8%) in the previously exposed group; and 1918 (2.5%) in the opioid-naïve group (Table 6-2).

**Table 6-2. Patients having early and persistent opioid use post-discharge**

		Opioid naïve n = 76,981	Currently exposed n = 13,172	Previously exposed n = 3109	p value*
Early post discharge opioid use	Yes	6791 (8.8%)	7528 (57.2%)	762 (24.5%)	< 0.001
	No	70,190 (91.2%)	5644 (42.8%)	2347 (75.5%)	
Persistent opioid use	Yes	1918 (2.5%)	5317 (40.4%)	305 (9.8%)	< 0.001
	No	75,063 (97.5%)	7855 (59.6%)	2804 (90.2%)	

Values are number (proportion)

\*Chi-square test.

### 6.6.3.1 Opioid-naïve group

For patients in the opioid-naïve group of both admission types, predictors associated with higher odds of PPOU included living in the most deprived quintile and having a high CCI. Conversely, minimally invasive surgery was associated with significantly lower odds of PPOU in opioid-naïve patients for both emergency and elective admission types. Variation over time was also present, with significantly lower odds of having opioid prescriptions from 2016 to 2019. Female sex and cancer surgery (adjusted odd ratio (aOR) 1.24, 95%CI 1.05–1.46) were only linked to higher odds of persistent use in the emergency setting (Table 6-3).

**Table 6-3: Univariable and multivariable logistic regression analysis investigating the predictors of persistent post-discharge opioid use for opioid naïve patients (n = 76,981), by surgical admission type.**

Predictors	Emergency n = 21,802			Elective n = 55,179		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	OR (95%CI)	OR (95%CI)	p value*	OR (95%CI)	OR (95%CI)	p value*
<b>Age</b>	1.01 (1.01–1.02)	1.00 (0.99–1.00)	0.192	1.01 (1.00–1.01)	0.99 (0.99–1.00)	0.595
<b>Sex</b>						
Male	reference	reference	–	reference	reference	–
Female	1.05 (0.90–1.21)	1.04 (0.89–1.21)	0.589	0.78 (0.69–0.88)	0.85 (0.76–0.96)	0.010
<b>Race</b>						
White	reference	reference	–	reference	reference	–
Black	0.56 (0.31–1.03)	0.54 (0.29–0.99)	0.050	1.16 (0.80–1.69)	1.11 (0.76–1.63)	0.564
Asian	0.79 (0.50–1.26)	0.84 (0.53–1.35)	0.486	1.09 (0.79–1.51)	1.18 (0.85–1.63)	0.320
Other	0.58 (0.36–0.94)	0.67 (0.41–1.09)	0.113	0.91 (0.66–1.25)	1.08 (0.78–1.48)	0.641
<b>IMD</b>						
1 (least deprived)	reference	reference	–	reference	reference	–
2	1.18 (0.92–1.51)	1.20 (0.93–1.54)	0.142	1.02 (0.85–1.22)	1.03 (0.85–1.22)	0.780
3	1.27 (0.99–1.63)	1.29 (1.12–1.66)	0.037	1.17 (0.98–1.40)	1.16 (0.97–1.39)	0.087
4	1.48 (1.16–1.88)	1.60 (1.26–2.04)	0.001	1.16 (0.96–1.39)	1.16 (0.97–1.40)	0.098
5 (most deprived)	1.37 (1.07–1.75)	1.45 (1.13–1.86)	0.003	1.46 (1.21–1.75)	1.45 (1.21–1.74)	0.001
<b>Charlson comorbidity index</b>						
0	reference	reference	–	reference	reference	–
1	1.64 (1.25–2.15)	1.55 (1.17–2.04)	0.002	1.96 (1.45–2.64)	1.88 (1.38–2.56)	0.001
≥2	1.96 (1.65–2.31)	1.83 (1.53–2.18)	0.001	2.61 (2.13–3.20)	2.45 (1.96–3.06)	0.001
<b>Cancer diagnosis</b>						
No	reference	reference	–	reference	reference	–
Yes	0.03 (0.02–0.03)	1.24 (1.05–1.46)	0.008	1.44 (1.26–1.64)	1.11 (0.95–1.29)	0.172

Predictors	Emergency n = 21,802			Elective n = 55,179		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	OR (95%CI)	OR (95%CI)	p value*	OR (95%CI)	OR (95%CI)	p value*
<b>Surgical approach</b>						
Open	reference	reference	–	reference	reference	–
Minimally invasive	0.58 (0.44–0.76)	0.66 (0.51–0.87)	0.003	0.62 (0.55–0.70)	0.69 (0.62–0.78)	0.001
<b>Year of surgery</b>						
2010	reference	reference	-	reference	reference	-
2011	0.92 (0.67–1.27)	0.89 (0.65–1.23)	0.499	1.13 (0.89–1.42)	1.12 (0.89–1.41)	0.326
2012	1.01 (0.74–1.38)	0.99 (0.73–1.35)	0.955	0.86 (0.68–1.10)	0.87 (0.69–1.12)	0.296
2013	0.81 (0.59–1.11)	0.81 (0.89–1.11)	0.190	0.84 (0.65–1.07)	0.87 (0.68–1.11)	0.268
2014	0.75 (0.53–1.04)	0.74 (0.53–1.03)	0.073	0.72 (0.56–0.92)	0.74 (0.58–0.95)	0.021
2015	0.73 (0.53–1.01)	0.74 (0.54–1.03)	0.072	0.69 (0.54–0.88)	0.73 (0.57–0.94)	0.017
2016	0.64 (0.46–0.88)	0.64 (0.46–0.88)	0.008	0.54 (0.42–0.70)	0.57 (0.44–0.75)	0.001
2017	0.62 (0.45–0.87)	0.62 (0.44–0.86)	0.005	0.47 (0.36–0.62)	0.51 (0.39–0.67)	0.001
2018	0.52 (0.37–0.72)	0.52 (0.37–0.73)	0.001	0.48 (0.37–0.63)	0.52 (0.40–0.68)	0.001
2019	0.53 (0.38–0.75)	0.55 (0.38–0.77)	0.001	0.44 (0.34–0.57)	0.48 (0.36–0.63)	0.001

Values are OR (95%CI)

IMD, Index of Multiple Deprivation. \*p values obtained from multivariable analysis

### 6.6.3.2 Currently exposed group

For the currently exposed group, pre-operative use of long-acting opioid formulations was associated with significantly greater odds of persistent opioid use than taking short-acting opioids (aOR 3.41, 95%CI 3.07–3.77). Female patients had higher odds of developing PPOU (aOR 1.13, 95%CI 1.05–1.22). Other predictors associated with higher odds included high deprivation index and high CCI (Table 6-4). Conversely, black, Asian and other races had lower odds of developing PPOU than white race. In contrast with the opioid-naïve group, a diagnosis of cancer was associated with lower odds of PPOU (aOR 0.84, 95%CI 0.77–0.91).

### 6.6.3.3 Previously exposed group

In the previously exposed group, having two or more comorbidities was the only predictor associated with higher odds of PPOU. Compared with open colectomy, minimally invasive surgery was associated with lower odds of PPOU (aOR 0.72, 95%CI 0.54–0.94). Patients who had a colectomy performed between 2014 and 2018 also had lower odds for PPOU compared with colectomy performed in 2010. The use of long-acting opioid formulations before colectomy was not associated with developing PPOU in this cohort (Table 6-4).

**Table 6-4: Univariable and multivariable logistic regression analysis investigating the predictors of persistent post-discharge opioid use for previously exposed patients (n = 16,281) in the post-discharge period following colectomy.**

Predictors	Currently exposed n = 13,172			Previously exposed n = 3109		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	OR (95%CI)	OR (95%CI)	p value*	OR (95%CI)	OR (95%CI)	p value*
<b>Age</b>						
	1.00 (1.00–1.01)	1.00 (1.00–1.01)	0.002	0.99 (0.98–1.00)	0.99 (0.98–0.99)	0.019
<b>Sex</b>						
Male	reference	reference	–	reference	reference	–
Female	1.19 (1.11–1.28)	1.13 (1.05–1.22)	<0.001	1.27 (0.99–1.61)	1.23 (0.96–1.57)	0.104
<b>Race</b>						
White	reference	reference	–	reference	reference	–
Black	0.71 (0.53–0.95)	0.64 (0.48–0.85)	0.003	0.95 (0.41–2.22)	0.80 (0.34–1.91)	0.632
Asian	0.72 (0.55–0.92)	0.72 (0.55–0.93)	0.015	0.68 (0.31–1.48)	0.56 (0.25–1.23)	0.152
Other	0.63 (0.49–0.83)	0.69 (0.53–0.91)	0.010	0.71 (0.28–1.77)	0.65 (0.25–1.65)	0.370
<b>IMD (patient level)</b>						
1 (least deprived)	reference	reference	–	reference	reference	–
2	1.08 (0.96–1.21)	1.08 (0.97–1.22)	0.173	1.16 (0.79–1.70)	1.15 (0.78–1.70)	0.477
3	1.22 (1.10–1.36)	1.23 (1.09–1.37)	<0.001	1.17 (0.78–1.73)	1.08 (0.73–1.61)	0.677
4	1.32 (1.18–1.48)	1.36 (1.21–1.52)	<0.001	1.42 (0.97–2.08)	1.38 (0.93–2.03)	0.100
5 (most deprived)	1.67 (1.50–1.87)	1.73 (1.54–1.93)	<0.001	1.49 (1.02–2.18)	1.41 (0.95–2.08)	0.083
Missing	0.74 (0.14–3.81)	0.73 (0.14–3.87)	0.716	-	-	–
<b>Charlson Comorbidity Index</b>						
0	reference	reference	–	reference	reference	–
1	1.24 (1.05–1.48)	1.23 (1.03–1.47)	0.024	1.33 (0.76–2.33)	1.71 (0.95–3.05)	0.069
≥ 2	1.61 (1.45–1.78)	1.46 (1.30–1.64)	<0.001	1.14 (0.81–1.63)	1.52 (1.03–2.25)	0.035

Predictors	Currently exposed n = 13,172			Previously exposed n = 3109		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	OR (95%CI)	OR (95%CI)	p value*	OR (95%CI)	OR (95%CI)	p value*
<b>Cancer diagnosis</b>						
No	reference	reference	–	reference	reference	–
Yes	0.93 (0.87–1.00)	0.84 (0.77–0.91)	<0.001	0.77 (0.61–0.98)	0.89 (0.68–1.19)	0.454
<b>Surgical approach</b>						
Open	reference	reference	–	reference	reference	–
Minimally invasive	0.96 (0.89–1.03)	0.99 (0.92–1.08)	0.940	0.66 (0.51–0.85)	0.72(0.54–0.94)	0.017
<b>Admission type</b>						
Emergency	reference	reference	–	reference	reference	–
Elective	1.14 (1.06–1.23)	1.22 (1.13–1.33)	<0.001	0.71 (0.55–0.93)	0.79 (0.59–1.06)	0.124
<b>Year of surgery</b>						
2010	reference	reference	-	reference	reference	-
2011	0.96 (0.82–1.12)	0.95 (0.82–1.11)	0.537	0.72(0.44–1.15)	0.71 (0.43–1.15)	0.166
2012	0.87 (0.75–1.02)	0.85 (0.73–0.99)	0.047	0.64 (0.38–1.05)	0.63 (0.38–1.03)	0.070
2013	1.08 (0.93–1.26)	1.07 (0.91–1.27)	0.376	0.68 (0.42–1.12)	0.69 (0.43–1.13)	0.148
2014	0.93 (0.79–1.08)	0.88 (0.76–1.07)	0.146	0.41 (0.24–0.72)	0.42 (0.24–0.73)	0.002
2015	0.99 (0.85–1.16)	0.95 (0.81–1.12)	0.597	0.59 (0.36–0.97)	0.57 (0.35–0.95)	0.031
2016	0.95 (0.81–1.11)	0.93 (0.79–1.09)	0.383	0.60 (0.36–0.98)	0.59 (0.36–0.97)	0.040
2017	0.97 (0.83–1.23)	0.92 (0.79–1.08)	0.356	0.41 (0.24–0.72)	0.41 (0.23–0.72)	0.002
2018	1.00 (0.96–1.17)	0.97 (0.83–1.14)	0.724	0.55 (0.33–0.92)	0.55 (0.33–0.94)	0.029
2019	1.08 (0.93–1.28)	1.05 (0.88–1.23)	0.596	0.71 (0.43–1.17)	0.73 (0.43–1.21)	0.223
<b>Long-acting opioid</b>						
No	reference	reference	–	reference	reference	–
Yes	3.50 (3.16–3.87)	3.41 (3.07–3.77)	<0.001	0.85 (0.47–1.52)	0.86 (0.47–1.54)	0.608

Values are OR (95%CI); IMD, Index of Multiple Deprivation. \*p values obtained from multivariable analysis.



## 6.7 Discussion

This nationwide study in patients undergoing colectomy in England contributes to a growing body of literature on post-discharge opioid use after surgery<sup>101, 324</sup>. The stratified analysis based on pre-operative opioid exposure has enabled quantification of the risk of PPOU with identification of predictors for developing this complication in three different groups of patients.

The study findings show that 16.2% of patients were issued prescriptions for opioid analgesics within 90 days of discharge. This finding aligns with a study from the US of 367 patients that reported a similar proportion (15%) of patients having post-discharge opioids following colorectal surgery<sup>325</sup>. However, it contrasts with the results from other population-based studies that examined opioid use after various surgical procedures. Another US-based study found that 80.3% of patients received post-discharge opioid prescriptions after a broad range of surgical procedures, including colectomy<sup>95, 326</sup>. Additionally, a study by Ladha *et al.* reported that the rate of filled opioid prescriptions following low-risk abdominal surgical procedures was seven times higher in the US and Canada than in Sweden, where only 11% of patients were given post-discharge opioids<sup>95</sup>, which is more consistent with this study. While the rate of opioid prescribing after surgical discharge was lower in China, a retrospective cohort study that included 438,128 patients found that 32,932 individuals (7.52%) were prescribed opioids upon discharge<sup>327</sup>.

Half of the patients in the study cohort who were discharged from the hospital with a prescription for opioids (8.1% of the overall cohort) continued to be prescribed opioids for up to 180 days following discharge. This overall finding was lower than the 10% prevalence reported in a prospective study from the US<sup>208</sup> and the figures determined by a US database analysis showing PPOU rates ranging between 13.5% and 21.2% following colectomy<sup>310</sup>. Furthermore, among opioid-naïve patients, 2.5% developed PPOU. This finding aligns with that reported by Clarke *et al.*<sup>141</sup>, who used the same definition of PPOU in a study that included different types of abdominopelvic procedures and was not strictly limited to colectomy.

It was found that patients with pre-operative opioid exposure accounted for the majority of persistent users. This result is similar to that of previous studies showing that PPOU is more common in patients with a history of opioid exposure before surgery<sup>171, 208, 314</sup>, although pre-operative opioid exposure is not defined consistently in terms of dose, recency, duration and continuity of use. While the definition adopted in the present study did not require evidence of long-term opioid use before surgery, a large proportion of patients in this group continued to use opioids for more than 90 days following discharge.

The odds of persistent opioid use were more than three times higher among individuals who used long-acting opioid formulations in the 180 days before colectomy than those who used short-acting formulations<sup>271, 311, 328</sup>. This finding contributes to the growing body of evidence suggesting that long-acting and modified-release formulations are a modifiable risk factor for PPOU<sup>329</sup>.

The association between PPOU and pre-operative opioid exposure is likely to be multifactorial. One possible explanation is that patients with previous opioid exposure can develop tolerance or hyperalgesia, which may make the management of their postoperative pain more challenging and lead to persistent use<sup>330, 331</sup>. Another possible explanation is that patients who were taking opioids pre-operatively had already adjusted to opioid-related side effects such as nausea, vomiting and constipation, while these side effects may have discouraged their opioid-naïve counterparts from continuing their opioids. In addition to the currently exposed group, patients with previous opioid exposure were also included. This is a distinct group with a potentially different trajectory of PPOU that is often overlooked. The current study found that despite their remote exposure to opioids before surgery, these patients were still at greater risk of PPOU than those in the naïve group. Although an association between the use of long-acting opioid formulations and PPOU in this group of patients was not found, it is essential to note that this finding may be limited by the small sample size in this group.

This extensive electronic health records analysis also reveals that amongst opioid-naïve and previously exposed patients with a history of remote opioid exposure, a minimally invasive surgical approach is associated with a significantly lower odds of PPOU than an open approach. In contrast, this protective effect is not seen in the currently exposed group. This finding supports literature from the US demonstrating that minimally invasive techniques attenuate the odds of developing PPOU and should be considered when skills and resources are

available, especially for opioid-naïve patients<sup>135, 208, 310</sup>. A possible explanation for this association may be that a minimally invasive approach is associated with reduced incision length<sup>135</sup> and less inflammation and nerve damage<sup>332</sup>, which may lead to lower levels of incisional pain and analgesic requirements. However, other studies examining the effect of surgical approach on opioid consumption have yielded contradictory findings that do not fully support this theory. For instance, while single-institution studies show decreased inpatient opioid use after minimally invasive surgery vs. open surgery<sup>333, 334</sup>, *Vu et al.*<sup>335</sup> report no difference in post-discharge opioid consumption by patients undergoing colectomies performed by these two approaches across many institutions. Additional factors may confound this finding including variations in surgical technique and enhanced recovery protocols, especially given inconsistent reductions in PPOU associated with minimally invasive surgery<sup>187</sup>. Further prospective studies are needed to assess the possible benefits of minimally invasive approaches on PPOU in specific surgical populations and pre-operative opioid use groups.

Having two or more comorbidities increases the odds of PPOU among all groups, while those in the most deprived quintiles have increased odds of PPOU in opioid-naïve patients and current users. These results align with previous studies that have evaluated these factors in major abdominal surgical procedures<sup>141, 144</sup>.

Ethnicity details were obtained for all patients undergoing colectomy between 2010 and 2019 from CPRD and HES. Among this cohort of patients (n=93,262), the ethnic distribution was as follows: White 85,335 (91.5%), Black 2,001 (2.2%), Asian 2,720 (2.9%), and Other 3,206 (3.4%)<sup>336</sup>. Similar ethnic distribution patterns were

observed in other UK studies conducted using CPRD, looking at different populations and different periods<sup>280, 290</sup>.

It is important to note that ethnic distribution in the UK varies based on age, with different ethnic groups exhibiting distinct age profiles. Age might play a significant role in influencing the ethnic composition of the included cohort in our study. The median (IQR [range]) age was 65 (51-75 [36-81]) years for all colectomy cohorts.

In 2019, the most common ethnic group in England and Wales was White (84.8%). Our study figures are more comparable to data from the 2019 census since in data spanning from 2011 to 2021, the proportion of individuals identifying as White ethnicity decreased from 86.0% to 81.7%<sup>316</sup>.

Variation was observed between racial groups. Opioid-naïve patients of black race had a significantly lower odds of PPOU, when compared with patients of white race, while current opioid users of white race were at higher risk of becoming persistent users compared with all other races. Previous research has identified racial disparities in pain diagnosis and treatment<sup>337</sup>, and white patients are more likely to be prescribed opioids than black patients<sup>338</sup>. In light of this evidence, it is necessary to consider that the present study's findings may have been confounded by clinicians' implicit bias in the assessment of pain severity and choice of treatment, implicit bias related to repeat opioid prescriptions<sup>339</sup>, hospital-level factors and surgical setting.

Over the 10-year study period, there were several changes to clinical practice that may have impacted the prescription of opioids and the incidence of PPOU. These

changes include: the widespread implementation of enhanced recovery programmes<sup>340</sup>; increased use of multimodal and opioid-sparing analgesia<sup>341</sup>; regional and neuraxial anaesthesia; and increased uptake of minimally invasive surgery. Additionally, there has been an increased awareness of the potential problems associated with opioids, which may have led to more responsible prescribing and stewardship practices.

### **6.7.1 Limitations**

This study has several limitations. First, although Aurum has longitudinal data on opioid prescription records before and after surgery, limiting the possibility of recall bias, it lacks clinical details such as in-hospital drug therapy, patient-reported outcome measures, and some complications (such as persistent postsurgical pain). Moreover, the assessment of PPOU using electronic health record data is limited by the inability to measure whether prescribed medicines were administered. Nevertheless, despite these limitations, the use of prescription data as a proxy for confirmed drug consumption is widespread in drug utilisation research<sup>133</sup>.

Additionally, data obtained from HES lack information on hospital-level factors such as pre-operative preparation, use of regional anaesthesia and availability of enhanced recovery protocols. It is unknown whether opioid prescribing guidance and discharge opioid tapering instructions were available for patients. While Daliya *et al.*<sup>101</sup> previously acknowledged the lack of these resources within hospitals in England, implementing these services along with opioid stewardship

programmes may be effective for minimising post-discharge opioid prescribing<sup>342, 343</sup>.

Another limitation is the lack of information on drugs prescribed privately or obtained via other sources. In addition, during the study period, some 'weak' opioids, such as dihydrocodeine and codeine, were available without a prescription, which may have led to the under-representation of the prevalence of PPOU related to these opioids. Other risk factors for PPOU reported in the literature such as history of depression, anxiety and pre-operative benzodiazepine and antidepressant use were not included in the current study<sup>271, 303</sup>. The dose, duration and type of opioids used before surgery may also be associated with the development of PPOU<sup>303</sup>, but these factors were not tested in the current analysis. Additionally, factors affecting the choice of surgical approach or admission type could not be controlled for. However, several patient- and surgery-specific predictors associated with long-term opioid use were identified, which had not been identified previously in a population from the UK.

## **6.8 Conclusion**

After undergoing colectomy in hospitals across England, 8.1% of patients continue to receive opioid prescriptions beyond 3 months after discharge. PPOU is more common in patients with pre-operative opioid exposure. Importantly, a minimally invasive surgical approach is associated with lower odds of persistent opioid use in opioid naïve and previously exposed patients compared with open colectomy and may present a modifiable risk factor meriting more clinical attention.

## **Chapter 7: Temporal trends and patterns in initial opioid prescriptions after hospital discharge following colectomy in England**

This chapter is an expanded version of published article: Baamer RM, Humes DJ, Toh LS, Knaggs RD, Lobo DN. Temporal trends and patterns in initial opioid prescriptions after hospital discharge following colectomy in England over ten years. *BJS Open* 2023;7(6): zrad136. doi: 10.1093/bjsopen/zrad136.



## **7.1 Abstract**

### **Background**

While opioid analgesics are often necessary for the management of acute postoperative pain, appropriate prescribing practices are crucial to avoid harm. The aim was to investigate the changes in the proportion of people receiving initial opioid prescriptions after hospital discharge following colectomy, and describe trends and patterns in prescription characteristics.

### **Methods**

This was a retrospective cohort study. Patients undergoing colectomy in England between 2010-2019 were included using electronic health record data from linked primary (CPRD) and secondary (HES) care. The proportion of patients having an initial opioid prescription issued in primary care within 90 days of hospital discharge was calculated. Prescription characteristics of opioid type and formulation were described.

### **Results**

Of the 95,155 individuals undergoing colectomy, 15,503 (16.3%) received opioid prescriptions. There was a downward trend in the proportion of patients with no prior opioid exposure (opioid naïve) who had a post-discharge opioid prescription ( $p < 0.001$ ), from 11.4% in 2010 to 6.7% in 2019 (-41.3%,  $p < 0.001$ ). Whereas the proportions remained stable for those prescribed opioids prior to surgery, from 57.5% in 2010 to 58.3% in 2019 ( $p = 0.637$ ). Codeine represented 44.5% of all prescriptions and prescribing increased by 14.5% between 2010 and 2019.

Prescriptions for morphine and oxycodone rose significantly by 76.6% and 31.0% respectively, while tramadol prescribing dropped by 48.0%. The most commonly prescribed opioid formulations were immediate-release (83.9%), followed by modified-release (5.8%) and transdermal (3.2%). There was a modest decrease in the prescribing of immediate-release formulations from 86.0% in 2010 to 82.0% in 2019 ( $p < 0.001$ )

### **Conclusion**

Over the 10 years studied, there was a changing pattern of opioid prescribing following colectomy, with a decrease in the proportion of opioid naïve patients prescribed post-discharge opioids.

## **7.2 Introduction**

While opioid analgesics are often necessary for the management of acute postoperative pain, appropriate prescribing practices are crucial to avoid harm<sup>271, 303, 344</sup>. Postoperative opioid prescribing may lead to PPOU<sup>95, 326</sup>, with dependence differing by opioid type and likeability<sup>198, 345</sup>. Our previous work demonstrated that 2.5% of opioid naïve patients who underwent colectomy in England developed PPOU, increasing to 40.4% in those with current opioid exposure (Chapter 6)<sup>336</sup>. Although definitions of PPOU vary<sup>133, 134</sup>, in North America the incidence of PPOU can range from 0.6% to 12% in opioid-naïve patients following abdominopelvic surgery and can be higher in those with previous opioid exposure<sup>133</sup>.

Differences in healthcare systems might have an impact on opioid prescribing practices. The UK has a publicly-funded NHS, which provides free healthcare to all

residents, including subsidised prescriptions<sup>346</sup>, mainly guided by national policies and drug formularies. In comparison, the US has a private healthcare system linked predominantly to insurance coverage. The variation in patterns of postoperative opioid use can also be linked to the promotion of certain opioids over others, leading to differences in the opioid selection, duration and quantity prescribed to each patient, and between countries<sup>194, 347, 348</sup>. For instance, the rate of filled opioid prescriptions in the US and Canada in the first week after discharge was seven times higher than in Sweden<sup>95</sup>. Although the frequency of filled prescriptions was similar between Canada and the US, patients in US hospitals received greater quantities of opioids<sup>95</sup>. Additionally, from 1994 to 2014, 80% of patients undergoing surgery, including colectomy, in the US received post-discharge opioid prescriptions<sup>326</sup>.

Opioid-related adverse events, which are related to potency, formulation and dose, can be reduced by avoiding long-acting and transdermal formulations<sup>271, 329, 349</sup>. Opioids should only be prescribed as immediate-release formulations for management of postoperative pain<sup>271, 329</sup>. Nevertheless, a recent UK study revealed that 10% of previously opioid-naïve patients were discharged with long-acting formulations<sup>101</sup>. Additionally, in the US, patients who were prescribed long-acting opioid formulations following surgical discharge were more likely to obtain prescriptions with higher doses compared with those prescribed short-acting formulations. Prescriptions with long-acting formulations resulted in a total OMEQ dose exceeding 350 mg<sup>326</sup>.

While evidence suggests a recent decline in postoperative opioid prescriptions in the US<sup>185, 350</sup>, it is unclear whether a similar trend exists in England. In addition, a comprehensive understanding of the specific opioids and formulations prescribed after surgical discharge and their variation over the years remains unexplored. This study aimed to investigate the changes in the proportion of people receiving initial opioid prescriptions after hospital discharge following colectomy, as well as describe trends and patterns in prescription characteristics, particularly temporal changes in analgesics, including potency and formulation choices.

### **7.3 Methods**

This retrospective cohort study followed the REporting of studies Conducted using Observational Routinely collected health Data Statement for Pharmacoepidemiology (RECORD-PE) guidelines<sup>351</sup>. A repeated cross-sectional analysis was used to describe temporal trends of patients undergoing colectomy and prescribed opioids within 90 days of hospital discharge following surgical procedure<sup>336</sup>, split by year-by-year data to describe trends and changes from 2010 to 2019. The 90-day duration was chosen to ensure that the prescribed opioid was associated with a surgical procedure, considering that the tissue healing process can take up to three months<sup>304</sup>. Moreover, this 90-day period aligns with the timeline used for the definition of chronic postoperative pain, which typically requires pain persistence at this stage to be considered chronic<sup>352</sup>.

Anonymised patient records were obtained from two previously validated<sup>285</sup> linked databases: primary CPRD Aurum<sup>277</sup> and linked secondary care HES<sup>276</sup> data

as previously described (Chapter 5)<sup>336</sup>.

Patients  $\geq 18$  years of age, who underwent colectomy between 1 January 2010 and 31 December 2019 were identified from HES using OPCS codes for colectomy procedures (Appendix S 9). The validity and reliability of codes to identify colectomy have been confirmed previously<sup>285</sup>. Patients were excluded if they did not have at least 12 months CPRD Aurum data before their date of surgery, to ensure complete preoperative opioid exposure data.

Patients issued opioid prescriptions were identified based on the presence of a prescription for an opioid within 90 days of hospital discharge after surgery. Opioid prescription records were identified using opioid product codes<sup>336</sup> (Appendix S 10) and extracted from the CPRD Aurum database then prepared for analysis using an adapted version of the DrugPrep algorithm which allows for identifying prescription errors, duplicate records, and dealing with missing data<sup>286</sup> (Chapter 5). Excluded opioids included higher-strength buprenorphine sublingual tablets (2, 4 and 8 mg), and methadone because they are primarily prescribed for opioid dependence in the UK. Injectable formulations were also excluded as these are typically administered by healthcare professionals rather than self-administered<sup>336</sup>.

### **7.3.1 Outcome measures**

#### **7.3.1.1 Primary outcome**

The primary outcome was the proportion of patients having initial opioid prescription issued from general practice within 90 days of hospital discharge

following colectomy. For this outcome, the method described previously (Chapter 6)<sup>336</sup> was employed to stratify the population based on opioid exposure before colectomy into three groups (opioid-naïve, currently exposed, and previously exposed). This stratification enabled description of the impact of previous opioid exposure on postoperative opioid use and determine if there were any differences in outcome between groups. Patients were categorised as opioid-naïve if they did not receive an opioid prescription in the year leading up to their surgical admission. Those who received an opioid prescription within the six months prior to their admission date were considered “currently exposed”, while those who received an opioid prescription within 7 to 12 months prior to admission were classified as “previously exposed”, forming two separate preoperative groups with no overlap (Chapter 6)<sup>321, 336</sup>.

### **7.3.1.2 Secondary outcome**

Several secondary outcomes were investigated: First, the potency of opioids in the initial prescription: opioids were classified as weak (codeine, dihydrocodeine, meptazinol, pentazocine, tramadol) and strong (morphine, oxycodone, fentanyl, buprenorphine, hydromorphone, pethidine, naloxone/oxycodone, cyclizine/dipipanone, hydromorphone, tapentadol), or combination of both<sup>294</sup>. Tramadol can be classed as a strong<sup>295</sup> or weak opioid<sup>294</sup>, and to allow comparison with other UK studies<sup>290, 296</sup> it was classified as a weak opioid.

Second, the opioid prescribed was determined as defined as the drug class (buprenorphine, codeine, dihydrocodeine, fentanyl, morphine, oxycodone,

tramadol, and other opioids). “Other opioids” represent opioids that were not commonly prescribed and combined in one category during drug preparation.

Third, opioid formulations were categorised into (immediate-release only, modified-release only, both immediate- and modified-release, transdermal only, and others).

Fourth, the amount of opioid in each prescription was described as OMEQ dose in mg/day. OMEQ dose was used to convert the doses of different opioids into a standard unit based on their analgesic potency to provide more easily comparable data across a range of opioid medicines. It warrants consideration as a standard prescribing measure<sup>291</sup> and is calculated by multiplying the daily dose of opioids in each prescription by the equivalent analgesic ratio as specified by the US Centers for Disease Control and Prevention<sup>292</sup> (Table 5-5). For those on a combination of opioids, OMEQ dose was calculated for each drug and combined to provide an overall OMEQ dose in mg/day for each patient, and was categorised into dose ranks:  $\leq 24$ , 25-49, 50-99, 100-249 and  $\geq 250$  mg/day. Patient characteristics were previously explained in Chapter 6 subheading 6.6.1.

## **7.4 Data analysis**

Characteristics of the colectomy population over time are presented as proportions for each year. For the primary outcome of the annual proportion of people receiving an opioid prescription, the analysis was stratified based on opioid exposure prior to colectomy. This was calculated as a percentage for each year (Equation 7-1).

**Equation 7-1. Proportion of patients receiving opioid prescription for each year**

$$\frac{\text{Number of individuals receiving at least one opioid prescription within 90 days of discharge in the year}}{\text{Number of individuals who had colectomy that year}} \times 100$$

Trend analysis over the years was performed using the Cochran Armitage test. Absolute and percentage changes between 2010 and 2019 were calculated and tested using unadjusted logistic regression.

For secondary outcomes, characteristics of patients having opioid prescriptions within 90 days of discharge are presented as proportions for each year. Descriptive statistics were used to describe the outcome measures as frequencies, proportions (percentage).

The yearly proportion of prescriptions containing an opioid formulation was calculated using Equation 7-2

**Equation 7-2. Yearly proportion of prescription containing an opioid formulation**

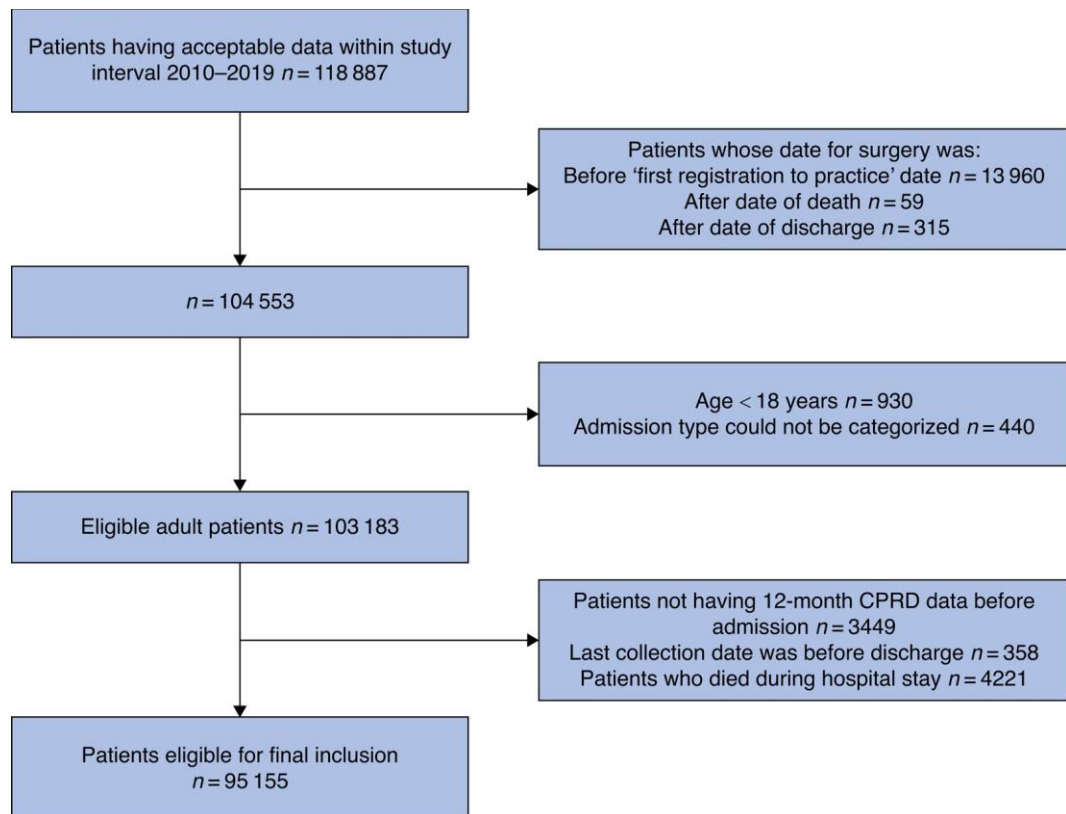
$$\frac{\text{Number of prescriptions in each opioid drug formulation category}}{\text{Total number of prescriptions for opioids within first 90 days of discharge in that year}} \times 100$$

The proportion of people who were dispensed an OMEQ dose in each category was calculated and the proportion of people prescribed an opioid in each category was calculated by dividing the number of people based on their daily OMEQ dose by the total number of people with repeated opioid prescriptions following surgery for that year. Utilisation measures were stratified based on opioid exposure before surgery into naïve, currently, and previously exposed.



## 7.5 Results

In total, 95 155 individuals had a colectomy during the study period and met the inclusion criteria (Figure 7-1). Over the study period, the surgical approach shifted toward open colectomy being less frequent than minimally invasive procedures. There was an increase in the number of opioid-naïve patients from 79.1% in 2010 to 86.9% in 2019 (percentage change +9.9%,  $p < 0.005$ ), whereas there was a fall in the currently opioid-exposed group (percentage change -40.5%,  $p < 0.001$ ), (Appendix S 11).



**Figure 7-1. Study flow diagram**

Of the 15,503 (16.3%) individuals who received opioid prescriptions from primary care after hospital discharge following colectomy, the ratio of opioid-naïve to currently exposed individuals and elective to emergency admission remained relatively stable over the study period. However, the proportions of individuals having two or more comorbidities, benign disease, and minimally invasive procedures increased over the study period (Table 7-1).

**Table 7-1. Baseline characteristics of patients having opioid prescriptions without 90 days following colectomy discharge between the years 2010 and 2019**

Variable	Years									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
<b>Whole colectomy</b>	n=8,001	n=8,470	n=8,850	N=8,963	n=9,038	n=9,614	n=10,009	n=10,286	n=10,794	n=11,130
<b>Issued initial opioid prescription</b>	n=1,607 (100%)	n=1,689 (100%)	n=1,663 (100%)	n=1,653 (100%)	n=1,537 (100%)	n=1,566 (100%)	N=1,466 (100%)	n=1,489 (100%)	N=1,435 (100%)	n=1,398 (100%)
<b>Age (mean ± SD)</b>	65.2 ± 14.3	64.9 ± 14.3	64.1 ± 15.3	63.7 ± 15.2	64.5 ± 15.0	63.7 ± 15.2	63.5 ± 15.4	63.4 ± 15.4	63.2 ± 14.8	63.4 ± 15.4
<b>Sex</b>										
Female	850 (52.9)	843 (49.9)	886 (53.3)	892 (54.0)	821 (53.4)	831 (53.1)	808 (55.1)	811 (54.5)	779 (54.3)	773 (55.3)
Male	757 (47.1)	846 (50.1)	777 (46.7)	761 (46.0)	716 (46.6)	735 (46.9)	658 (44.9)	678 (45.5)	656 (45.7)	625 (44.7)
<b>Ethnicity</b>										
White	1,530 (95.2)	1,600 (94.7)	1,563 (93.9)	1,560 (94.3)	1,437 (93.5)	1,452 (92.7)	1,355 (92.4)	1,370 (92.0)	1,328 (92.5)	1,258 (90.0)
Black	32 (1.9)	22 (1.3)	21 (1.3)	25 (1.5)	20 (1.3)	33 (2.1)	26 (1.8)	30 (2.01)	32 (2.2)	34 (2.4)
Asian	36 (2.2)	41 (2.4)	47 (2.8)	40 (2.4)	40 (2.6)	37 (2.4)	40 (2.7)	38 (2.6)	32 (2.2)	49 (3.5)
Others	9 (0.56)	26 (1.5)	32 (1.9)	28 (1.7)	40 (2.6)	44 (2.8)	45 (3.1)	51 (3.4)	43 (3.0)	57 (4.1)
<b>Index of Multiple Deprivation (1 most deprived, 5 least deprived)</b>										
1	315 (19.6)	338 (20.0)	316 (19.0)	323 (19.5)	298 (19.4)	324 (20.7)	276 (18.8)	305 (20.5)	305 (21.3)	265 (18.9)
2	335 (20.9)	343 (20.3)	334 (20.1)	349 (21.1)	311 (20.2)	305 (19.5)	295 (20.1)	293 (19.7)	258 (17.9)	270 (19.3)
3	348 (21.7)	325 (19.2)	326 (19.6)	316 (19.1)	318 (20.7)	315 (20.1)	330 (22.5)	289 (19.4)	298 (20.8)	285 (20.4)
4	306 (19.0)	347 (20.5)	324 (19.5)	351 (21.2)	325 (21.2)	291 (18.6)	299 (20.4)	289 (19.4)	282 (19.7)	275 (19.6)
5	301 (18.7)	332 (19.7)	363 (21.8)	314 (19.0)	283 (18.4)	330 (21.1)	263 (17.9)	311 (20.9)	291 (20.3)	303 (21.7)

Variable	Years									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Missing	2 (0.12)	4 (0.24)	-	-	-	-	3 (0.20)	2 (0.13)	1 (0.07)	-
<b>Charlson Comorbidity Index</b>										
0	261 (16.3)	252 (14.9)	279 (16.8)	282 (17.1)	248 (16.1)	262 (16.7)	220 (15.0)	204 (13.7)	206 (14.3)	198 (14.2)
1	119 (7.4)	120 (7.1)	110 (6.6)	104 (6.3)	99 (6.4)	103 (6.6)	88 (6.0)	114 (7.7)	87 (6.1)	82 (5.9)
≥2	1,227 (76.4)	1,317 (77.9)	1,274 (76.6)	1,267 (76.7)	1,190 (77.4)	1,201 (76.7)	1,158 (78.9)	1,171 (78.6)	1,142 (79.6)	1,118 (79.9)
<b>Preoperative opioid exposure</b>										
Opioid naïve	721 (44.9)	804 (47.6)	774 (46.5)	752 (45.5)	707 (46.0)	695 (44.4)	642 (43.8)	632 (42.5)	607 (42.3)	647 (46.3)
Currently exposed	808 (50.3)	795 (47.1)	800 (48.1)	823 (49.8)	755 (49.1)	794 (50.7)	753 (51.4)	789 (52.3)	753 (52.5)	677 (48.4)
Previously exposed	78 (4.9)	90 (5.3)	89 (5.4)	78 (4.7)	75 (4.9)	77 (4.9)	71 (4.8)	68 (4.6)	75 (5.2)	74 (5.3)
<b>Surgical approach</b>										
Open	1211 (75.4)	1259 (74.5)	1196 (71.9)	1140 (68.9)	1032 (67.1)	1026 (65.5)	932 (63.6)	900 (60.4)	831 (57.9)	781 (55.9)
Minimally invasive	396 (24.6)	430 (25.5)	467 (28.1)	513 (31.0)	505 (32.9)	540 (34.5)	534 (36.4)	589 (39.6)	604 (42.1)	617 (44.1)
<b>Cancer diagnosis</b>										
No	680 (42.3)	656 (38.8)	756 (45.5)	734 (44.4)	685 (44.6)	699 (44.6)	657 (44.8)	681 (45.7)	653 (45.5)	662 (47.4)
Yes	927 (57.7)	1,033 (61.2)	907 (54.5)	919 (55.6)	52 (55.4)	867 (55.4)	809 (55.2)	808 (54.3)	782 (54.5)	736 (52.6)
<b>Admission type</b>										
Emergency	453 (28.2)	497 (29.4)	531 (31.9)	526 (31.8)	486 (31.6)	503 (32.1)	464 (31.7)	452 (30.4)	438 (30.5)	468 (33.5)
Elective	1154 (71.8)	1192 (70.6)	1132 (68.1)	1127 (68.2)	1051 (68.4)	1063 (67.9)	1002 (68.4)	1037 (69.6)	997 (69.5)	930 (66.5)

### 7.5.1 Primary outcome

#### Trends in postoperative opioid prescribing

Overall, the percentage of patients issued an opioid prescription within 90 days of hospital discharge decreased by 37.3% between 2010 and 2019 ( $p < 0.001$ ). The opioid-naïve group mainly drove this downward trend, with the proportion of people prescribed any opioid decreasing from 11.4% in 2010 to 6.7% in 2019, (percentage change -41.3%,  $p < 0.001$ ). Whereas, for the currently exposed group, the percentage of individuals prescribed opioids remained stable, from 57.5% in 2010 to 58.3% in 2019 (percentage change +1.3%,  $p = 0.697$ ). Similarly, for the previously exposed group, percent change between 2010 and 2019 was not significant (percent change -12.85%,  $p < 0.322$ ) (Figure 7-2).

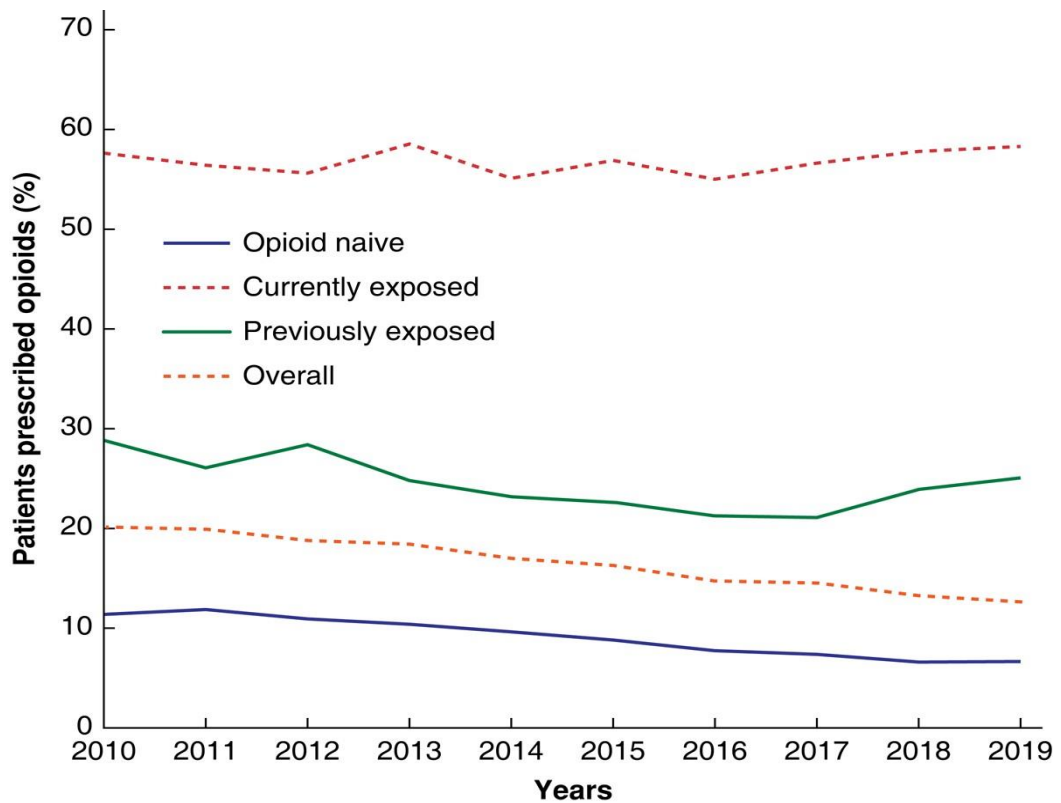


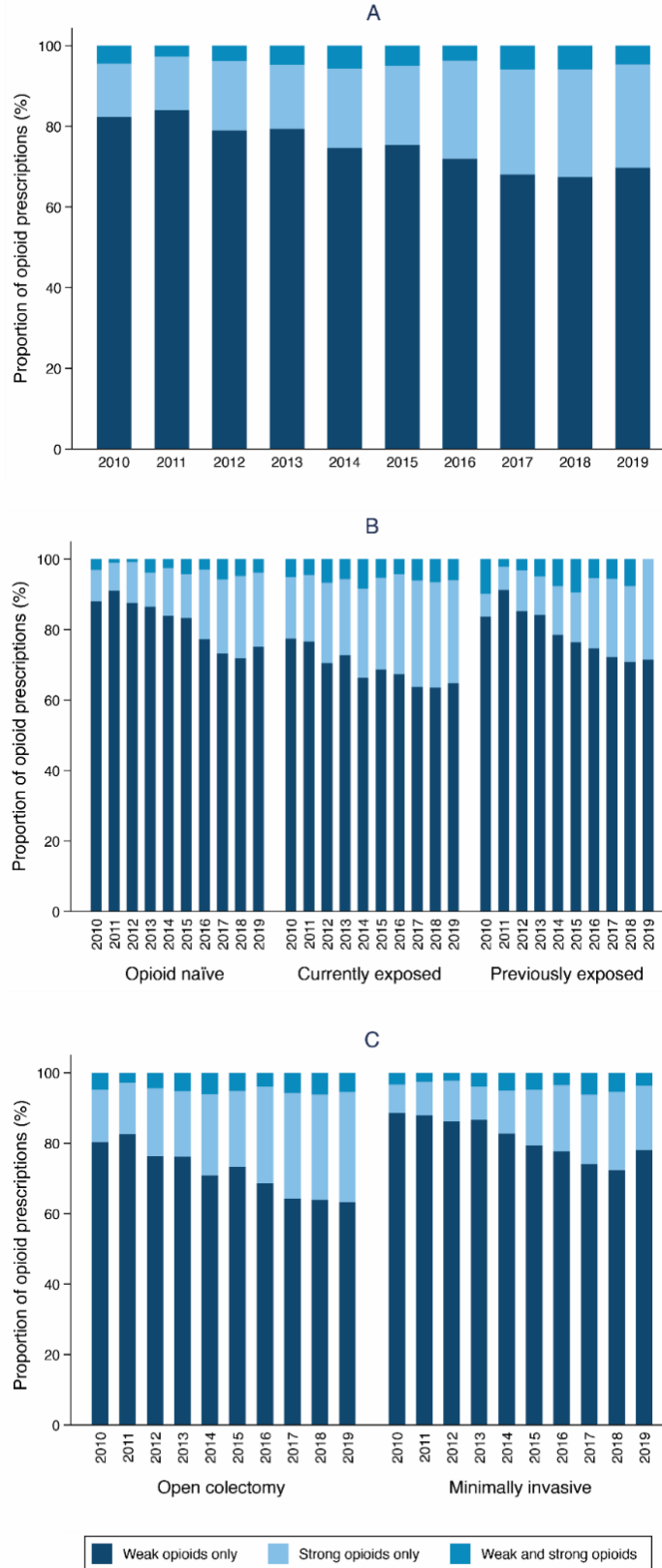
Figure 7-2. Temporal trend of percentage of patients who received opioid prescriptions after discharge

## 7.5.2 Secondary outcomes

### Trends in opioid prescriptions by opioid potency

For trends in opioid prescriptions by opioid potency, weak opioids were the most commonly prescribed category during the study period (75.5%), followed by strong opioids (19.9%), with the remainder (4.6%) prescribed a combination of weak and strong opioids. Notably, there was a downward trend in weak opioid prescribing prevalence over the years, with a decline from 82.3% in 2010 to 69.7% in 2019 (percentage change-15.3%,  $p < 0.001$ ). This decline remained statistically significant for all three strata of previous opioid exposure ( $p < 0.001$ ), and for both open and minimally invasive surgeries ( $p < 0.001$ ) (Figure 7-3 and Appendix S 6)

There was an upward trend in the prescribing prevalence of strong opioids, with a 94.0% increase (13.2% in 2010 to 25.6% in 2019,  $p < 0.001$ ). In addition, strong opioid prescribing was more common for currently opioid exposed (64.3%) than for the opioid-naïve (31.9%) and previously exposed groups (3.7%). However, the temporal changes were steeper for the opioid-naïve group, with a 133% increase from 2010 to 2019. Although strong opioid prescribing increased at a similar rate for both open and minimally invasive colectomy (15.0% in 2010 to 31.0% in 2019,  $p < 0.001$ ) and (8.1% in 2010 to 18.3% in 2019,  $p < 0.001$ ) respectively. Strong opioid prescribing remained lower in the minimally invasive colectomy group than in those having open colectomy (Figure 7-3 and Table 7-2).



**Figure 7-3. Yearly trend in potency of opioid prescribed in initial prescription received after discharge.**

Notes: (A) overall cohort, (b) cohort stratified by opioid exposure before colectomy, and (C) cohort stratified by surgical approach

**Table 7-2. Changes in the potency of opioid prescribed in initial prescription received after discharge**

		Opioid potency			
		Weak opioids	Strong opioids	Both weak & strong	
Stratified by Opioid exposure before colectomy	Opioid naïve N=6981	2010 n=721	87.9%	9.0%	3.0%
		2019 n=647	75.1%	20.9%	3.8%
		Percent change, p value	-14.8%, p < 0.001	+132.9%, p < 0.001	+26.3%, p < 0.436
	Currently exposed N=7747	2010 n=808	77.4%	17.5%	5.0%
		2019 n=677	64.8%	29.4%	5.9%
		Percent change, p value	-16.3%, p < 0.001	+67.9%, p < 0.001	+18.4%, p < 0.476
	Previously exposed N=775	2010 n=78	83.7%	6.5%	9.8%
		2019 n=74	71.4%	28.6%	0%
		Percent change, p value	14.7%, p < 0.055	+338.7%, p < 0.001	-100%, p < 0.005
Stratified by surgical approach	Open N=10,308	2010 n=1,326	80.0%	14.9%	4.8%
		2019 n=861	63.0%	30.9%	5.4%
		Percent change, p value	-21.3%, p < 0.001	+106.0%, p < 0.001	12.5%, p < 0.510
	Laparoscopic N=5,195	2010 n=420	88.5%	8.1%	3.3%
2019 n=662		78.1%	18.3%	3.6%	
Percent change, p value		-11.8%, p < 0.001	+125.9%, p < 0.001	+9%, p < 0.799	

Codeine was the most commonly prescribed opioid during the study period (44.5%), followed by tramadol (29.9%) and morphine (12.2%). Notably, prescribing of specific opioid medicines changed over time. For the overall population, the prescribing of codeine decreased from 43.5% in 2010 to 40% in 2014 and rose to 50.0% in 2019 ( $p < 0.001$ ). When people were stratified either by surgical approach or by opioid exposure before surgery, codeine remained the most commonly prescribed opioid. However, the significantly increased prescribing prevalence was mainly for the opioid-naïve group and minimally invasive surgery (Figure 7-4, Table 7-3, Table 7-4 and Table 7-5).



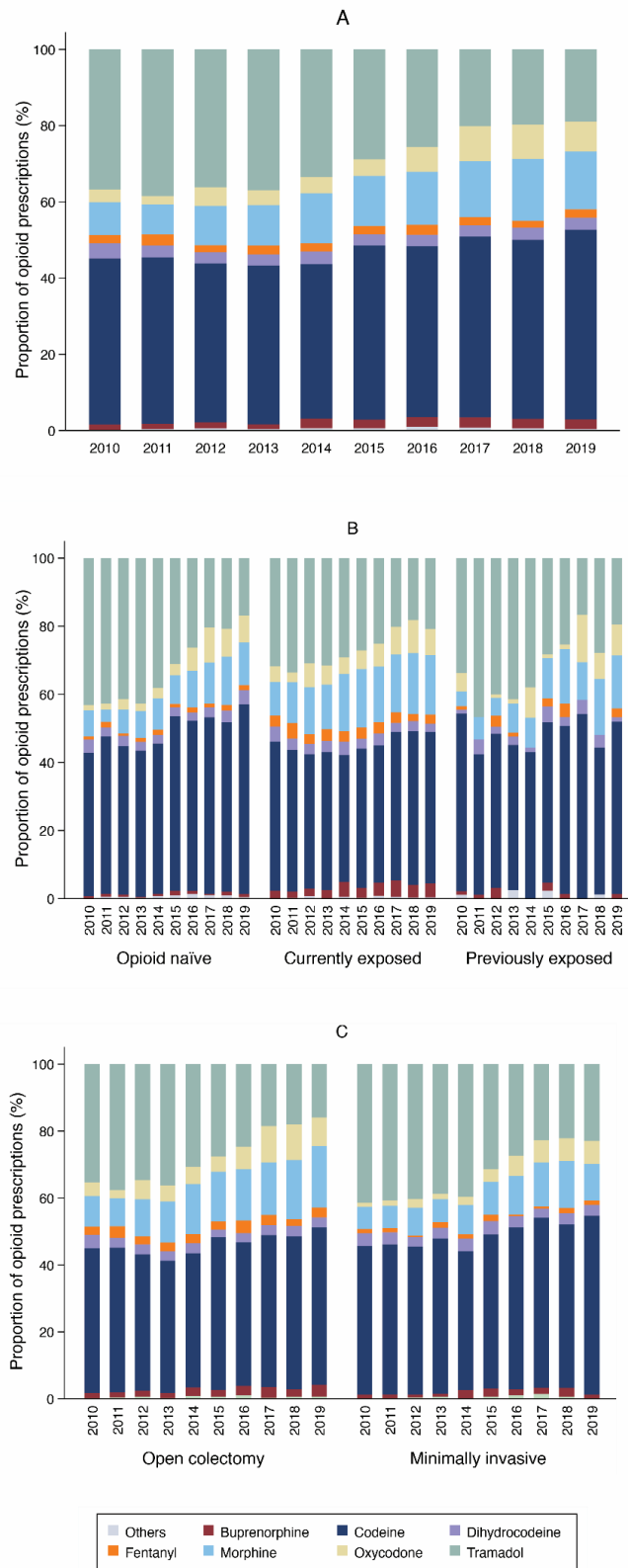
The proportion of prescriptions for oxycodone and morphine continued to increase. Oxycodone prescribing nearly trebled between 2010 and 2019 for opioid-naïve group and minimally invasive surgery (percentage change: +395% and +471% respectively). On the contrary, buprenorphine prescribing increased from 2.2% to 4.1% for currently opioid exposed group and from 4.1% to 8.6% for open colectomy. Among all the prescribed opioids, tramadol prescribing decreased significantly, with a steep decline starting in 2014. This decline was evident for all stratified groups.

### **Formulations**

Overall, immediate-release formulations were the most prescribed formulation over the study period (83.9%), followed by modified-release only (5.8%) and transdermal only (3.1%). Although immediate-release formulations were more prominent, their prevalence decreased from 86.0% in 2010 to 82.0% in 2019 (percentage change -4.7%,  $p < 0.001$ ).

Comparison within stratum of preoperative opioid exposure showed differences in formulation choices. Transdermal and modified-release formulations were prescribed more for the currently exposed group (76.8% and 69.0% respectively), compared with 20.0% and 27.6% respectively in the opioid-naïve group. For the currently exposed group, there was an increase in the prescribing of (immediate & modified formulations) from (5.4%) in 2010 to 8.6% in (2019), percent change (59.3%,  $p < 0.001$ ).

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**Figure 7-4. Yearly trend in the type of opioid prescribed in initial prescription received after discharge**

Note: (A) overall cohort, (B) cohort stratified by opioid exposure before colectomy, and (c) cohort stratified by surgical approach

**Table 7-3. Changes in the type of opioid prescribed in initial prescription received after discharge for overall cohort**

Opioids analgesics		2010 n=1746	2019 n=1523	Absolute change	Percent change	p value
<b>Weak Opioids</b>	Codeine	43.5%	49.8%	+6.3	+14.5%	<0.001
	Dihydrocodeine	4.0%	3.2%	-0.90	-21.5%	0.043
	Tramadol	36.8%	18.9%	-17.8	-48.4%	<0.001
<b>Strong opioids</b>	Morphine	8.6%	15.2%	+6.6	+76.9%	<0.001
	Oxycodone	3.4%	7.8%	+4.4	+131.1%	<0.001
	Buprenorphine	1.4%	2.5%	+ 1.1	+74.8%	0.041
	Fentanyl	2.1%	2.2%	+ 0.10	+2.4%	0.920

n = number of patients having opioid prescription

#### Oral morphine equivalent dose per day

Of the five dose ranks of total OMEQ dose, most people were in the lower dose ranks (43.6% in the 25-49 mg/day group and 30.8% in the 50-99 mg/day group). There was an increasing trend in the percentage of people prescribed opioids in the 25-49 mg/day group from 40.1% to 51.3% ( $p < 0.001$ ), with the increase being more predominant for the opioid-naïve and prior exposed groups. On the other hand, a downward trend started in 2013 was seen for doses of 50-99 mg/day (percentage change 34.5%) (Figure 7-5).

Table 7-4. Changes in type of opioid prescribed stratified by surgical approach

Opioid analgesics	Surgical approach									
	Open colectomy					Laparoscopic				
	2010 n=1326	2019 n=861	Absolute change	Percent change	p value	2010 n=420	2019 n=662	Absolute change	Percent change	p value
<b>Codeine</b>	43.2	46.9	+3.8	+8.9%	0.054	44.5	53.5	+9.0	+20.2%	<0.001
<b>Dihydrocodeine</b>	4.07	3.02	-1.9	-25.8%	0.0259	3.8	3.3	-0.49	-12.9	0.822
<b>Tramadol</b>	35.3	15.9	-19.4	-54.9%	<0.001	41.4	22.9	-18.5	-44.5%	0.326
<b>Morphine</b>	9.2	18.3	+9.2	+98.9%	<0.001	6.7	11.0	+4.3	+65.3%	0.007
<b>Oxycodone</b>	4.1	8.6	+4.5	+110.9%	<0.001	1.2	6.8	+5.6	+470.9	<0.001
<b>Buprenorphine</b>	1.5	3.5	+1.9	+130.0%	0.003	1.2	1.2	+0.02	+1.7%	0.925
<b>Fentanyl</b>	2.4	2.9	+0.49	+20.3%	0.317	1.2	1.2	+0.02	+1.7%	<0.001

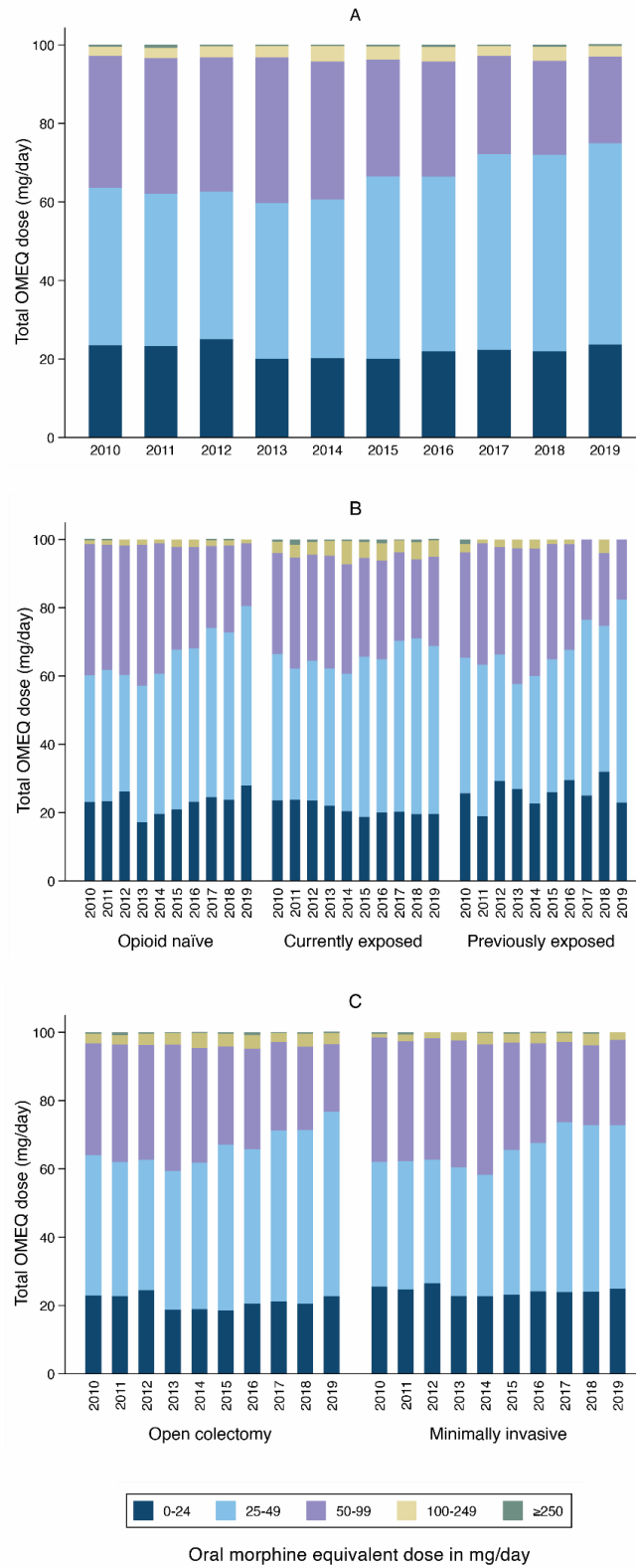
n represents number of patients each year

**Table 7-5. Changes in type of opioid prescribed stratified by opioid exposure before colectomy**

Opioid	Opioid exposure before surgery														
	Naïve n=7382					Currently exposed n=8676					Previously exposed n=828				
	2010	2019	Absolute	Percent	p	2010	2019	Absolute	Percent	p	2010	2019	Absolute	Percent	p
<b>analgesics</b>	N=756	N=686	change	change	value	N=898	N=760	change	change	value	N=92	N=77	change	change	value
<b>Codeine</b>	42.2%	55.7%	+13.5	+31.9%	<0.001	43.8%	44.5%	+0.73	+1.6%	0.779	52.1%	50.7%	-1.4	-2.7%	0.552
<b>Dihydrocodeine</b>	3.8%	4.2%	+0.39	+10.1%	0.904	4.5%	2.37%	-2.1	-46.7%	0.019	1.1%	1.3%	+0.21	+19.3%	0.054
<b>Tramadol</b>	43.1%	16.9%	-26.2	-60.8%	<0.001	31.7%	20.8%	-20.8	-34.4%	<0.001	33.7%	19.5%	-14.2	-42.1%	0.021
<b>Morphine</b>	7.7%	12.5%	+4.8	+62.9%	<0.001	9.8%	17.5%	+7.7	+78.6%	<0.001	4.4%	15.6%	+11.3	+258.1%	0.057
<b>Oxycodone</b>	1.6%	7.8%	+6.3	+395.3%	<0.001	4.7%	7.6%	+2.9	+63.2%	<0.001	5.4%	9.1%	+3.7	+67.4%	0.532
<b>Buprenorphine</b>	0.53%	0.87%	+0.34	+64.1%	0.429	2.2%	4.1%	+1.9	+82.9%	0.032	1.1%	1.3%	+0.21	+19.3%	0.667
<b>Fentanyl</b>	0.93%	1.5%	+0.53	+56.9%	0.275	3.2%	2.8%	-0.47	-14.5%	0.607	1.1%	2.6%	+1.5	+138.1%	0.540

n represents total number of patients in this strata, N = number of patients in this stratum in certain year.

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**Figure 7-5. Yearly trend in total oral morphine equivalent doses prescribed in initial prescription received after discharge**

Note: (A) overall cohort, (B) cohort stratified by opioid exposure before colectomy, and (C) cohort stratified by surgical approach

## 7.6 Discussion

There was a notable decrease in patients receiving opioid prescriptions in primary care following discharge after colectomy, particularly among opioid-naïve patients over time. These results are consistent with those of studies from the US that also showed a decline in opioid prescribing after major abdominal and orthopaedic procedures<sup>185, 350</sup>, despite the differences between postoperative prescribing practices in the US and the UK. It is essential to note that due to a dearth of studies on postoperative opioid prescribing practices in the UK, direct comparisons with current study findings are limited.

Codeine and tramadol were the most frequently prescribed opioids after colectomy, consistent with findings that codeine and tramadol accounted for approximately 58% and 45% of postoperative prescriptions in Canada and Sweden, respectively, compared with only 7% in the United States<sup>95</sup>. A similar trend was observed in a cross-sectional study that examined the type of opioid initiated for new users in different countries, where a higher proportion of patients was started on codeine and tramadol in the UK, while oxycodone was the most commonly prescribed opioid in the US<sup>300</sup>.

The current study also found a decrease in prescribing of tramadol after 2014, reaching a similar rate to morphine prescribing by the end of the study period. One possible explanation for this decline is the classification of tramadol as a Schedule 3 controlled substance in the UK in 2014<sup>353</sup>, prompted by safety concerns and potential risks of misuse. This decrease in tramadol prescribing is consistent with a UK study that assessed the impact of reclassification on the use of tramadol

for chronic pain<sup>354</sup>. Another observed change over time was the increase in prescribing of oxycodone and morphine, consistent with trends reported in contemporary prescribing literature from the UK for other indications<sup>300, 355</sup>.

While the data included in this study were obtained before the release of guidelines that advise against using transdermal and long-acting formulations for managing acute pain<sup>271</sup>, the findings are reassuring since immediate-release formulations accounted for most prescribed opioids. However, the unexpected modest decrease in the prescribing of immediate-release formulations in 2019 is noteworthy. It is also worth emphasising that prescribing transdermal formulations was more common among patients with previous opioid exposure, which could be attributed to the continuation of similar formulations after hospital discharge. Nevertheless, increased education and awareness are necessary to discourage the use of long-acting formulations in favour of immediate-release opioids due to their higher risk of misuse, addiction, and difficulty in dose adjustment.

Most patients were prescribed low opioid doses (OMEQ dose in the 25-49 and 59-99 mg/day categories), with an upward trend for patients prescribed OMEQ dose in the 25-49 mg/day category over the years. International guidelines vary in the OMEQ doses that require caution. Canadian guidelines recommend that prescribed OMEQ dose should be limited to <50 mg/day<sup>356</sup>, while US guidelines advise prescribers to avoid increasing the dose to  $\geq 90$  mg/day<sup>292</sup>. The UK Faculty of Pain Medicine advises that the potential harms outweigh the benefits when an



OMEQ dose of 120 mg/day is exceeded<sup>357</sup>. It is challenging to identify any specific intervention or policy that contributed to the observed trends in prescribing observed in this study. Possible interventions could be the improvement of perioperative pain management approaches and surgical techniques, particularly since there was an increase in the adoption of minimally invasive surgeries in this cohort. Other contributing factors include the promotion of non-opioid analgesia or opioid-sparing strategies, the availability of patient-provider education and discharge counselling services<sup>336</sup>.

Several clinical implications arise from the findings of this study. First, although the UK guidelines on perioperative opioid prescribing<sup>352, 358</sup> do not provide metrics on the proportion of patients on opioids to indicate best practice, the study findings may indicate a potential decrease in the reliance on opioids for managing acute pain following colectomy in England and could represent a trend towards improved opioid stewardship. Second, the consensus guidelines on preventing opioid-related harm suggest that post-discharge repeat prescriptions for opioids should be avoided, given the potential risks involved<sup>271, 358</sup>. This recommendation becomes particularly relevant as the current analysis showed that some patients still need opioids within 90 days after discharge, which might raise concerns about the possibility of developing chronic postoperative pain. As opioids are not recommended for managing chronic postoperative pain<sup>271</sup>, requests for additional opioids should prompt a comprehensive patient review by the GP or pain specialists for opioid weaning or assessment for chronic postoperative pain<sup>359, 360</sup>. Since the data used were collected before the release of these guidelines, future

studies should evaluate the impact of guideline implementation on reducing opioid prescribing and opioid-related adverse events for surgical patients.

Third, the study showed that codeine and tramadol were the most commonly prescribed opioids. Despite being classified as weak opioids, being prodrugs both can have different side effect profiles based on individual genetic polymorphisms<sup>84</sup>. The classification of opioids based on potency has been debated<sup>345</sup> as this alone does not protect patients from potential harm, including dependence and mortality<sup>361</sup>. Notably, while codeine-related deaths in the UK increased by 21-fold from 9 in 1994 to 188 in 2022<sup>362</sup>, the drug is still available over-the-counter. In contrast, the Australian Federal Government reclassified codeine as a prescription-only medicine in 2018, resulting in a subsequent reduction in harms associated with its use<sup>363, 364</sup>. We suggest that the results of the current study can indicate possible opportunities to re-evaluate analgesic selection practices and educate healthcare professionals about the variable effects and side effects profile of different opioids.

## **7.7 Limitations**

This study had some limitations. While it describes trends and patterns in opioid use, it did not assess the specific factors at the patient, provider or system level that influenced them. Accuracy of recorded data is a common concern when using electronic health records. Nevertheless, the databases used in this study have undergone thorough validation and have implemented various measures to ensure data quality and accuracy. Moreover, the opioid prescription data were prepared using a systematic approach with a prescription preparation algorithm.

This algorithm addresses missing data, accounts for overlapped prescriptions, and calculates OMEQ dose, allowing for more easily comparable data across different opioid medications since OMEQ dose is considered a standard prescribing measure.

Another shortcoming of electronic health record data is the lack of detailed clinical contexts, such as specific medication-use indications, patient preferences, and clinical decision-making processes. This limitation also applies to analgesics prescribed during hospital stay, which may impact the choice of opioid and prescribed doses. For example, the use of adjunctive paracetamol or non-steroidal anti-inflammatory drugs immediately after surgery is associated with decreased postoperative opioid requirements and reduced related adverse events<sup>365</sup>. Finally, while using prescription data as a proxy measure of drug consumption is a well-established practice in drug utilisation research<sup>133</sup>, it is essential to acknowledge its limitations. In the current study, the availability of issued opioid prescriptions was used as a surrogate marker to ascertain opioid consumption. However, as information on actual consumption and adherence was lacking, overall utilisation may have been overestimated.

## **Chapter 8: General discussion**

The overarching theme of this thesis is centred on advancing the comprehensive understanding of postoperative pain management, starting from pain assessment to patterns of opioid use and the development of PPOU. This thesis focuses on colectomy as a specific surgical procedure for in-depth analysis within the context of postoperative opioid use.

In order to achieve the overarching aim of this thesis, three distinct yet interrelated objectives were established and addressed through three studies using different epidemiological methods: a systematic review, a population-based cohort, and a cross-sectional study using linked primary and secondary care databases. Additionally, various descriptive and inferential analytical methods were used to analyse and report the findings.

This general discussion chapter summarises the key findings derived from the three studies in this thesis. It provides recommendations for clinical and policy implications, suggests directions for future research, and closes with an overall conclusion. The strengths and limitations of the data sources and those specific to each study have been discussed in their respective chapters.

## **8.1 Summary of the key findings**

### **Chapter 3: Utility of unidimensional and functional pain assessment tools in adult postoperative patients: A systematic review**

The first study presented in Chapter 3 reviewed and evaluated the available evidence on the measurement properties of different unidimensional and functional pain assessment tools when used to assess postoperative pain in

hospitalised adults. The robustness of this systematic review arises from challenging the validity and reliability of long-established tools that have been used for many years. The COSMIN methodology was employed, which is a tool that has been used to conduct high-quality systematic reviews to aid healthcare providers in selecting the best available tool for practice.

After a systematic search of four databases from their inception to August 2020, 31 studies involving 12,498 participants were included. The quality of evidence for the measurement properties and utility of the VAS, VDS, NRS, and FPS was suboptimal and failed to meet the required COSMIN methodological standards. Studies on functional assessment tools were scarce, with only one study including an 'objective pain score', a tool assessing pain interference with respiratory function after major abdominal surgery. Its quality was suboptimal, showing a very low quality of evidence.

#### **Chapter 4: Data source and cohort identification**

This chapter aimed to provide a rationale for selecting electronic health records, specifically the HES and CPRD databases, as the data source, identify the study cohort, and extract relevant study variables for the studies presented in this thesis.

Two datasets were generated. One contained all patients who underwent colectomy between 2010 and 2019, regardless of their opioid prescription status, and included opioid prescription records for one year before and after colectomy for patients with opioid prescriptions (used in Chapter 6). The second only included patients who underwent colectomy with opioid prescription records for one year before admission and one year after discharge (used in Chapter 5).

### **Chapter 5: Preparing opioid prescriptions records for analysis**

This chapter highlighted the importance of data preparation as a crucial step in generating a clean dataset suitable for analysis. In addition to addressing missing data for the duration and quantity variables, various data entry errors were identified, including typographical mistakes, incorrect quantity entries, and the use of different measurement units.

This chapter aimed to use the DrugPrep algorithm to prepare the opioid prescription records, expand the algorithm to produce a daily OMEQ dose variable, and generate variables that retain information about prescribed opioids and formulations when multiple prescriptions were prescribed on the same day.

### **Chapter 6: Predictors of persistent postoperative opioid use following colectomy: A population-based cohort study in England**

In this retrospective cohort study, an extensive electronic health record analysis was conducted using linked primary and secondary care data from England to determine the prevalence of PPOU after colectomy and identify predictors of associated with PPOU. This study identified 93,262 adult patients who underwent colectomy between 2010 and 2019.

This study found that 16.2% of patients were issued at least one opioid prescription within 90 days of discharge. Half of the patients who were issued opioid prescription after discharge (8.1% of the total cohort) continued to be prescribed opioids for up to 180 days after discharge. The incidence of PPOU was 2.5% in opioid-naïve patients, while patients with preoperative opioid exposure,

whether current or previous, had a significantly higher risk of developing PPOU (40.4% and 9.8%, respectively).

This study also highlighted the potential benefits of a minimally invasive surgical approach in mitigating PPOU risk, particularly for opioid-naïve patients and those with previous opioid exposure before colectomy. Minimally invasive surgery was associated with significantly lower odds of PPOU in opioid-naïve patients for both emergency (aOR 0.66, 95% CI 0.51–0.87) and elective (aOR 0.69, 95% CI 0.62–0.78) admissions.

In patients with current opioid exposure, the use of modified-release opioid formulations in the six months before colectomy had greater odds of leading to PPOU than the use of immediate-release formulations (aOR 3.41, 95% CI 3.07–3.77).

Having two or more comorbidities increased the odds of developing PPOU in all groups. However, those in the most deprived quintiles had increased odds of developing PPOU among opioid-naïve patients and the currently exposed group. Differences were observed between racial groups, with opioid-naïve patients with black race having significantly lower odds of developing PPOU compared with opioid-naïve patients of white race. In contrast, white patients with current opioid exposure were at higher risk of PPOU than those of all other races. These key findings highlight the complex interplay of patient characteristics, preoperative opioid exposure, and surgical approaches in persistent opioid use after colectomy.



## **Chapter 7: Temporal trends and patterns in initial opioid prescriptions after hospital discharge following colectomy in England**

This study used a repeated cross-sectional analysis to describe temporal trends and changes in patients who underwent colectomy and were prescribed opioids within 90 days of postoperative hospital discharge from 2010 to 2019. It found a significant downward trend in the proportion of opioid-naïve patients with a post discharge opioid prescription, from 11.4% in 2010 to 6.7% in 2019 (−41.3%,  $p < 0.001$ ), but a stable trend in patients prescribed opioids preoperatively in both currently and previously exposed groups.

This study also examined the trends and patterns in prescription characteristics, revealing significant shifts in opioid prescribing practices over the years. Codeine was the most commonly prescribed opioid, showing a notable increase from 2014 to 2019. Additionally, there was a substantial increase in oxycodone and morphine prescriptions, particularly for opioid-naïve patients (+395%) and those who underwent minimally invasive surgery (+471%). Buprenorphine prescriptions increased for patients with current opioid exposure and those who underwent open colectomy, while tramadol prescriptions declined steeply from 2014, which was evident in all patient groups.

Immediate-release opioid formulations were the most commonly prescribed throughout the study period. Transdermal and modified-release formulations were more frequently prescribed to currently exposed patients. Of the five total OMEQ dose ranks, most patients received lower opioid doses, with 43.6% falling into the OMEQ 25–49 mg/day dosage range and 30.8% in the 50–99 mg/day range.

There was a noticeable upward trend in the percentage of patients prescribed opioids in the 25–49 mg/day range, increasing from 40.1% to 51.3% ( $p < 0.001$ ) from 2010 to 2019.

## **8.2 Implications of the findings arising from this thesis**

### **8.2.1 Implications for clinical practice and policymakers**

#### **Functional pain assessment tools must be considered**

Findings from the three studies included in this thesis collectively have substantial implications for policy and practice and indicate that there may be opportunities to improve the safety of opioid prescribing to treat acute pain. In the postoperative setting, the initial step for pain management begins after pain assessment. Current postoperative pain assessments are focused on providing humanitarian pain relief by measuring pain intensity and guiding analgesic administration to reach zero pain intensity.

The findings from Chapter 3 showed that while cut-offs for unidimensional pain assessment tools are important, they are not validated to guide analgesic interventions. Some evidence also indicated that the complete reliance on these unidimensional assessment tools has resulted in unrestricted titration of opioid doses to reach zero pain, leading to increased opioid administration within the hospital settings<sup>41, 44, 217</sup>. Higher prescribed opioid doses may be associated with an increased risk of PPOU, as demonstrated in a previous study that showed a correlation between the quantity of opioids prescribed during a hospital stay and the development of PPOU<sup>366</sup>.

Based on the findings from Chapter 6, PPOU does occur following colectomy in the UK. Therefore, the commonly used indicators of pain relief based on pain intensity should be reconsidered to enhance postoperative pain management. Consequently, a growing emphasis is placed on promoting tools that guide analgesic dosing to restore and maximise functional capacity. These functional measures may include evaluating patients' ability to cough or breathe deeply. Additionally, elements of the DrEaMing concept, including drinking, eating and moving, are considered in Commissioning for Quality and Innovation (CQUIN) targets and indicator outcomes for recovery and can also be measured as pain relief indicators<sup>367</sup>.

Restoring function is an integral part of postoperative pain relief. It is not a new concept, first highlighted 25 years ago<sup>57</sup>, but it has yet to be adequately implemented in pain assessment. The findings from Chapter 3 confirmed this, showing the scarcity of studies that used functional pain assessment tools. Their scarcity underscores the need for policy initiatives that advocate for integrating and validating such tools in postoperative settings. Policymakers can play a pivotal role in supporting this research, encouraging the development of standardised functional pain assessment tools and fostering their implementation in clinical practice.

However, policymakers and healthcare providers must acknowledge the challenges of implementing functional pain assessment tools in clinical practice. Since pain is subjective, its impact on an individual's ability to function can vary widely from individual to individual. Therefore, functional assessment tools should

reflect this subjectivity, particularly since individuals perceive and express pain differently.

One significant challenge is the absence of clear guidelines about which functions to include and how to assess them, especially in the perioperative setting. Functional assessment tools must encompass a broad spectrum of daily activities and functions that pain can impact. Furthermore, these affected functions may vary depending on the type of surgery and stage of recovery, necessitating customisable activities tailored to the specific procedure.

Implementing functional pain assessment tools requires healthcare providers to be trained in their administration and interpretation. In busy acute postoperative settings, time constraints may limit the comprehensive assessment of interference of pain with function since healthcare providers must balance this with other clinical responsibilities. Patients' acceptance and willingness to engage in repeated functional pain assessments can vary, with some finding these assessments burdensome and, thus, may not comply with them.

Cooperative efforts among patients, researchers, and healthcare providers are needed to overcome the aforementioned challenges. These efforts should focus on developing and implementing practical, functional pain assessment tools that genuinely reflect the impact of pain on an individual's ability to function and provide guidance for analgesic dosages. This collaboration can ensure that these tools are effective, well-accepted, and appropriately tailored to patients' diverse experiences and needs in different surgical contexts.

### **Repeated opioid prescriptions should be monitored**

The findings from Chapters 6 and 7 are crucial for clinicians and policymakers since they shed light on the dynamics of postoperative opioid prescribing. In the UK, it is common for patients to receive an initial opioid prescription during their hospital stay<sup>101</sup>, often managed by the surgical team. However, this initial prescription may not cover the entire postoperative period, and patients may require additional opioid medicines after discharge.

In many cases, the responsibility for ongoing pain management transitions to GPs once patients return home. The HES data lack details on opioids prescribed within the hospital and before discharge. Therefore, including prescriptions written during the hospital stay was not feasible and only subsequent prescriptions issued by GPs were included. For policymakers involved in postoperative care, the findings from this thesis are crucial since they tracked opioid use beyond the immediate hospitalisation period. This is essential for assessing the degree of reliance on repeated opioid prescriptions after discharge, which was identified as a modifiable risk factor for persistent opioid use in the UK<sup>101, 358</sup>. Focusing on GPs prescriptions provided a comprehensive perspective on opioid prescribing patterns throughout the postoperative period that might extend to three months after discharge.

International consensus guidelines on preventing opioid-related harm suggest that repeat prescriptions for opioids should be avoided after discharge, given the potential risks involved<sup>271</sup>. This recommendation becomes particularly relevant since the findings from Chapter 6 showed that some patients still need opioids

within 90 days after discharge, with 1 in 12 patients continuing to use opioids for 180 days after discharge.

Policymakers should consider this finding carefully. Since the exact cause of persistent opioid use cannot be confirmed, these findings might raise concerns about the possibility of drug misuse, opioid use disorder, or chronic postoperative pain. Since opioids are not recommended for managing chronic postoperative pain<sup>271</sup>, requests for additional opioids should prompt a comprehensive patient review by the GP or pain specialists for opioid weaning or assessment for chronic postoperative pain<sup>359, 360</sup>. Policymakers should also promote these approaches, which align with the public health goals of minimising opioid-related harms in the postoperative period.

### **Inclusion of opioids in the New Medicine Service**

Another option for monitoring persistent opioid use could involve incorporating opioids prescribed postoperatively into the list of medicines covered by pharmacists under the New Medicine Service (NMS). This service commenced in English community pharmacies in October 2011<sup>368</sup>. Under the NMS, pharmacists are remunerated for offering advice on newly prescribed medicines to patients with certain long-term conditions (hypertension, type 2 diabetes, asthma/chronic obstructive pulmonary disease, and those taking anticoagulant/antiplatelet agents). The NMS aims to improve medication adherence and reduce medicine wastage<sup>369</sup>. It was recently proposed to expand the NMS to include antidepressants to manage expected side effects and educate patients on the expectations of using these medicines<sup>370</sup>. Policymakers may similarly explore

including opioids in the NMS. Their inclusion could help relieve some of the GP workload, allowing them to focus on more complex medical issues while pharmacists handle medication-related aspects, discuss any side effects, monitor pain management, and ensure patients adhere to prescribed regimens, potentially leading to better patient outcomes.

### **PPOU is an outcome after colectomy**

Chapter 6 showed that thousands of patients can be expected to become persistent opioid users following their first exposure to opioids after colectomy. However, the rate of PPOU in our data is lower than those reported in studies from the US. To our knowledge, no other patient population have been studied for this outcome in England or the UK. This thesis focused on colectomy. Therefore, its findings may inform the development of guidelines and practices to minimise PPOU and enhance the quality of care of patients who undergo colectomy. Additionally, policymakers can view its findings as a foundation for providing a benchmark to which healthcare providers in the UK can compare themselves within the acute pain context. Moreover, its findings can be helpful to policymakers in guiding the creation of interventions to prevent unintended transitions to PPOU.

### **Preoperative screening for predictors of PPOU**

The stratified analysis based on preoperative opioid exposure presented in Chapter 6 enabled the identification of predictors of PPOU development in three patient groups undergoing colectomy. The identified predictors are significant for healthcare providers and policymakers, allowing them to create risk stratification

approaches to support safe opioid prescribing and mitigate the harms associated with persistent opioid use. For example, if a patient is opioid-naïve and has one or more predictors that are associated with higher PPOU risks during preoperative screening, healthcare providers could discuss balancing the risks and benefits of opioid use with them and suggest non-opioid alternatives. Conversely, if their PPOU risk is expected to be low, this could prevent healthcare providers from withholding opioids when they can be prescribed safely and effectively.

**Promoting minimally invasive surgery for opioid-naïve patients and those with previous opioid exposure**

The findings from Chapter 6 indicated that opioid-naïve patients and those with previous opioid exposure might benefit from a minimally invasive surgical approach as it was associated with significantly lower odds of PPOU than an open approach. This finding is particularly important for surgeons and policymakers and suggests considering such surgical options for these patients when the necessary skills and resources are available. However, it is crucial to acknowledge the challenge of drawing firm conclusions about causality due to the retrospective nature of Chapter 6, especially considering additional factors that might confound its findings, including surgeons' expertise, variation in surgical techniques, and the availability of enhanced recovery programmes in the surgical setting. Therefore, future studies must determine whether minimally invasive techniques can reduce PPOU risk.



**Differences in the risk of PPOU between racial groups**

The findings from Chapter 6 showing variation in PPOU risk between racial groups have some clinical implications. Opioid-naïve patients of black race had significantly lower odds of PPOU than opioid-naïve patients of white race. In contrast, white patients with current opioid exposure were at higher risk of PPOU than all other races. On one hand, this finding could indicate that patients of white race are more likely to be prescribed opioids than patients of black race<sup>338</sup>. A previous study showed prejudice against patients of black race in the diagnosis and treatment of pain<sup>337</sup>. On the other hand, the lower odds of PPOU for patients of black race could be related to experiencing less pain. However, policymakers should also be aware that the current findings may have been confounded by clinicians' implicit bias in assessing pain severity and treatment choice, implicit bias in repeat opioid prescriptions<sup>339</sup>, hospital-level factors, and surgical settings. However, it is unclear why racial disparities in pain management exist and how they can be addressed. Policymakers should ensure that healthcare providers are appropriately educated on racial disparities in pain management and implement strategies to minimise bias and ensure equal access to care.

**Recommendations for currently opioid exposed patients**

Consistent with previous studies in other countries and distinct surgical populations<sup>171, 208, 371</sup>, Chapter 6 confirmed that most persistent users were patients with preoperative opioid exposure. Notably, this preoperative opioid exposure does not need to be chronic to increase risk, and even patients with previous opioid exposure within 7–12 months preoperatively still faced a

significant PPOU risk. Additionally, the use of modified-release opioid formulations within six months preoperatively was associated with a three-fold higher risk of persistent opioid use compared to the use of short-acting formulations. This aligns with the increasing evidence suggesting that long-acting and modified-release formulations are a modifiable risk factor for PPOU<sup>329</sup>.

This finding holds relevance for patient care since patients with preoperative opioid exposure might develop tolerance or hyperalgesia and require higher postoperative opioid doses. Therefore, for healthcare providers and policymakers, these findings underscore the importance of thorough preoperative assessment for these groups. Additionally, a patient-centred approach to preoperative opioid weaning can be considered, when possible, in consultation with the patient and a multidisciplinary healthcare team. Weaning can help reduce hyperalgesia or hypersensitivity resulting from opioid use, making postoperative pain management more effective with lower doses. While the benefits of preoperative opioid weaning may appear promising, there remains a need for future research<sup>372</sup>. Alternatively, healthcare providers may consider prioritising multimodal pain management strategies or opioid-sparing techniques for this group to reduce their reliance on opioids.

#### **Promote awareness of the use of specific opioid formulations**

The integration of modified-release opioids into postoperative pain management practice was driven by the belief that they provide enhanced and prolonged pain relief while minimising the occurrence of 'peak and trough' serum opioid concentrations, thereby reducing the potential for opioid dependence<sup>373</sup>.

Additionally, they were seen as a means to reduce nursing workload by decreasing the frequency of administering analgesic doses compared to immediate-release opioid formulations<sup>374</sup>.

The findings from Chapter 7 showed that immediate-release opioids are the most commonly prescribed formulation after colectomy. However, since both modified release and transdermal formulations are still prescribed in this patient population, it is essential not to become complacent about current opioid prescribing practices. Transdermal formulations were more common for patients with current opioid exposure than for opioid-naïve patients, suggesting that patients continue to use the same preoperative formulation based on their previous pain history. Nevertheless, transdermal formulations were also used for opioid-naïve patients, consistent with a multicentre study indicating that 10% of patients were discharged with modified-release opioid formulations after major abdominal surgeries in England<sup>101</sup>.

Besides being contraindicated in the immediate postoperative period, modified-release formulations were associated with worse acute pain scores than immediate-release opioids, indicating a risk of underdosing to prevent opioid-induced ventilatory impairment<sup>349</sup>. Additionally, these formulations were associated with a higher incidence of opioid-related adverse events, increased length of hospital stays, and higher readmission rates<sup>349</sup>. Therefore, the findings from this thesis indicate that policymakers should recognise the critical need to promote education and awareness of acute pain prescribing recommendations and discourage the postoperative use of modified-release and transdermal

opioids. It is also crucial to explain to healthcare providers that gradual weaning of these formulations may be impeded, increasing the PPOU risk.

### **Enhanced awareness of the potential problems associated with opioids**

The findings from Chapter 6 showed that 16.2% of patients were issued prescriptions for opioids within 90 days of discharge, potentially indicating that the rate of postoperative opioid prescribing is lower than that reported in EHR studies conducted in the US, Canada, and Australia. However, since the current findings do not show how many patients are discharged from the hospital with opioid prescriptions, it could be argued that prescriptions issued after discharge were not captured. Therefore, the prescribing rate might have been higher if a prospective cohort study design or audit discharge chart review were used.

Even if more patients were discharged from the hospital with an opioid prescription, the findings from Chapters 6 and 7 indicate that they may have discontinued or stopped their initial opioid prescription without the need for additional refills. For policymakers and healthcare providers, these findings could indicate an enhanced awareness of the potential problems associated with opioids, and making patient-provider education and discharge counselling services available may have been beneficial.

### **Revisit regulations around the availability of codeine as an Over-The-Counter medicine**

The findings from Chapter 7 suggest that codeine is preferred by healthcare providers, possibly because they perceive it as a weak opioid. This perception

could be mainly influenced by its over-the-counter OTC availability, leading to the misconception that codeine is entirely safe. However, like other opioids, codeine is associated with potential adverse effects such as constipation, respiratory depression, and sedation. The accessibility of codeine without a prescription and with no legal sales limit<sup>375</sup> could lead to patients continuing its use without proper monitoring, raising concerns about misuse, dependence, and the potential for exceeding recommended doses and PPOU, which cannot be tracked.

Due to codeine's potential for misuse, it was rescheduled as a prescription-only medicine in Australia, aligning with other countries such as Germany, Japan, and the US<sup>376</sup>. This change resulted in a reduction in harm associated with its use<sup>363, 364</sup>. In the UK, codeine-related deaths increased 21-fold from 9 in 1994 to 188 in 2022<sup>362</sup>. Despite arguments supporting scheduling codeine as prescription-only in the UK, it remains available OTC. One justification for this decision was concern about increased GP visits for self-limiting illnesses, contradicting the NHS policy of promoting self-care. Additionally, restricting access to codeine could lead to patients obtaining it from illegal sources<sup>361</sup>.

The findings from Chapter 7 indicated that tramadol prescribing started to decrease in 2014. That trend was explained by its classification as a Schedule 3 controlled substance in the UK in 2014<sup>377</sup>, prompted by safety concerns and potential risks of misuse. For policymakers, this finding might suggest a need for a future examination of the risks and benefits associated with up-scheduling codeine and its impact on the selection of other opioids.

**Careful prescribing of codeine**

This pharmacological aspect of codeine is clinically crucial since individual variations in CYP2D6 activity can cause variable analgesic responses among patients. While genetic testing can identify variations in the CYP2D6 gene, it is not routinely conducted; this may be because of a shortage of genetic counsellors, who are the only ones allowed to discuss genetic testing results with patients<sup>378</sup>. Alternatively, it could be potentially due to the additional costs and time burden it places on the NHS. As such, healthcare providers may need to weigh the potential benefits of codeine against the risks associated with variable responses in patients. Therefore, the main question is, would it not be much safer to simply prescribe morphine or an alternative opioid?

The broader implications of codeine prescribing are thought-provoking and warrant reflection within the context of current opioid prescribing practices in the UK. Healthcare providers must remain vigilant about these implications, especially in populations with a higher risk of opioid-related complications, such as older adults, who were the primary age group referred for colectomy.

**Re-evaluation of analgesic selection practices**

The increase in the prescribing of oxycodone and morphine shown in Chapter 7 is consistent with trends reported in contemporary studies on prescribing in the UK for other indications<sup>300, 355</sup>. The fact that oxycodone prescribing increased should raise some concerns among policymakers and healthcare providers. Oxycodone has distinct euphoric effects reported to be strikingly similar to heroin. Oxycodone

scored more favourably than fentanyl, buprenorphine, and morphine when compared to heroin<sup>379</sup>.

Previous studies have shown that the type of opioid initially prescribed can impact PPOU risk. A Danish study showed that tramadol, oxycodone, and fentanyl had a stronger association with PPOU development than morphine<sup>380</sup>. Jivraj *et al.* found that patients given oxycodone after surgery were less likely to discontinue chronic opioids than those given other opioids<sup>381</sup>. Even for similar formulations, the type of opioid and its likability can impact PPOU risk. Indeed, a recent Australian study found that modified-release oxycodone was associated with higher odds of PPOU compared to modified-release tapentadol<sup>382</sup>. Therefore, oxycodone might not be the optimal analgesic choice, especially in patients at a high risk of addiction<sup>379</sup>.

The findings from Chapter 7 might also suggest that current analgesic choices may reflect what is prescribed at hospital discharge. Since GPs are expected to repeat the initial prescription rather than change the type or formulation of the prescribed opioid, policymakers should use the findings from Chapter 7 to re-evaluate analgesic selection practices and educate healthcare professionals about the variable effects and side effects of different opioids. Healthcare providers should ensure that they are responsible for adhering to opioid stewardship principles, regardless of the specific opioid prescribed, providing patients with both verbal and written information, including an opioid discontinuation plan and the safe disposal of unused opioids.

## 8.2.2 Implications for patients

The findings from this thesis could help educate patients who wish to enrol in future pain research on the limitations of using unidimensional pain assessment tools. Patients' active role in collaborative efforts with healthcare providers and researchers is essential for developing and implementing practical and functional pain assessment tools. Patients' acceptance and engagement in repeated functional pain assessments are pivotal in achieving effective pain management.

Patients must be informed about the potential risks of opioids, including their risks of misuse and dependence, and proper monitoring is essential. Figure 8-1 provides an illustrated example of how to communicate the risk of PPOU to patients using an icon array based on Chapter 6 findings.



**Figure 8-1. Risk of PPOU among 100 patients prescribed opioid within 90 days following colectomy**

Note: green icons represent PPOU

Additionally, patients should be educated about distinctions between opioid formulations, with a specific focus on the potential risks associated with modified-



release opioids. Understanding these risks is crucial for patients since it empowers them to actively contribute to their postoperative well-being and collaborate effectively with healthcare professionals to optimise pain management strategies, ensuring a more informed and patient-centred care approach.

### **8.2.3 Implications for future studies**

The systematic review conducted in Chapter 3 provided a thorough and critical evaluation of the state of evidence for postoperative pain assessment tools. However, it is essential to note that the systematic search was concluded in 2020, and the review was published in 2021. Since then, the body of evidence in this field has continued to grow. A new search performed in 2023 identified 10 potentially relevant articles<sup>383-392</sup>, new tools for assessing pain based on function, and three evaluations of unidimensional tools in different surgical populations<sup>259, 387, 392</sup>.

It is important to apply the COSMIN methodology to these new studies, which involves multiple sequential steps, including assessing their methodology, risk of bias, measurement properties, and certainty of their findings, summarising and grading their quality of evidence. However, it is currently infeasible to integrate these new studies into our existing review due to the complex requirements of the COSMIN methodology. Therefore, an updated systematic review is needed to critically evaluate the methodology of the studies identified in the updated search and combine their findings with the current systematic review to provide updated recommendations for clinical practice.

Furthermore, prospective studies are needed to identify proper functional pain assessment tools and examine how the measured functions impact opioid dosing. Qualitative studies using approaches such as focus groups can provide valuable insights into patients' postoperative experiences and most impacted functions and offer a comprehensive perspective on pain and its impact on postoperative function. Additionally, studies examining the optimal cut-offs to administer opioid and non-opioid analgesics based on functional pain assessment tools are required.

### **Opioid utilisation and PPOU**

The findings in this thesis on opioid utilisation are focused on colectomy. Therefore, whether the results presented in this thesis can be generalised to other surgical contexts is unclear, particularly considering variations in pain intensity, surgical technique, and outcomes. Therefore, given the significant number of surgeries conducted in England, future studies should explore the incidence of PPOU after various surgical procedures with different expected trajectories for PPOU, for instance, arthroplasty and cholecystectomy.

The pharmacoepidemiological studies presented in this thesis used linked CPRD and HES data for the colectomy cohort and opioid prescriptions. Future studies could use other data sources to cross-validate these results and help identify any potential sampling bias. Primary data collection via discharge chart review and prospective follow-up using phone interviews could also be used. Additionally, further prospective studies are needed to assess the possible benefits of minimally invasive approaches on PPOU in specific surgical populations and preoperative opioid use groups. Future studies should also examine the impact of post

discharge opioid type and dose on PPOU. Opportunities for prospective future studies exist to identify the actual causes of PPOU to support recommendations and avoid imposing undue restrictions on opioid prescribing when they can be helpful and safely used by some patients.

In Australia, modified-release formulations accounted for over 30% of all opioids prescribed after surgery<sup>393</sup>. However, a reduction in modified-release opioid prescribing was observed in surgical inpatients after the release of a position statement advising against the discharge prescribing of these formulations<sup>394</sup>. Notably, the data in this thesis were collected before the publication of UK guidelines advising against using transdermal and long-acting formulations for managing acute pain<sup>352, 358</sup>. Therefore, future studies should explore the impact of guideline implementation on the choice of opioid formulations. Figure 8-2 provides suggestions for future research based on the findings from Chapters 6 and 7.

### **8.3 Conclusions**

This PhD thesis has used various methodologies to address several areas related to pain assessment and opioid utilisation that had been inadequately researched. The research presented in this thesis contributes to a deeper understanding of postoperative pain assessment and challenges the validity and reliability of unidimensional tools to quantify postoperative pain in adult patients. It emphasises the importance of continually improving pain measurement by incorporating functional assessment tools. It also identifies the need for psychometric validation studies of functional pain assessment tools to identify

patients needing additional interventions to promote recovery and improve postoperative pain assessment and management.

This thesis also showed that electronic health records play a significant role in opioid utilisation research. The research presented in this thesis has shown that 8% of patients who underwent colectomy continued to receive opioid prescriptions beyond three months after discharge. PPOU was more common in patients with preoperative opioid exposure than in opioid naïve patients.

The evidence provided in this thesis supports the findings of prior research from other countries that persistent opioid use can be an expected outcome after colectomy. Additionally, a changing pattern in opioid prescribing after colectomy was observed between 2010 and 2019, with a decrease in the proportion of opioid-naïve patients being prescribed opioids after discharge and variations in the type of opioid prescribed. Future research should consider the limitations of this PhD project as an opportunity to advance efforts to enhance the quality of care for surgical patients and contribute to improved patient outcome.

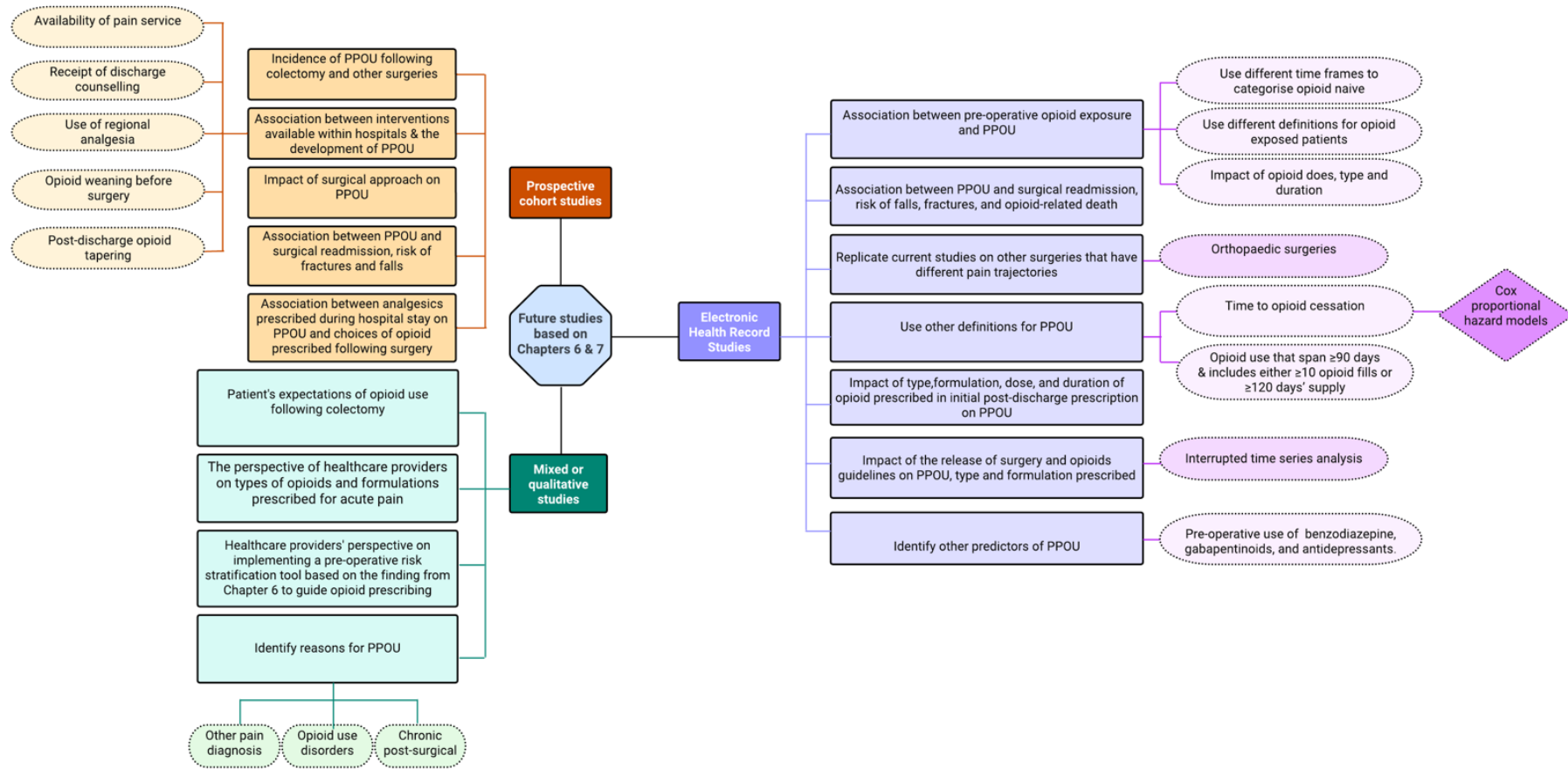


Figure 8-2. Suggestions for future research

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## Appendices

### Appendix S 1. PROSPERO notification of systematic review protocol registration

The protocol can be accessed at

[https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=213495](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=213495)

#### PROSPERO Registration message [213495]

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Dear Mrs Baamer,

Thank you for submitting details of your systematic review "Unidimensional and functional pain assessment tools in postoperative adult patients: a systematic review of development and utility" to the PROSPERO register. We are pleased to confirm that the record will be published on our website within the next hour.

Your registration number is: CRD42020213495

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility and remember to update your record when your review is published. You can log in to PROSPERO and access your records at <https://www.crd.york.ac.uk/PROSPERO>.

Comments and feedback on your experience of registering with PROSPERO are welcome at [crd-register@york.ac.uk](mailto:crd-register@york.ac.uk)

Best wishes for the successful completion of your review.

Yours sincerely,

Georgina MacKenzie  
PROSPERO Administrator  
Centre for Reviews and Dissemination  
University of York  
York YO10 5DD  
t: +44 (0) 1904 321049  
e: [CRD-register@york.ac.uk](mailto:CRD-register@york.ac.uk)  
[www.york.ac.uk/inst/crd](http://www.york.ac.uk/inst/crd)

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## **Appendix S 2. Search strategy**

**Search strategy for Ovid Medline** Version 15/08/20

### **PICO**

#### **Population**

Postoperative patients aged 18 years and over from all surgical disciplines.

#### **Intervention**

Unidimensional pain assessment tools including

5. Verbal or printed numerical pain rating scale.
6. Printed or verbal descriptor scale.
7. Visual analogue scale.
8. Faces scales: Wong-baker FACES, Faces Pain Scale – Revised.
9. Functional pain assessment tools

**Comparison:** -----

**Outcomes:** psychometric properties including validity and reliability

#### **Additional outcomes**

Instrument feasibility, interpretability, and ability to detect desire of analgesia.

Search concepts to be combined for Boolean AND, and used for unidimensional pain assessment tool and then repeated for functional pain assessment tools

1. Outcome terms
2. Pain assessment tool terms
3. Construct: acute postoperative pain
4. 1 AND 2 AND 3
5. 4 + Limits ( english , humans, adults > 18 years)

Did not apply limits full text, abstracts this might include bias in the results

Ovid MEDLINE(R) ALL < 1946 to August 15, 2022>

1.exp PSYCHOMETRICS/ or psychometr\*.mp. or measurement propert\*.mp. or Validity.mp. or valid\*.mp. or exp Validation Study/ or convergent validity.mp. or construct validity.mp. or content validity.mp. or criterion validity.mp. or reliab\*.mp. or unreliab\*.mp. or Comparative Study.mp. or Feasibility.mp. or Generalizability.mp. or generalisa\*.mp. or interpretab\*.mp. or Sensitiv\*.mp. or Responsive\*.mp. or 'Measurement Accuracy'.mp. or 'ease of use'.mp. or Analgesi\* response.mp. or 'desire of analgesi\*'.mp. or 'Request of analgesic\*'.mp. or 'hypotheses testing'.mp. or 'measurement error\*'.mp. or Internal consistency.mp. or Data accuracy.mp. or 'standard error of measurement'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]4890505

2.(pain scale\* or pain rating scale\* or (pain assessment and (instrument\* or tool\*)) or pain intensity scale\* or pain measurement instrument\* or Pain score\* or pain intensity assessment).mp. or exp Pain Measurement/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]113996

3.Visual Analog Scale.mp. or exp Visual analog? Pain scale/ or (visual analog? and (scale or score)).mp. or vas.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]146135

4.((numeric\* and rating and (scale or score)) or numeric scale or nrs or nprs).mp. or exp numerical pain rating scale/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]26611

5.exp verbal descriptor scale/ or Vds.mp. or exp verbal rating scale\*/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]1128

6.exp face\* pain scale\*/ or exp wong baker Face\*/ or wong baker face\*.mp. or exp faces pain scale revised/ or faces pain scale revised.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]594

7.(pain activity assessment or functional pain assessment scale or functional activity score\*or functional pain activity scale\* or functional assessment tool or objective pain score\* or movement evoked pain assessment or assessment of pain at movement or objective pain assessment or clinically aligned pain assessment tool).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]252

8.exp Pain, Postoperative/ or exp acute pain/ or post surgical pain.mp. or surgical pain.mp. or pain post procedure.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]46322

9.1 and 3 and 85987

10.1 and 4 and 8556

11.1 and 5 and 86

12.1 and 6 and 856

13.1 and 7 and 832

14.limit 9 to (Elanguage and humans and "all adult (19 plus years)")4358

15.limit 10 to (English language and humans and "all adult (19 plus years)")537

16.limit 11 to (English language and humans and "all adult (19 plus years)")

17.limit 12 to (English language and humans and "all adult (19 plus years)")12

18.limit 13 to (English language and humans and "all adult (19 plus years)")2



### Appendix S 3. Studies ineligible following full text review

Full paper examined: 38/ Exclusion after complete paper screening 19 papers.

#### Excluded papers:

1. Arnstein P, Gentile D, Wilson M. validating the functional pain scale for hospitalised adults. *Pain Manag Nurs*. 2019; **20**: 418-24.

**Explanation:** Paper validating functional scale for hospitalised chronic pain patient but did not report separate result for surgical patients.

**Reason for exclusion:** No separate results for postoperative pain assessment.

2. Barber MD, Janz N, Kenton K, et al. Validation of the surgical pain scales in women undergoing pelvic reconstructive surgery. *Female Pelvic Med Reconstr Surg*. 2012; **18**: 198-204.

**Explanation:** Surgical pain scale looked at long term functional outcome following surgery.

**Reason for exclusion:** Patients not assessed as inpatients/irrelevant outcome.

3. McCarthy Jr M, Chang CH, Pickard AS, et al. Visual analog scales for assessing surgical pain. *Jl Amn Coll Surg*. 2005; **201**: 245-52.

**Reason for exclusion:** Patients not assessed as inpatients or irrelevant outcome.

4. Blumstein HA, Moore D. Visual analogue pain scores do not define desire for analgesia in patients with acute pain. *Acad Emerg Med*. 2003; **10**: 211-4.

**Explanation:** VAS to detect desire of analgesia in acute emergency pain.

**Reason for exclusion:** Not surgical population.

5. Chiu LYL, Sun T, Ree R, et al. The evaluation of smartphone versions of the visual analogue scale and numeric rating scale as postoperative pain assessment tools: a prospective randomized trial. *Can J Anesth*. 2019; **66**: 706-15.

**Reason for exclusion:** Comparison between NRS smart version with paper version.

6. Neudecker J, Raue W, Schwenk W. High correlation but inadequate point-to-point agreement, between conventional mechanical and electronical visual

analogue scale for assessment of acute postoperative pain after general surgery. *Acute Pain*. 2006; **8**: 175-80.

**Reason for exclusion:** Comparison between electronic and mechanical VAS.

7. Erden S, Karadag M, Guler Demir S, et al. Cross-cultural adaptation, validity, and reliability of the Turkish version of revised American Pain Society patient outcome questionnaire for surgical patients. *Agri*. 2018; **30**: 39-50.

**Reason for exclusion:** Multidimensional tool (Revised American Pain Society Patient Outcome Questionnaire).

8. Keawnantawat P, Thanasilp S, Preechawong S. Translation and validation of the Thai version of a modified brief pain inventory: a concise instrument for pain assessment in postoperative cardiac surgery. *Pain Pract*. 2017; **17**: 763-73.

**reason for exclusion:** Multidimensional tool (modified brief pain inventory).

9. Mendoza TR, Chen C, Brugger A, et al. The utility and validity of the modified Brief Pain Inventory in a multiple-dose postoperative analgesic trial. *Clin J Pain*. 2004; **20**: 357-62.

**Reason for exclusion:** Multidimensional tool (Brief Pain Inventory).

10. Mwachiro M, Mwachiro E, Wachu M, et al. assessing post-operative pain with self-reports via the Jerrycan Pain Scale in Rural Kenya. *World J Surg*. 2020; **44**: 3636-42.

**Reason for exclusion:** Applicability of irrelevant tool (Jerrycan Pain Scale).

11. Jain R, Grewal A. A randomized comparative study assessing efficacy of pain versus comfort scores. *Saudi J Anaesth*. 2017; **11**: 396-401.

**Reason for exclusion:** Retracted paper.

12. Liu WH, Aitkenhead AR. Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale. *Br J Anaesth*. 1991; **67**: 768-71.

**Reason for exclusion:** Irrelevant outcome.

13. Salo D, Eget D, Lavery RF, Garner L, Bernstein S, on K. Can patients accurately read a visual analog pain scale? *Am J Emerg Med*. 2003; **21**: 515-9.

**Reason of exclusion:** Not surgical population.

14. Sills ES, Genton MG, Walsh APH, Wehbe SA. Who's asking? Patients may under-report postoperative pain scores to nurses (or over-report to surgeons) following surgery of the female reproductive tract. *Arch Gynecol Obstet.* 2009; **279**: 771-4.

**Explanation:** Looked at how patient communicate pain between nurse and physician.

**Reason for exclusion:** Irrelevant outcome.

15. Rothaug J, Weiss T, Meissner W. How simple can it get? Measuring pain with NRS items or binary items. *Clin J Pain.* 2013; **29**: 224-32.

**Explanation:** They used different answer format for (binary yes/no answers vs. NRS) in a subset of patients using Quality Improvement in Postoperative Pain Management (QUIPS).

**Reason for exclusion:** Multidimensional tool (QUIPS).

16. Zalon ML. Comparison of pain measures in surgical patients. *J Nurs Meas.* 1999; **7**: 135-52.

**Explanation:** This study aimed to establish the validity of brief pain inventory short form.

**Reason for exclusion:** Validation of multidimensional scale.

17. Halm M, Bailey C, St Pierre J, et al. Pilot evaluation of a functional pain assessment scale. *Clin Nurse Spec.* 2019; **33**: 12-21.

**Explanation:** Sample from medical/surgical, critical care, and rehabilitation units experiencing acute or chronic pain.

**Reason for exclusion:** No separate results for acute postoperative pain.

18. Martin WJMM, Ashton-James CE, Skorpil NE, et al. What constitutes a clinically important pain reduction in patients after third molar surgery? *Pain Res Manag.* 2013; **18**: 319-22.

**Reason for exclusion:** Dental surgery, not hospitalised patients.

19. Rago R, Forfori F, Materazzi G, et al. Evaluation of a preoperative pain score in response to pressure as a marker of postoperative pain and drugs consumption in surgical thyroidectomy. *Clin J Pain.* 2012; **28**: 382-6.

**Reason for exclusion:** Sensitivity of preoperative vas scores after tourniquet pressure inflation.

## **Appendix S 4. Newcastle Ottawa Quality Assessment Scale**

### **(adapted for cross sectional studies)**

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review.

#### **Selection:** (Maximum 4 stars)

##### **1) Representativeness of the sample:**

- a) Truly representative of the average in the target population. \* (all subjects or random sampling)
- b) Somewhat representative of the average in the target population. \* (non-random sampling)
- c) Selected group of users.
- d) No description of the sampling strategy.

##### **2) Sample size:**

- a) Justified and satisfactory. (by reporting appropriate sample size calculation) \*
- b) Not justified.

##### **3) Non-respondents: (adopted to details about patient refused assessment and reasons are described)**

- a) Comparability between assessed and non-assessed is established \*
- b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. removed
- c) No description of the number and reason for refusing assessment.

##### **4) Ascertainment of the assessment (risk factor):**

- a) Validated measurement tool. \*\*
- b) Non-validated measurement tool, but the tool is available or described. \*
- c) No description of the measurement tool.

#### **Comparability:** (Maximum 2 stars)

- 1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
  - a) The study controls for the most important factor (select one). \*
  - b) The study control for any additional factor. \*

#### **Outcome:** (Maximum 3 stars)

##### **1) Assessment of the outcome:**

- a) Independent blind assessment. \*\*

- b) Record linkage. \*\*
- c) Self report. \*
- d) No description.

**2) Statistical test:**

- a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). \*
- b) The statistical test is not appropriate, not described or incomplete.

## Appendix S 5. Updated criteria for Good Measurement Properties

Measurement property	Rating	Criteria
Reliability	+	ICC or weighted Kappa $\geq 0.70$
	?	ICC or weighted Kappa not reported
	-	ICC or weighted Kappa $< 0.70$
Measurement error	+	Smallest detectable change (SDC) or limits of agreement (LoA) $<$ minimal important change (MIC)
	?	MIC not defined
	-	SDC or LoA $>$ MIC
Hypotheses testing for construct validity	+	The result is in accordance with the hypothesis
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis
Cross-cultural validity/ measurement invariance	+	No important differences found between group factors (such as age, gender, language) in multiple group factor analysis OR no important DIF for group factors (McFadden's $R < 0.02$ )
	?	No multiple group factor analysis OR DIF analysis performed
	-	Important differences between group factors OR DIF was found
Criterion validity	+	Correlation with gold standard $\geq 0.70$ OR AUC $\geq 0.70$
	?	Not all information for '+' reported
	-	Correlation with gold standard $< 0.70$ OR AUC $< 0.70$
Responsiveness	+	The result is in accordance with the hypothesis OR AUC $\geq 0.70$
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis OR AUC $< 0.70$

Adapted from Prinsen CA, et al.<sup>224</sup> then modified by removing structural validity and internal consistency item.

## Appendix S 6. Modified GRADE approach for grading the quality of evidence

Quality of evidence	Lower if
High	Risk of bias
Moderate	-1 Serious
Low	-2 Very serious
Very low	-3 Extremely serious
	Inconsistency
	-1 Serious
	-2 Very serious
	Imprecision
	-1 total n = 50–100
	-2 total n < 50
	Indirectness
	-1 Serious
	-2 Very serious

The starting point is the assumption that the evidence is of high quality. The quality of evidence is subsequently downgraded with one or two levels for each factor (i.e., risk of bias, inconsistency, imprecision, indirectness) to moderate, low, or very low when there is risk of bias (low study quality), (unexplained) inconsistency in results, or indirect results.<sup>226</sup> Information on how to downgrade is described in detail in the COSMIN user manual.<sup>225, 395</sup> n = sample size.



## Appendix S 7. Definition of quality levels

Quality Level	Definition
High	We are very confident that the true measurement property lies close to that of the estimate of the measurement property
Moderate	We are moderately confident in the measurement property estimate: the true measurement property is likely to be close to the estimate of the measurement property, but there is a possibility that it is substantially different
Low	Our confidence in the measurement property estimate is limited: the true measurement property may be substantially different from the estimate of the measurement property
Very low	We have very little confidence in the measurement property estimate: the true measurement property is likely to be substantially different from the estimate of the measurement property

These definitions were adapted from the GRADE approach<sup>227</sup>. Information on how to downgrade is described in detail in the COSMIN user manual<sup>225</sup>.

## Appendix S 8. ISAC protocol approval notification

**Subject: Review of study 21\_000668 is now complete**

**Date:** 29 November 2021 at 14:08:26 GMT

**To:** [roger.knaggs@nottingham.ac.uk](mailto:roger.knaggs@nottingham.ac.uk)



Dear Dr Roger Knaggs,

Your study 21\_000668 – “Opioid prescriptions following discharge from hospital after abdominal and orthopaedic surgery: A cohort study from England ” has been approved by CPRD. You can view any additional feedback by logging on to eRAP at <https://www.erap.cprd.com/>.

If your study requires CPRD to extract the study dataset, please contact CPRD via [enquiries@cpdr.com](mailto:enquiries@cpdr.com) to initiate a single-study licence agreement and discuss the data specification.

If your amended study will access CPRD data via an Institutional multi-study licence and you require linked data, you will need to make a request for the linked data.

- If you require linked data to identify the study cohort, please complete the Linkage Request Form, available on eRAP, and return this to [enquiries@cpdr.com](mailto:enquiries@cpdr.com) with the code lists (in the form of a tab delimited text file) as soon as possible.
- If/when you require linked data for a cohort you have already defined, please complete the Linkage Request Form, available on eRAP, and return this to [enquiries@cpdr.com](mailto:enquiries@cpdr.com) with your patient identifiers (in the form of a tab delimited text file).

Linked data will be provided, by secure transfer, within 10 working days of receipt of a valid request.

Should you require any advice regarding the implementation of your approved amendment please don't hesitate to contact us at [enquiries@cpdr.com](mailto:enquiries@cpdr.com).

Kind Regards.

## My studies

ID	Study title	Status	Submission date
21_000668	Opioid prescriptions following discharge from hospital after abdominal and orthopaedic surgery: A cohort study from England	Approved	01/10/2021
Chief investigator: <b>Dr Roger Knaggs (Confirmed)</b>			<a href="#">View</a>
Corresponding applicant: <b>Mrs Reham Baamer (Owner)</b>			
Collaborators:			<a href="#">Download</a>
<b>Mr David Humes (Confirmed)</b>			
<b>Professor Dileep Lobo (Confirmed)</b>			
<b>Dr Li Shean Toh (Confirmed)</b>			

## Linkage requests for my studies

Application ID	Linkage request ID	Type	Requestor	Status	Date
#21_000668	2315	Type 2	Mrs Reham Baamer	Delivered	03/10/2022
Opioid prescriptions following discharge from hospital after abdominal and orthopaedic surgery: A cohort study from England					<a href="#">View</a>
#21_000668	2240	Type 1	Mrs Reham Baamer	Delivered	05/09/2022

## **Appendix S 9. OPCS and ICD codes used to identify colectomy, inflammatory bowel disease and diverticula disease**

### **Colectomy codes**

#### **H04 Total excision of colon and rectum (*Clean-Contaminated*)**

H04.1 Panproctocolectomy and ileostomy

Includes: Proctocolectomy not elsewhere classified

H04.2 Panproctocolectomy and anastomosis of ileum to anus and creation of pouch however further qualified

H04.3 Panproctocolectomy and anastomosis of ileum to anus not elsewhere classified

H04.8 Other specified

H04.9 Unspecified

#### **H05 Total excision of colon (*Clean-Contaminated*)**

H05.1 Total colectomy and anastomosis of ileum to rectum

H05.2 Total colectomy and ileostomy and creation of rectal fistula however further qualified

H05.3 Total colectomy and ileostomy not elsewhere classified

H05.8 Other specified

H05.9 Unspecified

#### **H06 Extended excision of right hemicolon (*Clean-Contaminated*)**

*Includes: Excision of right colon and other segment of ileum or colon and surrounding tissue*

H06.1 Extended right hemicolectomy and end to end anastomosis

H06.2 Extended right hemicolectomy and anastomosis of ileum to colon

H06.3 Extended right hemicolectomy and anastomosis not elsewhere classified

H06.4 Extended right hemicolectomy and ileostomy however further qualified

H06.5 Extended right hemicolectomy and end to side anastomosis

H06.8 Other specified

H06.9 Unspecified

#### **H07 Other excision of right hemicolon (*Clean-Contaminated*)**

*Includes: Limited excision of caecum and terminal ileum caecum*

H07.1 Right hemicolectomy and end to end anastomosis of ileum to colon

*Includes: Ileocaecal resection*

H07.2 Right hemicolectomy and side to side anastomosis of ileum to transverse colon

H07.3 Right hemicolectomy and anastomosis not elsewhere classified

H07.4 Right hemicolectomy and ileostomy however further qualified

H07.5 Right hemicolectomy and end to side anastomosis

H07.8 Other specified

H07.9 Unspecified

#### **H08 Excision of transverse colon (*Clean-Contaminated*)**

H08.1 Transverse colectomy and end to end anastomosis

H08.2 Transverse colectomy and anastomosis of ileum to colon

H08.3 Transverse colectomy and anastomosis not elsewhere classified

H08.4 Transverse colectomy and ileostomy however further qualified

H08.5 Transverse colectomy and exteriorisation of bowel not elsewhere classified\*

H08.6 Transverse colectomy and end to side anastomosis

H08.8 Other specified

H08.9 Unspecified

*\*Note: Use secondary code for exteriorisation of caecum (H14) or other exteriorisation of colon (H15)*

**H09 Excision of left hemicolon (Clean-Contaminated)**

H09.1 Left hemicolectomy and end to end anastomosis of colon to rectum

H09.2 Left hemicolectomy and end to end anastomosis of colon to colon

H09.3 Left hemicolectomy and anastomosis not elsewhere classified

H09.4 Left hemicolectomy and ileostomy however further qualified

H09.5 Left hemicolectomy and exteriorisation of bowel not elsewhere classified\*

H09.6 Left hemicolectomy and end to side anastomosis

H09.8 Other specified

H09.9 Unspecified

*\*Note: Use secondary code for exteriorisation of caecum (H14) or other exteriorisation of colon (H15)*

**H10 Excision of sigmoid colon (Clean-Contaminated)**

H10.1 Sigmoid colectomy and end to end anastomosis of ileum to rectum

H10.2 Sigmoid colectomy and anastomosis of colon to rectum

H10.3 Sigmoid colectomy and anastomosis not elsewhere classified

H10.4 Sigmoid colectomy and ileostomy however further qualified

H10.5 Sigmoid colectomy and exteriorisation of bowel not elsewhere classified\*

H10.6 Sigmoid colectomy and end to side anastomosis

H10.8 Other specified

H10.9 Unspecified

*\*Note: Use secondary code for exteriorisation of caecum (H14) or other exteriorisation of colon (H15)*

**H11 Other excision of colon (Clean-Contaminated)**

Includes: Excision of colon where segment removed is not stated

H11.1 Colectomy and end to end anastomosis of colon to colon not elsewhere classified

SSI H11.2 Colectomy and side to side anastomosis of ileum to colon not elsewhere classified

H11.3 Colectomy and anastomosis not elsewhere classified

H11.4 Colectomy and ileostomy not elsewhere classified

H11.5 Colectomy and exteriorisation of bowel not elsewhere classified\*

H11.6 Colectomy and end to side anastomosis NEC

H11.8 Other specified

**Please see minimum wound class against each procedure**

H11.9 Unspecified

*Includes: Colectomy or hemicolectomy not elsewhere classified*

*\*Note: Use secondary code for exteriorisation of caecum (H14) or other exteriorisation of colon (H15)*

**H29 Subtotal excision of colon and rectum (Clean contaminated)**

H29.1 Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus

H29.2 Subtotal excision of colon and rectum and creation of colonic pouch NEC

H29.3 Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum.

H29.4 Subtotal excision of colon and creation of colonic pouch NEC

H29.8 Other specified subtotal excision of colon

H29.9 Unspecified subtotal excision of colon

**H33 Excision of rectum (Clean contaminated)**

*Includes: Excision of whole or part of rectum with or without part of sigmoid colon*

H33.1 Abdominoperineal excision of rectum and end colostomy

H33.2 Proctectomy and anastomosis of colon to anus

H33.3 Anterior resection of rectum and anastomosis of colon to rectum using staples

*Includes: Rectosigmoidectomy and anastomosis of colon to rectum*

H33.4 Anterior resection of rectum and anastomosis not elsewhere classified

H33.5 Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel\*

H33.6 Anterior resection of rectum and exteriorisation of bowel\*

H33.7 Perineal resection of rectum HFQ

H33.8 Other specified

H33.9 Unspecified

*Includes: Rectosigmoidectomy not elsewhere classified*

**\*Note:** Use secondary code for creation of artificial opening into ileum (G74); exteriorisation of caecum (H14) or other exteriorisation of colon (H15)

**Inflammatory bowel disease codes**

K50, K500, K501, K508, K509, K51, K510, K512, K513, K514, K515, K518, K519, K520, K521, K522, K523, K528, K529

**Diverticular disease codes**

K57, K570, K571, K572, K573, K574, K575, K578, K579

## Appendix S 10. Opioid products code

Product Code Id	Code	Drug substance name	Formulation	Strength
12353941000033110	34535311000001107	Tramadol hydrochloride	Modified-release tablet	75mg
12353841000033119	34536311000001102	Tramadol hydrochloride	Modified-release tablet	200 mg
12353741000033112	34534911000001109	Tramadol hydrochloride	Modified-release tablet	150 mg
12353641000033115	34535811000001103	Tramadol hydrochloride	Modified-release tablet	100 mg
1850441000033112	461411000000000	Tramadol hydrochloride	Modified-release tablet	400 mg
1850341000033118	929211000000000	Tramadol hydrochloride	Modified-release tablet	300 mg
1850241000033111	142111000000000	Tramadol hydrochloride	Modified-release tablet	200 mg
1850141000033116	139611000000000	Tramadol hydrochloride	Modified-release tablet	150 mg
4259241000033118	11985311000001102	Tramadol hydrochloride	Modified-release tablet	50 mg
1564741000033116	315611000000000	Tramadol hydrochloride	Modified-release tablet	200 mg
1564641000033113	362111000000000	Tramadol hydrochloride	Modified-release tablet	150 mg
1564541000033112	306311000000000	Tramadol hydrochloride	Modified-release tablet	100 mg
1564841000033114	314411000000000	Tramadol hydrochloride	Soluble tablet	50 mg
1564341000033117	203811000000000	Tramadol hydrochloride	Capsule	50 mg
1561541000033114	3778011000001102	Morphine sulfate	Modified-release capsule	60 mg
1561441000033113	3651611000001107	Morphine sulfate	Modified-release capsule	30 mg
1561341000033119	4035511000001101	Morphine sulfate	Modified-release capsule	200 mg
1561141000033117	3652111000001109	Morphine sulfate	Modified-release capsule	10 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
1561241000033112	3881611000001107	Morphine sulfate	Modified-release capsule	100 mg
11243541000033111	32133511000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
11243141000033119	32138511000001108	Oxycodone hydrochloride	Modified-release tablet	5 mg
11243441000033110	32136711000001102	Oxycodone hydrochloride	Modified-release tablet	40 mg
11243341000033116	32140211000001108	Oxycodone hydrochloride	Modified-release tablet	20 mg
11243241000033114	32135311000001106	Oxycodone hydrochloride	Modified-release tablet	10 mg
4417541000033116	12871611000001108	Tramadol hydrochloride	Modified-release tablet	200 mg
4417641000033115	12871211000001106	Tramadol hydrochloride	Modified-release tablet	150 mg
4417741000033112	12869811000001101	Tramadol hydrochloride	Modified-release tablet	100 mg
2746141000033115	75011000000000	Codeine phosphate/ Paracetamol	Tablet	30 mg + 500 mg
2745941000033112	3141110000000000	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
1549541000033119	21011000000000	Tramadol hydrochloride	Modified-release capsule	50 mg
1549441000033115	94110000000000	Tramadol hydrochloride	Modified-release capsule	200 mg
1549341000033114	7115110000000000	Tramadol hydrochloride	Modified-release capsule	150 mg
1549241000033116	3310110000000000	Tramadol hydrochloride	Modified-release capsule	100 mg
2980441000033112	5197011000001105	Tramadol hydrochloride	Orodispersible tablet	50 mg
1548041000033116	4009110000000000	Tramadol hydrochloride	Capsule	50 mg
3344441000033113	9533211000001100	Tramadol hydrochloride	Modified-release tablet	400 mg
3344341000033119	9532911000001102	Tramadol hydrochloride	Modified-release tablet	300 mg



Product Code Id	Code	Drug substance name	Formulation	Strength
3344241000033112	9532611000001108	Tramadol hydrochloride	Modified-release tablet	200 mg
3344141000033117	9532211000001106	Tramadol hydrochloride	Modified-release tablet	150 mg
10598041000033118	30002211000001101	Fentanyl	Transdermal patch	50 mcg/ hr
10598141000033119	30002011000001106	Fentanyl	Transdermal patch	25 mcg/ hr
10598241000033114	30001711000001101	Fentanyl	Transdermal patch	12 mcg/ hr
10597841000033112	30003011000001102	Fentanyl	Transdermal patch	100 mcg/ hr
5007241000033117	15363611000001103	Fentanyl	Transdermal patch	75 mcg/ hr
5007541000033115	15363411000001101	Fentanyl	Transdermal patch	50 mcg/ hr
5007441000033116	15363211000001100	Fentanyl	Transdermal patch	25 mcg/ hr
11507641000033116	32520211000001103	Fentanyl	Transdermal patch	12 mcg/ hr
5007341000033110	15363811000001104	Fentanyl	Transdermal patch	100 mcg/ hr
1479641000033111	360311000000000	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
12428641000033115	34912111000001102	Buprenorphine	Transdermal patch	70 mcg/ hr
12428541000033116	34911911000001105	Buprenorphine	Transdermal patch	52.5 mcg/ hr
12428441000033117	34911711000001108	Buprenorphine	Transdermal patch	35 mcg/ hr
2738041000033119	3449311000001104	Buprenorphine	Transdermal patch	70 mcg/ hr
2737941000033117	3448811000001101	Buprenorphine	Transdermal patch	52.5 mcg/ hr
2737841000033113	3446611000001101	Buprenorphine	Transdermal patch	35 mcg/ hr
4459541000033117	12790811000001109	Tramadol hydrochloride	Modified-release tablet	200 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
4459441000033118	12790511000001106	Tramadol hydrochloride	Modified-release tablet	150 mg
4459341000033112	12790311000001100	Tramadol hydrochloride	Modified-release tablet	100 mg
4523041000033116	11592111000001101	Tramadol hydrochloride	Modified-release capsule	50 mg
4523341000033119	11592711000001100	Tramadol hydrochloride	Modified-release capsule	200 mg
4523241000033112	11592511000001105	Tramadol hydrochloride	Modified-release capsule	150 mg
4523141000033117	11592311000001104	Tramadol hydrochloride	Modified-release capsule	100 mg
1702041000033114	3242911000001107	Tramadol hydrochloride	Effervescent powder	50 mg
1701941000033115	3250111000001107	Tramadol hydrochloride	Effervescent powder	100 mg
1454541000033111	451511000000000	Tramadol hydrochloride	Capsule	50 mg
2078141000033115	35921211000001100	Tramadol hydrochloride	Modified-release tablet	75 mg
1465741000033113	322633008	Tramadol hydrochloride	Soluble tablet	50 mg
2980341000033118	5212811000001100	Tramadol hydrochloride	Orodispersible tablet	50 mg
4259141000033113	12037411000001103	Tramadol hydrochloride	Modified-release tablet	50 mg
1462941000033118	35940111000001103	Tramadol hydrochloride	Modified-release capsule	50 mg
1702241000033118	322645004	Tramadol hydrochloride	Effervescent powder	50 mg
1454241000033114	322623000	Tramadol hydrochloride	Capsule	50 mg
1850041000033115	35921011000001105	Tramadol hydrochloride	Modified-release tablet	400 mg
1849941000033112	35920911000001102	Tramadol hydrochloride	Modified-release tablet	300 mg
1462541000033112	35920811000001107	Tramadol hydrochloride	Modified-release tablet	200 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
1462841000033114	35920711000001104	Tramadol hydrochloride	Modified-release capsule	200 mg
1462441000033111	35920611000001108	Tramadol hydrochloride	Modified-release tablet	150 mg
1462741000033116	35920511000001109	Tramadol hydrochloride	Modified-release capsule	150 mg
6389141000033118	19200411000001106	Tramadol hydrochloride	Oral drops	100 mg/1 ml
1462341000033117	35920311000001103	Tramadol hydrochloride	Modified-release tablet	100 mg
1462641000033113	35920211000001106	Tramadol hydrochloride	Modified-release capsule	100 mg
1702141000033113	322646003	Tramadol hydrochloride	Effervescent powder	100 mg
3996641000033119	11055011000001100	Tramadol hydrochloride	Modified-release tablet	300 mg
3996541000033115	11054811000001105	Tramadol hydrochloride	Modified-release tablet	200 mg
3996441000033116	11054611000001106	Tramadol hydrochloride	Modified-release tablet	100 mg
3332841000033115	9508511000001103	Fentanyl	Transdermal patch	75 mcg/ hr
3332941000033111	9508211000001101	Fentanyl	Transdermal patch	50 mcg/ hr
3333041000033118	9508011000001106	Fentanyl	Transdermal patch	25 mcg/ hr
3333141000033119	9508911000001105	Fentanyl	Transdermal patch	100 mcg/ hr
12350241000033114	21695111000001100	Tramadol hydrochloride	Modified-release tablet	200 mg
12350141000033119	21694511000001108	Tramadol hydrochloride	Modified-release tablet	150 mg
12350041000033118	21692911000001105	Tramadol hydrochloride	Modified-release tablet	100 mg
6527741000033117	19957411000001103	Buprenorphine hydrochloride	Sublingual tablet	400 mcg
6527641000033114	19957211000001102	Buprenorphine hydrochloride	Sublingual tablet	200 mcg

Product Code Id	Code	Drug substance name	Formulation	Strength
1428641000033115	762111000000000	Buprenorphine hydrochloride	Sublingual tablet	400 mcg
1426141000033112	867611000000000	Buprenorphine hydrochloride	Sublingual tablet	200 mcg
5234441000033111	15850911000001105	Naloxone / Oxycodone	Modified-release tablet	2.5 mg + 5 mg
5234541000033112	15851311000001104	Naloxone / Oxycodone	Modified-release tablet	20 mg + 40 mg
4898341000033115	14976011000001107	Naloxone / Oxycodone	Modified-release tablet	10 mg + 20 mg
4898441000033114	14975711000001101	Naloxone / Oxycodone	Modified-release tablet	5 mg + 10 mg
6132141000033114	442341005	Tapentadol hydrochloride	Tablet	75 mg
6132041000033110	442472008	Tapentadol hydrochloride	Tablet	50 mg
6133141000033119	18672211000001103	Tapentadol hydrochloride	Modified-release tablet	50 mg
6133541000033111	18672111000001109	Tapentadol hydrochloride	Modified-release tablet	250 mg
9160141000033113	24408811000001107	Tapentadol hydrochloride	Oral solution	20 mg/ml
6133441000033110	18672011000001108	Tapentadol hydrochloride	Modified-release tablet	200 mg
6133341000033116	18671911000001101	Tapentadol hydrochloride	Modified-release tablet	150 mg
6133241000033114	18671811000001106	Tapentadol hydrochloride	Modified-release tablet	100 mg
1835541000033116	292611000000000	Buprenorphine hydrochloride	Sublingual tablet	400 mcg
1352541000033110	104110000000000	Codeine phosphate/ Paracetamol	Effervescent tablet	30 mg + 500 mg
1698041000033118	247311000000000	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
1363841000033114	341211000000000	Codeine phosphate/ Paracetamol	Tablet	30 mg + 500 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
9292941000033111	604311000000000	Codeine phosphate/ Paracetamol	Tablet	12.8mg + 500 mg
12187041000033117	34027611000001109	Oxycodone hydrochloride	Oral solution	1 mg/ ml
9061541000033116	23657811000001102	Oxycodone hydrochloride	Capsule	5 mg
9061741000033112	23658211000001104	Oxycodone hydrochloride	Capsule	20 mg
12187141000033118	34027811000001108	Oxycodone hydrochloride	Oral solution	10 mg/ml
9061641000033115	23658011000001109	Oxycodone hydrochloride	Capsule	10 mg
1276641000033119	3079311000001108	Morphine sulfate	Tablet	50 mg
1752041000033116	3451411000001107	Morphine sulfate	Oral solution	20 mg/ ml
1278641000033115	3077311000001103	Morphine sulfate	Tablet	20 mg
1752541000033114	3164111000001107	Morphine sulfate	Oral solution	2 mg/ml
1278541000033116	2898611000001107	Morphine sulfate	Tablet	10 mg
11756241000033110	33480711000001101	Buprenorphine	Transdermal patch	5 mcg/ hr
11756441000033111	33481111000001108	Buprenorphine	Transdermal patch	20 mcg/ hr
11756341000033117	33480911000001104	Buprenorphine	Transdermal patch	10 mcg/ hr
12637441000033118	35543311000001100	Oxycodone hydrochloride	Modified-release tablet	60 mg
12636441000033116	35541911000001100	Oxycodone hydrochloride	Modified-release tablet	5 mg
12637341000033112	35542911000001106	Oxycodone hydrochloride	Modified-release tablet	40 mg
12637241000033119	35542711000001109	Oxycodone hydrochloride	Modified-release tablet	30 mg
12636941000033114	35542511000001104	Oxycodone hydrochloride	Modified-release tablet	20 mg
12636741000033111	35542311000001105	Oxycodone hydrochloride	Modified-release tablet	15 mg
12636541000033115	35542111000001108	Oxycodone hydrochloride	Modified-release tablet	10 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
1164541000033115	6801110000000000	Dihydrocodeine / Paracetamol	Tablet	20 mg + 500 mg
1157541000033117	4199110000000000	Dihydrocodeine / Paracetamol	Tablet	30 mg + 500 mg
9176841000033112	24467911000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
9809841000033115	27993311000001101	Oxycodone hydrochloride	Modified-release tablet	60 mg
9177041000033115	24466911000001102	Oxycodone hydrochloride	Modified-release tablet	5 mg
9177141000033116	24467711000001101	Oxycodone hydrochloride	Modified-release tablet	40 mg
9809741000033113	27993011000001104	Oxycodone hydrochloride	Modified-release tablet	30 mg
9177241000033111	24467411000001107	Oxycodone hydrochloride	Modified-release tablet	20 mg
9809641000033116	27992811000001102	Oxycodone hydrochloride	Modified-release tablet	15 mg
9177341000033118	24467111000001102	Oxycodone hydrochloride	Modified-release tablet	10 mg
12195141000033111	34172111000001105	Buprenorphine	Transdermal patch	70 mcg/ hr
12195041000033112	34172311000001107	Buprenorphine	Transdermal patch	52.5 mcg/ hr
12194941000033112	34172511000001101	Buprenorphine	Transdermal patch	35 mcg/ hr
11732541000033112	33038711000001103	Buprenorphine	Transdermal patch	5 mcg/ hr
11732441000033111	33039311000001108	Buprenorphine	Transdermal patch	20 mcg/ hr
11732341000033117	33039111000001106	Buprenorphine	Transdermal patch	15 mcg/ hr
11732241000033110	33038911000001101	Buprenorphine	Transdermal patch	10 mcg/ hr
13751341000033119	38728711000001102	Buprenorphine	Transdermal patch	5 mcg/ hr
13751541000033114	38746011000001101	Buprenorphine	Transdermal patch	20 mcg/ hr

Product Code Id	Code	Drug substance name	Formulation	Strength
13751441000033113	38745611000001103	Buprenorphine	Transdermal patch	10 mcg/ hr
11577241000033114	32643711000001109	Buprenorphine	Transdermal patch	70 mcg/ hr
11577141000033119	32643211000001102	Buprenorphine	Transdermal patch	52.5 mcg/ hr
11507941000033111	32576211000001102	Buprenorphine	Transdermal patch	35 mcg/ hr
6527441000033112	19956611000001102	Buprenorphine hydrochloride	Sublingual tablet	400 microgram
13747241000033118	38956411000001100	Pethidine hydrochloride	Tablet	50 mg
1065641000033110	322612004	Pethidine hydrochloride	Tablet	50 mg
13300641000033110	12303411000001102	Pethidine hydrochloride	Capsule	50 mg
1044641000033117	322600003	Pentazocine hydrochloride	Capsule	50 mg
1068041000033114	322601004	Pentazocine hydrochloride	Tablet	25 mg
1043041000033113	4656111000001106	Dihydrocodeine / Paracetamol	Tablet	7.4 mg + 500mg
1030141000033119	655311000000000	Codeine phosphate/ Paracetamol	Effervescent tablet	8 mg + 500 mg
4432041000033115	772811000000000	Codeine phosphate/ Paracetamol	Capsule	8 mg + 500 mg
11730941000033119	33054211000001103	Buprenorphine	Transdermal patch	5 mcg/ hr
11730841000033110	33054611000001101	Buprenorphine	Transdermal patch	20 mcg/ hr
11730741000033117	33054411000001104	Buprenorphine	Transdermal patch	10 mcg/ hr
2968841000033110	841911000000000	Codeine phosphate/ Paracetamol	Tablet	12.8 mg + 500 mg
1037041000033119	3870411000001105	Hydromorphone hydrochloride	Modified-release capsule	8 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
1036941000033115	3838511000001105	Hydromorphone hydrochloride	Modified-release capsule	4 mg
1036741000033118	3869411000001108	Hydromorphone hydrochloride	Modified-release capsule	2 mg
1036841000033111	4004111000001104	Hydromorphone hydrochloride	Modified-release capsule	24 mg
1036641000033110	4001411000001107	Hydromorphone hydrochloride	Modified-release capsule	16 mg
1029241000033117	3837511000001106	Hydromorphone hydrochloride	Capsule	2.6 mg
1029141000033112	3836411000001105	Hydromorphone hydrochloride	Capsule	1.3 mg
6133841000033113	18663511000001100	Tapentadol hydrochloride	Modified-release tablet	50 mg
6134241000033111	18665211000001104	Tapentadol hydrochloride	Modified-release tablet	250 mg
6134141000033116	18664711000001107	Tapentadol hydrochloride	Modified-release tablet	200 mg
6134041000033115	18664411000001101	Tapentadol hydrochloride	Modified-release tablet	150 mg
6133941000033117	18664111000001106	Tapentadol hydrochloride	Modified-release tablet	100 mg
6132341000033112	18662911000001100	Tapentadol hydrochloride	Tablet	75 mg
6132241000033119	18662511000001107	Tapentadol hydrochloride	Tablet	50 mg
9160241000033118	24120811000001104	Tapentadol hydrochloride	Oral solution	20 mg/ml
12665241000033117	35847411000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
12665141000033112	35847211000001103	Oxycodone hydrochloride	Modified-release tablet	60 mg
12665041000033113	35846011000001105	Oxycodone hydrochloride	Modified-release tablet	5 mg
12664941000033113	35847011000001108	Oxycodone hydrochloride	Modified-release tablet	40 mg
12664841000033117	35846811000001104	Oxycodone hydrochloride	Modified-release tablet	30 mg



Product Code Id	Code	Drug substance name	Formulation	Strength
12664741000033110	35846611000001103	Oxycodone hydrochloride	Modified-release tablet	20 mg
12664641000033118	35846411000001101	Oxycodone hydrochloride	Modified-release tablet	15 mg
12664541000033119	35846211000001100	Oxycodone hydrochloride	Modified-release tablet	10 mg
1988441000033113	2898211000001105	Oxycodone hydrochloride	Oral solution	1 mg/1 ml
1988041000033116	2895711000001105	Oxycodone hydrochloride	Capsule	5 mg
1988241000033112	2896311000001101	Oxycodone hydrochloride	Capsule	20 mg
1988341000033119	2897511000001109	Oxycodone hydrochloride	Oral solution	10 mg/ml
1988141000033117	2896011000001104	Oxycodone hydrochloride	Capsule	10 mg
8048441000033119	20969411000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
8048041000033111	20968611000001105	Oxycodone hydrochloride	Modified-release tablet	5 mg
8048341000033113	20969211000001103	Oxycodone hydrochloride	Modified-release tablet	40 mg
8048241000033115	20969011000001108	Oxycodone hydrochloride	Modified-release tablet	20 mg
8048141000033110	20968811000001109	Oxycodone hydrochloride	Modified-release tablet	10 mg
1987941000033119	2898111000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
6125641000033111	18643311000001102	Oxycodone hydrochloride	Modified-release tablet	60 mg
2748541000033111	4074911000001106	Oxycodone hydrochloride	Modified-release tablet	5 mg
1987841000033110	2897211000001106	Oxycodone hydrochloride	Modified-release tablet	40 mg
6125541000033110	18644611000001105	Oxycodone hydrochloride	Modified-release tablet	30 mg
1987741000033117	2896611000001106	Oxycodone hydrochloride	Modified-release tablet	20 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
6125441000033114	18645111000001103	Oxycodone hydrochloride	Modified-release tablet	15 mg
6125741000033119	18641711000001104	Oxycodone hydrochloride	Modified-release tablet	120 mg
1987641000033114	2891711000001108	Oxycodone hydrochloride	Modified-release tablet	10 mg
1982541000033111	36131511000001104	Oxycodone hydrochloride	Modified-release tablet	80 mg
6125241000033113	36131311000001105	Oxycodone hydrochloride	Modified-release tablet	60 mg
1987441000033112	36131211000001102	Oxycodone hydrochloride	Oral solution	1 mg/1 ml
13708441000033111	38752411000001107	Oxycodone hydrochloride	Tablet	5 mg
2748441000033110	36131011000001107	Oxycodone hydrochloride	Modified-release tablet	5 mg
1987141000033116	322691007	Oxycodone hydrochloride	Capsule	5 mg
1982141000033119	36130911000001104	Oxycodone hydrochloride	Modified-release tablet	40 mg
6125141000033118	36130711000001101	Oxycodone hydrochloride	Modified-release tablet	30 mg
13708641000033113	38752311000001100	Oxycodone hydrochloride	Tablet	20 mg
1982041000033118	36130411000001107	Oxycodone hydrochloride	Modified-release tablet	20 mg
1987341000033118	322693005	Oxycodone hydrochloride	Capsule	20 mg
6125041000033117	36130211000001108	Oxycodone hydrochloride	Modified-release tablet	15 mg
6125341000033115	18645511000001107	Oxycodone hydrochloride	Modified-release tablet	120 mg
1987541000033113	36130011000001103	Oxycodone hydrochloride	Oral solution	10 mg/1 ml
13708541000033112	38752211000001108	Oxycodone hydrochloride	Tablet	10 mg
1981941000033112	36129511000001101	Oxycodone hydrochloride	Modified-release tablet	10 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
1987241000033111	322692000	Oxycodone hydrochloride	Capsule	10 mg
13708741000033116	38456711000001108	Oxycodone hydrochloride	Tablet	5 mg
13708941000033118	38455911000001103	Oxycodone hydrochloride	Tablet	20 mg
13708841000033114	38453311000001100	Oxycodone hydrochloride	Tablet	10 mg
10333841000033113	29676711000001106	Oxycodone hydrochloride	Modified-release tablet	80 mg
10333741000033115	29677411000001103	Oxycodone hydrochloride	Modified-release tablet	60 mg
10333141000033119	29650311000001107	Oxycodone hydrochloride	Modified-release tablet	5 mg
10333641000033112	29677611000001100	Oxycodone hydrochloride	Modified-release tablet	40 mg
10333541000033111	29677211000001102	Oxycodone hydrochloride	Modified-release tablet	30 mg
10333441000033110	29678311000001106	Oxycodone hydrochloride	Modified-release tablet	20 mg
10333341000033116	29678111000001109	Oxycodone hydrochloride	Modified-release tablet	15 mg
10333241000033114	29677811000001101	Oxycodone hydrochloride	Modified-release tablet	10 mg
4956241000033114	15302811000001106	Fentanyl	Transdermal patch	75 mcg/ hr
4956141000033119	15302611000001107	Fentanyl	Transdermal patch	50 mcg/ hr
4956041000033118	15302411000001109	Fentanyl	Transdermal patch	25 mcg/ hr
5300441000033116	16088911000001101	Fentanyl	Transdermal patch	12 mcg/ hr
4956341000033116	15303011000001109	Fentanyl	Transdermal patch	100 mcg/ hr
4503041000033113	13567911000001105	Fentanyl	Transdermal patch	75 mcg/ hr
4502941000033115	13567711000001108	Fentanyl	Transdermal patch	50 mcg/ hr

Product Code Id	Code	Drug substance name	Formulation	Strength
4502841000033111	13567511000001103	Fentanyl	Transdermal patch	25 mcg/ hr
4503141000033112	13568111000001108	Fentanyl	Transdermal patch	100 mcg/ hr
1014641000033112	3609711000001109	Morphine sulfate	Oral solution	6 mg/1 ml
1014941000033117	3453511000001105	Morphine sulfate	Oral solution	20 mg/1 ml
1014441000033110	3331611000001103	Morphine sulfate	Oral solution	2 mg/1 ml
1014841000033113	3164311000001109	Morphine sulfate	Oral solution	2 mg/1 ml
1014541000033111	3608411000001106	Morphine sulfate	Oral solution	20 mg/1 ml
8884741000033112	37975411000001101	Fentanyl	Transdermal patch	75 mcg/ hr
8884641000033115	37974911000001105	Fentanyl	Transdermal patch	50 mcg/ hr
8884541000033116	37973911000001108	Fentanyl	Transdermal patch	25 mcg/ hr
8884441000033117	37972611000001107	Fentanyl	Transdermal patch	12 mcg/ hr
8884341000033111	37975711000001107	Fentanyl	Transdermal patch	100 mcg/ hr
12185741000033114	34052211000001105	Oxycodone hydrochloride	Modified-release tablet	80 mg
12185641000033117	34051311000001106	Oxycodone hydrochloride	Modified-release tablet	40 mg
12185541000033118	34051911000001107	Oxycodone hydrochloride	Modified-release tablet	20 mg
12185341000033113	34051611000001101	Oxycodone hydrochloride	Modified-release tablet	10 mg
12347141000033118	14983611000001104	Tramadol hydrochloride	Modified-release tablet	200 mg
12347041000033117	14983411000001102	Tramadol hydrochloride	Modified-release tablet	150 mg
12346941000033118	14983211000001101	Tramadol hydrochloride	Modified-release tablet	100 mg
4424241000033116	12948411000001105	Tramadol hydrochloride	Modified-release tablet	100 mg
9204541000033110	24560811000001101	Fentanyl	Transdermal patch	75 mcg/ hr

Product Code Id	Code	Drug substance name	Formulation	Strength
9204441000033114	24560611000001100	Fentanyl	Transdermal patch	50 mcg/ hr
10336841000033116	24560411000001103	Fentanyl	Transdermal patch	25 mcg/ hr
9204341000033115	24560211000001102	Fentanyl	Transdermal patch	12 mcg/ hr
9204641000033111	24561011000001103	Fentanyl	Transdermal patch	100 mcg/ hr
944541000000000	3882611000001101	Morphine sulfate	Modified-release capsule	90 mg
944441000000000	3778211000001107	Morphine sulfate	Modified-release capsule	60 mg
944341000000000	3651811000001106	Morphine sulfate	Modified-release capsule	30 mg
944241000000000	4388011000001106	Morphine sulfate	Modified-release capsule	200 mg
944141000000000	3882911000001107	Morphine sulfate	Modified-release capsule	150 mg
944041000000000	3883211000001109	Morphine sulfate	Modified-release capsule	120 mg
940341000000000	4088311000001108	Morphine sulfate	Modified-release granules	60 mg
940841000000000	4380011000001109	Morphine sulfate	Modified-release granules	30 mg
940741000000000	4379311000001107	Morphine sulfate	Modified-release granules	20 mg
940241000000000	4089211000001105	Morphine sulfate	Modified-release granules	200 mg
940141000000000	4088611000001103	Morphine sulfate	Modified-release granules	100 mg
941241000000000	2883211000001103	Morphine sulfate	Modified-release tablet	60 mg
940441000000000	922411000000000	Morphine sulfate	Modified-release tablet	5 mg
922411000000000	3078711000001103	Morphine sulfate	Modified-release tablet	30 mg
941341000000000	394011000000000	Morphine sulfate	Modified-release tablet	200 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
940041000000000	272811000000000	Morphine sulfate	Modified-release tablet	15 mg
275334000000000	3077711000001104	Morphine sulfate	Modified-release tablet	10 mg
275364000000000	2883611000001101	Morphine sulfate	Modified-release tablet	100 mg
4434241000033119	12143711000001107	Morphine sulfate	Oral solution	1 mg/ ml
13754841000033114	12300511000001109	Morphine sulfate	Oral solution	100 mcg/ ml
931941000000000	3631511000001107	Morphine sulfate	Oral solution	6 mg/1 ml
933941000000000	322455007	Morphine sulfate	Suppository	30 mg
931641000000000	36128611000001106	Morphine sulfate	Oral solution	20 mg/ ml
934241000000000	322433004	Morphine sulfate	Suppository	20 mg
933841000000000	322428003	Morphine sulfate	Suppository	15 mg
931741000000000	3521311000001108	Morphine sulfate	Oral solution	2 mg/ml
931541000000000	36128311000001101	Morphine sulfate	Oral solution	2 mg/ml
934141000000000	322432009	Morphine sulfate	Suppository	10 mg
931841000000000	3631411000001108	Morphine sulfate	Oral solution	20 mg/ml
934641000000000	322446009	Morphine hydrochloride	Suppository	15 mg
7859941000033112	12140711000001103	Morphine hydrochloride	Oral solution	2 mg/1 ml
2068441000033118	36127811000001106	Morphine sulfate	Modified-release capsule	90 mg
936741000000000	36127711000001103	Morphine sulfate	Modified-release tablet	60 mg
930241000000000	4110911000001104	Morphine sulfate	Modified-release granules	60 mg
1924141000033115	36127611000001107	Morphine sulfate	Modified-release capsule	60 mg
930341000000000	36127511000001108	Morphine sulfate	Modified-release tablet	5 mg
938241000000000	322728004	Morphine sulfate	Tablet	50 mg
2068841000033115	36127411000001109	Morphine sulfate	Modified-release capsule	50 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
936641000000000	36127311000001102	Morphine sulfate	Modified-release tablet	30 mg
3032941000033110	4389511000001109	Morphine sulfate	Modified-release granules	30 mg
1924041000033119	36127211000001105	Morphine sulfate	Modified-release capsule	30 mg
939541000000000	322709006	Morphine sulfate	Tablet	20 mg
3032841000033119	4389411000001105	Morphine sulfate	Modified-release granules	20 mg
2068741000033113	36127111000001104	Morphine sulfate	Modified-release capsule	20 mg
933141000000000	36127011000001100	Morphine sulfate	Modified-release tablet	200 mg
930141000000000	4110811000001109	Morphine sulfate	Modified-release granules	200 mg
1924341000033117	36126911000001104	Morphine sulfate	Modified-release capsule	200 mg
929941000000000	36126811000001109	Morphine sulfate	Modified-release tablet	15 mg
2068641000033116	36126711000001101	Morphine sulfate	Modified-release capsule	150 mg
2068541000033117	36126611000001105	Morphine sulfate	Modified-release capsule	120 mg
936441000000000	322708003	Morphine sulfate	Tablet	10 mg
929741000000000	36126511000001106	Morphine sulfate	Modified-release tablet	10 mg
1923941000033116	36126411000001107	Morphine sulfate	Modified-release capsule	10 mg
936541000000000	36126211000001108	Morphine sulfate	Modified-release tablet	100 mg
930041000000000	4110711000001101	Morphine sulfate	Modified-release granules	100 mg
1924241000033110	36125811000001101	Morphine sulfate	Modified-release capsule	100 mg
13118741000033113	36022611000001104	Morphine anhydrous	Oral drops/ Oral solution	10 mg/ml
2912341000033119	4527211000001108	Morphine sulfate	Modified-release tablet	60 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
2912241000033112	4526811000001107	Morphine sulfate	Modified-release tablet	30 mg
2912141000033117	4525911000001109	Morphine sulfate	Modified-release tablet	10 mg
2912441000033113	4527911000001104	Morphine sulfate	Modified-release tablet	100 mg
930941000000000	4035011000001109	Morphine sulfate	Modified-release capsule	50 mg
930841000000000	3881711000001103	Morphine sulfate	Modified-release capsule	20 mg
930741000000000	3882211000001103	Morphine sulfate	Modified-release capsule	100 mg
4386841000033114	12882411000001107	Fentanyl	Transdermal patch	75 mcg/ hr
4386741000033116	12882011000001103	Fentanyl	Transdermal patch	50 mcg/ hr
8962341000033111	23682311000001104	Fentanyl	Transdermal patch	37.5 mcg/ hr
4387041000033117	12881711000001108	Fentanyl	Transdermal patch	25 mcg/ hr
4386641000033113	12881511000001103	Fentanyl	Transdermal patch	12 mcg/ hr
4386941000033118	12882611000001105	Fentanyl	Transdermal patch	100 mcg/ hr
896441000000000	234611000000000	Meptazinol hydrochloride	Tablet	200 mg
896341000000000	333936002	Meptazinol hydrochloride	Tablet	200 mg
3331541000033110	9529311000001109	Codeine phosphate/ Paracetamol	Effervescent tablet	30 mg + 500 mg
3334541000033113	987110000000000	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
4899141000033112	14977411000001101	Tramadol hydrochloride	Modified-release capsule	50mg
4899441000033116	14976811000001101	Tramadol hydrochloride	Modified-release capsule	200 mg
4899341000033110	14977011000001105	Tramadol hydrochloride	Modified-release capsule	150 mg



Product Code Id	Code	Drug substance name	Formulation	Strength
4899241000033117	14977211000001100	Tramadol hydrochloride	Modified-release capsule	100 mg
4022941000033111	11085711000001108	Fentanyl	Transdermal patch	75 mcg/ hr
4022841000033115	11085311000001109	Fentanyl	Transdermal patch	50 mcg/ hr
4022741000033113	11084911000001106	Fentanyl	Transdermal patch	25 mcg/ hr
4022641000033116	11084511000001104	Fentanyl	Transdermal patch	12 mcg/ hr
4023041000033118	11085911000001105	Fentanyl	Transdermal patch	100 mcg/1 hr
4824441000033111	19624411000001108	Tramadol hydrochloride	Modified-release tablet	200 mg
4824341000033117	19624611000001106	Tramadol hydrochloride	Modified-release tablet	150 mg
4824241000033110	19624811000001105	Tramadol hydrochloride	Modified-release tablet	100 mg
11568441000033118	24637511000001102	Tramadol hydrochloride	Modified-release tablet	200 mg
11568141000033114	24637211000001100	Tramadol hydrochloride	Modified-release tablet	150 mg
11567841000033116	24636911000001106	Tramadol hydrochloride	Modified-release tablet	100 mg
3909741000033117	20475411000001106	Tramadol hydrochloride	Modified-release tablet	200 mg
3909641000033114	20475211000001107	Tramadol hydrochloride	Modified-release tablet	150 mg
3909541000033113	20475011000001102	Tramadol hydrochloride	Modified-release tablet	100 mg
8537341000033111	22686511000001102	Oxycodone hydrochloride	Capsule	5 mg
8537541000033116	22686911000001109	Oxycodone hydrochloride	Capsule	20 mg
8537441000033117	22686711000001107	Oxycodone hydrochloride	Capsule	10 mg
7886641000033116	20938311000001108	Oxycodone hydrochloride	Modified-release tablet	80 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
10492041000033114	29838811000001108	Oxycodone hydrochloride	Modified-release tablet	60 mg
7886241000033119	20937511000001101	Oxycodone hydrochloride	Modified-release tablet	5 mg
7886541000033117	20938111000001106	Oxycodone hydrochloride	Modified-release tablet	40 mg
10491641000033110	29838611000001109	Oxycodone hydrochloride	Modified-release tablet	30 mg
7886441000033118	20937911000001108	Oxycodone hydrochloride	Modified-release tablet	20 mg
10491541000033114	29838411000001106	Oxycodone hydrochloride	Modified-release tablet	15 mg
10492241000033118	29838211000001107	Oxycodone hydrochloride	Modified-release tablet	120 mg
7886341000033112	20937711000001106	Oxycodone hydrochloride	Modified-release tablet	10 mg
11808641000033119	33630211000001100	Oxycodone hydrochloride	Modified-release tablet	80 mg
11808541000033115	33630011000001105	Oxycodone hydrochloride	Modified-release tablet	60 mg
11808441000033116	33629011000001104	Oxycodone hydrochloride	Modified-release tablet	5 mg
11808341000033110	33629811000001105	Oxycodone hydrochloride	Modified-release tablet	40 mg
11808241000033117	33629611000001106	Oxycodone hydrochloride	Modified-release tablet	30 mg
11808141000033112	33629411000001108	Oxycodone hydrochloride	Modified-release tablet	20 mg
11808041000033113	33629211000001109	Oxycodone hydrochloride	Modified-release tablet	10 mg
4028641000033118	9101211000001104	Tramadol hydrochloride	Modified-release tablet	200 mg
4028541000033119	9101011000001109	Tramadol hydrochloride	Modified-release tablet	150 mg
4028341000033114	9100811000001106	Tramadol hydrochloride	Modified-release tablet	100 mg
1741241000033116	3251511000001105	Codeine phosphate/ Paracetamol	Effervescent powder	60 mg + 1 g

Product Code Id	Code	Drug substance name	Formulation	Strength
1621841000033112	3253711000001104	Codeine phosphate/ Paracetamol	Effervescent powder	30 mg + 500 mg
796641000000000	232711000000000	Codeine phosphate/ Paracetamol	Tablet	30 mg + 500 mg
3057541000033118	7336011000001106	Codeine phosphate/ Paracetamol	Effervescent tablet	30 mg + 500 mg
1830841000033114	737111000000000	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
6137941000033114	17572011000001107	Codeine phosphate/ Paracetamol	Tablet	15 mg + 500 mg
12667041000033119	35859011000001101	Oxycodone hydrochloride	Modified-release tablet	80 mg
12666941000033115	35858711000001108	Oxycodone hydrochloride	Modified-release tablet	60 mg
12666841000033111	35853511000001107	Oxycodone hydrochloride	Modified-release tablet	5 mg
12666741000033118	35857911000001109	Oxycodone hydrochloride	Modified-release tablet	40 mg
12666641000033110	35857411000001101	Oxycodone hydrochloride	Modified-release tablet	30 mg
12666541000033114	35858311000001109	Oxycodone hydrochloride	Modified-release tablet	20 mg
12666441000033113	35857811000001104	Oxycodone hydrochloride	Modified-release tablet	15 mg
12666341000033119	35857611000001103	Oxycodone hydrochloride	Modified-release tablet	10 mg
4425741000033111	32463511000001109	Fentanyl	Transdermal system	40 mcg/1 dose
12346741000033116	21964611000001108	Tramadol hydrochloride	Modified-release tablet	200 mg
12346641000033113	21964411000001105	Tramadol hydrochloride	Modified-release tablet	150 mg
12346441000033111	21964211000001106	Tramadol hydrochloride	Modified-release tablet	100 mg
5300041000033113	16034111000001104	Fentanyl citrate	Spray	50 mcg/1 dose

Product Code Id	Code	Drug substance name	Formulation	Strength
5300241000033117	16035311000001103	Fentanyl citrate	Spray	200 mcg/1 dose
5300141000033112	16034711000001103	Fentanyl citrate	Spray	100 mcg/1 dose
3229141000033111	36045211000001108	Codeine phosphate/ Ibuprofen	Modified-release tablet	20 mg + 300 mg
738641000000000	36057711000001109	Hydromorphone hydrochloride	Modified-release capsule	8 mg
738541000000000	36057611000001100	Hydromorphone hydrochloride	Modified-release capsule	4 mg
738341000000000	36057411000001103	Hydromorphone hydrochloride	Modified-release capsule	2 mg
738441000000000	36057311000001105	Hydromorphone hydrochloride	Modified-release capsule	24 mg
728741000000000	322667003	Hydromorphone hydrochloride	Capsule	2.6mg
738241000000000	36057211000001102	Hydromorphone hydrochloride	Modified-release capsule	16 mg
728641000000000	322665006	Hydromorphone hydrochloride	Capsule	1.3 mg
8882941000033118	23446611000001104	Buprenorphine	Transdermal patch	70 mcg/ hr
8882841000033114	23446411000001102	Buprenorphine	Transdermal patch	52.5 mcg/ hr
8882741000033116	23446211000001101	Buprenorphine	Transdermal patch	35 mcg/ hr
624441000000000	3446911000001107	Codeine phosphate	Oral solution	3 mg/1 ml
10045741000033116	28491211000001101	Buprenorphine hydrochloride	Sublingual tablet	400 mcg
609341000000000	3792511000001104	Pentazocine hydrochloride	Tablet	25 mg
2753541000033116	934110000000000	Morphine sulfate	Modified-release tablet	60 mg
2753441000033117	3078911000001101	Morphine sulfate	Modified-release tablet	30 mg
4817241000033113	14930611000001104	Morphine sulfate	Modified-release tablet	200 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
2753341000033111	3075211000001103	Morphine sulfate	Modified-release tablet	10 mg
2753641000033115	219511000000000	Morphine sulfate	Modified-release tablet	100 mg
575241000000000	36120311000001103	Fentanyl	Transdermal patch	75 mcg/ hr
575141000000000	36120211000001106	Fentanyl	Transdermal patch	50 mcg/ hr
11469241000033116	421136001	Fentanyl	Transdermal system	40 mcg/ hr
8962241000033118	23707711000001107	Fentanyl	Transdermal patch	37 mcg/ hr
575041000000000	36120011000001101	Fentanyl	Transdermal patch	25 mcg/ hr
3839341000033117	9752311000001101	Fentanyl	Transdermal patch	12 mcg/ hr
574941000000000	36119911000001103	Fentanyl	Transdermal patch	100 mcg/ hr
4893141000033110	14951911000001104	Fentanyl citrate	Sublingual tablet	100 mcg
4426141000033117	12875011000001104	Fentanyl	Transdermal patch	75 mcg/ hr
4426241000033112	12874911000001104	Fentanyl	Transdermal patch	50 mcg/ hr
4426341000033119	12874811000001109	Fentanyl	Transdermal patch	25 mcg/ hr
4426041000033116	12875111000001103	Fentanyl	Transdermal patch	100 mcg/ hr
6441041000033119	19487311000001103	Fentanyl	Transdermal patch	75 mcg/ hr
6440941000033112	19487111000001100	Fentanyl	Transdermal patch	50 mcg/ hr
6440841000033116	19486911000001100	Fentanyl	Transdermal patch	25 mcg/ hr
6440741000033114	19486711000001102	Fentanyl	Transdermal patch	12 mcg/ hr
6441141000033115	19487511000001109	Fentanyl	Transdermal patch	100 mcg/ hr
12347241000033113	34577211000001109	Dihydrocodeine / Paracetamol	Tablet	10 mg + 500 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
7859141000033110	20474611000001108	Dihydrocodeine / Paracetamol	Tablet	30 mg + 500 mg
7859041000033111	20474311000001103	Dihydrocodeine / Paracetamol	Tablet	20 mg + 500 mg
3248241000033114	9090111000001109	Fentanyl	Transdermal patch	75 mcg/ hr
3248141000033119	9089911000001100	Fentanyl	Transdermal patch	50 mcg/ hr
3248041000033118	9089711000001102	Fentanyl	Transdermal patch	25 mcg/ hr
3839441000033111	9751111000001108	Fentanyl	Transdermal patch	12 mcg/ hr
3248341000033116	9090311000001106	Fentanyl	Transdermal patch	100 mcg/ hr
4905410000000000	2836711000001108	Fentanyl	Transdermal patch	75 mcg/ hr
4904410000000000	2836411000001102	Fentanyl	Transdermal patch	50 mcg/ hr
4903410000000000	2837011000001109	Fentanyl	Transdermal patch	25 mcg/ hr
4902410000000000	2838111000001106	Fentanyl	Transdermal patch	100 mcg/ hr
13118841000033115	37122911000001104	Morphine anhydrous	Oral drops/ Oral solution	10 mg/1 ml
2183741000033111	8055110000000000	Tramadol hydrochloride	Modified-release tablet	400 mg
2183641000033119	1741100000000000	Tramadol hydrochloride	Modified-release tablet	300 mg
2183541000033115	1092110000000000	Tramadol hydrochloride	Modified-release tablet	200 mg
2183441000033116	8478110000000000	Tramadol hydrochloride	Modified-release tablet	150 mg
2078241000033110	4246110000000000	Tramadol hydrochloride	Modified-release tablet	75 mg
2078541000033112	2784110000000000	Tramadol hydrochloride	Modified-release tablet	200 mg
2078441000033111	9196110000000000	Tramadol hydrochloride	Modified-release tablet	150 mg

Product Code Id	Code	Drug substance name	Formulation	Strength
2078341000033117	216911000000000	Tramadol hydrochloride	Modified-release tablet	100 mg
8838541000033116	23047311000001100	Oxycodone hydrochloride	Modified-release tablet	5 mg
8838741000033112	23020811000001107	Oxycodone hydrochloride	Modified-release tablet	40 mg
8838641000033115	23020611000001108	Oxycodone hydrochloride	Modified-release tablet	20 mg
8838841000033119	23366811000001104	Oxycodone hydrochloride	Modified-release tablet	10 mg
3179641000033116	322556006	Cyclizine/ Dipipanone	Tablet	30 mg + 10 mg
469541000000000	39112511000001108	Dihydrocodeine tartrate	Modified-release tablet	90 mg
468741000000000	39112411000001109	Dihydrocodeine tartrate	Modified-release tablet	60 mg
462841000000000	322553003	Dihydrocodeine tartrate	Tablet	40 mg
468541000000000	322539003	Dihydrocodeine tartrate	Tablet	30 mg
469441000000000	39112611000001107	Dihydrocodeine tartrate	Modified-release tablet	120 mg
13582941000033117	8457311000001105	Dihydrocodeine tartrate	Oral suspension	2 mg/1 ml
442841000000000	36098611000001109	Dihydrocodeine tartrate	Oral solution	2 mg/1 ml
433541000000000	3037511000001107	Dihydrocodeine tartrate	Modified-release tablet	90 mg
433341000000000	3037111000001103	Dihydrocodeine tartrate	Modified-release tablet	60 mg
433441000000000	3037811000001105	Dihydrocodeine tartrate	Modified-release tablet	120 mg
433141000000000	3038211000001108	Dihydrocodeine tartrate	Tablet	40 mg
3851441000033111	8427711000001105	Dihydrocodeine / Paracetamol	Oral suspension	2 mg/ml + 100 mg/ml
5891241000033112	13893011000001104	Dihydrocodeine / Paracetamol	Oral solution	2 mg/ ml + 100 mg/ml

Product Code Id	Code	Drug substance name	Formulation	Strength
2850041000033116	3803111000001102	Codeine phosphate/ Paracetamol	Tablet	15 mg + 500 mg
6386541000033119	19207211000001106	Codeine phosphate/ Paracetamol	Effervescent tablet	15 mg + 500 mg
6431441000033110	19191911000001105	Codeine phosphate/ Paracetamol	Capsule	15 mg + 500 mg
3713410000000000	322504003	Codeine phosphate	Tablet	60 mg
3712410000000000	322503009	Codeine phosphate	Tablet	30 mg
3711410000000000	322502004	Codeine phosphate	Tablet	15 mg
3367410000000000	3420111000001109	Codeine phosphate/ Ibuprofen	Modified-release tablet	20 mg + 300 mg
3729410000000000	322307006	Codeine phosphate/ Paracetamol	Tablet	8 mg + 500 mg
13497541000033118	38555211000001104	Codeine phosphate/ Paracetamol	Effervescent tablet	8 mg + 500 mg
3730410000000000	322343000	Codeine phosphate/ Paracetamol	Effervescent tablet	8 mg + 500 mg
2948410000000000	322344006	Codeine phosphate/ Paracetamol	Capsule	8 mg + 500 mg
4590641000033113	11579211000001107	Codeine phosphate/ Paracetamol	Tablet	8 mg + 500 mg
12356141000033117	34625311000001101	Codeine phosphate/ Paracetamol	Tablet	60mg + 1 gram
13417741000033113	38063911000001100	Codeine phosphate/ Paracetamol	Oral solution	6 mg/ml + 100 mg/ml
3706410000000000	322341003	Codeine phosphate/ Paracetamol	Tablet	30 mg + 500 mg



Product Code Id	Code	Drug substance name	Formulation	Strength
32614100000000	322365000	Codeine phosphate/ Paracetamol	Effervescent tablet	30 mg + 500 mg
1588741000033112	322323006	Codeine phosphate/ Paracetamol	Effervescent powder	30 mg + 500 mg
29544100000000	322366004	Codeine phosphate/ Paracetamol	Capsule	30 mg + 500 mg
2875341000033110	3805611000001109	Codeine phosphate/ Paracetamol	Tablet	15 mg + 500 mg
6386441000033115	19230711000001108	Codeine phosphate/ Paracetamol	Effervescent tablet	15 mg + 500 mg
6431341000033116	19200211000001107	Codeine phosphate/ Paracetamol	Capsule	15 mg + 500 mg
5334541000033117	322379008	Codeine phosphate/ Paracetamol	Tablet	12.8 mg + 500 mg
12603741000033113	35544111000001100	Buprenorphine	Transdermal patch	70 mcg/ hr
12603641000033116	35543911000001104	Buprenorphine	Transdermal patch	52.5 mcg/ hr
12603541000033117	35543711000001101	Buprenorphine	Transdermal patch	35 mcg/ hr
11489841000033119	32197311000001107	Oxycodone hydrochloride	Modified-release tablet	80 mg
10984841000033113	31322211000001103	Oxycodone hydrochloride	Modified-release tablet	5 mg
11489741000033112	32196811000001100	Oxycodone hydrochloride	Modified-release tablet	40 mg
10985141000033118	31324011000001102	Oxycodone hydrochloride	Modified-release tablet	20 mg
10984941000033117	31323511000001107	Oxycodone hydrochloride	Modified-release tablet	10 mg
3343641000033113	9565311000001104	Buprenorphine	Transdermal patch	5 mcg/ hr
3343841000033114	9565911000001103	Buprenorphine	Transdermal patch	20 mcg/ hr

Product Code Id	Code	Drug substance name	Formulation	Strength
11077241000033112	31877211000001103	Buprenorphine	Transdermal patch	15 mcg/ hr
3343741000033116	9565611000001109	Buprenorphine	Transdermal patch	10 mcg/ hr
11029341000033114	31279211000001103	Buprenorphine	Transdermal patch	5 mcg/ hr
11029541000033119	31278611000001105	Buprenorphine	Transdermal patch	20 mcg/ hr
12106841000033113	34027411000001106	Buprenorphine	Transdermal patch	15 mcg/ hr
11029441000033115	31278911000001104	Buprenorphine	Transdermal patch	10 mcg/ hr
12409541000033116	34838811000001108	Buprenorphine	Transdermal patch	5 mcg/ hr
12409741000033112	34839211000001102	Buprenorphine	Transdermal patch	20 mcg/ hr
12409641000033115	34839011000001107	Buprenorphine	Transdermal patch	10 mcg/ hr
2737741000033115	35913911000001101	Buprenorphine	Transdermal patch	70 mcg/ hr
3343341000033117	9567211000001104	Buprenorphine	Transdermal patch	5 mcg/ hr
2737641000033112	35913811000001106	Buprenorphine	Transdermal patch	52.5 mcg/ hr
174241000000000	322492007	Buprenorphine hydrochloride	Sublingual tablet	400 mcg
2737541000033111	35913711000001103	Buprenorphine	Transdermal patch	35 mcg/ hr
2922641000033116	35913611000001107	Buprenorphine hydrochloride	Solution for injection	300 micg/1 ml
3343541000033112	9567311000001107	Buprenorphine	Transdermal patch	20 mcg/ hr
172641000000000	322498006	Buprenorphine hydrochloride	Sublingual tablet	200 mcg
11077041000033116	32038411000001102	Buprenorphine	Transdermal patch	15 mcg/ hr
3343441000033111	9567411000001100	Buprenorphine	Transdermal patch	10 mcg/ hr

Product Code Id	Code	Drug substance name	Formulation	Strength
12325741000033112	34551811000001100	Buprenorphine	Transdermal patch	5 mcg/ hr
12326041000033117	34552211000001108	Buprenorphine	Transdermal patch	20 mcg/ hr
12325941000033110	34552011000001103	Buprenorphine	Transdermal patch	10 mcg/ hr
11780841000033116	33548111000001103	Buprenorphine	Transdermal patch	70 mcg/ hr
11780741000033114	33546411000001107	Buprenorphine	Transdermal patch	52.5 mcg/ hr
11780641000033117	33546611000001105	Buprenorphine	Transdermal patch	35 mcg/ hr
11484541000033117	32484611000001108	Buprenorphine	Transdermal patch	70 mcg/ hr
11484441000033118	32484411000001105	Buprenorphine	Transdermal patch	52.5 mcg/ hr
11484341000033112	32484211000001106	Buprenorphine	Transdermal patch	35 mcg/ hr
12603441000033118	35544311000001103	Buprenorphine	Transdermal patch	5 mcg/ hr
12603341000033112	35545111000001101	Buprenorphine	Transdermal patch	20 mcg/ hr
12603241000033119	35544511000001109	Buprenorphine	Transdermal patch	10 mcg/ hr
13712041000033119	38811311000001100	Tramadol hydrochloride	Modified-release tablet	200 mg
12389041000033115	34733411000001103	Tramadol hydrochloride	Modified-release tablet	100 mg
10642141000033119	30721711000001109	Oxycodone hydrochloride	Modified-release tablet	80 mg
10642041000033118	30721411000001103	Oxycodone hydrochloride	Modified-release tablet	60 mg
10641441000033119	30719311000001101	Oxycodone hydrochloride	Modified-release tablet	5 mg
10641941000033112	30720811000001109	Oxycodone hydrochloride	Modified-release tablet	40 mg
10641841000033116	30721111000001108	Oxycodone hydrochloride	Modified-release tablet	30 mg

<b>Product Code Id</b>	<b>Code</b>	<b>Drug substance name</b>	<b>Formulation</b>	<b>Strength</b>
<b>10641741000033114</b>	30720511000001106	Oxycodone hydrochloride	Modified-release tablet	20 mg
<b>10641641000033117</b>	30720111000001102	Oxycodone hydrochloride	Modified-release tablet	15 mg
<b>10641541000033118</b>	30719811000001105	Oxycodone hydrochloride	Modified-release tablet	10 mg
<b>1063141000033116</b>	322604007	Pentazocine lactate	Suppository	50 mg
<b>26500000000000000</b>	36566111000001100	Codeine phosphate	Oral solution	5 mg/ ml
<b>2645041000033118</b>	38896411000001100	Codeine phosphate	Oral solution	3 mg/ ml

## Appendix S 11. Yearly characteristics of the colectomy cohort between 2010 and 2019

Variable	Years									
	2010 N= 8001	2011 N= 8470	2012 N= 8850	2013 N= 8963	2014 N= 9038	2015 N= 9614	2016 N= 10 009	2017 N= 10 286	2018 N= 10 794	2019 N= 11 130
Age, years	66.8	66.9	66.3	65.8	66.3	65.2	65.0	65.0	63.9	63.9
<b>Sex</b>										
Female	3938 (49.2)	4087 (48.3)	4377 (49.5)	4417 (49.3)	4489 (49.7)	4853 (50.5)	5130 (51.3)	5150 (50.1)	5561 (51.5)	5776 (51.9)
Male	4063 (50.8)	4383 (51.8)	4473 (50.5)	4546 (50.7)	4549 (50.3)	4761 (49.5)	4879 (48.8)	5136 (50.1)	5233 (48.5)	5354 (48.1)
<b>Preoperative opioid</b>										
Naïve	6326 (79.1)	6715 (79.3)	7097 (80.2)	7242 (80.8)	7345 (81.3)	7878 (81.9)	8307 (83.0)	8571 (83.3)	9178 (85.1)	9674 (86.9)
Currently	1404 (17.6)	1410 (16.7)	1440 (16.3)	1406 (15.7)	170 (15.2)	1396 (14.5)	1368 (13.7)	1393 (13.5)	1302 (12.1)	1161 (10.4)
Previously	271 (3.4)	345 (4.1)	313 (3.5)	315 (3.5)	323 (3.6)	340 (3.54)	334 (3.3)	322 (3.13)	314 (2.9)	295 (2.7)
<b>Index of Multiple Deprivation</b>										
1	1775 (22.2)	1934 (22.8)	1979 (22.4)	2015 (22.5)	2035 (22.5)	2154 (22.4)	2198 (21.9)	2328 (22.6)	2415 (22.4)	2459 (22.1)
2	1795 (22.4)	1820 (21.8)	1835 (20.7)	1928 (21.5)	1857 (20.6)	2005 (20.9)	2125 (21.2)	2203 (21.4)	2304 (21.4)	2390 (21.5)
3	1677 (20.9)	1719 (20.3)	1842 (20.8)	1768 (19.7)	1810 (20.0)	1957 (20.4)	2063 (20.6)	2064 (20.1)	2099 (19.5)	2270 (20.4)
4	1439 (17.9)	1617 (19.1)	1608 (18.2)	1726 (19.3)	1777 (19.7)	1786 (18.6)	1898 (18.9)	1961 (19.1)	2138 (19.8)	2116 (19.0)
5	1307 (16.3)	1370 (16.2)	1572 (17.8)	1519 (16.9)	1550 (17.2)	1703 (17.7)	1706 (17.0)	1710 (16.6)	1827 (16.9)	1883 (16.9)
Missing	8 (0.10)	10 (0.12)	14 (0.16)	7 (0.08)	9 (0.10)	9 (0.09)	19 (0.19)	20 (0.19)	11 (0.10)	12 (0.11)
<b>Charlson comorbidity index</b>										
0	1968 (24.6)	1859 (21.9)	2090 (23.6)	2249 (25.1)	2178 (24.1)	2433 (25.3)	2412 (24.1)	2361 (22.9)	2588 (23.9)	2591 (23.3)
1	608 (7.6)	649 (7.7)	668 (7.55)	648 (7.2)	639 (7.1)	725 (7.5)	772 (7.7)	791 (7.7)	791 (7.3)	789 (7.1)
≥2	5425 (67.8)	5962 (70.4)	6092 (68.8)	6066 (67.7)	6221 (68.8)	6456 (67.2)	6825 (68.2)	7134 (69.4)	7415 (68.7)	7750 (69.6)

Variable	Years									
	2010 N= 8001	2011 N= 8470	2012 N= 8850	2013 N= 8963	2014 N= 9038	2015 N= 9614	2016 N= 10 009	2017 N= 10 286	2018 N= 10 794	2019 N= 11 130
<b>Surgical approach</b>										
<b>Open</b>	5812 (72.6)	5915 (69.8)	5973 (67.5)	5796 (64.7)	5606 (62.0)	5661 (58.9)	5707 (57.0)	5523 (53.7)	5661 (52.5)	5385 (48.4)
<b>Minimally invasive</b>	2189 (27.4)	2555 (30.2)	2877 (32.5)	3167 (35.3)	3432 (37.9)	3953 (41.1)	4302 (42.9)	4763 (46.3)	5133 (47.5)	5745 (51.6)
<b>Cancer diagnosis</b>										
<b>No</b>	3367 (42.1)	3419 (40.4)	3725 (42.1)	3913 (43.7)	3947 (43.7)	4369 (45.4)	4452 (44.5)	4610 (44.8)	4858 (45.0)	5028 (45.2)
<b>Yes</b>	4634 (57.9)	5051 (59.6)	5125 (57.9)	5050 (56.3)	5091 (56.3)	5245 (54.6)	5557 (55.5)	5676 (55.2)	5936 (54.9)	6102 (54.8)
<b>Admission type</b>										
<b>Elective</b>	5735 (71.7)	5948 (70.2)	6229 (70.4)	6185 (69.0)	6340 (70.2)	6715 (69.8)	6963 (69.6)	7348 (71.4)	7609 (70.5)	7977 (71.7)
<b>Emergency</b>	2266 (28.3)	2522 (29.8)	2621 (29.6)	2778 (30.9)	2698 (29.9)	2899 (30.2)	3046 (30.4)	2938 (28.6)	3185 (29.5)	3153 (28.3)