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Health Technology Assessment

Extended Research Article

Gabapentin as an adjunct to multimodal pain regimens in surgical patients: the GAP placebo-controlled RCT and economic evaluation

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This article

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Abstract

Background: Gabapentin is an anticonvulsant medication with a United Kingdom licence to treat partial seizures and neuropathic pain. It is used off-licence for acute pain and is frequently added to multimodal analgesic regimens after surgery to try and reduce opioid use while controlling pain effectively.

Objective: To test the hypothesis that gabapentin reduces opioid use after major surgery and speeds up recovery, thereby reducing postoperative hospital length of stay compared to standard multimodal analgesia.

Design, setting and participants: The GAP study was a multicentre, blinded, randomised controlled trial in patients aged ≥ 18 years, undergoing cardiac, thoracic or abdominal surgery with an expected postoperative stay of ≥ 2 days in seven National Health Service hospitals. The trial was designed to provide 90% power to detect a difference of 12.5% in the proportion of participants discharged by the median length of stay in each specialty (500 participants/specialty), which was reduced to 80% (340 participants/specialty) due to COVID-19-related recruitment challenges.

Interventions: Participants were randomised 1 : 1 (stratified by surgical specialty) to receive either gabapentin (600 mg before surgery, 300 mg twice daily for 2 days after surgery) or placebo as an adjunct to multimodal pain regimens.

Main outcome measures: Primary outcome was length of stay. Secondary outcomes included acute and chronic (Brief Pain Inventory) pain, total opioid use, adverse health events, health-related quality of life (-EQ-5D-5L, Short Form questionnaire-12 items physical component score and mental component score), resource use; cost-effectiveness (outcome measure quality-adjusted life-years using EQ-5D, five-level version).

Results: One thousand one hundred and ninety-six (cardiac 500, thoracic 346, abdominal 350) participants consented and were randomised. Baseline characteristics were well balanced across the two groups: median age: 68 years; male sex 796/1195 (66.4%). Of the participants, 223/1195 (18.7%) did not receive all prescribed medication or received medication out of window. There was no difference in length of stay; median placebo (n = 589): 6.15, gabapentin (n = 595): 5.94 days [hazard ratio for discharge 1.07, 95% confidence interval (0.95 to 1.20), p = 0.26]. Opioid use *in-hospital* differed between surgical specialties (p = 0.001); in the abdominal specialty, it was significantly lower in the gabapentin group in 4 of the first 5 postoperative days [range −26% (−46% to 0%) to −36% (−52% to −14%)], with no differences in the cardiac specialty nor in the thoracic specialty beyond day 2. *During follow-up*, opioid use was similar in the two groups across all specialties. Acute pain beyond 24 hours was similar (p ≥ 0.15). The incidence of one or more serious adverse events was placebo: 189/595 (31.7%); gabapentin: 195/599 (32.6%). Health-related quality of life was similar [EQ-5D: mean difference −0.014 (−0.036 to 0.009), Short Form questionnaire-12 items physical component score: −0.87 (−1.71 to −0.04), Short Form questionnaire-12 items mental component score: at 4 weeks 0.74 (−1.71 to 0.42) and 4 months −0.55 (−1.61 to 0.51)]. Differences in costs and quality-adjusted life-years favoured placebo, and gabapentin was not considered cost-effective.

Limitations:

- GAP study tests the application of gabapentin to major body cavity surgery, but not major *non-body cavity* surgery, or *non-major* surgery.
- The fixed dose and limited duration of gabapentin may reduce applicability to certain populations.
- Reducing the power to 80% reduced the ability of the trial to detect a beneficial effect of gabapentin.

Conclusions: Among patients undergoing major cardiac, thoracic and abdominal surgery, adding gabapentin to multimodal analgesic regimes did not result in a change in length of stay, opiate use in two specialties, acute pain, or health-related quality of life, nor was it cost-effective.

Future work: Trials to assess the place of gabapentin in major *non-body cavity* surgery (e.g. joint replacement), or *non-major* (e.g. day-care) surgery should be considered.

Trial registration: This trial is registered as Current Controlled Trials ISRCTN63614165.

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Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
ASA	American Society of Anaesthesiologists
BPI	Brief Pain Inventory
CEAC	cost-effectiveness acceptability curve
COVID-19	coronavirus disease 2019
CRF	case report form
DMSC	Data Monitoring and Safety Committee
eMIT	electronic market information tool
EQ-5D-5L	EQ-5D five-level version
GAP	trial acronym
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
LoS	length of stay
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NRS	numerical rating scale (for measuring pain scores)
PCS	physical component score
PI	principal investigator
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SF-12	Short Form - 12 questionnaire
SmPC	summary of product characteristics
TSC	Trial Steering Committee

Plain language summary

Background

Gabapentin is a medicine used to treat epilepsy and pain caused by damaged nerves. Doctors have recently been using gabapentin to treat pain after an operation, with the intention of reducing the amount of morphine-type drugs (called 'opioids') needed while maintaining good pain relief. Doctors want to try to reduce the amount of opioid drugs because they cause side effects (such as dizziness and reduced breathing rate), often delaying discharge from hospital and leading to slower recovery. There is uncertainty about whether adding gabapentin to the usual painkilling drugs will result in good pain relief, with fewer side effects, and therefore faster recovery after surgery.

Who participated?

One thousand one hundred and ninety-five adults having major heart, lung or abdominal surgery who were expected to stay in hospital for at least 2 days after their surgery.

What was involved?

The participants were given either gabapentin or placebo (the same tablet but with no active drug) just before and twice daily for 2 days after their surgery. We measured how long they stayed in hospital after the surgery, the amount of opioid drugs they used, the amount of pain they had, what their quality of life was and how much they cost the National Health Service. We measured these during their hospital stay and at 4 weeks and 4 months after the surgery.

What did the trial find?

The trial found that there was no difference in the length of hospital stay, the number of adverse health events, or National Health Service costs between people who took gabapentin and those who took the placebo. People who took gabapentin for abdominal and thoracic surgery used fewer opioid-type drugs in-hospital after their surgery – but this did not translate into better pain control or fewer side effects. Therefore, this trial tells us that doctors should stop routinely giving gabapentin to people to reduce their pain after major surgery.

Scientific summary

Background

There are around 4.9 million episodes of surgery per year in the UK – 1.5 million of these are classified as *major* surgery, procedures which cost the NHS upwards of £5.5B per year. Up to 40% of patients report severe pain after surgery that negatively impacts their recovery. Optimal postoperative pain management not only meets the humanitarian imperative to alleviate suffering, but also provides benefits in terms of reduced length of hospital stay and reduced chronic postsurgical pain. These have consequent positive impacts on quality of life and well-being.

Gabapentin is a medicine frequently added to multimodal analgesic regimens after surgery to try and reduce the use of opioid drugs (which can cause somnolence, dizziness and respiratory depression) while controlling pain effectively. It is an anticonvulsant medication with a UK licence to treat partial seizures and neuropathic pain. It is also used off-licence for acute pain. It reduces voltage-gated calcium channel activity in the central neurones and therefore reduces neuronal firing and neurotransmitter release.

There are over 130 randomised controlled trials (RCTs) that have investigated gabapentin versus placebo in different surgical populations. Most are small (< 200 patients, median 80) and highly heterogeneous, both statistically and clinically. Because of the absence of evidence for both the benefits and harms of gabapentin in the perioperative setting, the UK National Institute for Health and Care Excellence issued a 'recommendation for research' in the most recent guidance for perioperative care.

Objectives

The GAP study aimed to test the hypothesis that gabapentin reduces opioid use after major surgery and speeds up recovery, thereby reducing postoperative hospital stay compared to standard multimodal analgesia.

Methods

Study design

A multicentre, parallel-group, placebo-controlled, pragmatic RCT comparing the effectiveness, cost-effectiveness and safety of gabapentin as an adjunct to standard multimodal analgesia.

Settings and participants

Participants were recruited from three surgical specialties (cardiac, thoracic and abdominal) in NHS secondary care centres. They were ≥ 18 years of age undergoing non-emergency surgery and were expected to stay in hospital and be able to swallow for at least 2 days after their surgery. Participants were excluded if they were already taking gabapentinoids or other anti-epileptics or receiving planned epidural anaesthesia/analgesia.

Interventions

The trial intervention was 600 mg gabapentin – two capsules – given preoperatively and 600 mg/day (300 mg in the morning and 300 mg in the evening) given postoperatively for 2 days when clinically able to swallow following extubation, within the multimodal analgesic regimens specified by local analgesic protocols. The comparator was a placebo capsule taken at the same time points as the active tablet.

Randomisation and blinding

Participants were randomly allocated to placebo or gabapentin in a 1 : 1 ratio stratified by surgical specialty. Randomisation was via a secure internet-based randomisation system, as close to the start of surgery as possible.

Participants, the clinical care team and the research nurse(s) responsible for participant follow-up were not informed of the allocation. Gabapentin capsules were over-encapsulated so that the capsules for active drug and placebo looked identical.

Follow-up

Patients were followed up daily until hospital discharge and then at 4 weeks and 4 months after surgery.

Outcomes

Primary outcome

The primary outcome was the time from start of surgery to hospital discharge in hours.

Secondary outcomes

- Opioid consumption in the period from surgery until hospital discharge.
- Opioid consumption from discharge until 4 months.
- Acute postoperative pain assessed using the numerical rating scale (NRS) completed at 1, 4 and 12 hours post surgery and then twice daily to discharge.
- Adverse events (AEs) from randomisation to discharge and serious adverse events (SAEs) up to 4 months post surgery.
- Health-related quality of life (HRQoL) measured using the EQ-5D, five-level version (EQ-5D-5L) questionnaire and Short Form -12 (SF-12) questionnaire completed pre-randomisation (baseline) and at follow-up at approximately 4 weeks and 4 months.
- Resource use to 4 months.
- Pain measured at baseline, 4 weeks and 4 months using the Brief Pain Inventory (BPI).

Sample size

The trial was designed to provide 90% power to detect a difference of 12.5% in the proportion of participants discharged by the median LoS in each specialty (500 participants per specialty). Due to recruitment challenges in the coronavirus disease 2019 (COVID-19) pandemic, and after discussion with the funder and Trial Steering Committee, the power was reduced to 80% (340 participants per specialty).

Statistical analyses

Analyses were directed by a pre-specified statistical analysis plan. Participants were grouped according to the randomised allocation (intention to treat). Those not undergoing surgery were excluded from the primary outcome analyses.

Specialty, treatment and the specialty by treatment interaction were included in all statistical models as fixed effects. For longitudinal outcomes, interactions with time were examined. Model fit was assessed graphically. Outcomes are adjusted for baseline where measured.

Time from surgery to hospital discharge (in hours) was compared using a Cox proportional hazards model. In-hospital deaths were censored at the specialty-specific maximum observed time-to-discharge for survivors. Opioid consumption was compared using log-linear models, and mixed-effects regression was used to compare NRS scores up to 30 days and HRQoL scores to 4 months. BPI pain scores (pain severity index and pain interference index) were compared using a two-part model, one for the occurrence of pain and the other a log-linear model for the pain score when present. The incidence of one or more SAE was compared using a generalised linear model. Subgroup analyses for the primary outcome included minimally invasive versus open surgery, sex and randomisation before or after the start of the COVID-19 pandemic. An exploratory analysis adjusting NRS scores for magnesium use was also included. Results are presented as treatment effects with 95% confidence intervals with placebo as the reference category. Analyses were performed using Stata, version 17.0 (StataCorp, College Station, TX, USA).

Economic evaluation

The within-trial economic evaluation was conducted from an NHS and Personal Social Services perspective, with the primary outcome of quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L. Resource use from day of surgery to 4 months was costed using published reference costs. The area under the curve was used to calculate QALYs accrued by each participant. Missing data were imputed. The incremental cost-effectiveness ratio was derived from the average costs and QALYs in each group, producing an incremental cost per QALY gained of using gabapentin compared to placebo. Bootstrapping was used to quantify uncertainty in costs and effects.

Results

Patient screening and recruitment

Recruitment took place at seven NHS Secondary care centres. Between 12 April 2018 and 20 May 2022, 3405 patients were assessed for eligibility, of whom 2209 were excluded. Therefore, 1196 patients (cardiac 500, thoracic 346, abdominal 350) were recruited and randomised; 596 to placebo and 600 to the gabapentin group. The numbers in the two groups were well balanced across surgical specialties.

Withdrawals

Twenty-seven participants withdrew after randomisation; 1 withdrew consent for their data to be used before surgery, 10 did not receive surgery in the study and 2 had their surgery moved to a non-study hospital (operative and primary outcome data provided for one). Two withdrawals were due to clinicians deeming the participant no longer eligible and 12 were patient decisions.

Protocol deviations

The most common deviation was where participants received fewer than the prescribed six doses of trial medication or received medication outside of window (223/1195, 18.7%). The deviations were well balanced across the groups. Thirteen of 16 ineligible participants recruited to the cardiac cohort were ineligible because the surgery was not carried out via a midline sternotomy, all having surgery via a thoracotomy incision. The were two ineligible participants recruited in the thoracic and abdominal specialties.

Patient follow-up

Follow-up data at 4 weeks and 4 months were available for 1153/1196 (96.4%) and 1120/1196 (93.6%) of randomised participants, respectively.

Numbers analysed

The analysis population consisted of 1195 randomised participants, (596 placebo group, 599 gabapentin group). One participant withdrew consent prior to surgery, at which point data collection stopped. This participant was excluded. In total, 1184 participants were included in the analysis of the primary outcome (589 placebo group, 595 gabapentin group). Ten of the 1195 participants were omitted as they did undergo surgery in the study and data were unavailable for a further one who had their surgery moved to a non-study hospital.

Baseline data

Baseline characteristics were well balanced across the placebo and gabapentin groups: median age was 69 (interquartile range 60–75) and 68 (59–74) years; male sex 388/596 (65.1%) and 406/599 (67.8%); White ethnicity 585/595 (98.3%) and 589/598 (98.5%) and body mass index 27.4 (24.4–31.2) and 27.1 (24.5–30.5) kg/m^2, respectively.

Primary outcome: hospital length of stay from surgery to discharge

There was no difference in LoS stay [median 6.15 and 5.94 days in the placebo and gabapentin groups, respectively, hazard ratio for discharge gabapentin:placebo, 1.07, (95% confidence interval 0.95 to 1.20), p = 0.26]. The hazard ratio for discharge was similar across the three surgical specialties (p = 0.94). The effect of gabapentin on time to discharge was similar in the open and minimal access subgroups, between males and females and between those operated before and after the start of the COVID-19 pandemic across all specialties.

Secondary outcomes

Opioid consumption

Opioid use (intravenous morphine equivalents) *in-hospital* differed between surgical specialties (p = 0.001) and over time (p = 0.010); in the abdominal specialty, it was significantly lower in the gabapentin group in 4 of the first 5 postoperative days [range −26% (−46%, 0%) to −36% (−52%, −14%)], with no differences in the cardiac specialty ($p \geq 0.21$ across each of the first 5 days) nor in the thoracic specialty beyond day 2 [day 1–27% (−46%, 2%); day 2–30% (−48%, −5%); range days 3–5, −5% (−31%, 29%) to −24% (−46%, 7%)]. *During follow-up*, opioid use was similar in the two groups across all specialties [−15% (−40%, 21%)].

Numerical rating of acute pain

In all specialties, acute pain (higher scores) reduced over time. The difference in mean NRS scores between the placebo and gabapentin groups also reduced over time; in the first 24 hours, the mean scores at rest and on movement were lower in the gabapentin group [median NRS placebo 3 (1–5), gabapentin 2 (0–4), mean difference (MD) −0.25 (−0.42, −0.08) at rest and NRS placebo 5 (3–7), gabapentin 5 (2–6), MD −0.25(−0.44, −0.069) on movement]. Beyond 24 hours, they were similar to the placebo group [e.g. median NRS at 48 hours: placebo 2 (0–4), gabapentin 2 (0–3), MD −0.12 (−0.28, 0.043) at rest and NRS placebo 4 (2–6), gabapentin 4 (2–6), MD -0.13 (−0.30, 0.041) on movement]. The pattern was the same across the three surgical specialties (p > 0.80). The conclusions were unchanged when accounting for magnesium use.

Short Form -12 questionnaire physical and mental component scores

The pattern of physical component scores over time differed across the three surgical cohorts, but the difference between the placebo and gabapentin groups was similar both over time (p = 0.53) and across the surgical cohorts (p = 0.47). On average, the physical component score was 0.87 points lower (−1.71, −0.04) in the gabapentin group compared to placebo.

The difference in the mental component score between the two groups changed over time (p = 0.056). At 4 weeks it was on average 0.74 points higher (−0.39, 1.87) in the gabapentin group and at 4 months it was 0.55 points lower (−1.61, 0.51) in the gabapentin group.

EQ-5D

The difference between the placebo and gabapentin groups was similar at 4 weeks and 4 months (p = 0.39) and across surgical cohorts (p = 0.83). On average, the score was 0.014 points lower (−0.033, 0.0095) in the gabapentin group compared to placebo.

Brief Pain Inventory

The number of participants reporting pain at both 4 weeks and 4 months was higher in the gabapentin group compared to the placebo group in all surgical specialties. However, where pain was reported, the severity of the pain [geometric mean ratio 0.99 (0.90, 1.08)] and interference of the pain [geometric mean ratio 1.07 (0.94, 1.22)] was similar.

Adverse events

Overall, 1453 AEs were reported in 433 participants in the placebo group compared to 1488 AEs in 420 participants in the gabapentin group. Additionally, 414 SAEs were reported in the placebo group and 505 in the gabapentin group. The events reported were reflective of the different surgeries, with more cardiac disorders in the cardiac specialty, and gastrointestinal disorders in the abdominal specialty. Most SAEs were considered to be either expected with gabapentin and/or anticipated after surgery. Less than 4% were considered unexpected (14/414, 3.4% in the placebo group, 16/505, 3.2% in the gabapentin group). There were 18 deaths, 8 in the placebo group and 10 in the gabapentin group. None were related to the intervention. The number of participants experiencing at least one SAE was similar in the two groups for participants having cardiac surgery [risk difference 0.015 (−0.21, 0.05)], higher in the gabapentin group for those having thoracic surgery [risk difference 0.06 (0.13, 0.107)] and lower in the gabapentin group for those having abdominal surgery [risk difference -0.051 (−0.095, −0.008)].

Economic evaluation

Mean QALYs to 4 months were 0.247 and 0.243 in the placebo and gabapentin groups, respectively, [MD −0.003 (−0.010, + 0.003)]. Total costs were £12,634 and £13,011 in the placebo and gabapentin groups, respectively [MD +£377 (−£790, +£1519)]. The probability that gabapentin is cost-effective at a willingness-to-pay threshold of £20,000 per QALY is 0.26. Gabapentin was unlikely to be cost-effective across a broad range of willingness-to-pay thresholds explored.

Discussion

Main findings

The GAP study has shown that among patients undergoing major surgery, the addition of gabapentin (600 mg preoperatively and 300 mg twice a day postoperatively 2 days) to multimodal analgesic regimes did not result in a change in hospital LoS, opiate use, acute pain, SAEs, quality of life or resource use, and it was not cost-effective. Overall, patients who took gabapentin had a higher incidence of pain at 4 months, albeit with similar severity to the placebo group when they did have pain. Those undergoing abdominal and thoracic surgery used less opioid medication while in-hospital, but not after discharge from hospital during follow-up. The lower opioid use did not translate into significant reductions in pain, but fewer patients suffered serious adverse effect(s) in the abdominal specialty. The increased incidence of pain at 4 months in the gabapentin group was also not seen in the abdominal surgery cohort. There were no other signals of either benefit or harm.

Strengths and limitations

The main study strength is the pragmatic trial design integrated in existing usual care pathways for a number of major surgical specialties across a number of NHS sites. It is also the first trial to assess the impact of gabapentin on hospital stay, quality of life and resource use after surgery. The major limitations were that the trial does not test the application of gabapentin to other major non-body cavity surgery (e.g. joint replacement), or non-major (e.g. day-care) surgery. It also included a non-variable dose of gabapentin, and the time-period of the intervention was restricted to 2 days after surgery.

Conclusion

Among patients undergoing major cardiac, thoracic and abdominal surgery, the addition of gabapentin (600 mg pr-operatively and 300 mg twice a day postoperatively for 48 hours) to multimodal analgesic regimes did not result in a change in hospital LoS, opiate use, acute pain, or quality of life, nor was it cost-effective.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN63614165.

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Chapter 1 Introduction

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Background

There are around 4.9 million episodes of surgery per year in the UK.[2] Up to 40% of patients report severe pain after surgery that negatively impacts their recovery.[3] Optimal postoperative pain management not only meets the humanitarian imperative to alleviate suffering, but also provides outcome benefits in terms of reduced length of hospital stay, and reduced chronic postsurgical pain.[4] These have consequent positive impacts on quality of life and well-being.[5,6] Many of the benefits of optimal analgesia come from its facilitation of earlier mobilisation, drinking and eating.[7] Pragmatic approaches to postoperative pain have moved management from unimodal to multimodal in an attempt to treat the multiple causes and modulators of pain (e.g. tissue damage, inflammation, neuronal damage, psychology), while minimising the adverse effects of high-dose single agents.

Current multimodal analgesic regimens used for major surgery include simple analgesics, opioids, regional analgesia and adjuvants.[8] Opioids are the key analgesic agents for managing moderate to severe pain.[8] However, they have poor efficacy for movement-associated pain and up to 80% of patients will experience side effects including confusion, nausea, vomiting, itching, constipation and respiratory depression. Opioid side effects increase the length of hospital stay, delay overall recovery and impact on quality of life.[9] Reliance on opioids after surgery also increases the risk of opioid dependence and long-term use.[10] Using this rationale, multiple agents have been applied in order to manage moderate and severe postoperative pain while minimising the use of systemic opioids. These include non-steroidal anti-inflammatory drugs, ketamine, neuraxial nerve stabilisers (e.g. tricyclic antidepressants and gabapentinoids), regional and neuraxial analgesia.[8]

Gabapentin

Gabapentin is an anticonvulsant medication with a UK licence to treat partial seizures and neuropathic pain. It is also used off-licence for acute pain, menopausal symptoms and oscillopsia.[11] It reduces voltage-gated calcium channel activity in the central neurones and therefore reduces neuronal firing and neurotransmitter release.[12–14] It is added to multimodal analgesic regimens after surgery to try and reduce opioid use while still controlling pain efficiently, although there is a large variation in its use in the perioperative setting across the UK.[15] There are over 130 randomised controlled trials (RCTs) that have investigated gabapentin versus placebo in different surgical populations. Most of these trials are small (< 200 patients, median 80) and highly heterogeneous, both statistically and clinically. These RCTs have been included in 18 systematic reviews that aimed to assess the effectiveness of gabapentin versus placebo in the perioperative period; 11 of these in surgical populations.[16–26] Gabapentin reduced opioid consumption and postoperative pain scores at 24 hours ($p < 0.001$) in all the reviews. No review assessed its impact on quality of life. The most recent systematic review was published in 2020[24] while recruitment to the GAP trial was ongoing. This review assessed the impact of gabapentin on length of hospital stay using data from eight trials ($n = 1165$), all of which provided very low to moderate quality evidence, and found no statistically significant difference in the length of hospital stay between the gabapentin and controls. Because of the absence of evidence for both the benefits and harms of gabapentin in the perioperative setting, the UK National Institute for Health and Care Excellence (NICE) issued a ‘recommendation for research’ in the most recent guidance for perioperative care.[8]

Major surgery

The use of gabapentin in the perioperative setting is most likely to yield benefits in major surgery which causes moderate to severe pain and therefore use of high-dose opiates. Increasing operative severity is associated with increased postoperative length of stay (LoS) and complications.[27] There are around 1.5 million of these procedures per year in the UK with a median LoS of 3.8 days and an interquartile range (IQR) of 3.6–4.0 days.[2] These major procedures cost the NHS around £5.5B per year. Reductions in length of postoperative hospital stay improve bed turnover, allowing hospitals to match demand with capacity for elective and emergency care. Reduced postoperative stays are also associated with reduced healthcare costs.[28]

Rationale

Optimal analgesia is critical for both patients and healthcare systems. Optimal analgesia allows patients to get out of bed faster and improves patient experience. This leads to more rapid discharge and thus improved efficiency and flow to the healthcare system. Reducing opioid use after surgery is a priority for both doctors and patients and is one of the central tenets of enhanced recovery programmes.[29] However, the current evidence base for gabapentin is not robust enough to allow for definitive evidence-based national guidelines in the perioperative setting.

Aims and objectives

The GAP trial aimed to compare the effectiveness, cost-effectiveness and safety of gabapentin as an adjunct to standard multimodal analgesia versus placebo for the management of pain following three types of major surgery (cardiac, thoracic and abdominal). The hypothesis to be tested was that gabapentin reduces opioid use after surgery and speeds up recovery, thereby reducing postoperative hospital stay compared to standard multimodal analgesia (usual care). Specific objectives were to estimate:

1. The difference between groups in the average length of hospital stay following surgery.
2. The difference between groups with respect to a range of secondary outcomes including assessment of efficacy (total opioid use, pain), measures of safety (adverse health events) and health-related quality of life (HRQoL) in the 4 months following randomisation.
3. The cost-effectiveness of gabapentin compared to usual care.

Chapter 2 Methods

Trial design

A multicentre, parallel-group, placebo-controlled, pragmatic RCT to compare the effectiveness, cost-effectiveness and safety of gabapentin as an adjunct to standard multimodal analgesia. Participants, clinical care teams and all members of the research team were blinded to the random allocation (*Figure 1*).

Criteria for progression from phase 1 to phase 2

During the first phase (12 months duration), integrated monitoring and feedback was used to maximise recruitment and adherence with the study medication. Progression from phase 1 to phase 2 was dependent on the following criteria being met when assessed 9 months after the start of recruitment:

- At least 60% of patients undergoing surgery were considered eligible for the trial (revising the eligibility criteria if necessary).
- At least 50% of eligible patients consented to randomisation after 6 months of active recruitment (lower consent rate expected initially as the trial team became familiar with the trial and how best to embed it in the clinical pathway).

In phase 2, the number of sites was increased.

Changes to trial design after commencement of the trial

There were several substantial amendments made to the protocol throughout the course of the trial. The changes relating to the trial design are summarised below. The approved protocol version in use when the trial opened to recruitment was version 5.0. Two substantial amendments prior to opening clarified.

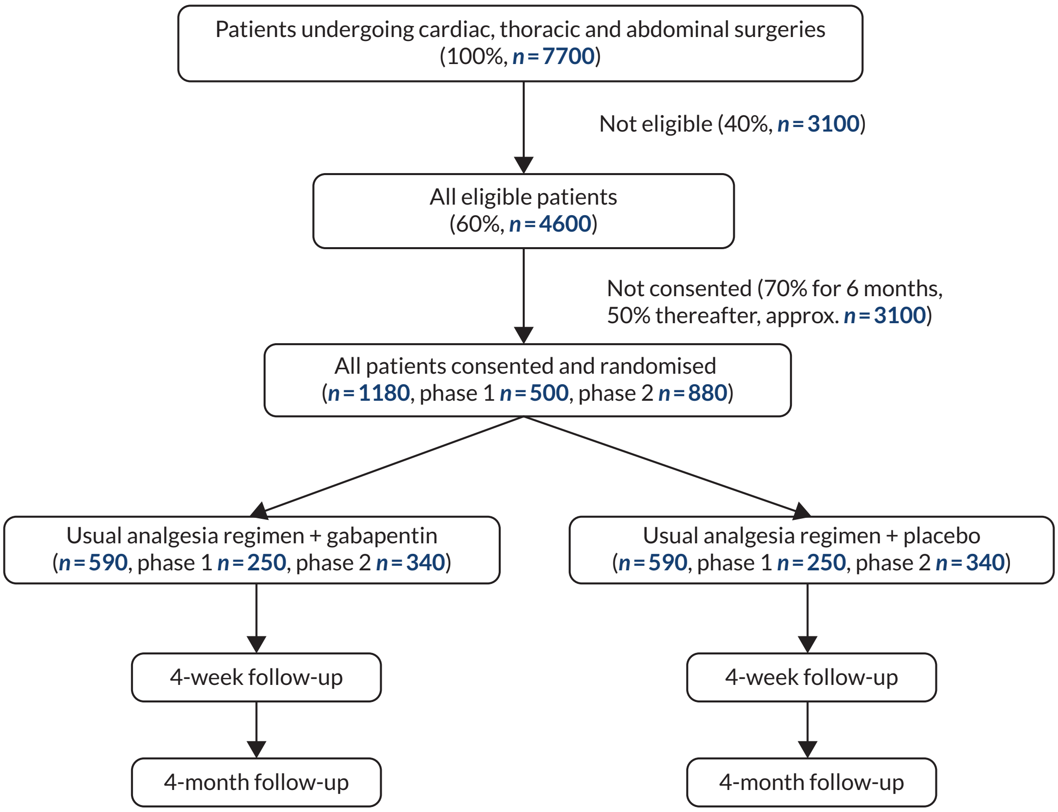

FIGURE 1 The trial schema for the GAP study. Note: the data shown in this figure relate to the planned number of participants, not the number actually recruited.

- how updates to the summary of product characteristics (SmPC) impacted the Reference Safety Information (RSI) in the protocol
- which serious adverse events (SAEs) were to be reported to the Sponsor
- which adverse events (AEs) were anticipated events of chemotherapy or radiotherapy and which were expected events of gabapentin

In addition, the trial medication packs were changed from eight to six capsules per pack. This was to reduce the chance of participants receiving extra doses of trial medication. Participants were due to receive six capsules in total: two as a loading dose preoperatively, and four postoperatively over 2 days. Packs originally contained eight capsules to allow for an extra loading dose to be given when surgery was delayed by more than 12 hours. Following this amendment, when a second loading dose was required, an additional pack of trial medication containing the same allocation as per the randomisation was dispensed.

Amendments to the protocol after the trial opened to recruitment were as follows:

Third amendment (approved 14 March 2019)

- Update to RSI to reflect updates to the SmPC.
- Clarification that appropriately trained/qualified non-medical clinicians were able to confirm and sign-off eligibility of participants.
- Addition of an optional diary for participants to record medication use following discharge from hospital.
- Revision to which SAEs were to be reported to the Sponsor.

Fourth amendment (approved 13 August 2019)

- Update to the number of sites participating in the trial.
- Update to RSI and further clarification as to which SAEs were to be reported to the Sponsor.

Fifth amendment (approved 17 January 2020)

- Clarification that the first postoperative dose of trial medication was due once the patient was deemed clinically able to swallow.
- Update to RSI to reflect updates to the SmPC.

Sixth amendment (approved 15 July 2021)

- Reduction of the sample size from 1500 to 1180, reflecting a reduction in power from 90% to 80% after agreement with the Funder and Sponsor as part of a recovery plan.
- Extension of the recruitment period by 20 months granted due delays in set-up of sites and impact of the COVID-19 pandemic on surgery in the NHS.
- Amendment to the consent process to allow consent to be given remotely; previously the protocol required consent to be given during a face-to-face consultation [developed in consultation with patient and public involvement (PPI) group, see Chapter 6 for further details].

Participants

Patient population

Patients were eligible to enter the study if all the following applied:

- Over 18 years of age.
- Undergoing non-emergency surgery:
  - Cardiac (surgery on the heart and great vessels carried out via midline sternotomy).

    - Thoracic (open or minimal access surgery on the lungs and surrounding tissues).
    - Abdominal (open or minimal access surgery within the abdominal cavity).

- Expected to stay in hospital at least until day 2 after surgery (where day 0 was the day of surgery).
- Expected to be able to swallow during the time period the study intervention was delivered.

Patients were not eligible to enter the study if any of the following applied:

- Taking anti-epileptic medication(s).
- Allergy to gabapentin.
- Already taking gabapentin or gabapentinoids.
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption.
- Planned epidural analgesia.
- Intended use of any gabapentinoids in the perioperative analgesic protocol other than the study medication (this includes but is not restricted to: pregabalin, enacarbil, gabapentin, 4-methylpregabalin and phenibut).
- Known renal impairment [for such patients, estimated glomerular filtration rate < 30 ml/minute/1.73 m^2].
- Weight < 50 kg.
- Unable to provide written informed consent to participate in the trial.
- Unwilling to participate in follow-up.
- A prisoner.
- Enrolled in another clinical trial and: (a) the patient is currently taking an investigational medicinal product as part of the other trial; or (b) co-enrolment is not permitted by the other trial; or (c) co-enrolment would be burdensome for the patient.

Changes to trial eligibility criteria after commencement of the trial

A non-substantial amendment to the protocol was approved in January 2018 (before the trial opened to recruitment) to add the inclusion criterion 'expected to be able to swallow during the time of the study intervention' for clarity. No other changes were made to trial eligibility.

Settings

Participants were recruited from three surgical specialties in NHS secondary care centres. One principal investigator (PI) was identified for each site. For sites where multiple specialties were open to recruitment, a clinical lead was identified for each specialty. Sites were permitted to open the trial in any or all the surgical specialties.

Trial interventions

Trial drug

The trial drug, gabapentin, is licensed to treat epileptic convulsions and neuropathic pain. It was used off-licence as part of the multimodal analgesic regimen. The trial drug comprised capsules containing 300 mg gabapentin or placebo, over-encapsulated to achieve blinding. The encapsulated trial medication was packaged into numbered packs, each containing six capsules, prepared by the trial pharmacy at the Sponsor NHS Trust.

Trial drug administration

The trial intervention was 600 mg gabapentin – two capsules – given preoperatively (ideally with the participant's premedication) and 600 mg/day (300 mg in the morning and 300 mg in the evening) given postoperatively for 2 days when clinically able to swallow following extubation (if applicable, see below), within the multimodal analgesic regimens specified by local analgesic protocols. Expert opinion and data from a systematic review (incorporating over 100 studies) were sought when establishing the study drug regimen. The comparator was a placebo capsule taken at the same time points as the active tablet within the multimodal analgesic regimens specified by local analgesic protocols. The preoperative loading dose was delivered by research staff and the postoperative doses could be delivered either by the clinical care teams or by research staff.

If the preoperative dose was administered and then the surgery postponed by more than 12 hours, a second preoperative dose of 600 mg of gabapentin was given preoperatively (ideally with the patient's premedication) for the rescheduled surgery. If a postoperative dose of trial medication was missed by < 6 hours, participants were given the 'missed' dose and continued the next scheduled dose as per the protocol. If a dose was missed by more than 6 hours, the dose was not given, the next scheduled dose was then given as per the protocol. If a participant was intubated for longer than 48 hours after the end of the operation, none of the postoperative study medication was administered.

Compliance with trial medication

Intervention compliance and trial medication accountability were checked locally at the study site and were monitored centrally. Compliance and reasons for non-compliance were also monitored by the Trial Steering Committee (TSC) and Data Monitoring and Safety Committee (DMSC).

Outcomes

Primary outcome

The primary outcome was the time in hours from start of surgery to hospital discharge. Postoperative hospital stay was chosen as it reflects the anticipated earlier recovery with gabapentin.

Secondary outcomes

Secondary outcomes were selected to assess the efficacy and safety of gabapentin and were as follows:

- Opioid consumption in the period from surgery until hospital discharge.
- Opioid consumption from discharge until 4 months.
- Acute postoperative pain assessed using the numerical rating scale (NRS) completed at 1 hour, 4 hours, 12 hours post surgery and then twice daily to discharge.
- Adverse health events from randomisation to discharge and SAEs up to 4 months post surgery.
- HRQoL measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) Short Form questionnaire-12 items (SF-12) questionnaires completed pre-randomisation (baseline) and at follow-up at approximately 4 weeks and 4 months. The EQ-5D-5L questionnaire comprises five questions and a visual analogue scale and the SF-12 comprises 12 questions. Responses to the five questions in the EuroQol-5 Dimensions (EQ-5D) are used to derive a utility score and the SF 12 responses are used to derive a summary physical component score (PCS) and a mental component score (MCS). For both instruments, higher scores indicate better quality of life. Minimal important differences in scores vary by participant population/intervention. For the EQ-5D utility score, differences in the range 0.04–0.08 have been suggested,[30] For the PCS and MCS of the SF-12, differences of 5 and 2 points, respectively, after surgery have been suggested.[31]
- Resource use to 4 months (measured during the hospital stay, at 4 weeks and 4 months).
- Pain measured at baseline, 4 weeks and 4 months using the Brief Pain Inventory (BPI). The BPI comprises 15 questions. Responses are used to derive a pain intensity index and a pain interference index. Higher scores indicate greater pain intensity/interference. For these indices, a difference of 2 points has been suggested as clinically important for chronic pain[32] but it is not defined for acute surgical pain.

Sample size

The study hypothesised that, on average, the postoperative hospital stay for participants allocated gabapentin will be shorter than for participants allocated the placebo medication. The sample size was chosen to test this hypothesis. To estimate the sample size, the median time to discharge was considered; taken as 5 days for cardiac and abdominal surgery, and 3 days for thoracic surgery. The target difference was set at 12.5%; this was the increase in the proportion of participants discharged by this median time that clinicians on the trial team felt would persuade clinicians to change practice. The sample sizes required to achieve 80% and 90% power, assuming a constant hazard ratio (HR) for the time to discharge, 5% statistical significance, a two-sided test, and allowing for 5% censoring due to death were 280 and 376 participants per surgical specialty, respectively. The sample size was set at 1500 in total, with a minimum of 376 per surgical stratum, which provided at least 90% power to detect a difference of 12.5% in each stratum and 80% power to detect a difference of 10% in any surgical strata recruiting in excess of 430 participants.

Changes to the sample size after commencement of the trial

Following minimal recruitment due to the COVID-19 pandemic in 2020–1, the trial progress was reviewed by the TSC and the Funder. At this stage, recruitment to the cardiac stratum was complete (500 participants randomised), but the thoracic and abdominal strata were incomplete. As part of the recovery plan, the trial team suggested that the power of the study should be reduced to 80%, reducing the recruitment target in the thoracic and abdominal strata from a minimum of 376 to 340 per stratum after adjusting for an observed non-compliance rate of 27%, giving a revised total sample of 1180 participants (500 cardiac, 340 thoracic, 340 abdominal).

Interim analyses

There were no interim analyses planned nor undertaken for GAP.

Randomisation

Participants were randomly allocated to either placebo or gabapentin in a 1 : 1 ratio. Randomisation took place through a secure internet-based randomisation system, as close to the commencement of surgery as possible. Randomisation was performed by an authorised member of the local research team after eligibility had been confirmed and written informed consent given. The randomisation scheme was prepared by a statistician independent of the trial team; the random allocations to gabapentin or placebo were stratified by site and specialty, so that each specialty at each site had approximately equal numbers of participants allocated to placebo and gabapentin, and allocations were blocked with varying block sizes. The randomisation system provided a unique pack code that was used to identify the trial medication. The mapping of the pack code to the randomised allocation was only known to the statistician who prepared the scheme and the trial pharmacy. It was not disclosed to any other member of the research team.

Blinding

Participants, clinical care and research teams

Participants, the clinical care team (i.e. their surgeon, anaesthetist and those responsible for their postoperative care) and the research nurse(s) responsible for participant follow-up were not informed of the allocation. Capsules containing gabapentin or placebo do not have a particularly strong or unusual smell or taste, so unblinding due to the characteristics of the drug was considered unlikely. Gabapentin capsules were over-encapsulated so that the capsules for active drug and placebo looked identical. We were aware that gabapentin may induce side effects that may inadvertently unblind participants. However, given that the side effects of gabapentin (e.g. drowsiness, dizziness and difficulty concentrating) are similar to those of morphine, and that participants were likely to view side effects as resulting from their whole experience (surgery and postoperative care), it was felt unlikely that any participant would definitively be able to attribute a specific side effect to gabapentin.

Trial statistician and core research team

The trial statistician and core team were blinded to the randomised allocation until all the primary analyses were completed; the allocations were labelled ‘A’ and ‘B’ in all data extracts and in all reports prepared during the conduct of the trial.

Assessment of blinding

The success of blinding was assessed using the Bang-blinding Index.[33] Participants were asked to complete the assessment at discharge and at the 4-month follow-up. The research nurse(s) responsible for data collection and follow-up of participants completed the Bang-blinding Index when the participant was ready for discharge.

Data collection

Overview

Data collection included the following elements:

1. a screening log of all non-emergency patients referred for cardiac, thoracic and abdominal surgery, and those who are approached for the trial (including the date when they were given the patient information leaflet)
2. patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility
3. consent information collected prior to randomisation in all participating patients
4. baseline information (e.g. history and planned operation and response to health status questionnaires) collected in all participating patients before randomisation
5. data relating to the participant's surgery and hospital stay (including opioid consumption and AEs) collected in all participating patients
6. study medication prescribed for all participating patients
7. data on acute postoperative pain (measured via NRS), persistent postsurgical pain (measured via the BPI), AEs and health status questionnaires collected during the hospital stay, at 4 weeks and at 4 months for all participating patients.

An overview of the schedule of data collection is given in *Table 1*.

Collection of health-related quality of life data

Baseline HRQoL and pain questionnaires were administered prior to randomisation. HRQoL and pain questionnaire data collected at 4 weeks and 4 months were completed on paper and/or by telephone according to participant preference.

Collection of resource use, medication and adverse event data

Resource use, medication data and SAEs after hospital discharge were captured by telephone; the research team contacted participants at mutually agreed times.

TABLE 1 Schedule of data collection

Data item	Pre randomisation	Pre surgery	Intraoperative	Post-surgery (until discharge)	Discharge	4 weeks	4 months
Sociodemographic details	✔						
Comorbidities	✔						
Routine clinical measures	✔				✔		
Resource use schedule					✔	✔	✔
SF-12	✔					✔	✔
EQ-5D-5L	✔					✔	✔
NRS pain score	✔[a]			✔[a]	✔		
Study medication		✔		✔[b]			
Opioid use	✔		✔	✔	✔	✔	✔
AEs				✔	✔		
SAEs				✔	✔	✔	✔
BPI	✔					✔	✔

a Routinely collected NRS pain scores as close as possible to the following time points were collected: pre randomisation, 1 hour, 4 hours, 12 hours post surgery and twice daily post surgery until discharge. NRS pain assessments were not possible in intubated patients.
b Trial medication was given morning and evening for 2 days following extubation (where applicable).

Serious and other AEs were recorded and reported in line with Good Clinical Practice guidelines. Data were collected from the time of consent until 4 months post randomisation. Events listed in the SmPC of gabapentin were considered *expected*. Events related to the surgery were considered *anticipated*, and these were deemed *unexpected* unless they were also listed in the SmPC. Many participants would go on to receive adjuvant chemotherapy or radiotherapy after surgery. Such treatments have a range of common serious side effects and toxicities, which were also considered *anticipated* for participants undergoing adjuvant chemotherapy and/or radiotherapy. The *expected* and *anticipated* events were listed in the trial protocol. Events that occurred that were not listed in the protocol were considered *unexpected*.

Safety data were reviewed regularly by the trial team and at least annually by the DMSC. Reporting to the Sponsor was required if an AE was considered serious (i.e. resulted in a hospital admission, prolonged a hospital admission, was life-threatening, resulted in persistent of significant disability or death) and *causally related* to the trial medication OR fatal. Reporting to the Medicines and Healthcare products Regulatory Agency, Research Ethics Committee and DMSC was required if a SAE was found to be both *unexpected and causally related* to trial medication.

Statistical methods

All analyses were directed by a pre-specified statistical analysis plan (SAP), which was finalised before the database was locked for analysis. The data are reported in line with the Consolidated Standards of Reporting Trials reporting guidelines.[34]

Summary statistics and analysis population

Data were described using summary statistics; mean and standard deviation (SD) for continuous variables (or median and IQR if distributions were skewed) and number and percentage for categorical variables. HRQoL questionnaires were scored according to the developer's scoring instructions, summary scales derived from the questionnaires are reported in summary tables.

Participants were grouped according to the randomised allocation (intention to treat). The analysis population consisted of all randomised participants, excluding those who withdrew and were unwilling for data already collected to be used. Data from any participant who withdrew and was unwilling for their data to be used were included in the study flow chart but not in any subsequent data tables or figures. Participants who did not undergo surgery (or had surgery at a non-study hospital and operative and outcome data were not available) were excluded from analyses of the primary outcome.

Modelling strategy

Specialty, treatment and the specialty by treatment interaction were included in all models as fixed effects. If statistically significant at the 10% level or less (i.e. between specialty differences are suggested), treatment effects for the whole cohort are omitted; otherwise, treatment estimates for the trial cohort as a whole are presented alongside the specialty-specific estimates.

For longitudinal outcomes, interactions with time (treatment by time, specialty by time and specialty by treatment by time) were examined. If statistically significant at the 10% level or less, results are presented for each time period separately; otherwise, overall estimates are given. Alternative covariance structures were considered and structure giving the lowest Akaike information criterion was chosen. Model fit was assessed graphically (e.g. plots of predicted values vs. residuals and normal probability plots). If the model was a poor fit, transformations (e.g. log transformation for data following a log-normal distribution) were considered.

All secondary outcome models are adjusted for baseline values fitted as a fixed effect. Missing baseline values were imputed using the specialty-specific median value.

Models used to compare primary and secondary outcomes

Primary outcome

Time from surgery to hospital discharge (in hours) was compared using a Cox proportional hazards model and treatment estimates are presented as HRs. In-hospital deaths were censored at the specialty-specific maximum observed time-to-discharge for survivors. Withdrawals before discharge were censored at withdrawal (if censored on the day of surgery, the time to withdrawal was assumed to be half a day). Any time spent in another hospital following discharge from the surgical unit but before discharge home was included (if the date of discharge from this hospital was not known, the time to discharge was censored at discharge from the surgical unit). The Efron method was used to account for tied times. Model assumptions were assessed graphically (e.g. using Schoenfeld residuals to assess proportionality of the hazards and Martingale residuals to assess model fit). Models were stratified by specialty and site.

Secondary outcomes

Derivation of opioid consumption is described in *Appendix 1*. Opioid consumption in the period to hospital discharge was compared between groups using a log-linear mixed-effects model with site and participant fitted as random effects, and indicators for each postoperative day (up to day 10). This analytical approach (as compared to analysing total consumption) allowed for the differing postoperative stays across the surgical specialties. Opioid consumption during follow-up was compared between groups using log-linear regression model, with clustering by site. Both models included daily opioid use at baseline (pre randomisation) fitted as a fixed effect.

Mixed-effects regression was used to compare NRS scores between groups up to 30 days. The effect of time since surgery (in hours) was modelled using fractional polynomial functions and an unstructured covariance structure. A two-dimensional polynomial was used for NRS at rest and a three-dimensional polynomial was used for NRS on movement. Site, participant and time (at the participant level) were included as random effects.

Longitudinal HRQoL scores (EQ-5D-5L and SF-12) were compared between groups using a linear mixed-effects model with site and participant fitted as random effects.

Brief Pain Inventory pain scores (pain severity index and pain interference index) were compared between groups using a two-part model; a mixed-effects logistic regression model comparing occurrence of pain versus no pain and a log-linear mixed effects model for the pain score, conditional on pain being present. Regression models of pain scores with no pain given a score of zero were explored but were a poor fit to the data.

Adverse events were all coded using Medical Dictionary for Regulatory Activities (MedDRA) and are reported by system organ class and preferred term. The incidence of one or more SAEs was compared between groups using generalised linear models to obtain risk differences and risk ratios with clustering by site.

The total dose of each non-opioid analgesic, over the hospital stay, was derived for each participant. Mean ratios were derived for each analgesic group and 95% confidence intervals (CIs) were estimated using bootstrapping (10,000 replications).

Subgroup analysis

Pre-specified subgroup analyses, comparing the primary outcome by minimally invasive versus open surgery, sex and randomisation before or after the start of the COVID-19 pandemic (taken as 23 March 2020), were performed. These were implemented by adding a treatment by subgroup interaction term into the Cox model. The subgroup analysis by minimally invasive versus open surgery was specified in the protocol. The others were not in the protocol but were added to the SAP at the request of the TSC.

Sensitivity and exploratory analyses

Two sensitivity analyses of the primary outcome, excluding ineligible participants and excluding participants from one site where there were concerns over data quality, were added to the SAP at the request of the Sponsor. They were not pre-specified in the protocol. An exploratory analysis adjusting the analyses of NRS at rest and on movement for magnesium use was also added to the SAP but was not included in the protocol. This was added because magnesium can be used as a form of pain relief in this patient population. Total magnesium use (in mmol/l) from baseline to discharge (fitted as a time-varying covariable) was included in the model.

Missing data

Missing data are described in footnotes to all tables. Rules for imputing missing data outlined in the SAP were dependent on the level of missing data. HRQoL scores (EQ-5D-5L, SF-12, BPI) met the threshold for multiple imputation. For other outcomes, participants with missing data were excluded. For HRQoL analyses, each subscale was imputed separately. Multivariable imputation by chained equations using predictive mean matching (of 10 nearest neighbours) was used to generate multiple complete data sets and results were combined using Rubin's rules. Factors included in the matching were baseline HRQoL score, treatment allocation, site and specialty. Results with and without imputation are presented.

Significance levels and adjustment for multiplicity

For hypothesis tests of treatment effects, two-tailed *p*-values of < 0.05 were considered statistically significant. Likelihood ratio tests were used in preference to Wald tests. No formal adjustment for multiplicity was made and the number of statistical tests performed should be considered when interpreting results.

The placebo is the reference group for all analyses. Results are presented as treatment effects with 95% CI.

All statistical analyses were performed with the use of Stata software, version 17.0 (StataCorp, College Station, TX, USA).

Economic evaluation

Aim

The economic evaluation aimed to estimate the incremental cost-effectiveness of gabapentin compared to placebo for the management of pain after major surgery, in line with the GAP trial.

Overview

The perspective of the evaluation was the UK NHS and Personal Social Services, and the perspective for outcomes was the patients' undergoing treatment. The primary outcome measure for the cost-effectiveness analysis was quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L.[35,36] Established guidelines on conducting economic evaluations set out by NICE were followed.[37] *Table 2* summarises the key aspects of the economic evaluation, and further details are provided below.

Form of analysis, primary outcome and cost-effectiveness decision rules

A cost-effectiveness analysis (specifically a cost–utility analysis) using QALYs as the primary outcome measure was conducted. QALYs combine both quantity and quality of life into a single measure. Incremental costs (the difference in mean costs between the gabapentin and placebo groups) were divided by incremental QALYs (the difference in mean QALYs between groups) and presented as the incremental cost-effectiveness ratio (ICER), which quantifies the incremental cost per QALY gained by switching from placebo to gabapentin. The economic evaluation analyses were performed on an intention-to-treat basis.

Gabapentin was considered cost-effective if the ICER fell below £20,000, which is generally considered as the threshold which NICE adopts for considering an intervention to be cost-effective.

Time horizon

A within-trial analysis, taking a 4-month time horizon from day-of-surgery, was conducted. It was anticipated that all major resource use for surgery and pain and complications relating to surgery would occur within this time frame, and therefore be captured.

TABLE 2 Summary of economic evaluation methods

Aspect of methodology	Strategy used in base-case analysis
Form of economic evaluation	Cost-effectiveness analysis for comparison between gabapentin and placebo
Perspective	NHS and Personal Social Services
Time horizon	A within-trial analysis, taking a 4-month time horizon
Data set	All randomised participants were included (see Patient population for eligibility criteria)
Costs included in analysis	Index admission:
	• Surgery
	• Preoperative, intraoperative and postoperative analgesics and local anaesthetics
	• LoS by ward type (including intensive care unit and high-dependency unit)
	• Investigations and treatments relating to complications, and SAEs
	Post-discharge:
	• Analgesia
	• Adjuvant therapy
	• Re-admissions to hospital
	• Outpatient and emergency department attendances
	• Community health and social care contacts
Utility measurement	EQ-5D-5L, administered at baseline (pre randomisation), and 4 weeks and 4 months post randomisation
QALY calculations	Assume that participants' utility changes linearly between utility measurements[a]
Adjustment for baseline utility	Regression used to adjust QALY calculations for differences in baseline utility
Missing data	Multiple imputation

a Participants' utility changes at a constant rate (in a straight line) between measurements.

Collection of resource use and costs

Resource use data were collected on all significant health service resource inputs for participants to the end of the 4-month follow-up period. Detailed resource use data collection was integrated into the trial case report forms (CRFs) for the index admission, and captured from participants at follow-ups at 4 weeks and 4 months post randomisation. The main resource use categories captured and costed are listed in *Table 3*, along with details of the sources of unit costs for each resource category. Costing decisions (such as resource use assumed for complications) were made without knowing the trial group allocation.

Surgery

Time in theatre was captured on the trial CRFs and used to cost the index surgery.

Treatment complications and serious adverse events

Trial CRFs captured postoperative complications that participants experienced, including cardiac, respiratory, gastrointestinal, renal, infective and neurological complications, and the need for reoperations. Clinical opinion was sought on the likely additional resource implications of each complication captured (CRF L), that were not already being captured. The CRFs also captured resource use around SAEs. SAEs were individually reviewed, and additional resources were costed, only if not already captured in complication costs, to avoid double counting. *Appendix 1*, *Table 25* through to *Appendix 1*, *Table 34* show all the complications, and the corresponding diagnostic tests and treatments assumed, and their unit costs.

TABLE 3 Resource use categories and sources of unit cost information

Resource	Source[a]	Sources of unit cost information
Initial surgery	CRF C1	ISD Scotland theatre costs[38]
Pre-, intra- and postoperative analgesics and local anaesthetics; analgesia prescribed at discharge and during follow-up	CRFs D1–D11, D13, D16, E2–E3, F2–F3	Electronic Marketing Information Tool;[39] Prescription Cost Analysis[40]
Initial stay in hospital post surgery by ward type	CRF D17	National Schedule of NHS Costs 2021–2[41]
Complications, including re-operations and SAEs	CRFs D14, E5, F6, S0–S4	National Schedule of NHS Costs 2021–2[41]
Adjuvant therapy	CRFs E4, F4	National Schedule of NHS Costs 2021–2[41]
Hospital re-admissions	CRFs E1, E5, F1, F6	National Schedule of NHS Costs 2021–2[41]
Outpatient and emergency department attendances	CRFs E1, E7, F1, F8	National Schedule of NHS Costs 2021–2[41]
Community health and social care contacts	CRFs E1, E8, F1, F9	Unit Costs of Health and Social Care 2022[42]

ISD, Information Services Division.
a C1–S4 are labels used to distinguish CRFs.

Hospital re-admissions, and other post-discharge primary and secondary health and social care visits

We reviewed the reasons for hospital re-admission, outpatient attendance and other primary and secondary care, and sought clinical opinion to clarify whether unexpected complications or events were unrelated to the index surgery. Any care totally unlinked to the trial was excluded, but given the range of surgery received by participants, there was very little health care we could be certain was unrelated.

Attaching unit costs to resource use

Unit costs for hospital and community healthcare resource use were largely obtained from national sources, for example, the National Schedule of NHS Costs for ward costs, scans and many complications; and Unit Costs of Health and Social Care for community costs.[41,42] Resources were valued in 2021–2 Great British pounds, and any unit costs from earlier years have been adjusted to 2021–2 prices using the NHS cost inflation index (NHSCII).[42] Costs of drugs given in hospital were taken where available from the electronic market information tool (eMIT), which provides the reduced prices paid for generic drugs in hospital, or from Prescription Cost Analysis data.[39,40] For a summary of the sources of unit cost information, see *Table 3*. For further details on all unit costs and their source, see *Appendix 1*, *Table 25* through to *Appendix 1*, *Table 34*.

Measurement of health-related quality of life and quality-adjusted life-years

Measurement of health-related quality of life

The EuroQol EQ-5D-5L questionnaire was used to measure HRQoL.[35,36] The EQ-5D is a generic measure of health outcome covering five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L was completed by participants at baseline (pre randomisation), and at 4 weeks and 4 months post randomisation. While data were gathered using the EQ-5D-5L (the five-level version, with five possible responses for each dimension), responses recorded on the instrument were converted into a single index value using the original three-level UK valuation set;[45] scores were then used to facilitate the calculation of QALYs. Utility values were calculated by mapping the five-level descriptive system to the three-level valuation set using the mapping function developed by Hernández-Alava and Pudney,[46] in line with NICE recommendations at the time of analysis.[37]

Calculation of quality-adjusted life-years

The QALY profile for each participant was estimated from surgery to 4 months, and the area under the curve of utility measurements was used to calculate the number of QALYs accrued by each participant. QALYs were calculated assuming that each participant's utility changes linearly (at a constant rate, i.e. in a straight line) between each measurement (baseline, 4 weeks and 4 months). For participants who died during the trial, their utility was assumed to change linearly between the preceding time point and the time of death, and to take the value of zero from death onwards.

Missing data

We first summarised the number of missing data for resource use and outcomes (EQ-5D-5L scores) descriptively. Exploratory analyses were conducted to explore the possible mechanisms and patterns of missing data.[47] Logistic regressions were used to explore associations between missingness and baseline variables, and missingness and previously observed outcomes. If the number of missing data was small (< 1% of cases), then unconditional or conditional mean imputation was considered as sufficient. However, we anticipated that it would be necessary to use multiple imputation to impute missing values. Multiple imputation is a flexible approach, which is valid if data are assumed to be missing at random (the probability that data are missing does not depend on the unobserved values, conditional on the observed data).[47,48]

Multiple imputation uses regression to predict *m* values for each missing data cell, and enables all key variables used in the economic evaluation and demographic data (both complete and incomplete) to be used to predict the values of missing data cells. In accordance with guidelines,[47,49] multiple imputation using chained equations was conducted, and the number of imputations set to be at least equal to the percentage of incomplete cases.[49] Multiple imputation was performed separately for each treatment group.

Multiple imputation can be conducted at an aggregated level of total costs for example, or at a disaggregated level of individual resource use items or EQ-5D domains. Given that imputing large numbers of variables may make the model difficult to estimate, a balance between the two is likely to be required. The patterns of missing data for resource use/costs and outcomes were used to determine the approach to multiple imputation. For example, data collected on a patient follow-up questionnaire may have similar patterns of missing data, in which case the total costs for that follow-up can be imputed rather than individual resource use items. For each variable with missing data, individual regressions were specified and tailored to the type of data being predicted. Linear regression with prediction mean matching was used, as it is particularly flexible.

Once multiple imputation had been conducted, tabulations and summaries of the observed and imputed data were compared to check the validity of the imputations. Rubin's rule was then used to summarise data across the *m* data sets.[50] This approach accounts for the variability both within and between imputed data sets and takes uncertainty in the estimated mean into account.

Adjustment for baseline utility

Given that baseline utility directly contributes to QALY calculations, it is important to control for any potential imbalances in baseline utility in the estimation of the mean difference in QALYs between treatment groups, to avoid introducing bias.[51] Regression adjustment also allows for regression to the mean and increases precision. If there was an imbalance at baseline, QALYs would be adjusted for baseline EQ-5D-5L.

Within-trial statistical analysis of cost-effectiveness results

Analyses were conducted in Stata version 18 and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

Initially descriptive summaries of resource use, costs and HRQoL were produced using means, SDs and standard errors (SEs) around the means. Cost data are typically positively skewed, but regardless of this, costs were summarised using the arithmetic mean, since it is this combined with the total number of patients which relates to the total budget impact of an intervention.

The ICER was derived from the average costs and QALYs gained in each trial group, producing an incremental cost per QALY gained of the gabapentin compared to placebo. Non-parametric bootstrapping of costs and QALYs was used to quantify the degree of uncertainty around the ICER. The number of bootstraps per imputed data set was set such that approximately 5000 bootstraps were run. Results are expressed in terms of a cost-effectiveness acceptability curve (CEAC), which indicates the likelihood that gabapentin is cost-effective for different levels of willingness to pay for health gain. While gabapentin is considered cost-effective if the ICER falls below £20,000, the ICERs and CEACs presented allow decision-makers to assess cost-effectiveness at a willingness-to-pay threshold of their choice.

Discounting

Costs and effects were not discounted as our time horizon was 4 months.

Sensitivity analysis

Univariate sensitivity analyses were used to investigate the impact on costs and cost-effectiveness results of variation in key parameters and major cost drivers, for example the unit costs of time in surgery and ward stays (see *Appendix 1*, *Table 35* for details). We also explored the impact of any high-cost participants (outliers).

Subgroup analysis

Two pre-planned subgroup analyses were undertaken for the cost-effectiveness analyses: the first compared gabapentin with placebo by specialty (cardiac, thoracic, abdominal) and the second compared gabapentin with placebo by specialty and type of surgery (open vs. minimal access). The impact of subgroups was evaluated using ordinary least squares regression predicting costs and QALYs, conditional on treatment group, subgroup and a treatment by subgroup interaction.

Chapter 3 Results: trial cohort

Study sites

Two sites opened to recruitment in phase 1 of the trial and recruited to all three surgical specialties. A further five sites were opened in phase 2. The study sites, surgical specialties and dates they opened to recruitment are given below:

Phase 1: Study sites and dates opened to recruitment

- Bristol Royal Infirmary, University Hospitals Bristol and Weston NHS Foundation Trust. Recruitment opened in the cardiac specialty 12 April 2018, abdominal specialty 21 May 2018, and thoracic specialty 15 June 2018.
- Southampton General Hospital, University Hospital Southampton NHS Foundation Trust. Recruitment opened in all three specialties 24 August 2018.

Phase 2: Study sites and dates opened to recruitment

- Musgrove Park, Somerset NHS Foundation Trust. Recruitment opened in the abdominal specialty 14 August 2019.
- Basildon University Hospital, Basildon and Thurrock University Hospitals NHS Foundation Trust. Recruitment opened in the abdominal specialty 16 August 2019.
- Blackpool Victoria Hospital, Blackpool Teaching Hospitals NHS Foundation Trust. Recruitment opened to the cardiac and thoracic specialties 21 August 2019.
- Royal United Hospitals Bath, Royal United Hospitals Bath NHS Foundation Trust. Recruitment opened to the abdominal specialty 6 December 2019.
- Royal Liverpool University Hospital, Liverpool University Hospital Foundation NHS Trust. Recruitment opened to the abdominal specialty 10 December 2021.

Patients screened and recruited

Between 12 April 2018 and 20 May 2022, a total of 3405 patients were assessed for eligibility, of which 2209 were excluded; 533 (15.7%) because they were ineligible at screening, 776 were not given study information/approached by the local team, 806 were approached but declined to take part, and 94 agreed to take part but did not proceed to randomisation. Therefore, 1196 patients (41.6% of eligible patients, 57.1% of patients approached) were recruited and randomised. The main reasons for screened patients not being recruited and randomised, by surgical specialty are shown in *Appendix 2*, *Table 36*. The eligibility rate and proportion of eligible patients approached were similar across the three surgical specialties (see *Appendix 2*, *Table 37*). The consent rate was slightly lower in the cardiac specialty (520/932, 56%) compared to the thoracic and abdominal specialties (384/600, 64% and 386/564, 68% respectively). Participant flow through the trial is shown in *Figure 2*.

Recruitment

Between 24 April 2018 and 20 May 2022, 1196 (cardiac 500, thoracic 346 abdominal 350) participants consented to take part and were randomised, 596 to the placebo group and 600 to the gabapentin group. The numbers in the two groups were well balanced in each surgical specialty. One participant withdrew consent for their data to be used after randomisation. A further 11 participants who did not undergo surgery (or had the surgery moved to a non-study hospital) were excluded from the primary analysis (see *Figure 2*). The final follow-up for the last participant was completed on 25 October 2022.

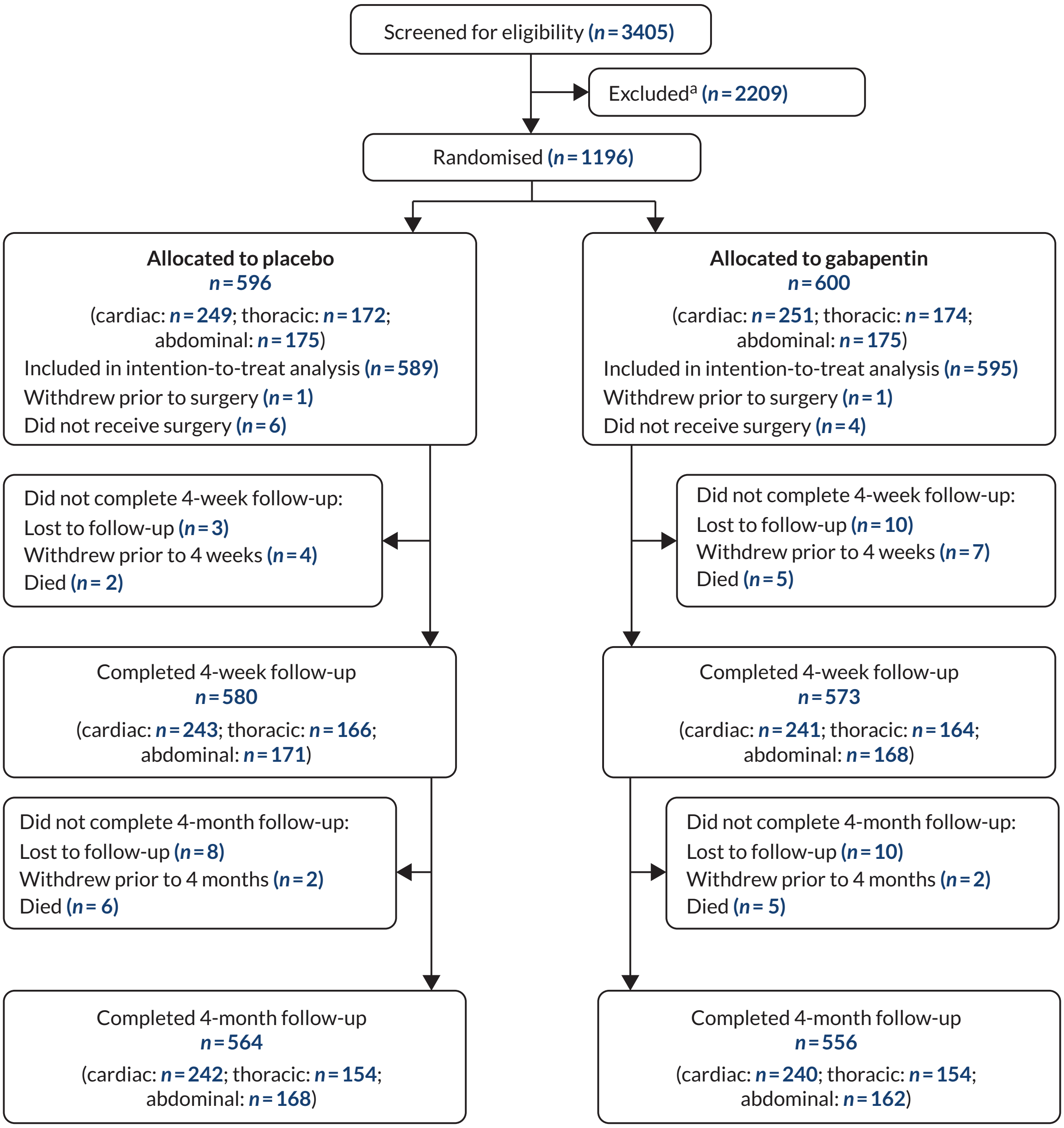

FIGURE 2 Participant flow. a, Reasons for exclusion are summarised in *Appendix 2*, *Table 36*.

Recruitment rate

When the trial was designed, the estimated recruitment rate was expressed in terms of the proportion of eligible patients recruited rather than as a recruitment per site per month. The proposed trial sites were asked to estimate the number of eligible surgeries performed each year and from this the anticipated recruitment rate was derived, allowing for a staggered opening of sites. It was estimated that 60% of patients would be eligible for the trial and that the participating surgical teams would initially recruit 30% of eligible patients but that as the trial became embedded in the clinical pathway this might increase to 50% after 6 months. The anticipated recruitment rate for each specialty at the two sites opened in phase 1 is given in the trial protocol (see https://fundingawards.nihr.ac.uk/award/15/101/16).

Progression from phase 1 to phase 2

The trial was assessed for progression approximately 9 months after the start of recruitment and used data to the end of January 2019. At that point, five of the six research teams (two sites, three specialties in each) had been actively screening and recruiting for a total of 28 months. No screening for potential participants had taken place at the abdominal specialty in Southampton due to insufficient resources. Over the 28 recruitment months, 916 patients had been screened and 697 (76%) were eligible so the first progression criterion was met. Over this time, 282 patients (40% eligible, 61% of patients approached to take part) had consented to join the trial, and 245 had been randomised compared to a target of 292. With 10 fewer consented than anticipated the Funder agreed the trial could continue to phase 2. The sites had opened later than expected and to address the recruitment shortfall further sites were opened in phase 2. The observed recruitment rate at each site over the full duration of the trial is given in *Appendix 2*, *Table 38*.

Impact of the COVID-19 pandemic on trial recruitment

Recruitment was severely impacted by the pandemic. Having randomised an average of 126 participants per quarter in 2019 and in the first quarter of 2020, recruitment dropped to just 9 randomisations in the period from April to June 2020. It increased slightly to 31 and 29 randomisations in the third and fourth quarters of the year, respectively, before declining again. In the first quarter of 2021, the trial was effectively paused as staff were redeployed to work on COVID-19-related research. No recruitment took place during this period (*Figure 3*). A request to extend the recruitment period was requested from the National Institute for Health and Care Research (NIHR). This was granted but with a reduced sample size. Recruitment to the cardiac cohort was complete (500 randomised). The sample size for the thoracic and abdominal cohorts was reduced to 340 providing 80% power rather than the original 90%.

Comparison of recruited and non-recruited patients

The age of trial participants was similar to those who were screened but did not join the trial because of ineligibility, non-approach or they did not wish to take part (see *Appendix 2*, *Table 39*).

Participant withdrawals

In total, 27 participants withdrew after randomisation. One withdrew consent for their data to be used, is excluded from all analyses, and is not shown in *Table 4*. Of the remaining 26, 11 did not undergo surgery (9 cancelled completely, 1 postposed and rescheduled after the study finished, 1 operated at a non-study hospital and no data available). The remaining 15 all underwent surgery (1 was moved to a non-study hospital, but operative and primary outcome data were provided). Twelve withdrawals were participant decisions, 2 were a clinical decision and 12 were for reasons related to the surgery (see *Table 4*).

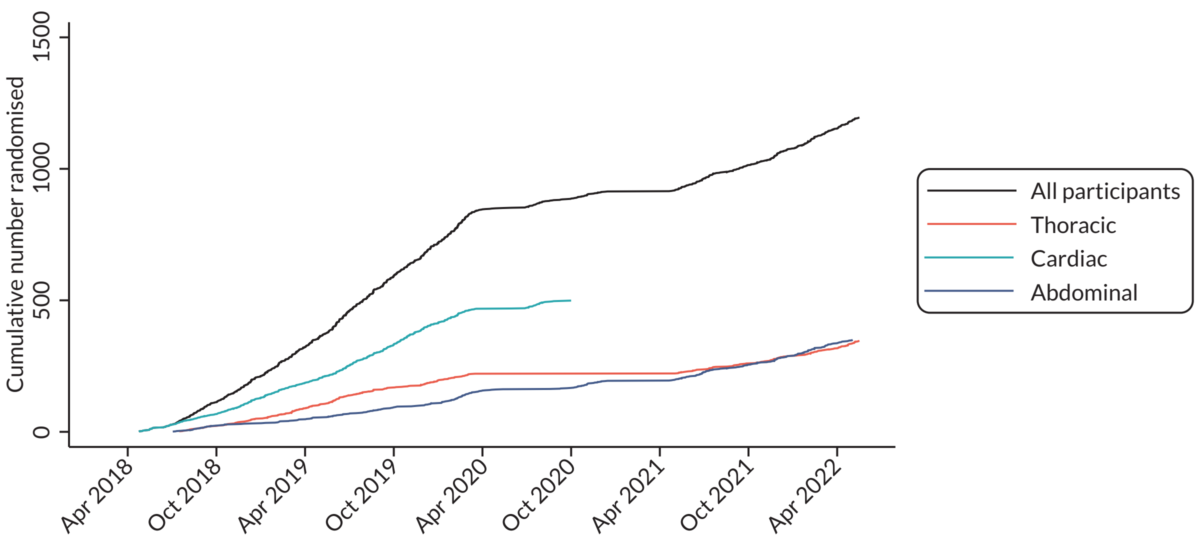

FIGURE 3 Trial recruitment.

TABLE 4 Reasons for withdrawal

Reasons for withdrawal	All participants (*n* = 1195) Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Number of withdrawals	13/596 (2.2%)	13/599 (2.2%)
Participant choice	***5/13 (38.5%)***	***7/13 (53.8%)***
Changed their mind about the trial	1/5 (20.0%)	2/7 (28.6%)
Does not wish to take the trial medication	1/5 (20.0%)	1/7 (14.3%)
No longer wishes to participate in follow-up	2/5 (40.0%)	1/7 (14.3%)
Other	1/5 (20.0%)	3/7 (42.9%)
Clinician choice		***2/13 (15.4%)***
Participant no longer eligible		2/2 (100.0%)
Other	***8/13 (61.5%)***	***4/13 (30.8%)***
Surgery cancelled	5/8 (62.5%)	4/4 (100%)
Surgery took place after the study ended	1/8 (12.5%)	
Surgery moved to another hospital[a]	2/8 (25.0%)	

a Operative details, including the primary outcome, were collected for one participant.

Protocol deviations

Protocol deviations are summarised in *Table 5*. The most common deviation was where participants received fewer than the prescribed six tablets of trial medication or received medication outside of window. Reasons for doses being missed included clinical decisions (18% of all prescribing deviations), participant refusal/withdrawal (18%), unable to swallow (17%), administrative errors (15%), logistical reasons (9%) and because the participant was discharged home earlier than anticipated (2%). The deviations were well balanced across the groups.

Thirteen of the 16 ineligible participants recruited to the cardiac cohort were ineligible because the surgery was not carried out via a midline sternotomy; they all had surgery via a thoracotomy incision. This occurred because the screening CRF specified 'non-emergency surgery' as an eligibility criterion but did not include 'midline sternotomy' (due to space limitations) and the full eligibility criteria in the protocol were not checked. Other reasons for ineligibility were surgery cancelled (preoperative doses given), taking antiepileptic topiramate (preoperative doses given), taking pregabalin (preoperative doses given), lactose intolerance (no trial medication given), allergy to gabapentin/pregabalin (no trial medication given), epidural anaesthesia (no trial medication given) and participation not permitted by another trial (all doses received).

Success of blinding

The Bang Blinding assessment of blinding asks for individuals to guess which treatment (i.e. gabapentin or placebo) received. If the blinding is successful, the proportion of correct guesses should be close to 50%. Results of the assessment of blinding of participants and research nurses responsible for outcome data collection are presented in *Table 6*. At discharge, 394/1145 (34.4%) of participants correctly identified the medication they had received and at 4 months 340/1102 (30.9%) were correct. A similar proportion of research nurses correctly identified the study medication received at discharge (368/1163, 31.6%). In all specialties, the percentage of correct responses was higher in the gabapentin group than in the placebo group but did not exceed 52% in any specialty. Reasons for the Bang Blinding assessment not being done are given in *Appendix 2*, *Table 40*.

TABLE 5 Protocol deviations

Deviations	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Any deviation	**43/249 (17.3%)**	**55/250 (22.0%)**	**29/172 (16.9%)**	**30/174 (17.2%)**	**37/175 (21.1%)**	**44/175 (25.1%)**	**109/596 (18.3%)**	**129/599 (21.5%)**
Ineligible patient randomised	10/249 (4.0%)	6/250 (2.4%)	0/172 (0.0%)	2/174 (1.1%)	2/175 (1.1%)	0/17 (0.0%)	12/596 (2.0%)	8/599 (1.3%)
Ineligible patient randomised and received at least one dose of trial medication	10/249 (4.0%)	6/250 (2.4%)	0/172 (0.0%)	0/174 (0.0%)	1/175 (0.6%)	0/175 (0.0%)	11/596 (1.8%)	6/599 (1.0%)
Participant received more than the prescribed doses of trial medication (including use of gabapentin from hospital stock)	4/249 (1.6%)	1/250 (0.4%)	1/172 (0.6%)	3/174 (1.7%)	4/175 (2.3%)	2/175 (1.1%)	9/596 (1.5%)	6/599 (1.0%)
Participant less than the prescribed doses of trial medication or received trial medication outside of specified time windows	35/249 (14.1%)	52/250 (20.8%)	29/172 (16.9%)	29/174 (16.7%)	35/175 (20.0%)	43/175 (24.6%)	99/596 (16.6%)	124/599 (20.7%)

TABLE 6 Bang Blinding index

Bang Blinding assessment	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Participant								
Guessed correctly – discharge	58/239 (24.3%)	112/236 (51.7%)	47/167 (28.1%)	69/165 (41.8%)	43/169 (25.4%)	55/169 (32.5%)	148/575 (25.7%)	246/570 (43.2%)
Guessed correctly – 4-month follow-up	45/237 (19.0%)	106/235 (45.1%)	42/151 (27.8%)	66/151 (43.7%)	33/166 (19.9%)	48/162 (29.6%)	120/554 (21.7%)	220/548 (40.1%)
Research nurse								
Guessed correctly – discharge	58/247 (23.5%)	102/244 (41.8%)	30/167 (18.0%)	73/167 (43.7%)	38/169 (22.5%)	67/169 (39.6%)	126/583 (21.6%)	242/580 (41.7%)

Note
Data are *n*/*N* (%).

Patient follow-up

The number of participants for whom follow-up data were available is presented in *Figure 2*. Follow-up data at 4 weeks and 4 months were available for 96.4% and 93.6% of randomised participants, respectively. Of the 66 participants not followed to 4 months, 27 had withdrawn (11 did not have surgery) and 18 had died.

Numbers analysed

The analysis population consisted of 1195 randomised participants. One randomised participant withdrew consent prior to surgery, at which point data collection stopped. This patient was excluded from the analysis population. The number of participants included in the analyses of each outcome is presented in *Table 7*.

Baseline characteristics

Baseline characteristics are summarised in *Table 8*. Characteristics were well balanced across the two groups. Overall, the median age was 68 years. The majority of participants were male (794/1195, 66.4%) and White ethnicity (1174/1193, 98.4%). In the thoracic and abdominal cohorts, most participants were American Society of Anaesthesiologists (ASA) grade II (mild systemic disease), while in the cardiac cohort, most were ASA grade III (severe systemic disease). Participants had a range of comorbidities (see *Table 8*). Overall, 497/1193 (41.7%) participants were taking analgesic medication at baseline, most were taking simple analgesia (see *Appendix 2*, *Table 41*). A quarter of those taking analgesia were taking opioids (128/497, 25.8%).

Surgical details are given in *Appendix 2*, *Table 42*. The median time from randomisation to surgery was 1.8 hours (IQR 1.5–2.4) in the placebo group and 1.7 hours (IQR 1.3–2.5) in the gabapentin group.

TABLE 7 Numbers included in primary analyses

Outcome	Number included in analysis, *n* (%)
Postoperative hospital stay (primary)	1184 (99%)[a]
Opioid consumption – from surgery to discharge	1183 (99%)
Opioid consumption – follow-up	1179 (99%)
Numerical rating scale – at rest	1175 (98%)[b]
Numerical rating scale – on movement	1173 (98%)[b]
SF-12 PCS	1102 (92%)[c]
SF-12 MCS	1102 (92%)[c]
EQ-5D questionnaire	1106 (93%)[d]
BPI – severity index	1096 (92%)[e]
BPI – interference index	1104 (92%)[f]
Any SAE	1195 (100%)

PCS, physical component score.
a Twelve participants did not undergo surgery (including the participant who did not permit their data to be used).
b Number with outcome data available. Missing baseline data were imputed using the specialty median score (*n* = 95).
c Number with outcome data available. Missing baseline data were imputed using the specialty median score (*n* = 48).
d Number with outcome data available. Missing baseline data were imputed using the specialty median score (*n* = 54).
e Number with outcome data available. Missing baseline data were imputed using the specialty median score (*n* = 78).
f Number with outcome data available. Missing baseline data were imputed using the specialty median score (*n* = 38).

TABLE 8 Baseline characteristics

Characteristic	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)[a]	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Demographics								
Age (years)[b]	70.0 (62–76)	69.0 (61–74)	69.0 (60–75)	67.0 (59–74)	66 (57–73)	66 (57–72)	69 (60–75)	68 (59–74)
Male sex	190/249 (76.3%)	196/250 (78.4%)	95/172 (55.2%)	94/174 (54%)	103/175 (58.9%)	116/175 (66.3%)	388/596 (65.1%)	406/599 (67.8%)
White	242/248 (97.6%)	242/249 (97.2%)	171/172 (99.4%)	173/174 (99.4%)	172/175 (98.3%)	174/175 (99.4%)	585/595 (98.3%)	589/598 (98.5%)
Asian/Asian British	3/248 (1.2%)	2/249 (0.8%)	1/172 (0.6%)	0/174 (0.0%)	0/175 (0.0%)	0/175 (0.0%)	4/595 (0.7%)	2/598 (0.3%)
Black/Black British	1/248 (0.4%)	0/249 (0.0%)	0/172 (0.0%)	0/174 (0.0%)	2/175 (1.1%)	1/175 (0.6%)	3/595 (0.5%)	1/598 (0.2%)
Mixed/multiple ethnic groups	1/248 (0.4%)	2/249 (0.8%)	0/172 (0.0%)	1/174 (0.6%)	0/175 (0.0%)	0/175 (0.0%)	1/595 (0.2%)	3/598 (0.5%)
Other ethnic group	1/248 (0.4%)	3/249 (1.2%)	0/172 (0.0%)	0/174 (0.0%)	1/175 (0.6%)	0/175 (0.0%)	2/595 (0.3%)	3/598 (0.5%)
Body mass index[c]	27.4 (24.3–31.3)	27.8 (25.3–30.8)	26.8 (24.1–30.8)	26.2 (23.1–29.7)	27.8 (24.9–31.5)	27.3 (24.6–30.7)	27.4 (24.4–31.2)	27.1 (24.5–30.5)
ASA grade								
I	5/245 (2.0%)	1/249 (0.4%)	5/171 (2.9%)	7/174 (4.0%)	8/174 (4.6%)	5/175 (2.9%)	18/590 (3.1%)	13/598 (2.2%)
II	22/245 (9.0%)	26/249 (10.4%)	106/171 (62.0%)	104/174 (59.8%)	125/174 (71.8%)	125/175 (71.4%)	253/590 (42.9%)	255/598 (42.6%)
III	203/245 (82.9%)	210/249 (84.3%)	60/171 (35.1%)	63/174 (36.2%)	40/174 (23.0%)	45/175 (25.7%)	303/590 (51.4%)	318/598 (53.2%)
IV	15/245 (6.1%)	12/249 (4.8%)	0/171	0/174	1/174 (0.6%)	0/175	16/590 (2.7%)	12/598 (2.0%)
Surgery received								
Lower GI surgery					137/175 (78.3%)	132/175 (75.4%)	137/596 (11.5%)	132/599 (11.0%)
Upper GI surgery					38/175 (21.7%)	43/175 (24.6%)	38/596 (3.2%)	43/599 (3.6%)
Medical history								
Non-diabetic	203/248 (81.9%)	204/249 (81.9%)	147/172 (85.5%)	154/173 (89%)	151/175 (86.3%)	151/175 (86.3%)	501/595 (84.2%)	509/597 (85.3%)
Oral medication	26/248 (10.5%)	28/249 (11.2%)	15/172 (8.7%)	10/173 (5.8%)	9/175 (5.1%)	12/175 (6.9%)	50/595 (8.4%)	50/597 (8.4%)
Injected medication	9/248 (3.6%)	8/249 (3.2%)	6/172 (3.5%)	6/173 (3.5%)	5/175 (2.9%)	9/175 (5.1%)	20/595 (3.4%)	23/597 (3.9%)
Diet controlled	10/248 (4.0%)	9/249 (3.6%)	4/172 (2.3%)	3/173 (1.7%)	10/175 (5.7%)	3/175 (1.7%)	24/595 (4.0%)	15/597 (2.5%)
Non-smoker	124/248 (50.0%)	124/249 (49.8%)	54/172 (31.4%)	52/174 (29.9%)	98/175 (56%)	92/175 (52.6%)	276/595 (46.4%)	268/598 (44.8%)
Ex smoker > 1 month	105/248 (42.3%)	97/249 (39%)	91/172 (52.9%)	83/174 (47.7%)	62/175 (35.4%)	69/175 (39.4%)	258/595 (43.4%)	249/598 (41.6%)
Current smoker	19/248 (7.7%)	28/249 (11.2%)	27/172 (15.7%)	39/174 (22.4%)	15/175 (8.6%)	14/175 (8%)	61/595 (10.3%)	81/598 (13.5%)

TABLE 8 Baseline characteristics (*continued*)

Characteristic	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)[a]	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Congestive cardiac failure	15/248 (6.0%)	23/249 (9.2%)	4/174 (2.3%)	4/174 (2.3%)	2/175 (1.1%)	4/175 (2.3%)	23/595 (3.9%)	31/598 (5.2%)
Peripheral vascular disease	11/248 (4.4%)	10/249 (4.0%)	3/172 (1.7%)	13/174 (7.5%)	1/175 (0.6%)	1/175 (0.6%)	15/595 (2.5%)	24/598 (4.0%)
Cerebrovascular disease	22/248 (8.9%)	18/249 (7.2%)	9/172 (5.2%)	5/174 (2.9%)	8/175 (4.6%)	6/175 (3.4%)	39/595 (6.6%)	29/598 (4.8%)
Hypertension requiring treatment	154/248 (62.1%)	172/249 (69.1%)	68/172 (39.5%)	60/174 (34.5%)	49/175 (28%)	49/175 (28%)	271/595 (45.5%)	281/598 (47%)
Myocardial infarction	40/248 (16.1%)	48/249 (19.3%)	11/172 (6.4%)	14/174 (8.0%)	7/175 (4.0%)	4/175 (2.3%)	58/595 (9.7%)	66/598 (11.0%)
Chronic pain syndrome	18/248 (7.3%)	19/249 (7.6%)	30/172 (17.4%)	17/174 (9.8%)	12/175 (6.9%)	10/175 (5.7%)	60/595 (10.1%)	46/598 (7.7%)
Neurological dysfunction	5/248 (2.0%)	9/249 (3.6%)	6/172 (3.5%)	3/174 (1.7%)	2/175 (1.1%)	5/175 (2.9%)	13/595 (2.2%)	17/598 (2.8%)
Chronic pulmonary disease	17/248 (6.9%)	20/249 (8.0%)	34/172 (19.8%)	40/174 (23.0%)	10/175 (5.7%)	14/175 (8.0%)	61/595 (10.3%)	74/598 (12.4%)
Rheumatological disease	7/248 (2.8%)	13/249 (5.2%)	21/172 (12.2%)	26/174 (14.9%)	14/175 (8.0%)	15/175 (8.6%)	42/595 (7.1%)	54/598 (9.0%)
Liver disease	2/248 (0.8%)	3/249 (1.2%)	5/172 (2.9%)	3/174 (1.7%)	12/175 (6.9%)	20/175 (11.4%)	19/595 (3.2%)	26/598 (4.3%)
Hemiplegia or paraplegia	0/248 (0.0%)	3/249 (1.2%)	0/172 (0.0%)	1/174 (0.6%)	0/175 (0.0%)	0/175 (0.0%)	0/595 (0.0%)	4/598 (0.7%)
AIDS/HIV infection	0/248 (0.0%)	1/249 (0.4%)	0/172 (0.0%)	0/174 (0.0%)	0/175 (0.0%)	0/175 (0.0%)	0/595 (0.0%)	1/598 (0.2%)
Renal disease	11/248 (4.4%)	7/249 (2.8%)	6/172 (3.5%)	3/174 (1.7%)	7/175 (4.0%)	2/175 (1.1%)	24/595 (4%)	12/598 (2.0%)
Malignancies (other than squamous skin cancer)	35/248 (14.1%)	31/249 (12.4%)	120/172 (69.8%)	117/174 (67.2%)	141/175 (80.6%)	144/175 (82.3%)	296/595 (49.7%)	292/598 (48.8%)

GI, gastrointestinal; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.
a One participant excluded as consent to use data withdrawn.
b Missing (placebo, gabapentin): cardiac (1, 0).
c Missing (placebo, gabapentin): cardiac (1, 1).

Note
Data are *n*/*N* (%) or median and IQR.

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Chapter 4 Results: primary and secondary outcomes

Primary outcome: time from surgery to hospital discharge

Primary analysis

Participants allocated to placebo had a median time to discharge of 6.15 days versus 5.94 days for those allocated to gabapentin. Six participants died before discharge, four underwent cardiac surgery (one placebo group, three gabapentin group) and two had thoracic surgery (both gabapentin group). As anticipated, the median stay was longest for those undergoing cardiac surgery with the participants undergoing thoracic surgery having the shortest median stay (*Figure 4* and *Table 9*). The HR for hospital discharge was similar across the three surgical specialties ($p = 0.94$) and did not differ significantly between the gabapentin and placebo groups (see *Table 9*).

Overall, 30 participants were delayed being discharged from hospital (17 placebo group, 13 gabapentin group), with similar numbers in each group in each of the specialties. The reasons for delayed discharge are summarised by group and specialty in *Appendix 2*, *Table 43*. Seventeen participants were discharged from the surgical unit to another hospital before being discharged home (11 in the placebo group, 6 in the gabapentin group). Fifteen of the 17 participants had undergone cardiac surgery. The other two (one in each group) had received thoracic surgery.

The numbers of participants discharged by 5 days after cardiac or abdominal surgery and by 3 days after thoracic surgery (the medians assumed in the trial power calculation) are shown in *Table 9*. The target 12.5% difference in favour of gabapentin was not met in any surgical specialty.

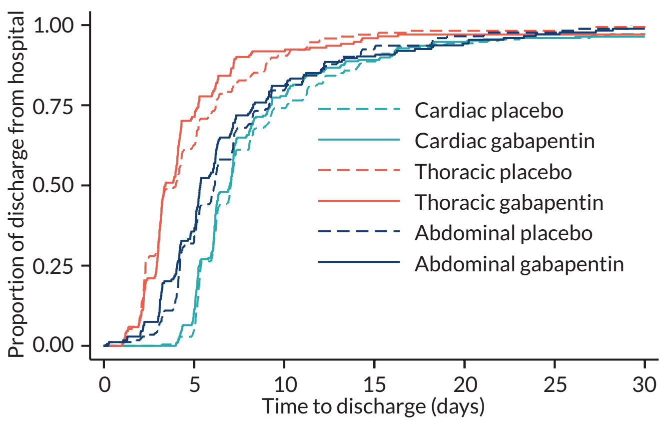
Sensitivity analyses

Sensitivity analyses excluding ineligible participants who underwent surgery and abdominal participants from one site where there had been concerns over data quality during the conduct of the trial were consistent with the primary analysis (see *Appendix 2*, *Table 44*)

Subgroup analyses

Minimal access versus open surgery

Use of minimal access versus open surgery is summarised in *Appendix 2*, *Table 45*. All cardiac procedures were open procedures. Approximately two-thirds of procedures in the thoracic specialty and half the procedures in the abdominal



Number at risk				
Cardiac placebo	247	64	14	7
Cardiac gabapentin	248	55	13	9
Thoracic placebo	169	16	3	1
Thoracic gabapentin	173	14	5	5
Abdominal placebo	173	35	6	0
Abdominal gabapentin	174	33	10	2

FIGURE 4 Time from surgery to discharge from hospital.

TABLE 9 Primary outcome: time to discharge from hospital after surgery

Time from surgery to hospital discharge (days)	Randomised to placebo	Randomised to gabapentin	HR (95% CI)	*p*-value
All participants (*N*)	589	595		
Median (IQR)	6.15 (4.22–8.97)	5.94 (4.08–8.04)	1.07 (0.95 to 1.20)	0.26
Cardiac (*N*)	247	248		
Median (IQR)	7.04 (5.38–10.24)	6.97 (5.27–9.20)	1.07 (0.89 to 1.28)	0.44
Discharged within 5 days	26.3%	27.0%		
Thoracic (*N*)	169	173		
Median (IQR)	3.99 (2.31–6.21)	3.41 (2.93–5.25)	1.09 (0.88 to 1.36)	0.42
Discharged within 3 days	48.5%	50.9%		
Abdominal (*N*)	173	174		
Median (IQR)	6.15 (4.21–9.17)	5.35 (4.06–8.29)	1.03 (0.83 to 1.29)	0.76
Discharged within 5 days	44.2%	52.3%		
Treatment by specialty interaction				0.94

N, number.

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specialty were minimal access procedures. The number of minimal access procedures was well balanced across the two groups. The effect of gabapentin on time to discharge was similar in the open and minimal access subgroups across all specialties (see *Appendix 2*, *Figure 21* and *Table 46*).

Male versus female participants

Approximately three-quarters of cardiac participants were male compared to around 50% males in the thoracic specialty and around two-thirds male in the abdominal specialty (see *Table 8*). The effect of gabapentin on the time to discharge was similar for male and female participants in all three specialties (see *Appendix 2*, *Figure 22* and *Table 46*).

Randomised before COVID-19 pandemic versus after the start of the pandemic

Over 90% of cardiac participants were randomised pre COVID-19 compared to around 65% in the thoracic specialty and around 45% in the abdominal specialty (see *Appendix 2*, *Table 47*). The effect of gabapentin on the time to discharge was similar for participants randomised pre and post the start of the pandemic in all three specialties (see *Appendix 2*, *Figure 23* and *Table 46*).

Secondary outcome: opioid consumption

Total opioid consumption in the two groups is summarised in *Table 10* and *Figure 5*. In the period from surgery to hospital discharge, the difference in total opioid consumption between the placebo and gabapentin groups differed by surgical specialty (p = 0.001) and over time (p = 0.010). In the cardiac specialty, total opioid use was similar in the two groups (see *Figure 5*). In the 2 days following thoracic surgery, there was a trend towards lower consumption in gabapentin group, while in the abdominal specialty, opioid consumption was lower in the gabapentin group, except at day 3 (see *Table 10* and *Figure 5*). After discharge, opioid consumption was similar in the two groups and across the three surgical specialty (see *Table 10* and *Figure 5*).

Non-opioid pain medication received is summarised in *Figure 6*. In the abdominal specialty, there is a trend towards less ibuprofen and aspirin use in hospital in the gabapentin group. Cardiac participants are routinely prescribed aspirin.

Further details of the opioid and simple analgesia and adjuvants received during participation in the trial are given in *Appendix 2*, *Table 48*.

Secondary outcome: numerical rating scale of pain

Primary analysis

A median of 14 NRS pain assessments were carried out on each participant (IQR: 11–21) in the period from surgery to hospital discharge. Pain at rest and on movement is summarised in *Figures 7* and *8*, respectively. In all specialties, acute pain (higher NRS scores) reduced over time. The difference in mean NRS scores between the placebo and gabapentin groups also reduced over time; in the first 24 hours, the mean scores at rest and on movement were lower in the gabapentin group, but beyond 24 hours they were similar to the placebo group (*Table 11*, *Figures 9* and *10*). The pattern was the same across the three surgical specialties (p > 0.80).

Numerical rating scale of pain: accounting for magnesium use

Use of magnesium is summarised in *Appendix 2*, *Table 49*. Almost half of all cardiac participants were given magnesium compared to 10% or less in the thoracic and abdominal specialties. Magnesium use was well balanced across the placebo and gabapentin groups. The impact of accounting for magnesium use in the analyses of pain scores at rest and on movement is shown in *Figures 9* and *10*. The adjustment had minimal impact on the treatment effect estimates and the conclusions are consistent with the primary analysis.

TABLE 10 Secondary outcome: opioid consumption

Outcome	Randomised to placebo Mean (median, IQR)	Randomised to gabapentin Mean (median, IQR)	Geometric mean ratio (95% CI)	*p*-value
Surgery to hospital discharge[a]				
All participants				
Day 0	15.1 (10.6, 4.9–20.9)	13.7 (9.0, 4.0–17.2)		
Day 1	26.4 (16.5, 8.1–33.0)	23.4 (13.2, 5.3–27.3)		
Day 2	17.1 (6.6, 2.0–17.0)	13.5 (6.6, 1.7–13.2)		
Day 3	13.2 (2.2, 0–9.9)	9.2 (3.0, 0–7.9)		
Day 4	9.0 (1.7, 0–6.6)	7.4 (1.4, 0–6.6)		
Day 5	8.3 (0, 0–6.6)	6.7 (0, 0–5.0)		
Cardiac				
Day 0	11.0 (7.0, 4.0–13.0)	12.2 (7.0, 2.6–12.0)	0.92 (0.71 to 1.19)	0.51
Day 1	27.5 (14.3, 7.3–27.7)	27.4 (13.7, 6–27.0)	0.88 (0.68 to 1.14)	0.34
Day 2	13.8 (5.0, 1.7–12.6)	13.3 (4.3, 0–9.9)	0.85 (0.65 to 1.10)	0.21
Day 3	12.4 (0, 0–5.3)	8.87 (1.0, 0–5.0)	1.14 (0.88 to 1.49)	0.32
Day 4	5.55 (0, 0–3.0)	6.4 (0, 0–3.6)	0.97 (0.74 to 1.27)	0.82
Day 5	5.4 (0, 0–2.0)	5.1 (0, 0–3.3)	0.91 (0.69 to 1.21)	0.53
Thoracic				
Day 0	18.6 (15.4, 8.3–24.3)	16.3 (13.2, 6.6–23.2)	0.76 (0.56 to 1.02)	0.07
Day 1	21.0 (16.5, 9.1–26.4)	17.0 (12.7, 5.3–21.5)	0.73 (0.54 to 0.99)	0.04
Day 2	13.5 (6.8, 3.0–17.2)	12.4 (6.6, 3.0–15.4)	0.70 (0.52 to 0.95)	0.02
Day 3	9.7 (4.0, 1.0–13.2)	10.4 (3.3, 0-9.9)	0.95 (0.69 to 1.29)	0.73
Day 4	7.9 (4.2, 1.7–10.7)	9.8 (3.6, 1.0–10.9)	0.80 (0.58 to 1.11)	0.19
Day 5	8.6 (4.0, 1.0–11.6)	13.1 (3.6, 1.7-9.9)	0.76 (0.54 to 1.07)	0.11
Abdominal				
Day 0	17.7 (16.2, 7.3–24.6)	13.2 (9.6, 3.3–18.5)	0.70 (0.52 to 0.93)	0.02
Day 1	30.3 (21.8, 9.9–40.3)	24.1 (14.5, 4.4–32.1)	0.67 (0.50 to 0.90)	0.007

continued

TABLE 10 Secondary outcome: opioid consumption (*continued*)

Outcome	Randomised to placebo Mean (median, IQR)	Randomised to gabapentin Mean (median, IQR)	Geometric mean ratio (95% CI)	*p*-value
Day 2	25.1 (11.8, 5.0–25.6)	14.9 (6.9, 1.7–19.8)	0.64 (0.48 to 0.86)	0.003
Day 3	16.9 (6.6, 0–13.2)	8.6 (3.3, 0–13.2)	0.87 (0.65 to 1.17)	0.35
Day 4	15.2 (4.0, 0–10.0)	7.9 (2.1, 0–10.0)	0.74 (0.54 to 1.00)	0.05
Day 5	13.8 (3.3, 0–12.8)	7.1 (0, 0–7.8)	0.69 (0.50 to 0.96)	0.03
Treatment by time by specialty interaction				0.80
Treatment by time interaction				0.010
Treatment by specialty interaction				0.001
Time by specialty interaction				< 0.001
During follow-up[b]				
All participants	116.4 (4.0, 0–87.1)	89.7 (3.3, 0–72.6)	0.85 (0.60 to 1.21)	0.30
Cardiac	76.1 (0, 0–59.4)	71.2 (0, 0–55.4)	1.12 (0.94 to 1.34)	0.16
Thoracic	142.1 (53.5, 3.96–153.9)	138.8 (32.1, 0–178.2)	0.66 (0.27 to 1.62)	0.30
Abdominal[c]	149.1 (0, 0–79.2)	68.3 (0, 0–41.6)	0.72 (0.39 to 1.35)	0.25
Treatment by specialty interaction				0.22

GMR, geometric mean ratio.
a Unable to calculate due to missing data (placebo, gabapentin): cardiac (2, 1), thoracic (4, 3), abdominal (2,1).
b Unable to calculate due to missing data (placebo, gabapentin): cardiac (3, 1), thoracic (4, 4), abdominal (3,1).
c Two extreme outliers were excluded from the analysis.

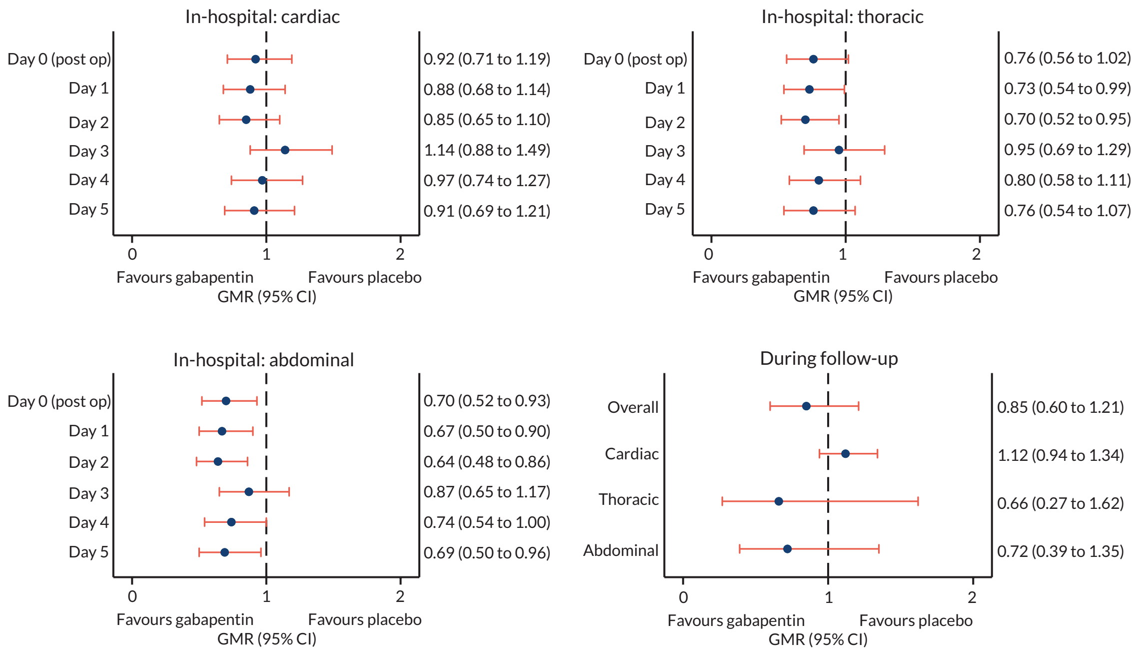

FIGURE 5 Opioid consumption following surgery to discharge and during follow-up. GMR, geometric mean ratio.

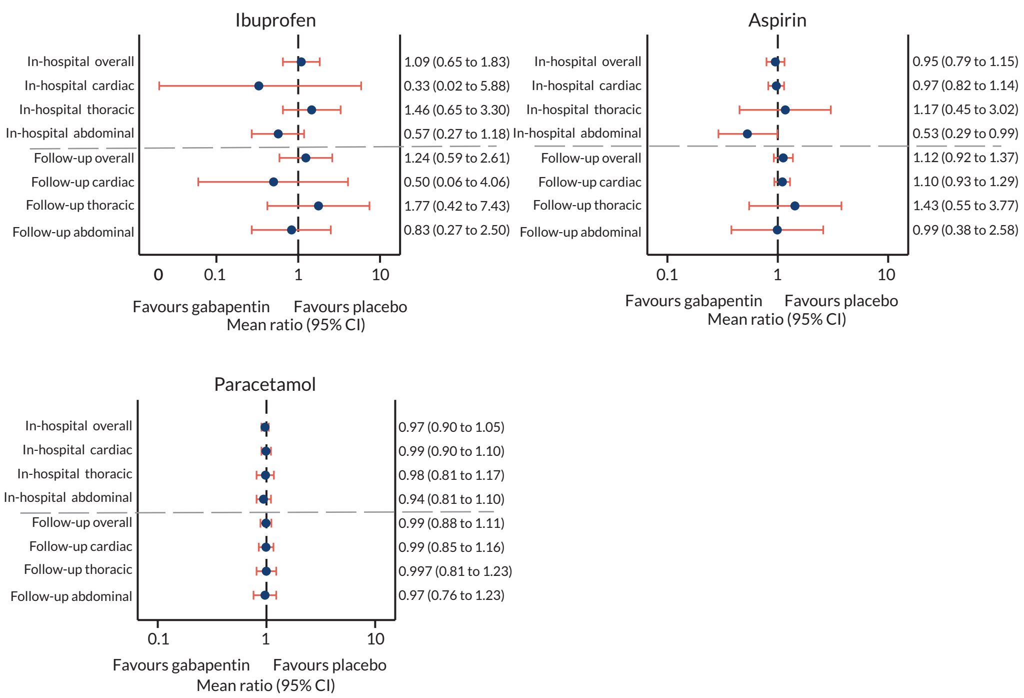

FIGURE 6 Non-opioid medication following surgery to discharge and during follow-up. Note: Plots show the mean ratio with CIs estimated using bootstrapping.

Secondary outcome: Short Form questionnaire-12 items physical and mental component scores

The PCS and MCS at baseline, 4 weeks and 4 months are summarised in *Table 12*, *Figures 11* and *12*. The pattern of PCSs over time differed across the three surgical cohorts, but the difference between the placebo and gabapentin groups was similar both over time ($p = 0.53$) and across the surgical cohorts ($p = 0.47$). On average, the PCS was 0.87 points lower (95% CI −1.71 to −0.04) in the gabapentin group than in the placebo group. In contrast, the difference in

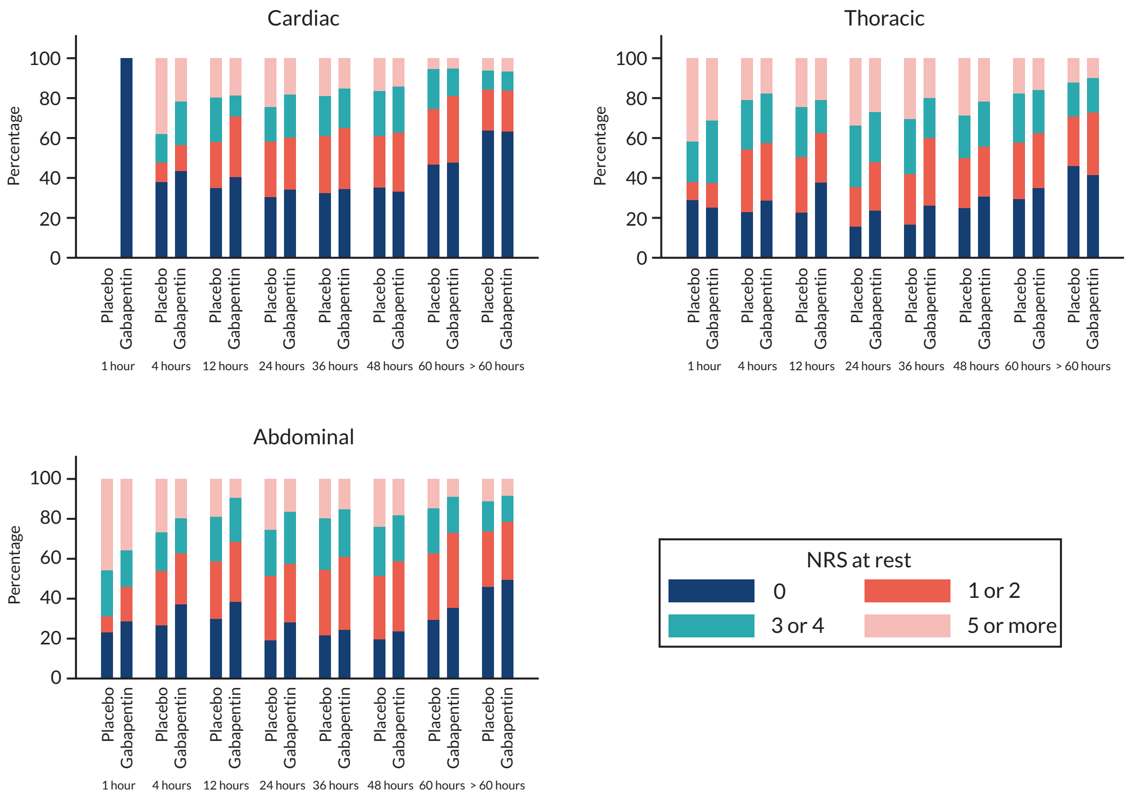

FIGURE 7 Numerical rating scale at rest.

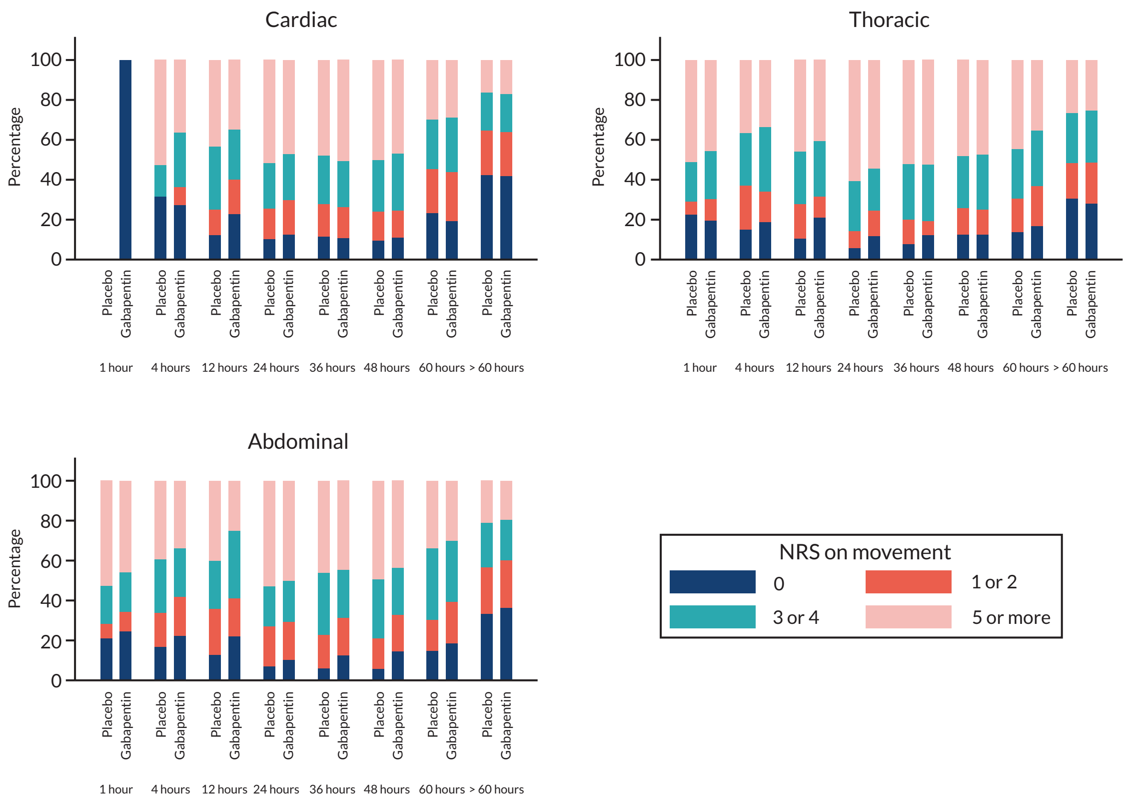

FIGURE 8 Numerical rating scale on movement.

TABLE 11 Secondary outcome: numerical rating scale of pain

Outcome	Randomised to placebo Mean (median, IQR)	Randomised to gabapentin Mean (median, IQR)	Mean difference (95% CI)	*p*-value
NRS at rest				
All participants				
1 hour[a]	3.99 (4, 1–6)	3.48 (4, 1–5)	−0.81 (−1.12 to −0.51)	< 0.001
24 hours[b]	2.87 (3, 1–5)	2.51 (2, 0–4)	−0.25 (−0.42 to −0.080)	0.004
48 hours[c]	2.43 (2, 0–4)	2.22 (2, 0–3)	−0.12 (−0.28 to 0.043)	0.15
72 hours[d]	1.72 (1, 0–3)	1.66 (1, 0–3)	−0.065 (−0.22 to 0.087)	0.40
96 hours[e]	1.33 (1, 0–2)	1.53 (1, 0–2)	−0.046 (−0.19 to 0.10)	0.54
120 hours[f]	1.32 (0, 0–2)	1.20 (0, 0–2)	−0.040 (−0.19 to 0.11)	0.59
Cardiac				
1 hour[g]				
24 hours	2.51 (2, 0–4)	2.28 (2, 0–4)	−0.082 (−0.31 to 0.14)	0.48
48 hours	2.02 (2, 0–3)	1.94 (1, 0–3)	−0.031 (−0.25 to 0.18)	0.78
72 hours	1.48 (1, 0–2)	1.34 (0, 0–2)	−0.013 (−0.22 to 1.94)	0.90
96 hours	1.01 (0, 0–2)	1.39 (0, 0–2)	−0.0097 (−0.22 to 0.20)	0.93
120 hours	0.88 (0, 0–1)	1.02 (0, 0–2)	−0.21 (−0.45 to 0.027)	0.082
Thoracic				
1 hour	3.96 (4, 0–6)	3.25 (3, 1–5)	−0.88 (−1.26 to −0.50)	< 0.001
24 hours	3.37 (3.5, 2–5)	2.88 (2, 1–5)	−0.33 (−0.62 to −0.035)	0.028
48 hours	2.77 (2, 1–5)	2.49 (2, 0–4)	−0.20 (−0.49 to 0.10)	0.187
72 hours	2.02 (1, 0–4)	1.91 (2, 0–3)	−0.14 (−0.44 to 0.15)	0.33
96 hours	1.88 (1, 0–3)	1.55 (1, 0–2)	−0.13 (−0.42 to 0.17)	0.40
120 hours	2.17 (1.5, 0–4)	1.84 (2, 0–3)	−0.12 (−0.42 to 0.17)	0.42
Abdominal				
1 hour	4.04 (4, 1–7)	3.88 (4, 2–6)	−0.79 (−1.17 to −0.42)	< 0.001
24 hours	2.85 (2, 1–5)	2.45 (2, 0–4)	−0.23 (−0.51 to 0.042)	0.097

continued

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Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 11 Secondary outcome: numerical rating scale of pain (*continued*)

Outcome	Randomised to placebo Mean (median, IQR)	Randomised to gabapentin Mean (median, IQR)	Mean difference (95% CI)	*p*-value
48 hours	2.73 (2, 1–4)	2.35 (2, 0–3)	−0.10 (−0.37 to 0.17)	0.46
72 hours	1.90 (1, 0–3)	1.95 (1, 0–3)	−0.05 (−0.31 to 0.21)	0.70
96 hours	1.53 (1, 0–2)	1.76 (1, 0–3)	−0.033 (−0.29 to 0.23)	0.80
120 hours	1.73 (1, 0–3)	1.30 (1, 0–2)	−0.030 (−0.29 to 0.23)	0.82
Treatment by time by specialty interaction				0.67
Treatment by time interaction				< 0.001
Treatment by specialty interaction				0.81
Time by specialty interaction				< 0.001
NRS on movement				
All participants				
1 hour[h]	4.76 (5, 3–7)	4.21 (5, 2–6)	−0.82 (−1.20 to −0.44)	< 0.001
24 hours[i]	4.86 (5, 3–7)	4.46 (5, 2–6)	−0.25 (−0.44 to −0.069)	0.007
48 hours[j]	4.32 (4, 2–6)	4.08 (4, 2–6)	−0.13 (−0.30 to 0.041)	0.14
72 hours[k]	3.20 (3, 1–5)	3.22 (3, 1–5)	−0.059 (−0.23 to 0.12)	0.51
96 hours[l]	2.67 (2, 0–4)	2.98 (3, 1–5)	−0.009 (−0.19 to 0.17)	0.92
120 hours[m]	2.28 (2, 0–4)	2.40 (2, 0–4)	0.032 (−0.15 to 0.22)	0.73
Cardiac				
1 hour[g]				
24 hours	4.63 (5, 3–7)	4.40 (5, 2–6)	−0.26 (−0.54 to 0.016)	0.065
48 hours	4.20 (4, 2–6)	4.15 (4, 2–6)	−0.14 (−0.40 to 0.12)	0.30
72 hours	3.17 (3, 1–5)	2.99 (3, 1–4)	−0.06 (−0.32 to 0.19)	0.63
96 hours	2.29 (2, 0–4)	2.92 (3, 1–5)	−0.013 (−0.27 to 0.25)	0.92
120 hours	1.82 (1, 0–3)	2.17 (2, 0–4)	0.029 (−0.23 to 0.29)	0.83
Thoracic				
1 hour	4.79 (5, 3–7)	3.97 (4, 1–6)	0.78 (−1.23 to −0.33)	0.001
24 hours	5.14 (5, 4–7)	4.71 (5, 3–7)	−0.21 (−0.55 to 0.13)	0.23

TABLE 11 Secondary outcome: numerical rating scale of pain (*continued*)

Outcome	Randomised to placebo Mean (median, IQR)	Randomised to gabapentin Mean (median, IQR)	Mean difference (95% CI)	*p*-value
48 hours	4.27 (4, 2–7)	4.13 (4, 2–6)	−0.086 (−0.43 to 0.26)	0.63
72 hours	3.25 (3, 0–5)	3.70 (3.5, 2–5)	−0.012 (−0.36 to 0.34)	0.95
96 hours	3.69 (3, 0–6)	3.23 (3, 1–5)	0.038 (−0.32 to 0.39)	0.83
120 hours	3.46 (3, 1–5.5)	3.34 (3, 1–5.50)	0.080 (−0.28 to 0.44)	0.67
Abdominal				
1 hour	4.71 (5, 2–7)	4.63 (5, 3–7)	−0.86 (−1.32 to −0.40)	< 0.001
24 hours	4.89 (5, 3–7)	4.29 (4, 2–6)	−0.29 (−0.61 to 0.035)	0.080
48 hours	4.56 (4, 3–7)	3.93 (4, 2–6)	−0.16 (−0.48 to 0.15)	0.31
72 hours	3.22 (3, 1–5)	3.23 (3, 1–5)	−0.09 (−0.41 to 0.023)	0.58
96 hours	2.71 (2.5, 1–4)	2.95 (2.5, 0–5)	−0.040 (−0.36 to 0.28)	0.81
120 hours	2.55 (2, 0–4)	2.47 (2, 0–4)	0.0013 (−0.32 to 0.33)	0.99
Treatment by time by specialty interaction				0.79
Treatment by time interaction				< 0.001
Treatment by specialty interaction				0.94
Time by specialty interaction				< 0.001

a Not recorded in time window (placebo, gabapentin): thoracic (74, 69), abdominal (123, 116).
b Not recorded in time window (placebo, gabapentin): cardiac (31, 37), thoracic (13, 20), abdominal (14, 18).
c Missing in time window (placebo, gabapentin): cardiac (28, 39), thoracic (39, 32), abdominal (21, 20).
d Missing in time window (placebo, gabapentin): cardiac (39, 56), thoracic (84, 85), abdominal (31, 42).
e Not recorded in time window (placebo, gabapentin): cardiac (62, 56), thoracic (107, 121), abdominal (53, 62).
f Missing in time window (placebo, gabapentin): cardiac (76, 86), thoracic (124, 142), abdominal (86, 87).
g Not captured as participants were ventilated after surgery.
h Not recorded in time window (placebo, gabapentin): thoracic (78, 72), abdominal (124, 118).
i Not recorded in time window (placebo, gabapentin): cardiac (36, 38), thoracic (14, 22), abdominal (15, 17).
j Missing in time window (placebo, gabapentin): cardiac (30, 41), thoracic (40, 34), abdominal (24, 21).
k Missing in time window (placebo, gabapentin): cardiac (40, 57), thoracic (84, 86), abdominal (33, 43).
l Not recorded in time window (placebo, gabapentin): cardiac (64, 58), thoracic (107, 121), abdominal (53, 65).
m Missing in time window (placebo, gabapentin): cardiac (77, 87), thoracic (124, 142), abdominal (87, 90).

Note
Statistical models used to obtain treatment estimates use all NRS assessments (median 14 assessments), not just those summarised here.

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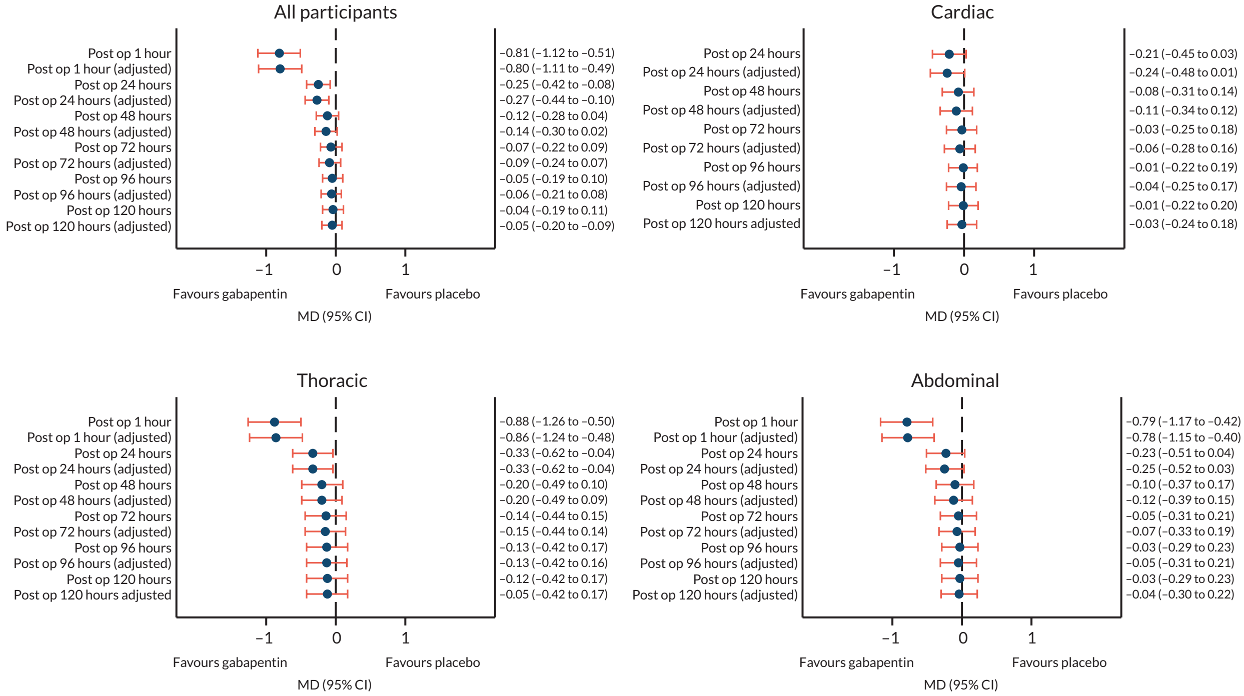

FIGURE 9 Numerical rating scale of pain at rest treatment effects. Adjusted, adjusted for magnesium use.

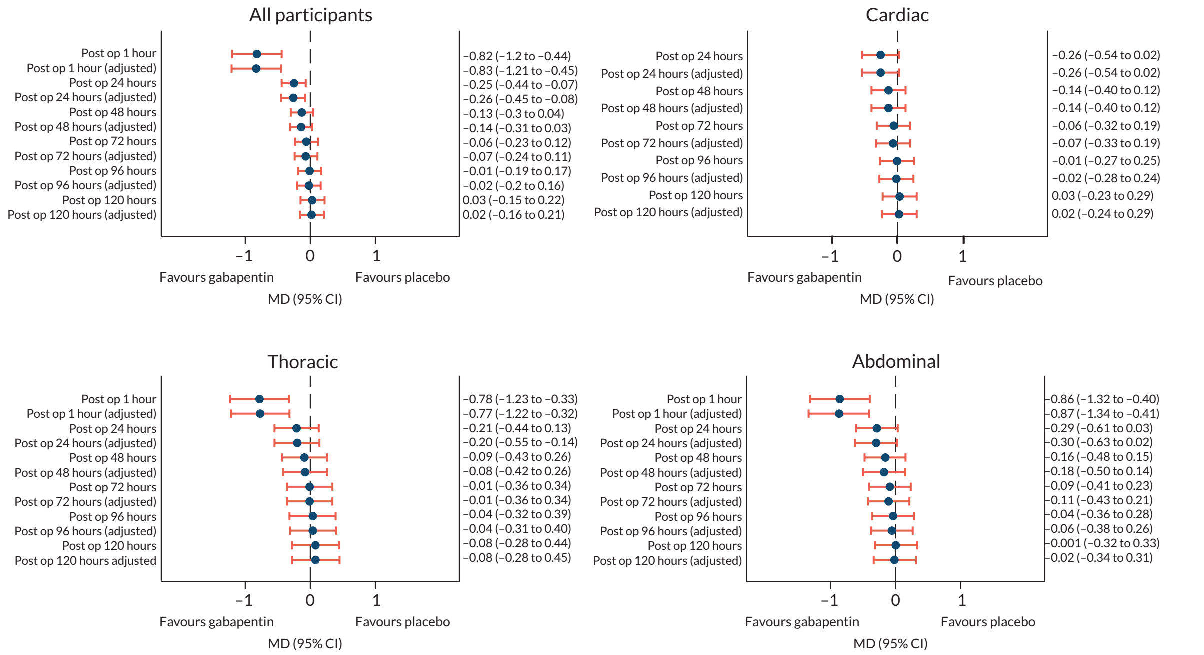

FIGURE 10 Numerical rating scale of pain on movement treatment effects. Adjusted, adjusted for magnesium use.

the MCS between the two groups changed over time (p = 0.056). At 4 weeks, the score was on average 0.74 points higher (95% CI −0.39 to + 1.87) in the gabapentin group and at 4 months it was 0.55 points lower (95% CI −1.61 to + 0.51) in the gabapentin group (see *Table 12* and *Figure 13*). Imputing missing scores provided results consistent with the primary analysis (see *Appendix 2*, *Table 50*).

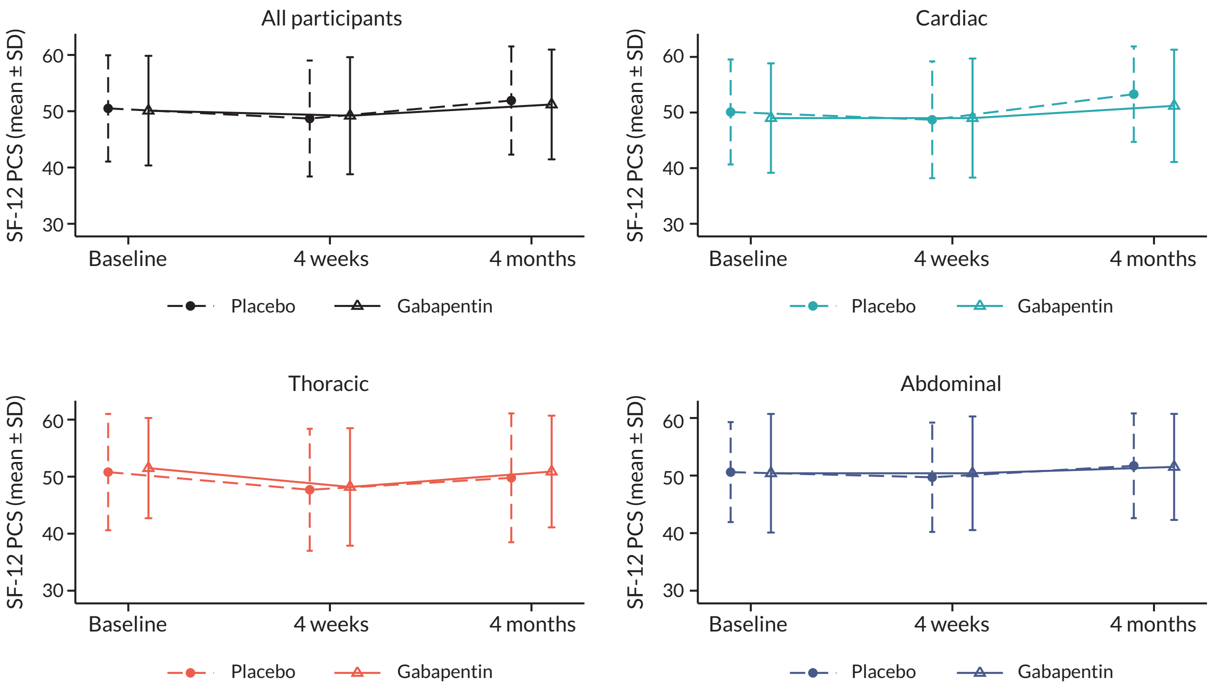

FIGURE 11 Short Form questionnaire-12 items PCS over time.

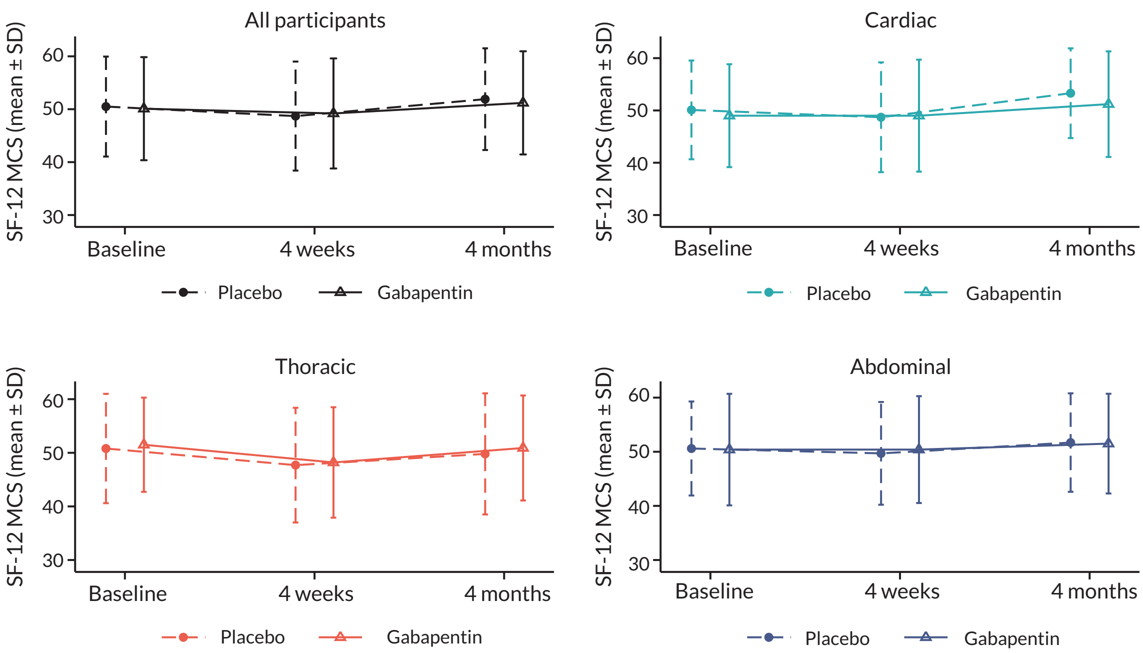

FIGURE 12 Short Form questionnaire-12 items MCS over time.

Secondary outcome: EuroQol-5 Dimensions, five-level version

The EQ-5D-5L utility score at baseline, 4 weeks and 4 months are summarised in *Table 13* and *Figure 14*. The pattern of scores over time differed across the three surgical cohorts, but the difference between the placebo and gabapentin groups was similar at 4 weeks and 4 months (p = 0.39) and across the surgical cohorts (p = 0.83). On average, the score was 0.014 points lower (95% CI −0.033 to + 0.005) in the gabapentin group than in the placebo group (see *Table 13* and *Figure 13*). Imputing missing utility scores provided results consistent with the primary analysis (see *Appendix 2*, *Table 50*).

TABLE 12 Secondary outcome: SF-12 PCS and mental component scores

Outcome	Randomised to placebo Mean (SD)	Randomised to gabapentin Mean (SD)	Mean difference (95% CI)	*p*-value
SF-12 PCS				
All participants				
Baseline	46.0 (10.2)	46.3 (10.6)		
4 weeks[a]	39.1 (8.83)	38.5 (9.63)	−0.87 (−1.71 to −0.04)	0.04
4 months[b]	47.3 (9.54)	46.3 (9.98)		
Cardiac				
Baseline	42.9 (9.66)	42.0 (9.73)		
4 weeks	37.2 (7.97)	36.6 (8.94)	−0.63 (−1.89 to + 0.63)	0.33
4 months	48.3 (8.82)	47.0 (10.1)		
Thoracic				
Baseline	48.0 (10.0)	48.0 (10.7)		
4 weeks	39.7 (8.59)	37.8 (9.45)	−1.73 (−3.33 to −0.12)	0.035
4 months	45.2 (9.24)	43.1 (9.99)		
Abdominal				
Baseline	48.4 (10.1)	50.8 (9.17)		
4 weeks	41.4 (9.71)	42.0 (9.92)	−0.30 (−1.86 to + 1.26)	0.38
4 months	47.6 (10.6)	47.9 (9.21)		
Treatment by time by specialty interaction				0.98
Treatment by time interaction				0.53
Treatment by specialty interaction				0.47
Time by specialty interaction				< 0.001
SF-12 MCS				
All participants				
Baseline	50.5 (9.45)	50.1 (9.74)		
4 weeks[a]	48.7 (10.3)	49.2 (10.4)	0.74 (−0.39 to 1.87)	0.20
4 months[b]	51.9 (9.61)	51.2 (9.75)	−0.55 (−1.61 to 0.51)	0.31
Cardiac				
Baseline	50.1 (9.44)	49.0 (9.84)		
4 weeks	48.7 (10.5)	49.0 (10.7)	−0.0006 (−1.51 to 1.51)	1.00
4 months	53.3 (8.58)	51.2 (10.1)	−1.28 (−2.72 to 0.16)	0.08
Thoracic				
Baseline	50.8 (10.2)	51.5 (8.79)		
4 weeks	47.7 (10.7)	48.2 (10.3)	1.45 (−0.37 to 3.28)	0.12
4 months	49.8 (11.3)	50.9 (9.79)	0.17 (−1.61 to 1.96)	0.85

TABLE 12 Secondary outcome: SF-12 PCS and mental component scores (*continued*)

Outcome	Randomised to placebo Mean (SD)	Randomised to gabapentin Mean (SD)	Mean difference (95% CI)	*p*-value
Abdominal				
Baseline	50.6 (8.68)	50.4 (10.3)		
4 weeks	49.7 (9.49)	50.4 (9.87)	1.18 (−0.60 to 2.95)	0.19
4 months	51.7 (9.10)	51.5 (9.21)	−0.10 (−1.83 to 1.62)	0.91
Treatment by time by specialty interaction				0.20
Treatment by time interaction				0.056
Treatment by specialty interaction				0.35
Time by specialty interaction				0.070

MCS, mental component scores.
a Missing (placebo, gabapentin): cardiac (24, 23), thoracic (25, 40), abdominal (29, 23).
b Missing (placebo, gabapentin): cardiac (20, 26), thoracic (34, 43), abdominal (26, 33).

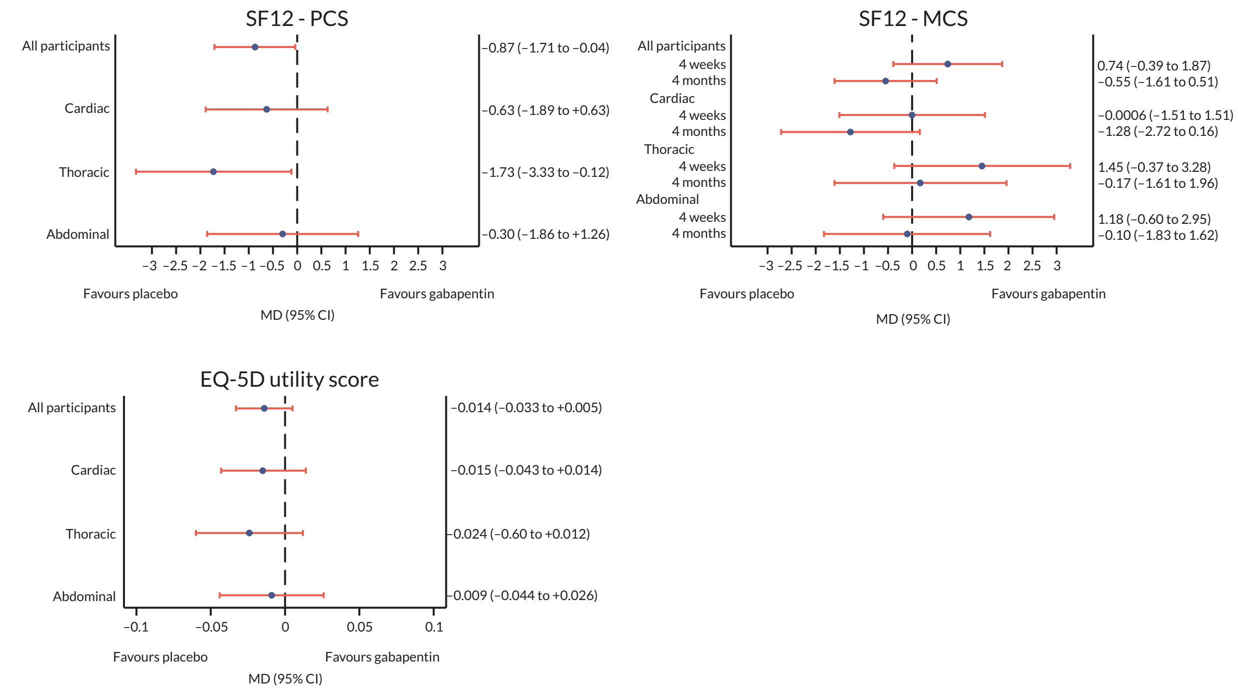

FIGURE 13 Short Form questionnaire-12 items and EQ-5D-5L treatment effects. MCS, mental component scores.

Secondary outcome: Brief Pain Inventory

Results for the BPI are summarised in *Table 14*, *Figures 15* and *16*. At both 4 weeks and 4 months, the number of participants reporting pain was higher in the gabapentin group compared to the placebo group (see *Table 14*, *Figures 15* and *17*). However, where pain was reported, the severity of the pain was similar in the two groups (ratio 0.99, 95% CI 0.90 to 1.08, *Figure 17*). A similar pattern was seen for how pain interfered with life. At both postoperative time points, more participants reported pain interference in the gabapentin group than in the placebo group but where reported the degree of inference was similar (ratio 1.07, 95% CI 0.94 to 1.22, *Figure 17*). Again, imputing missing BPI responses provided results consistent with the primary analysis (see *Appendix 2*, *Table 51*).

TABLE 13 Secondary outcome: EQ-5D-5L

Outcome	Randomised to placebo Mean (SD)	Randomised to gabapentin Mean (SD)	Mean difference (95% CI)	*p*-value
EQ-5D-5L utility score				
All participants				
Baseline	0.77 (0.20)	0.77 (0.19)		
4 weeks[a]	0.79 (0.20)	0.69 (0.20)	−0.014 (−0.033 to + 0.005)	0.16
4 months[b]	0.74 (0.22)	0.73 (0.22)		
Cardiac				
Baseline	0.74 (0.21)	0.73 (0.19)		
4 weeks	0.68 (0.21)	0.66 (0.21)	−0.015 (−0.043 to + 0.014)	0.31
4 months	0.81 (0.20)	0.79 (0.21)		
Thoracic				
Baseline	0.80 (0.19)	0.82 (0.16)		
4 weeks	0.70 (0.19)	0.67 (0.20)	−0.024 (−0.060 to + 0.012)	0.19
4 months	0.71 (0.25)	0.72 (0.23)		
Abdominal				
Baseline	0.79 (0.19)	0.79 (0.20)		
4 weeks	0.75 (0.18)	0.74 (0.19)	−0.009 (−0.044 to + 0.026)	0.63
4 months	0.72 (0.21)	0.79 (0.22)		
Treatment by time by specialty interaction				0.35
Treatment by time interaction				0.39
Treatment by specialty interaction				0.83
Time by specialty interaction				< 0.001
EQ-5D-5L visual analogue scale				
All participants				
Baseline	70.8 (19.4)	70.1 (20.9)		
4 weeks[c]	67.2 (18.6)	66.3 (19.5)		
4 months[d]	75.3 (18.5)	74.4 (19.0)		
Cardiac				
Baseline	65.4 (19.2)	63.1 (21.3)		
4 weeks	64.8 (18.7)	63.9 (20.5)		
4 months	77.1 (17.1)	76.5 (17.2)		
Thoracic				
Baseline	76.4 (17.7)	75.5 (17.9)		
4 weeks	68.6 (18.5)	65.2 (18.1)		
4 months	71.9 (21.4)	69.8 (19.8)		

TABLE 13 Secondary outcome: EQ-5D-5L (*continued*)

Outcome	Randomised to placebo Mean (SD)	Randomised to gabapentin Mean (SD)	Mean difference (95% CI)	*p*-value
Abdominal				
Baseline	73.0 (19.5)	74.8 (20.3)		
4 weeks	69.3 (18.3)	71.0 (18.5)		
4 months	75.5 (17.5)	75.1 (20.1)		

a Missing (placebo, gabapentin): cardiac (24, 21), thoracic (23, 35), abdominal (27, 22).
b Missing (placebo, gabapentin): cardiac (20, 26), thoracic (35, 43), abdominal (31, 35).
c Missing (placebo, gabapentin): cardiac (23, 21), thoracic (22, 36), abdominal (27, 22).
d Missing (placebo, gabapentin): cardiac (20, 29), thoracic (41, 49), abdominal (30, 38).

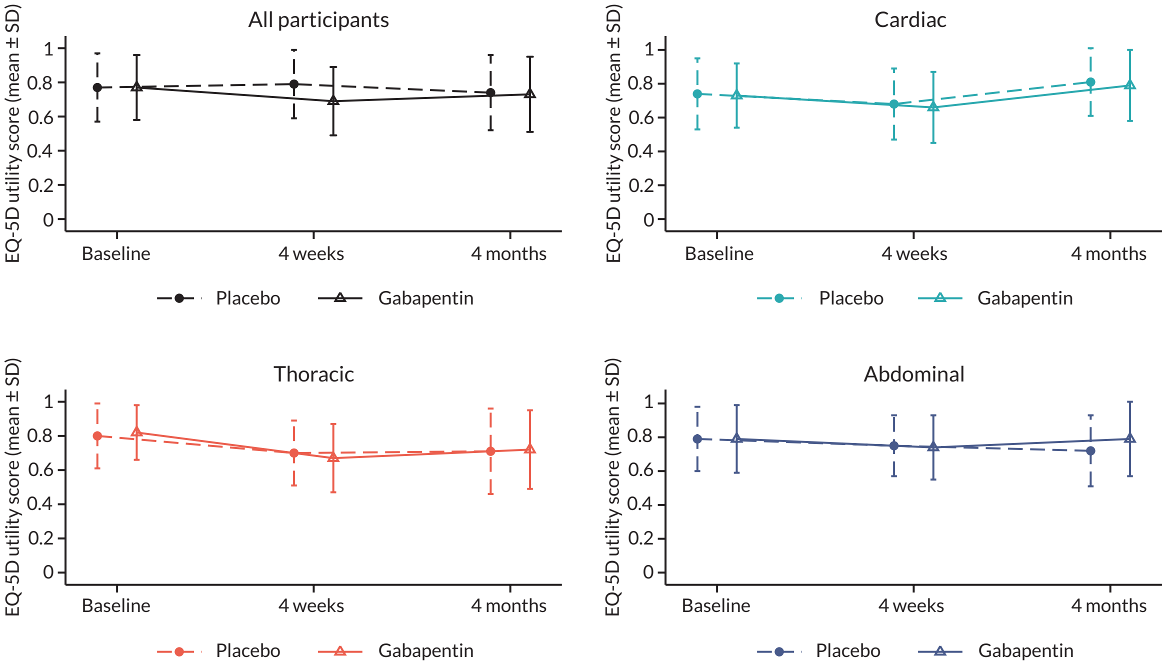

FIGURE 14 EuroQol-5 Dimensions, five-level version utility score over time.

Secondary outcome: safety

Adverse and SAEs experienced by the trial participants are summarised by MedDRA system organ class in *Table 15*. A breakdown of the events within each system organ class is given in *Appendix 2*, *Tables 52* and *53*. Overall, 1453 AEs were reported in 433 participants in the placebo group compared to 1488 AEs in 420 participants in the gabapentin group. In addition to these AEs, 414 SAEs were reported in the placebo group and 505 were reported in the gabapentin group. The events reported were reflective of the different surgeries, with more cardiac disorders in the cardiac specialty, and gastrointestinal disorders in the abdominal specialty. Similar numbers of respiratory events were reported in thoracic participants in the two groups (49 events in the placebo group, 55 in the gabapentin group), but a higher proportion were classified as serious in the gabapentin group (11/49 placebo, 33/55 gabapentin, *Table 15*). Most SAEs were considered to be either expected with gabapentin and/or anticipated after surgery. Less than 4% were considered unexpected (14/414, 3.4% in the placebo group, 16/505, 3.2% in the gabapentin group, *Appendix 2*, *Table 54*). Three SAEs were classified as a possible serious adverse reaction (SAR) to gabapentin, the remainder were considered not related (565/918, 61.5%) or unlikely to be related (350/918, 38.1%, *Appendix 2*, *Table 54*). The three SARs were all in the gabapentin group; they were loss of consciousness (1 day), respiratory depression (1 day) and vomiting (3 days). All resolved without sequelae.

TABLE 14 Secondary outcome: Brief Pain Inventory

Outcome	Randomised to placebo		Randomised to gabapentin		Odds ratio for pain present (95% CI)	*p*-value	Geometric mean ratio where present (95% CI)	*p*-value
	Present	If present	Present	If present				
	n (%)	Median (IQR)	*n* (%)	Median (IQR)				
Pain severity index								
All participants								
Baseline	216/571 (37.8%)	12 (7–19)	205/585 (35.0%)	10 (6–16)				
4 weeks[a]	295/506 (53.3%)	11 (7–18)	319/503 (63.4%)	11 (7–18)	1.42 (1.15 to 1.75)	0.001	0.99 (0.90 to 1.08)	0.77
4 months[b]	182/505 (33.2%)	12.5 (7–20)	211/485 (40.6%)	11 (6–19)				
Cardiac								
Baseline	82/233 (35.2%)	10 (6–16)	87/243 (35.8%)	10 (6–14)				
4 weeks	131/215 (60.9%)	11 (7–16)	148/222 (66.7%)	11 (7–16)	1.35 (0.98 to 1.86)	0.07	0.98 (0.86 to 1.12)	0.78
4 months	74/223 (33.2%)	12 (7–19)	88/217 (40.6%)	10 (6–15)				
Thoracic								
Baseline	57/166 (34.3%)	14 (9–20)	53/173 (30.6%)	10 (6–19)				
4 weeks	94/150 (62.7%)	14 (8–19)	90/132 (68.2%)	15 (9–20)	1.63 (1.10 to 2.42)	0.014	1.08 (0.93 to 1.26)	0.33
4 months	50/133 (37.6%)	14 (7–20)	66/128 (51.6%)	13 (7–21)				
Abdominal								
Baseline	77/172 (44.8%)	12 (8–20)	65/169 (38.5%)	12 (5–17)				
4 weeks	70/141 (49.6%)	10.5 (7–19)	81/149 (54.4%)	9 (5–16)	1.34 (0.91 to 1.97)	0.14	0.90 (0.73 to 1.10)	0.29
4 months	58/149 (38.9%)	12 (8–20)	57/140 (40.7%)	11 (4–20)				
Treatment by time by specialty interaction								0.34
Treatment by time interaction								0.77
Treatment by specialty interaction								0.24
Time by specialty interaction								0.003

TABLE 14 Secondary outcome: Brief Pain Inventory (*continued*)

Outcome	Randomised to placebo: Present *n* (%)	Randomised to placebo: If present Median (IQR)	Randomised to gabapentin: Present *n* (%)	Randomised to gabapentin: If present Median (IQR)	Odds ratio for pain present (95% CI)	*p*-value	Geometric mean ratio where present (95% CI)	*p*-value
Pain interference index								
All participants								
Baseline	214/584 (36.6%)	19.5 (9–34)	185/592 (31.3%)	19 (8–33)				
4 weeks[c]	299/525 (57.0%)	23 (10–37)	320/516 (62.0%)	22 (11–36)	1.38 (1.12 to 1.70)	0.003	1.07 (0.94 to 1.22)	0.30
4 months[d]	186/331 (36.0%)	21.5 (7–36)	206/390 (41.5%)	21 (8–35)				
Cardiac								
Baseline	86/242 (35.5%)	16.5 (9–33)	86/247 (34.8%)	17 (8–34)				
4 weeks	135/227 (59.5%)	21 (9–36)	148/228 (64.9%)	22.5 (12–36)	1.31 (0.94 to 1.82)	0.11	1.14 (0.93 to 1.39)	0.21
4 months	77/229 (33.6%)	19 (5–35)	87/223 (39.0%)	18 (7–30)				
Thoracic								
Baseline	56/169 (33.1%)	25 (8.5–34)	45/174 (25.9%)	19 (7–34)				
4 weeks	93/152 (61.2%)	25 (11–38)	92/136 (67.6%)	23.5 (14.5–37)	1.70 (1.15 to 2.51)	0.008	1.14 (0.93 to 1.40)	0.21
4 months	51/138 (37.0%)	26 (9–39)	65/130 (50.0%)	23 (12–36)				
Abdominal								
Baseline	72/173 (41.6%)	18.5 (9–35)	54/171 (31.6%)	18 (8–28)				
4 weeks	71/146 (48.6%)	22 (11–39)	80/152 (52.6%)	16 (9–33.5)	1.22 (0.84 to 1.76)	0.30	0.90 (0.69 to 1.16)	0.41
4 months	58/150 (38.7%)	22.5 (8–36)	54/143 (37.8%)	18 (7–35)				
Treatment by time by specialty interaction								0.44
Treatment by time interaction								0.92
Treatment by specialty interaction								0.28
Time by specialty interaction								0.002

GMR, geometric mean ratio; OR, odds ratio.
a Missing (placebo, gabapentin): cardiac (24, 21), thoracic (23, 35), abdominal (27, 22).
b Missing (placebo, gabapentin): cardiac (20, 26), thoracic (35, 43), abdominal (31, 35).
c Missing (placebo, gabapentin): cardiac (23, 21), thoracic (22, 36), abdominal (27, 22).
d Missing (placebo, gabapentin): cardiac (20, 29), thoracic (41, 49), abdominal (30, 38).

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Health Technology Assessment 2026 Vol. 30 No. 9

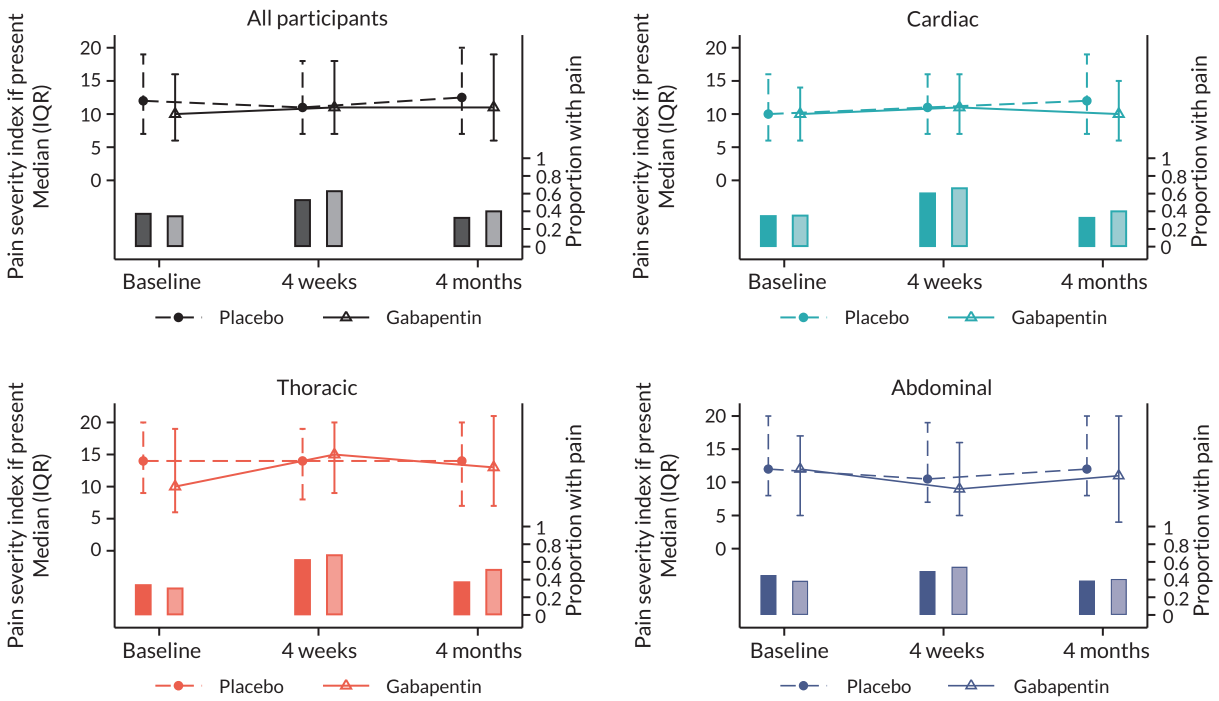

FIGURE 15 Brief Pain Inventory pain severity over time.

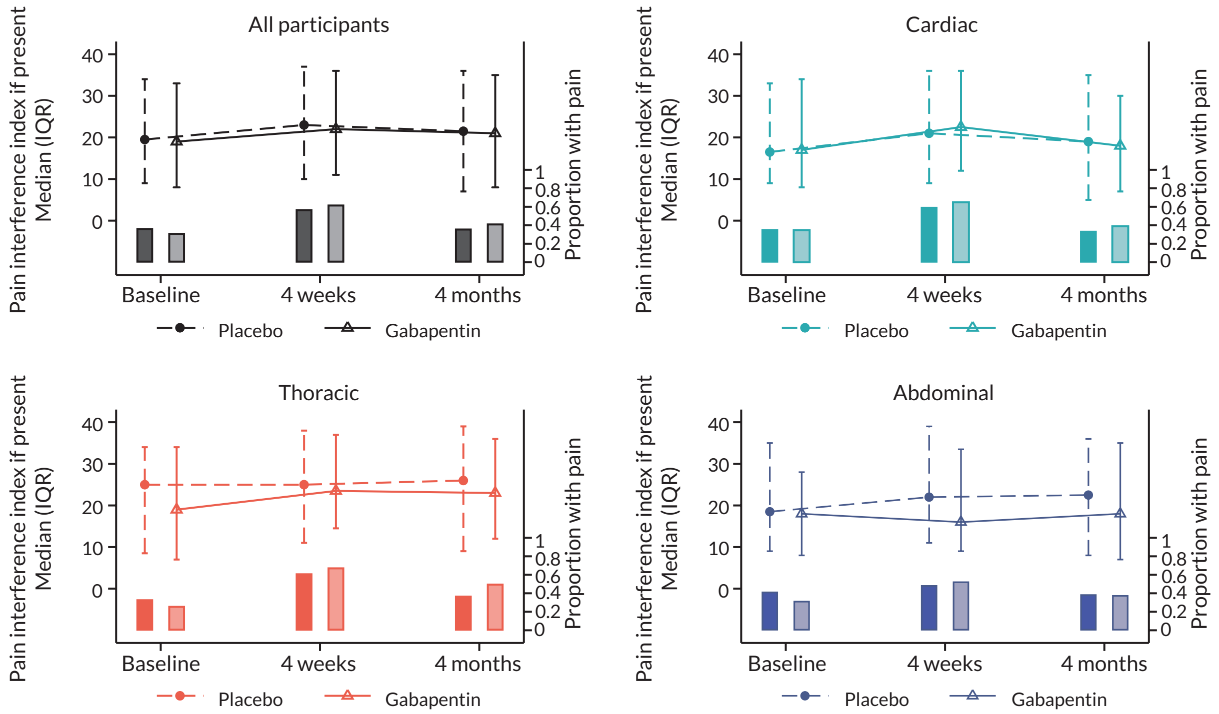

FIGURE 16 Brief Pain Inventory pain interference over time.

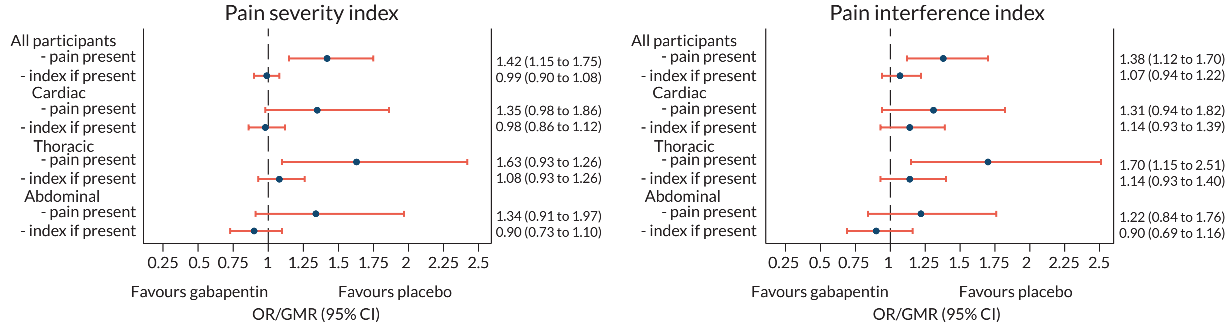

FIGURE 17 Brief Pain Inventory treatment effects. GMR, geometric mean ratio; OR, odds ratio.

Almost one-third of participants experienced at least one SAE (*Table 16*). The risk of at least one differed across the surgical specialties (p = 0.006). In the cardiac specialty, the risk was similar in the two groups (difference 1.5%, 95% CI −2.1% to + 5.0%, in favour of placebo), while in the thoracic and abdominal specialties, the difference was more marked; in the thoracic specialty, 6.0% more participants had at least one SAE in the gabapentin group compared to placebo (95% CI 1.3% to 10.7%), while in the abdominal specialty, the reverse trend was seen with fewer participants in the gabapentin group having a SAE (difference 5.1%, 95% CI 0.8% to 9.5%, in favour of gabapentin).

There were 18 participant deaths in the trial, 8 in the placebo group and 10 in the gabapentin group. Four deaths were in the cardiac specialty (1 placebo, 3 gabapentin), 12 were in the thoracic specialty (7 placebo, 5 gabapentin) and 2 were in the abdominal specialty (both gabapentin group). None of the deaths were deemed to be related to the trial intervention.

TABLE 15 Adverse events experienced during trial participation

Event (MedDRA system organ class)	Cardiac (*n* = 499)				Thoracic (*n* = 346)				Abdominal (*n* = 350)				Overall (*n* = 1195)[a]			
	Randomised to placebo (*n* = 249)		Randomised to gabapentin (*n* = 250)		Randomised to placebo (*n* = 172)		Randomised to gabapentin (*n* = 174)		Randomised to placebo (*n* = 175)		Randomised to gabapentin (*n* = 175)		Randomised to placebo (*n* = 596)		Randomised to gabapentin (*n* = 599)	
	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE
One or more events	243/249 (97.6%)	78/249 (31.3%)	245/250 (97.7%)	82/250 (32.7%)	91/172 (53.0%)	44/172 (25.6%)	75/346 (43.2%)	55/174 (31.6%)	99/175 (56.6%)	67/175 (38.3%)	100 (57.2%)	58/175 (33.1%)	433/596 (72.2%)	189/599 (31.7%)	420/599 (70.0%)	195/599 (32.5%)
Number of events	1082	187	1335	216	164	83	133	111	207	144	220	178	1453	414	1488	505
Blood and lymphatic system disorders	14/14 (5.6%)	2/1 (0.4%)	6/6 (2.4%)	1/1 (0.4%)	1/1 (0.6%)		1/1 (0.6%)	1/1 (0.6%)	4/4 (2.3%)	1/1 (0.6%)	3/3 (1.7%)	2/1 (0.6%)	19/19 (3.2%)	3/2 (0.3%)	10/10 (1.7%)	4/3 (0.5%)
Cardiac disorders	149/131 (52.6%)	43/33 (13.3%)	139/116 (46.2%)	40/30 (12.0%)	19/19 (11.0%)	2/2 (1.2%)	2/2 (1.1%)	2/2 (1.1%)	3/3 (1.7%)	2/2 (1.1%)	6/6 (3.4%)	7/6 (3.4%)	171/153 (25.7%)	47/37 (6.2%)	147/124 (20.7%)	49/38 (6.3%)
Ear and labyrinth disorders	1/1 (0.4%)					1/1 (0.6%)							1/1 (0.2%)	1/1 (0.2%)		
Eye disorders	9/9 (3.6%)	1/1 (0.4%)	9/9 (3.6%)				1/1 (0.6%)	0/0 (.)	1/1 (0.6%)				10/10 (1.7%)	1/1 (0.2%)	10/10 (1.7%)	0/0 (.)
Gastrointestinal disorders	82/59 (23.7%)	11/8 (3.2%)	90/64 (25.5%)	12/11 (4.4%)	28/22 (12.8%)	3/3 (1.7%)	27/22 (12.6%)	6/6 (3.4%)	98/62 (35.4%)	43/30 (17.1%)	102/62 (35.4%)	79/42 (24.0%)	208/143 (24.0%)	57/41 (6.9%)	219/148 (24.7%)	97/59 (9.8%)
General disorders and administration site conditions	69/59 (23.7%)	7/7 (2.8%)	85/72 (28.7%)	8/6 (2.4%)	10/10 (5.8%)	2/1 (0.6%)	10/9 (5.2%)	5/5 (2.9%)	15/15 (8.6%)	14/13 (7.4%)	15/14 (8.0%)	4/4 (2.3%)	94/84 (14.1%)	23/21 (3.5%)	110/95 (15.8%)	17/15 (2.5%)
Hepatobiliary disorders				2/2 (0.8%)							1/1 (0.6%)				1/1 (0.2%)	2/2 (0.3%)
Immune system disorders			1/1 (0.4%)												1/1 (0.2%)	
Infections and infestations	47/41 (16.5%)	36/25 (10.0%)	58/52 (20.7%)	35/27 (10.8%)	9/8 (4.7%)	27/18 (10.5%)	10/9 (5.2%)	15/14 (8.0%)	10/9 (5.1%)	24/21 (12.0%)	19/15 (8.6%)	22/20 (11.4%)	66/58 (9.7%)	87/64 (10.7%)	87/76 (12.7%)	72/61 (10.2%)
Injury, poisoning and procedural complications	82/67 (26.9%)	10/7 (2.8%)	73/60 (23.9%)	20/13 (5.2%)	14/14 (8.1%)	18/14 (8.1%)	7/7 (4.0%)	16/13 (7.5%)	12/11 (6.3%)	40/30 (17.1%)	12/12 (6.9%)	34/21 (12.0%)	108/92 (15.4%)	68/51 (8.6%)	92/79 (13.2%)	70/47 (7.8%)
Investigations	48/46 (18.5%)	4/3 (1.2%)	46/44 (17.5%)	4/4 (1.6%)	2/2 (1.2%)		1/1 (0.6%)	2/2 (1.1%)	2/2 (1.1%)	1/1 (0.6%)	6/6 (3.4%)	2/1 (0.6%)	52/50 (8.4%)	5/4 (0.7%)	53/51 (8.5%)	8/7 (1.2%)

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TABLE 15 Adverse events experienced during trial participation (*continued*)

Event (MedDRA system organ class)	Cardiac (*n* = 499)				Thoracic (*n* = 346)				Abdominal (*n* = 350)				Overall (*n* = 1195)[a]			
	Randomised to placebo (*n* = 249)		Randomised to gabapentin (*n* = 250)		Randomised to placebo (*n* = 172)		Randomised to gabapentin (*n* = 174)		Randomised to placebo (*n* = 175)		Randomised to gabapentin (*n* = 175)		Randomised to placebo (*n* = 596)		Randomised to gabapentin (*n* = 599)	
	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE	AE	SAE
Metabolism and nutrition disorders	37/35 (14.1%)	3/3 (1.2%)	31/31 (12.4%)	5/4 (1.6%)	3/3 (1.7%)		5/5 (2.9%)	1/1 (0.6%)	4/4 (2.3%)	1/1 (0.6%)	1/1 (0.6%)		44/42 (7.0%)	4/4 (0.7%)	37/37 (6.2%)	6/5 (0.8%)
Musculoskeletal and connective tissue disorders	3/3 (1.2%)	1/1 (0.4%)	2/2 (0.8%)	1/1 (0.4%)		1/1 (0.6%)			0/0 (.)			2/1 (0.6%)	3/3 (0.5%)	2/2 (0.3%)	2/2 (0.3%)	3/2 (0.3%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)				1/1 (0.4%)		8/7 (4.1%)	2/2 (1.1%)	6/5 (2.9%)	1/1 (0.6%)				1/1 (0.2%)	8/7 (1.2%)	2/2 (0.3%)	7/6 (1.0%)
Nervous system disorders	30/25 (10.0%)	6/6 (2.4%)	32/27 (10.8%)	5/5 (2.0%)	8/7 (4.1%)	1/1 (0.6%)	10/10 (5.7%)	5/5 (2.9%)	12/12 (6.9%)		16/14 (8.0%)	5/5 (2.9%)	50/44 (7.4%)	7/7 (1.2%)	58/51 (8.5%)	15/15 (2.5%)
Psychiatric disorders	29/26 (10.4%)	4/4 (1.6%)	27/25 (10.0%)	9/7 (2.8%)	8/6 (3.5%)	3/1 (0.6%)	9/8 (4.6%)	3/2 (1.1%)	12/10 (5.7%)		9/9 (5.1%)	1/1 (0.6%)	49/42 (7.0%)	7/5 (0.8%)	45/42 (7.0%)	13/10 (1.7%)
Renal and urinary disorders	22/22 (8.8%)	8/6 (2.4%)	35/31 (12.4%)	5/5 (2.0%)	17/15 (8.7%)	1/1 (0.6%)	22/21 (12.1%)		12/12 (6.9%)	6/6 (3.4%)	9/9 (5.1%)	6/6 (3.4%)	51/49 (8.2%)	15/13 (2.2%)	66/61 (10.2%)	11/11 (1.8%)
Reproductive system and breast disorders									1/1 (0.6%)				1/1 (0.2%)			
Respiratory, thoracic and mediastinal disorders	106/85 (34.1%)	24/15 (6.0%)	105/89 (35.5%)	31/22 (8.8%)	38/35 (20.3%)	11/10 (5.8%)	22/20 (11.5%)	33/23 (13.2%)	8/7 (4.0%)	7/5 (2.9%)	12/12 (6.9%)	7/5 (2.9%)	152/127 (21.3%)	42/30 (5.0%)	139/121 (20.2%)	71/50 (8.3%)
Skin and subcutaneous tissue disorders	4/4 (1.6%)		6/6 (2.4%)		1/1 (0.6%)		1/1 (0.6%)		4/4 (2.3%)		6/6 (3.4%)		9/9 (1.5%)		13/13 (2.2%)	
Surgical and medical procedures	126/117 (47.0%)	18/11 (4.4%)	126/112 (44.6%)	24/18 (7.2%)	3/3 (1.7%)	1/1 (0.6%)		9/5 (2.9%)	2/2 (1.1%)	1/1 (0.6%)		5/5 (2.9%)	131/122 (20.5%)	20/13 (2.2%)	126/112 (18.7%)	38/28 (4.7%)
Vascular disorders	224/186 (74.7%)	9/7 (2.8%)	264/201 (80.1%)	13/10 (4.0%)	3/3 (1.7%)	4/4 (2.3%)	3/3 (1.7%)	7/5 (2.9%)	6/4 (2.3%)	4/4 (2.3%)	3/3 (1.7%)	2/1 (0.6%)	233/193 (32.4%)	17/15 (2.5%)	270/207 (34.5%)	22/16 (2.7%)

a One participant withdrew consent for their data to be used. Data are number of events in number of participants (% of participants).

TABLE 16 Secondary outcome: one or more SAEs

SAEs	Randomised to placebo		Randomised to gabapentin		Risk difference (95% CI)	*p*-value	Risk ratio (95% CI)	*p*-value
	n/*N*	%	*n*/*N*	%				
All participants								
One or more SAEs	189/596	31.7	195/599	32.6				
Cardiac								
One or more SAEs	78/249	31.3	82/250	32.8	+ 0.015 (−0.021 to + 0.050)	0.41	1.05 (0.92 to 1.20)	0.47
Thoracic								
One or more SAEs	44/172	25.6	55/174	31.6	+ 0.060 (± 0.013 to + 0.107)	0.011	1.23 (1.04 to 1.47)	0.013
Abdominal								
One or more SAEs	67/175	38.3	58/175	33.2	−0.051 (−0.095 to −0.008)	0.020	0.86 (0.76 to 0.98)	0.022
Treatment by specialty interaction						0.0006		0.0027

Chapter 5 Results: economic evaluation

Analysis data set

All randomised participants were included in the health economic evaluation except 1 participant who withdrew consent, and a further 11 who did not have surgery in the study. Therefore, 1184 participants (589 placebo group, 595 gabapentin group) were included in our analyses.

Missing data

The amount of complete data for resource use and outcomes (individual EQ-5D scores and QALYs) for participants in each group is summarised in *Appendix 2*, *Table 55*. Seventy-four per cent of participants in both groups had complete resource use data, and 78% (79% randomised to placebo, 77% randomised to gabapentin) had complete EQ-5D scores across the three time points. Overall, 41% of cases were incomplete (40% and 42% in the placebo and gabapentin groups, respectively), so multiple imputation with $m = 45$ imputations was conducted to handle missing data. Given this, when uncertainty is considered in *Base-case cost-effectiveness results*, 110 bootstraps per imputation were run.

Quality-adjusted life-years

Table 17 reports the EQ-5D scores at each of the time points and QALYs for all participants, with missing data imputed. There were 17 participants who died by the end of 4 months (1%), 7 of whom died by 4 weeks. Participants who had died by the time of follow-up were given an EQ-5D score of zero. There was no difference in EQ-5D scores at baseline, but at 4 weeks and 4 months scores were slightly higher in the placebo group. This results in a slight gain in QALYs to 4 months in the placebo group compared to the gabapentin group, but this difference is not statistically significant.

Resource use and costs

Table 18 reports information on the main resource use items. In the index admission, this includes time in theatre and the length of hospital stay by ward type. Post-hospital discharge includes hospital re-admissions, and other primary and secondary care resource use over the 4 months follow-up.

Resource use during the index admission was very similar between the groups. On average, time in theatre differed by just 5 minutes; surgery took 3.4 and 3.3 hours for participants in the placebo and gabapentin groups, respectively. Participants spent a mean of 7.6 and 7.2 days in hospital after surgery in the placebo and gabapentin groups, respectively. Resource use post-hospital discharge was also very similar between the groups.

TABLE 17 EuroQol-5 Dimensions scores and QALYs to 4 months for all participants

Outcomes	Randomised to placebo (n = 589) Mean (SE)	Randomised to gabapentin (n = 595) Mean (SE)	Gabapentin vs. placebo Mean difference (95% CI)
EQ-5D[a]			
Baseline	0.771 (0.008)	0.774 (0.008)	+ 0.003 (-0.019 to + 0.025)
4 weeks	0.701 (0.009)	0.683 (0.009)	−0.018 (-0.042 to + 0.007)
4 months	0.777 (0.009)	0.773 (0.009)	−0.004 (-0.031 to + 0.022)
QALYs to 4 months	**0.247 (0.003)**	**0.243 (0.002)**	**−0.003 (-0.010 to + 0.004)**

a Deaths included as zero.

TABLE 18 Observed resource use for participants

Resource use	Randomised to placebo (*n* = 589)		Randomised to gabapentin (*n* = 595)		Gabapentin vs. placebo
	n **(%)**	**Mean (SD)**	***n*** **(%)**	**Mean (SD)**	**Mean difference (95% CI)**
Index admission					
Time in theatre (hours)	589 (100)	3.4 (1.5)	595 (100)	3.3 (1.5)	−0.1 (−0.2 to + 0.1)
Intensive care unit stay (days)	587 (100)	0.6 (2.2)	593 (100)	0.9 (3.0)	+ 0.2 (−0.0 to + 0.6)
High-dependency unit stay (days)	587 (100)	1.6 (2.4)	593 (100)	1.5 (2.1)	−0.2 (−0.4 to + 0.1)
Ward stay (days)	587 (100)	4.9 (3.8)	592 (99)	4.7 (4.0)	−0.2 (−0.7 to + 0.2)
Ward stay at another hospital (days)[a]	587 (100)	0.5 (3.8)	595 (100)	0.2 (2.3)	−0.2 (−0.6 to + 0.1)
Total stay (days)	587 (100)	7.6 (7.9)	592 (99)	7.2 (6.8)	−0.4 (−1.2 to + 0.5)
Post-hospital discharge to 4 weeks					
Further inpatient days	572 (97)	0.7 (3.5)	577 (97)	0.9 (3.8)	+ 0.2 (−0.3 to + 0.6)
Hospital visits	565 (96)	0.8 (1.2)	565 (95)	0.8 (1.1)	−0.0 (−0.2 to + 0.1)
Community visits	565 (96)	2.5 (2.4)	564 (95)	2.6 (2.8)	+ 0.1 (−0.2 to + 0.4)
4 weeks to 4 months					
Further inpatient days	566 (96)	0.9 (3.8)	567 (95)	1.2 (6.1)	+ 0.2 (−0.4 to + 0.8)
Hospital visits	566 (96)	2.1 (2.3)	562 (94)	1.9 (2.1)	−0.2 (−0.4 to + 0.1)
Community visits	566 (96)	3.7 (6.8)	560 (94)	3.0 (5.0)	−0.7 (−1.4 to −0.0)

HDU, high-dependency unit; ICU, intensive care unit.
a Length of stay at another hospital if discharged there after surgery.

A breakdown of total costs for all participants is provided in *Figure 18* (with missing data imputed). The key cost drivers were surgery, time in critical care and on a ward. The cost of the intervention is included in the analgesia component; this costs just 6p per participant. Costs are slightly higher in the gabapentin group, but there are no material differences in any of the cost components between the groups. Greater detail on these costs is provided in *Table 19*. Total costs to 4 months are on average £12,634 in the placebo group and £13,011 in the gabapentin group, (mean difference −£377, 95% CI −£797 to + £1550).

Base-case cost-effectiveness results

Table 20 combines the cost and outcome results and presents the cost-effectiveness. The differences in costs and QALYs both favour the placebo group, but are small and not statistically significant. Based on the point estimates of the cost and QALY differences, placebo is considered cost-effective: placebo is *dominant* over gabapentin, as it is both more effective and less costly. However, it is important to consider the uncertainty around this result. *Figure 19* shows the cost-effectiveness plane, with the bootstrap replicates of the cost and QALY differences. The black dot is the point estimate of the cost and QALY difference. The majority of the bootstrap replicates are in the north-west quadrant, where costs are higher and QALYs are lower in the gabapentin group, indicating that gabapentin is not cost-effective.

The CEAC in *Figure 20* shows the probability that gabapentin is cost-effective for a range of willingness-to-pay thresholds. At a willingness-to-pay threshold of £20,000 per QALY, which is generally considered as the threshold which NICE adopts for considering an intervention to be cost-effective, the probability that gabapentin is cost-effective is 0.26 (at a threshold of £30,000 per QALY, the probability is 0.25). Across the broad range of willingness-to pay-thresholds shown, gabapentin is unlikely to be considered as cost-effective.

Sensitivity analyses

The results of the sensitivity analyses around unit costs for time in theatre and bed-day costs in the index admission (which together accounted on average for more than 80% of total costs) are shown in *Appendix 2*, *Table 56*. Varying the cost of time in theatre and critical care by ± 50% had the greatest impact on total costs in each group, but none of the sensitivity analyses had a great impact on the cost difference between groups. The cost differences across the

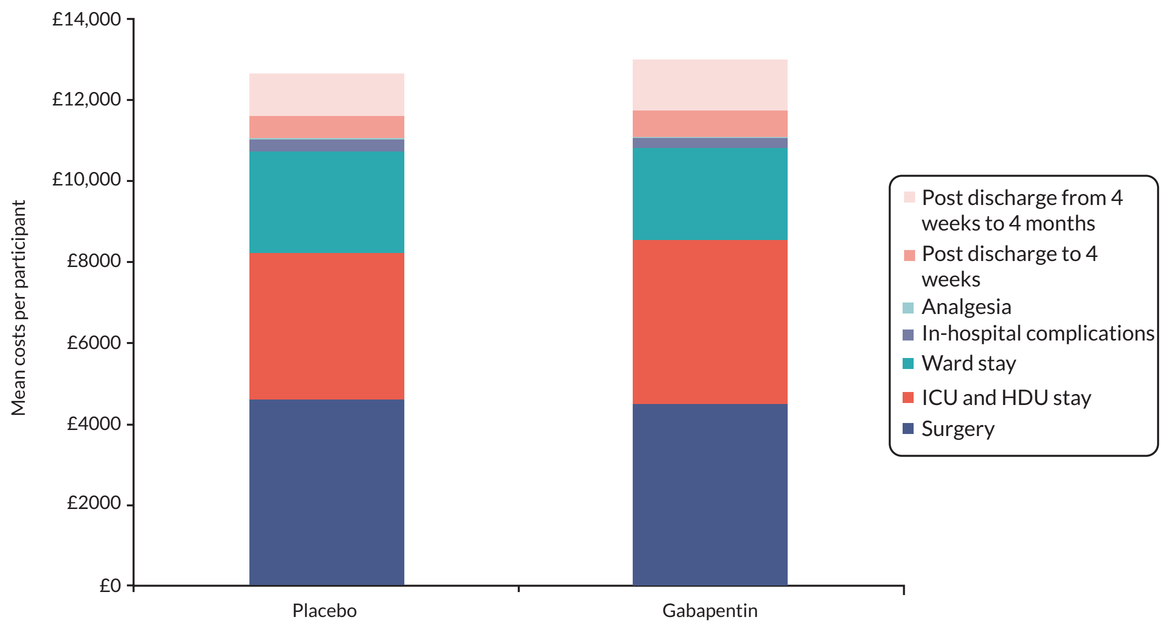

FIGURE 18 Total costs to 4 months for all participants. HDU, high-dependency unit; ICU, intensive care unit.

TABLE 19 Costs for all participants to 4 months

Resource	Randomised to placebo (*n* = 589) Mean (SE) costs	Randomised to gabapentin (*n* = 595) Mean (SE) costs	Gabapentin vs. placebo Mean cost difference (95% CI)
Index admission			
Surgery			
Time in theatre	4598 (84)	4495 (83)	−104 (−336 to + 128)
Hospital stay[a]			
Intensive care unit	1423 (262)	2077 (261)	+ 654 (−73 to + 1380)
High-dependency unit	2199 (123)	1956 (122)	−243 (−582 to + 97)
Ward	2314 (77)	2206 (76)	−108 (−320 to + 104)
Ward stay at another hospital	171 (49)	83 (49)	−89 (−225 to + 47)
Total	6108 (344)	6322 (342)	+ 214 (−738 to + 1166)
Analgesia	20 (1)	19 (1)	−1 (−4 to + 2)
In-hospital complications and SAEs	310 (31)	232 (30)	−77 (−162 to + 7)
Index admission total	**11,035 (387)**	**11,067 (385)**	**+ 32 (−1040** to **+ 1104)**
Post discharge to 4 weeks			
Analgesia	3 (0)	2 (0)	−1 (−3 to −0)
Re-admissions	312 (73)	444 (75)	+ 132 (−74,+ 338)
Hospital visits	167 (10)	164 (10)	−3 (−32 to + 25)
Community visits	67 (4)	74 (4)	+ 7 (−5 to + 19)
4-week total	**549 (75)**	**683 (76)**	**+ 134 (−76** to **+ 344)**
4 weeks to 4 months			
Analgesia	3 (0)	3 (0)	−0 (−1 to + 0)
Re-admissions	418 (118)	650 (128)	+ 232 (−111 to + 575)
Hospital visits	546 (23)	535 (22)	−11 (−73 to + 51)
Community visits	83 (5)	73 (5)	−10 (−25 to + 4)
4 weeks to 4 months total	**1050 (124)**	**1260 (134)**	**+ 210 (−148** to **+ 569)**
Total Costs	**12,634 (422)**	**13,011 (423)**	**+ 377 (−797** to **+ 1550)**

HDU, high-dependency unit; ICU, intensive care unit.
a Length of stay at another hospital if discharged there after surgery.

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TABLE 20 Base-case cost-effectiveness results

Cost-effectiveness element	Randomised to placebo (*n* = 589) Mean (95% CI)	Randomised to gabapentin (*n* = 595) Mean (95% CI)	Gabapentin vs. placebo Mean difference (95% CI)
Total costs	**£12,634** (£11,999 to £13,384)	**£13,011** (£12,042 to £13,887)	+ £377 (–£790 to + £1519)
QALYs	**0.247** (0.241 to 0.251)	**0.243** (0.238 to 0.247)	**-0.003 (–0.010 to + 0.003)**
ICER (cost/QALY)			**Placebo dominant (–£113 to 283)**

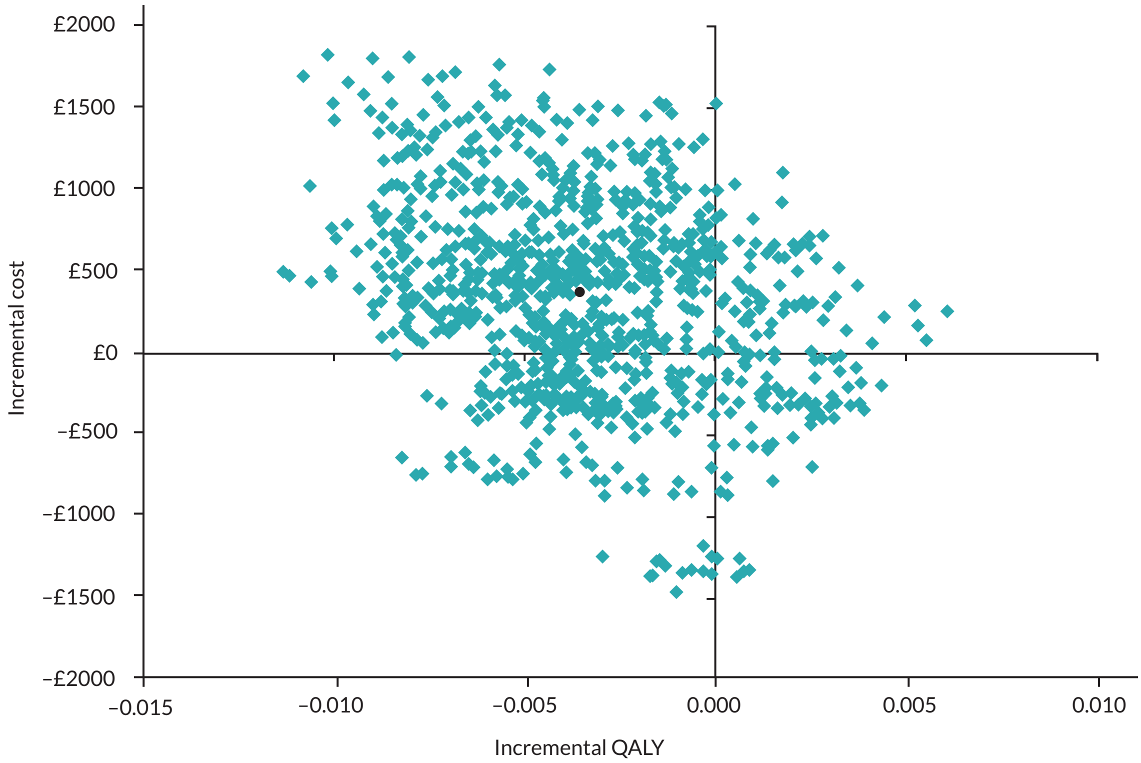

FIGURE 19 Cost-effectiveness plane.

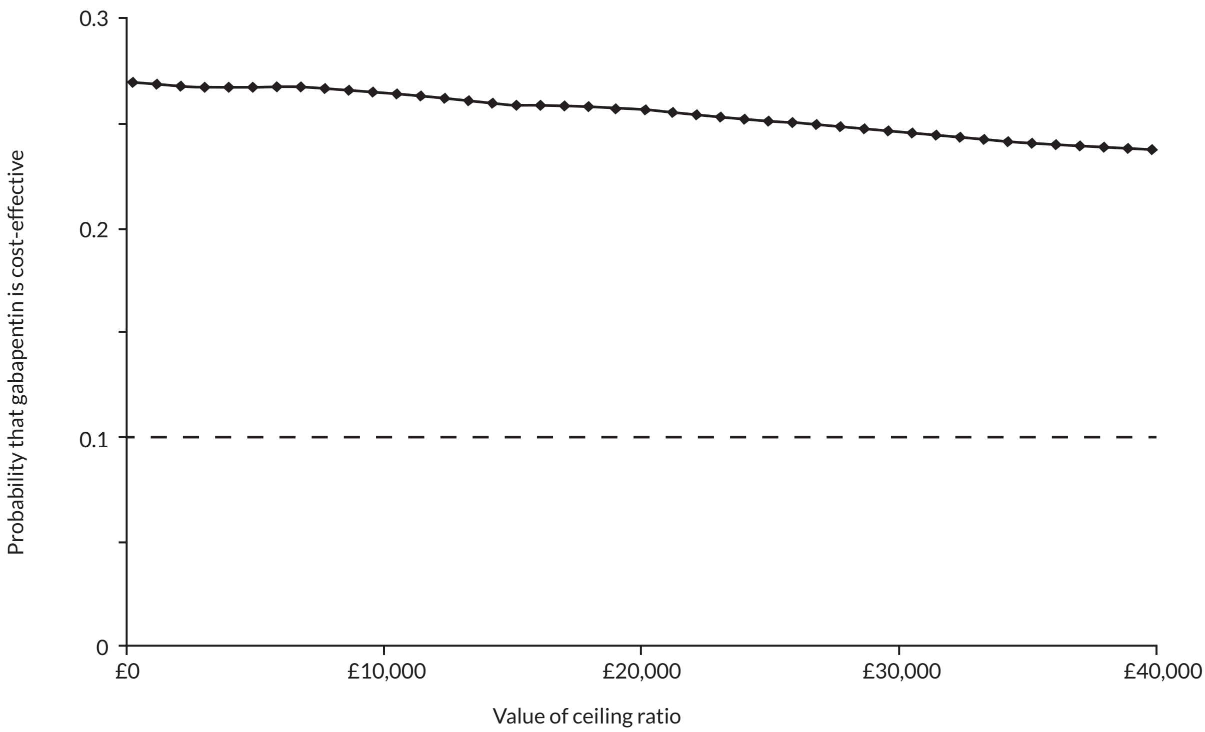

FIGURE 20 Cost-effectiveness acceptability curve.

sensitivity analyses ranged from + £171 to + £582, bracketing and all very similar to the base-case cost difference of + £377. These findings reinforce how similar resource use is between the groups.

As the distribution of total costs per participant is positively skewed in both groups, it is possible that a few high-cost outliers are exerting significant influence on the overall findings. As such, we examined the existence of outliers and their effects. There were four participants with costs over £70,000, three of whom were in the gabapentin group. Two participants had costs of £114,000 and £159,000 in the gabapentin and placebo groups, respectively. These participants had long stays in hospital, with significant time spent in intensive care and high-dependency units. There are no grounds for excluding these participants from the analyses; nevertheless, it is instructive to investigate the impact they are having on the cost results, as an imbalance across groups of these outliers could easily have arisen by chance. *Table 21* shows the effects on costs in each treatment group of excluding the highest cost participants. When the two highest cost outliers with total costs over £100,000 and the four high-cost participants with costs over £70,000 are excluded, uncertainty reduces but cost results remain similar to the base case: costs are slightly higher in the gabapentin group. Although these participants exert a significant impact on the cost results, they do not alter conclusions.

Subgroup analyses

The results of the first subgroup analysis assessing whether cost-effectiveness results for gabapentin versus placebo varied by specialty are presented in *Table 22*. In all cases, the differences between costs and QALYs between the groups are small, and not statistically significant. Results for thoracic and abdominal specialties follow the pattern of the main results: based on point estimates of the differences in costs and QALYs, gabapentin is more costly and less effective than placebo, and gabapentin is therefore dominated by placebo. In the cardiac specialty, costs as well as QALYs were slightly lower in the gabapentin group compared to placebo, resulting in a trade-off between costs and effects: based on the point estimates, we would need to be willing to accept £30,314 to forgo a QALY to consider gabapentin cost-effective. As this is above the £20,000 threshold which NICE adopts for considering an intervention to be cost-effective, gabapentin would not be considered cost-effective in the cardiac specialty. Conclusions are therefore consistent between the base case analysis and by specialty, gabapentin is not cost-effective.

The results of the second subgroup analysis assessing whether cost-effectiveness results for gabapentin versus placebo varied by specialty and type of surgery (minimally invasive vs. open surgery) are presented in *Appendix 2*, *Table 57*. There were no minimally invasive cardiac procedures. As in the base case analysis and subgroup analysis by specialty, the differences between costs and QALYs between the groups are small. Conclusions are consistent with the subgroup analysis by speciality; gabapentin is dominated by placebo for the thoracic and abdominal specialties.

Summary

There were very small differences in costs and QALYs in favour of the placebo group, and when combined, results suggest gabapentin is not cost-effective.

TABLE 21 Sensitivity analyses around high-cost participants

Sensitivity analysis	Randomised to placebo (*n* = 589) Mean cost (£) (SE)	Randomised to gabapentin (*n* = 595) Mean cost (£) (SE)	Gabapentin vs. placebo Mean cost (£) difference (95% CI)
Base case (all participants)	12,634 (422)	13,011 (423)	+ 377 (−797 to + 1550)
Exclude two highest cost participants (> £100,000)	12,385 (365)	12,842 (367)	+ 457 (−559 to + 1473)
Exclude four highest cost participants (> £70,000)	12,385 (346)	12,611 (349)	+ 227 (−739 to + 1192)

TABLE 22 Costs, QALYs and cost-effectiveness results by surgical specialty

	Randomised to placebo Mean (SE)	Randomised to gabapentin Mean (SE)	Gabapentin vs. placebo Mean difference (95% CI)	ICER (cost/QALY)
All participants	*n* = 589	*n* = 595		
Total cost (£)	12,634 (422)	13,011 (423)	+ 377 (−797 to + 1550)	Placebo dominant (−£113,283)
QALYs	0.247 (0.003)	0.243 (0.002)	−0.003 (−0.010 to + 0.004)	
Cardiac	*n* = 247	*n* = 248		
Total cost (£)	15,493 (632)	15,302 (632)	−190 (−1944 to + 1563)	£30,314
QALYs	0.246 (0.004)	0.239 (0.004)	−0.006 (−0.017 to + 0.004)	
Thoracic	*n* = 169	*n* = 173		
Total cost (£)	8835 (765)	9802 (770)	+ 967 (−1165 to + 3099)	Placebo dominant (£−675,276)
QALYs	0.238 (0.005)	0.237 (0.005)	−0.001 (−0.014 to + 0.011)	
Abdominal	*n* = 173	*n* = 174		
Total cost (£)	12,265 (757)	12,935 (756)	+ 670 (−1429 to + 2770)	Placebo dominant (£−773,032)
QALYs	0.255 (0.005)	0.255 (0.005)	−0.001 (−0.014 to + 0.012)	

Chapter 6 Patient and public involvement

Trial design and set-up

The trial was designed in collaboration with a wide team, including a co-applicant who was a patient with extensive PPI experience. In addition, representatives from the three surgical specialties included in the trial were consulted on the study design. These groups were:

- Abdominal surgery – The NIHR Bristol Nutrition Biomedical Research Unit colorectal PPI group.
- Thoracic surgery – The Royal Brompton Hospital Cancer Consortia PPI group.
- Cardiac surgery – two patients who underwent cardiac surgery at the Bristol Heart Institute.

Patient and public involvement participants were asked about the importance of the study, trial design (including how we planned to approach patients and the outcomes we are measuring), and whether patients were likely to find the study burdensome. PPI participants unanimously agreed that the study is important and that the duration of the dosing and pain scores would not be burdensome. As a result of their feedback, some changes were made to the study design and information, including removing adherence from the progression criteria to phase 2, re-assessing expected screening and eligibility rates and minimum participant recruitment numbers per specialty.

Detailed feedback on draft patient-facing documents were obtained from our PPI group. The group suggested changes to the contents and style of these documents; these changes were incorporated into the final versions submitted for regulatory approval. The PPI group also reviewed the study questionnaires (EQ-5D-5L, SF-12, BPI) and advised on order of completion. Modes of completion and schedule for follow-ups and reminders were also discussed. In general, the PPI felt that the suggested follow-up was an acceptable level of burden for participants.

Management of the research

The GAP study TSC included two members of the public from the outset. The TSC met regularly throughout the study and the public members were encouraged to share their feedback. In addition, the study management team met regularly with PPI representatives throughout the duration of the study, to review patient-facing documents, amendments and newsletters, and to provide study updates.

While the study was recruiting, it was highlighted by participants and research nurses that providing optional diaries would aid participant's recall about analgesia medications taken during the follow-up period. To respond to this feedback, the study management team developed several diaries which were provided to the PPI group and TSC members for feedback. The final version implemented in the study was developed with extensive feedback from these groups.

As well as proactively seeking out PPI feedback from TSC and PPI group members, the study management team also actively sought to obtain information about the experience of the trial from study participants themselves. The 4-month questionnaire was amended to include three optional questions to allow participants to feedback positive and negative experiences of being part of the GAP study, these responses were monitored throughout the study.

Positive feedback fell into themes, the first was around helping others, the NHS and furthering research, with comments such as '*without research we cannot go forward*', '*I think everyone should take part in studies to help research*' and '*good to do something positive in a bad situation*'. The second was centred on the positive experience of engaging with and support provided by the research team, and the care and attention received particularly in the follow-up phase of the trial. The third was about how easy it was to take part ('*just one more tablet*' and '*no needles*'), the positive pain management experience ('*I expected to have pain, I had none!*') and the benefits of reflecting on one's health when completing questionnaires. Responses also suggested the trial was well explained ('*50/50 opportunity that pain relief could be improved assisting with speedier recovery*').

Things the participants did not like were the size of the tablets (too big) and the questionnaires. While some just did not like completing the questionnaires (too long, boring, annoying), other comments were directed at the instruments used. Several participants reported that they had ongoing pain, not from their surgery but from comorbid conditions (e.g. arthritis) or chemotherapy, and this led to uncertainty as to how to answer some questions. Others commented that many questions were not applicable to their current situation/age or that they struggled to see the relevance of the questions to the taking of six tablets 4 months before. Some participants also struggled with the concept of rating their pain/health – one participant commented '*I put 90 for my health today but I have a cough*'. There were a few comments about completing questionnaires online, over the telephone etc., with different preferences expressed. Some expressed a preference for providing free-text responses rather than ticking boxes. Several indicated that they would like to know if they received the gabapentin or placebo (this information will be included with the summary of results to participants).

In terms of taking part in future research, 89% of respondents said yes, but several clarified that it would depend on what the research involved, with travel a factor for some. Several interpreted the question as being specifically related to surgery and hoped not need surgery again!

The changes implemented as part of the recovery plan were reviewed by the TSC and were endorsed by the PPI members. The remote consent pathway, introduced to the study at this time, was developed with extensive feedback from the PPI group. The PPI group suggested patients being approached remotely should be sent a 'frequently asked questions' document alongside study information, to answer questions specifically relating to the process of consenting remotely. This suggestion was implemented fully and was reviewed by the PPI group before being submitted for regulatory approval.

Dissemination of the research

Participants of the GAP study were sent regular updates in the format of newsletters. Each newsletter was developed with extensive PPI input regarding content, format and style before sending to study participants.

The management team worked to raise the profile of the study among patients and the public in a variety of ways, for example, the study was featured in the University Hospital's Bristol and Weston NHS Trust 'Voices' magazine, which was supplied to Trust staff and patients. Important study updates and milestones were also communicated via the Bristol Trials Centre's Twitter (Twitter, Inc., San Francisco, CA, USA) page and website.

The study results will be communicated to all study participants who opted to receive them. The results will be summarised and developed in collaboration with PPI contributors to ensure they are relevant, understandable and clear.

Chapter 7 Discussion

Trial conduct

The trial successfully recruited to the revised target and time set out after the COVID-19 pandemic. To ensure the trial completed and provided useful information, the funder agreed to reducing the power of the study from 90% to 80% which would reduce the number of participants required and would allow recruitment to be completed within the funding envelope.

The trial was significantly impacted by the COVID-19 pandemic for five major reasons:

1. Planned surgery stopped during the initial COVID-19 restrictions of March 2020.
2. When planned surgery restarted, this took place at a significantly lower rate – reducing the ability to recruit to the trial.
3. Clinical research staff were diverted back to clinical care during 2020.
4. Trials Centre staff were diverted into COVID-19 vaccine research.
5. High rates of site staff sickness/isolation reduced capacity for both the surgery itself and the recruitment and follow-up of participants.

We made changes to the trial procedures during the COVID-19 pandemic (including moving consent from face-to-face to remote). This allowed recruitment after the initial restrictions of the COVID-19 pandemic (Quarter 1 of 2020) to continue, albeit at a slower rate.

The study sites were engaged with the trial throughout, and data completion rates were good. Similarly, protocol deviations were low except for 16.6% of participants in the placebo group and 20.7% of participants in the gabapentin group who received less than the prescribed amount of medication or received the medication out of dosing window. This is not all drug error. Changes in the clinical condition of the patient (e.g. prolonged ventilation, clinical deterioration and somnolence) account for 38% of these. The GAP study was designed to be a pragmatic trial and reflects the patient pathways that exist in the real world. This represents reduced adherence to the protocol but makes the findings more applicable to NHS practice.

Blinding of participants and research staff was successful. While the research nurses were much better than the patients at 'guessing' the correct treatment group, they were still no better than would be expected by chance. Participants were worse at 'guessing' than would be expected by chance, which implies that their prior beliefs about how they would feel after the operation, as well as their perceived impact of gabapentin, were incorrect. The difference in number of correct guesses between the research nurses and the patients is likely to be the elimination of prior beliefs about the state of patients after any operation. As is to be expected, research nurses have more experience at looking at postoperative patients and knowing subjectively how they look and feel.

The trial team faced challenges from the research governance framework not aligning with the practicalities of delivering a pragmatic clinical trial as part of usual clinical care. Regulatory requirements for trials of investigational medical products require reporting of SAEs to the Sponsor – including all those expected of the study medication and anticipated of the surgery. Around 70% of people in the trial had at least one AE and over 30% of people had at least one SAE. Those expected of the medication include all of those listed on the SmPC, and in the case of gabapentin include those for chronic use in a primary care environment. This presents a serious administrative challenge when this is applied in the major surgery context. For example, one of the events expected of the medication is 'palpitations'. Around 30–50% of patients undergoing cardiac surgery will have atrial fibrillation (or supraventricular tachycardia) after their surgery.[52] Given the sample size, there will be around 200–250 'palpitation' events reportable just in the cardiac surgery cohort. Given the wide variety of local and systematic complications that major surgery can precipitate, SAE reporting is a significant administrative burden in the major surgery context and uses considerable resources without improving the signal-to-noise ratio. We agreed a matrix with the Medicines and Healthcare products Regulatory Agency and Sponsor of SAEs of 'expected of the medication only'/'medically anticipated only'/'medically anticipated AND expected of the medication'. Only SAEs expected of the medication or unexpected were subject to expedited reporting to the Sponsor. Events which were anticipated of the surgery, or both the surgery and the drug, were logged and reviewed periodically by the Sponsor during safety reviews.

Site PIs are recognised by NHS Trusts and taking on the role of PI may count towards individual recognition or remuneration. Having a single PI for each hospital (a governance requirement), even if recruitment was taking place across several unrelated (and in many cases geographically separate) specialties, disincentivised some clinicians from participation, as they did not feel they would get the appropriate recognition for their work. PIs were required to delegate responsibilities (e.g. assessing eligibility/safety) to colleagues in other specialties. This placed additional burden on local teams to deliver these training sessions and obtain copies of the required documentation. Where feasible, specialty leads and associate PIs were appointed to champion the study in their departments. The Sponsor, while viewing each hospital as a single centre, monitored specialties separately. This created additional work for the local site PI and central co-ordination team. The system used for capturing local research activity (Local Portfolio Management Systems – EDGE) does not allow recruitment to be easily attributed to different specialties (for site payments) within one hospital Trust, and any discrepancies at one centre had to be checked by all specialties resulting in additional work and frustration for local teams.

Equality, diversity and inclusion

The age groups of the participants are representative of those undergoing major surgery and the male/female split overall is heavily influenced by the inclusion of cardiac surgery – where over 70% of the surgical population are male (this is representative of the national and international picture[53]). The sex make-up of the other surgical specialties is representative of population contained within them. The trial included relatively few non-white participants which is not representative of the whole UK surgical population (see below).

This study was designed and opened before the prioritisation of equality, diversity and inclusion and, as such, there was no incentive to be inclusive and no specific costs allocated. Therefore, our approach was reactive rather than proactive. We did not actively search out under-represented populations or translate trials materials into languages other than English (although if patients did present, we made every effort to include them in the trial – including the use of interpreters). In subsequent studies (e.g. Prehab-UK: PDG NIHR203304 in cardiac surgery), we have carried out routine data analysis to ensure that our research directly reflects and targets the population who it is designed to serve. While we cannot comment on other specialties (as we have no direct comparators), certainly in the UK cardiac surgery population only around 90–95% of the population are white with around 5% South Asian (compared with > 97% in the GAP study). Therefore, it is likely that the GAP study is not entirely representative of the UK population.

Trial results

The GAP study has shown that, among patients undergoing major surgery, the addition of gabapentin (600 mg preoperatively and 300 mg twice a day postoperatively 2 days) to multimodal analgesic regimes did not result in a change in hospital LoS, opiate use, acute pain, SAEs, quality of life or resource use, and it was not cost-effective. Overall, patients who took gabapentin had a higher incidence of pain at 4 months, albeit with similar severity to the placebo group when they did have pain. Those undergoing abdominal and thoracic surgery used less opioid medication while in-hospital, but not after discharge from hospital during follow-up. The lower opioid use did not translate into significant reductions in pain, but fewer patients suffered serious adverse effect(s) in the abdominal specialty. The increased incidence of pain at 4 months in the gabapentin group was also not seen in the abdominal surgery cohort. There were no other signals of either benefit or harm. None of the differences in patient-reported outcomes met the suggested thresholds for clinical importance.

Gabapentinoids such as gabapentin and pregabalin are often included in perioperative multimodal analgesia regimens in an attempt to reduce acute, subacute and chronic pain after surgery. Over the last decade, the off-label use of gabapentinoids for the control of acute nociceptive or neuropathic pain has drastically increased in several countries,[54–56] and they are now routinely used for the management of postoperative analgesia to decrease pain and opioid use. There have been serious concerns about the trade-off between the potential adverse effects of gabapentinoids (e.g. risk of abuse and respiratory depression) and the clinical benefits.[57–62] Gabapentin is included as a 'strong recommendation' as a component of multimodal analgesia for the management of postoperative pain in the USA,[63] but not in Europe.[64] NICE made a 'recommendation for research' for the use of gabapentin for postoperative pain control.[8] However, this was because of uncertainties regarding dose and timing, rather than its clinical effectiveness – which NICE perceived to be effective based on systematic review.

The GAP study confirms the findings of the last comprehensive, multispecialty systematic review and meta-analysis published in 2020[24] showing no *clinically* significant benefit of gabapentinoids in the perioperative setting [albeit with some small statistically significant reductions in postoperative pain (MD, −6 on a 100-point scale; 95% CI −9 to −3; I^2 = 98%; 18 trials; 1392 participants) and opiate use (MD −5.46 in mg of intravenous morphine equivalent at 48 hours, 95% CI, −9.60 to −1.33, I^2 = 80%; 12 trials, 642 patients)]. There were a small number of single-centre, small trials since this meta-analysis[65–67] – none of which have shown a clinically significant reduction in pain. None of these recently published trials examined length of hospital stay and indeed only 17/281 trials in the 2020 meta-analysis examined length of hospital stay (and in none of those studies was it the primary outcome to which the study was powered). Almost all studies were powered for changes in pain scores or reduction in opiates. While many studies show a statistically significant difference in these, very few show *clinically* important differences in pain (10 mm difference on a 100-mm visual analogue score[68]). Our study was subject to this whereby the mean difference in NRS favoured the gabapentin group at all *in-hospital* time points. However, at no time point or specialty, at rest, or on movement was the mean difference in NRS more than 1 (the equivalent of 10 mm difference on a 100-mm visual analogue score). Therefore, while at time points within 2 days of surgery this is statistically significant, and at no point was it *clinically* significant. While opiate use between the two groups was similar in the cardiac specialty, there was statistically less opiate use in the gabapentin group in both the thoracic specialty in the first 2 days after the surgery and the abdominal specialty in four of the first 5 days after surgery. It is clear from enhanced recovery pathways[69–71] that targeting *optimal* pain control (i.e. the patient can ambulate, deep breathe and cough) in the postoperative period rather than *complete* suppression of pain leads to improved clinical outcomes. This is because many analgesics (gabapentin included) have somnolence and sedation as an adverse effect – patients may be pain free, but they are sleepy and non-ambulating – placing them at risk of a variety of postoperative complications such as pneumonia and venous thromboses. In the thoracic and abdominal specialties, gabapentin reduced opioid use, but not enough to reduce the number of AEs. The most cited risk of gabapentin in the postoperative period is that of somnolence and respiratory depression. The number of AEs in the neurological and respiratory MedDRA classes is broadly similar (and inconsistently distributed) between gabapentin and placebo groups. Interpreting the pain and opioid outcomes across the GAP study would imply that similar outcomes are reached (i.e. similar pain experience) both *in-hospital* and at *follow-up*, regardless of whether gabapentin is used or not.

The high number of AEs is reflective of the setting of major surgery in which the trial was conducted. Even within this, there were higher AE rates in cardiac surgery compared to the other surgical specialties (almost all cardiac patients suffered at least one AE). A large proportion of patients (almost one-third) suffered at least one SAE; again, which is as expected following major surgery. While there were differences in the numbers of AEs between the two groups at the individual specialty level (higher rate of SAEs in the gabapentin group in thoracic surgery and placebo group in abdominal surgery), this was balanced over both groups at the whole trial level. This indicates that gabapentin does not present a serious risk of harm in the perioperative period.

The dose chosen within the GAP trial was based on consensus centred on the systematic reviews of trials chosen at the time of design.[72,73] There was (and still is) considerable heterogeneity among previous RCTs about what dose (100–1500 mg/day), timing (preoperatively, postoperatively or both) and duration (single dose to 30 days, although most commonly 2–5 days) of gabapentin were administered. These reviews highlighted that the variability around any pain control was not due to the dose of gabapentin, but baseline pain after the surgery and that any opiate-sparing effect occurred regardless of timing of the dose. There has been no evidence since that contravenes this. A mid-range dose was chosen encompassing pre- and postoperative administration. Sustained pain relief after surgery is achieved in most patients by 2 days after the operation[74] and so this duration was chosen for the intervention. These parameters are as applicable now as when the trial was designed.

The GAP study is the first to provide any cost-effectiveness evidence for the use of gabapentin in the perioperative setting.[8] Previous studies and trials have probably not included this type of analysis due to gabapentin being a low-cost intervention (each 300 mg tablet costs the NHS around 1 pence[39]) and many of the trials have been small and of low quality.[8,24] They are therefore unlikely to have had the resources or expertise to carry out this type of analysis. The *in-hospital* healthcare costs have been calculated based on existing NHS unit costs and fit within the envelope of plausibility for the types of surgery that were included (NHS Tariff for major, general abdominal surgery £5000–10,000, cardiac surgery £10,000–15,000, major thoracic surgery £5000–£8000[75]). Given that gabapentin had no impact on clinical outcomes either *in-hospital* or at *follow-up*, it is therefore not surprising that it also had no impact on resource use and hence costs at these time points.

Strengths and limitations

The major strength of this study is that it is a pragmatic trial design integrated in existing usual care pathways for major surgery across a number of NHS sites. It is also the first trial to assess the impact of gabapentin on hospital stay, quality of life and cost-effectiveness. This makes the findings generalisable to the NHS as a whole and ensures it has implications for health policy.

It was also conducted across a number of major surgical specialties, making its findings generalisable to all major body cavity surgeries. No other study of gabapentin in the perioperative setting has included such a wide variety of surgery types.[24] Most previous studies were limited to a single specialty and in many cases a single operation (e.g. hysterectomy, knee replacement). That said, clearly there were more patients recruited from the cardiac specialty (500) than thoracic (346) and abdominal (350) specialties – which may represent a limitation. However, the trial was powered (minimum 80%, reduced from 90% due to complete recruitment within an acceptable time and funding envelope after the COVID-19 pandemic) to detect a difference in hospital LoS *in each specialty* and therefore this will have a minimal impact on the conclusions, given the small difference (< 5 hours difference in median stay) between the two groups in hospital LoS.

The GAP study does not test the application of gabapentin to other major non-body cavity surgery (e.g. joint replacement), or non-major (e.g. day-care) surgery. Care pathways and analgesic regimens for these other types of surgery are different and therefore we cannot fully assess the impact of the addition of gabapentin to them. However, given the lack of impact of gabapentin on pain scores within the GAP study, we would not anticipate that it would impact postoperative pain significantly in other settings as indicated by the most recent meta-analysis.[24]

Other limitations of the trial include the non-compliance in terms of missed or delayed doses of study medication, the non-variable dose of gabapentin and the restricted time period of the intervention. Therefore, we cannot assess the impact of higher doses of gabapentin on pain or the impact of a reduced dose on adverse effects in vulnerable populations such as the elderly and frail. However, since the pain scores on rest were below 2 and pain scores on movement were below 4 from 48 hours after the surgery, the impact of prolonged treatment with gabapentin beyond the current intervention time period is likely to be limited.

Patient and public involvement

The main impacts of PPI in the trial were with respect to:

- Designing the study to make the study less burdensome for patients.
- Developing information for participants.

- Making significant changes in the way in which trial follow-up was conducted and hence promoting the completeness of the outcome data.
- Disseminating information about the findings of the trial to participants (ongoing).

The study was funded and started before our current PPI strategy and implementation was developed with the NIHR Bristol Biomedical Research Centre and other existing collaborations (University of the West of England). PPI participants came to GAP study investigators' meetings and Trial management group meetings but were not involved in the study the way we work with them now. In other studies, funded since the GAP study (e.g. PRACTISE-AF NIHR156028 and Prehab-UK: NIHR203304), our PPI members are now truly embedded in the research team. They have participated in systematic review data extraction, chair stakeholder meetings and provide administrative support to their own PPI meetings as well as the usual core PPI activities. This has been as a result of developing collaborations with PPI participants (some of whom were involved with the GAP study) and national groups (e.g. the National Cardiac Surgery PPI group). These collaborations needed time to develop, and they were not in place for the start of the GAP study. The training provided by the Biomedical Research Centre and People in Health West of England to PPI members means that the understanding of research methodology has improved. Questions from PPI members are valuable and often highlight gaps in knowledge or omissions by the research team – even in methodology. Had this been in place at the start of the GAP study, we may have avoided some of the negative feedback, particularly in relation to the choice of patient-reported outcome measures expressed by some participants. Several participants found it difficult to complete the BPI, a questionnaire designed to assess chronic pain, when they were no longer in pain.

Potential implications for policy-makers

This trial has shown that gabapentin has minimal impact as part of a multimodal analgesic regimen for major body-cavity surgery. It has few benefits for patients in terms of pain control, reduction of AEs or quality of life, and no benefits for healthcare providers in terms of LoS, resource use or costs. Whilst it may have small impacts on opiate use in the short term, this was not reflected inimprovement to pain control. Gabapentin is addictive and can be abused – it is implicated in 15% of drug-related deaths in Scotland[76] and around 10% in the USA (but is detected in around 85–90% of opioid deaths).[77] This has resulted in its UK classification into a Schedule 3 Controlled Drug of the Misuse of Drugs Act (1971)[78] during the lifetime of the GAP study. The prescribing of gabapentinoids in the postoperative period has been found to increase the risk of their prolonged use.[79] Additionally, the risk of prolonged *opioid* use has also been found with the use of any perioperative gabapentinoid.[80] In the USA, 20% of gabapentin-naive people prescribed the medication for postoperative pain were still taking them at 90 days postoperatively.[79] These societal harms traded-off against the lack of clinical or cost-effectiveness further compound the argument that there should be a reduction in prescription of gabapentin for acute postoperative pain.

Unanswered questions and future research

1. The GAP study has answered many of the questions associated with the use of gabapentin – particularly those associated with change in LoS. It is difficult to see a mechanism by which gabapentin could reduce hospital LoS in non-major and major non-body cavity surgery, as these types of surgery use less opiate than those included in the GAP study and surgical-site pain control impacts less on respiratory function (the biggest source of postoperative morbidity[81]) after these types of surgery. However, there is still potential for an RCT of gabapentin versus placebo in major joint replacement surgery but is likely that the driver (and therefore outcomes) would be quality of recovery rather than avoidance of complications or healthcare efficiency.
2. The GAP study was not designed to test the place of gabapentin in rescue therapy for those whose pain is not controllable using conventional multimodal analgesia. Therefore, there is potential for research in this area. However, the differences in NRS between gabapentin and placebo at rest and on movement were small and clinically insignificant. It is therefore unlikely that it will be effective at controlling pain after major surgery – even as a rescue therapy. Also, a trial of gabapentin as a rescue therapy for uncontrolled pain after major surgery would be challenging in both design and conduct. Relatively few people have uncontrolled pain after major surgery; thus, identifying and recruiting these people to a RCT would be difficult.

3. Other opiate-reducing techniques such as regional analgesia for pain control after major surgery exist and these warrant testing. These are beginning to happen with studies such as CAMELOT (NIHR133554), a trial of rectus sheath block for abdominal surgery and ORIGIN (NIHR201150), a trial of pectus-intercostal-rectus sheath block for sternotomy. However, there are an array of both single-nerve and fascial-plane blocks which have not been tested in a RCT. These deserve testing but must focus on the composite outcome of LoS to ensure a complete picture of risks and benefits.

Chapter 8 Conclusion

Among patients undergoing major cardiac, thoracic and abdominal surgery, the addition of gabapentin (600 mg preoperatively and 300 mg twice a day posoperatively for 48 hours) to multimodal analgesic regimes did not result in a clinically signigicant change in hospital LoS, opiate use, acute pain, or quality of life, nor was it cost-effective. Patients who took gabapentin had a higher incidence of pain at 4 months.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

Following publication, anonymised individual participant data will be made available upon request to the corresponding author for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. Only data from participants who have consented for their data to be shared with other researchers will be provided.

Ethics statement

The trial was given a favourable ethical opinion (reference IRAS 225986) by the Yorkshire and the Humber – Sheffield Research Ethics Committee on 23 November 2017.

Information governance statement

The University of Bristol is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Bristol is the Data Processor; University Hospitals Bristol and Weston NHS Foundation Trust is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for University Hospitals Bristol and Weston NHS Foundation Trust Data Protection Officer here: InformationGovernance@uhbw.nhs.uk.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/PLMH9787.

Primary conflicts of interest: Chris A Rogers reports membership of a Clinical Trials Unit funded by the UK National Institute for Health Research (NIHR) and reports grants from NIHR during the conduct of the study. She also reports membership of the NIHR Health Technology Assessment Funding Committee Policy Group (formally CSG) (2017–21) and the Health Technology Assessment Commissioning Committee (2016–21). She has no other competing interests.

No other authors report competing interests.

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Publications

Rogers CA, Baos S, Culliford L, Pufulete M, Gibbison B; on behalf of the GAP study investigators. Challenges of conducting trials across multiple clinical specialties. *Trials* 2019;**20**:268.

Baos S, Rogers CA, Abbadi R, Alzetani A, Casali G, Chauhan N, *et al*. Effectiveness, cost-effectiveness and safety of gabapentin versus placebo as an adjunct to multimodal pain regimens in surgical patients: protocol of a placebo controlled randomised controlled trial with blinding (GAP study). *BMJ Open* 2020;**10**:e041176.

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Appendix 1 Additional details on methods used

Statistical methods: derivation of opioid consumption

Opioid consumption in the period from surgery to hospital discharge was derived by first calculating the amount (e.g. milligram) of each opioid taken each day, converting these to intravenous morphine equivalents and summing to give a total intravenous morphine equivalent dose for the day. Morphine equivalents used for each drug is given in *Table 23*. During follow-up the same approach was taken using doses and dates when drugs were started/changed/stopped to derive the total amount of drug received before converting to intravenous morphine equivalents. Assumptions applied if drug data were missing at follow-up are given in *Table 24*.

TABLE 23 Intravenous morphine equivalents for each drug

Drug	Oral morphine equivalent[a]	IV morphine equivalent
Morphine (oral[b])	10 mg of oral morphine to 3.33–5 mg IV morphine	Dose (mg)*0.33
Codeine (oral)	100 mg to 10 mg of oral morphine	Dose (mg)*0.1*0.33
Tramadol (oral)	50–100 mg to 10 mg of oral morphine	Dose (mg)*(10/100)*0.33
Tramadol (IV)	25–50 mg to 10 mg of oral morphine	Dose (mg)*(10/50)*0.33
Fentanyl (oral[c])	100 mcg to 15 mg of oral morphine	Dose (mcg)*(15/100)*0.33
Fentanyl (IV[d])	0.067 mg to 10 mg of oral morphine	Dose (mg)*(10/0.067)*0.33
Fentanyl (patch)	12 mcg/hour to 30 mg/day of oral morphine	Dose (mcg/hour)*(30/12)*0.33
Dihydrocodeine (oral)	100 mg to 10 mg of oral morphine	Dose (mg)*0.1*0.33
Diamorphine (IV)	3.33 mg to 10 mg of oral morphine	Dose (mg)*(10/3.33)*0.33
Oxycodone (oral[b])	5–7.5 mg to 10 mg of oral morphine	Dose (mg)*(10/7.5)*0.33
Oxycodone (IV)	3.33–5 mg to 10 mg of oral morphine	Dose (mg)*(10/5)*0.33
Buprenorphine (sublingual)	0.1–0.125 mg to 10 mg of oral morphine	Dose (mg)*(10/0.125)
Buprenorphine (patch)	35 mcg/hour to 63 mg of oral morphine	Dose [(mcg/hour)/5]*9*0.33
Alfentenyl (IV)	0.25–0.33 mg to 10 mg of oral morphine	Dose (mg)*(10/0.33)*0.33
Pethidine (IV)	25 mg to 10 mg of oral morphine	Dose (mg)*(10/25)*0.33

i.v., intravenous.
a From www.gloshospitals.nhs.uk/gps/treatment-guidelines/opioid-equivalence-chart/
b Short acting and prolonged release.
c www.palliativecareguidelines.scot.nhs.uk/guidelines/pain/choosing-and-changing-opioids.aspx
d Includes epidural.

DOI: 10.3310/PLMH9787

TABLE 24 Assumptions applied when drug data were incomplete

4-week follow-up completed	4-month follow-up completed	Medication at 4 weeks	Medication at 4 months	Assumption
✔	✔	Blank	Blank	Medication not taken during follow-up
✔	✔	Yes	Blank	Assumed stopped at 2.5 months (mid-way between 4 weeks and 4 months)
✔	✔	Yes	No, stop date not given	Assumed stopped at 2.5 months (mid-way between 4 weeks and 4 months)
✘ (remained in hospital)	✔	–	No, stop date not given	Assumed stopped at 2.5 months (mid-way between 4 weeks and 4 months)
✘ (remained in hospital)	✔	–	Yes	Assumed taken throughout
✘	✔	–	No, stop date given	Assume taken from discharge to stop date
✔	✘	? information incomplete	–	Assume stopped mid-way between discharge and 4 weeks
✘	✘	–	–	Missing

Note
If medication end date corresponded to discharge date, it was assumed that the drug was not taken during follow-up. If dose and/or frequency were given as a range, the lowest dose and highest frequency was assumed. If the frequency was given as 'when required' (pro re nata, PRN), half the maximum daily dose was assumed.

Health economic methods: unit costs used in the economic evaluation

Note that unit costs not in 2021–2 prices have been adjusted to 2021–2 prices using the NHSCII.[42]

TABLE 25 Unit costs associated with surgery and inpatient stays in the index admission

Resource	Unit cost (£)	Reference
Surgery		
Surgery – time in theatre (per hour)	1356	Public Health Scotland.[38] Costs Book 2019–20 – R140 Number of theatres, expenditure and usage. Average cost per theatre hour used across general hospital (mainly acute).
Inpatient stay		
Ward day	471	NHS Reference Costs 2017–8.[43] Weighted average of elective inpatient excess bed-day costs across all activities
High-dependency day – cardiac specialty	1246	NHS Reference Costs 2021–2.[41] Critical Care. CCU06, Cardiac surgical adult PATIENTS predominate. Weighted average of XC06Z – XC07Z, Adult Critical Care, 0–1 organs supported.
High-dependency day – thoracic/ abdominal specialties	1664	NHS Reference Costs 2021–2.[41] Critical Care. Weighted average of CCU01 Non-specific, general adult critical care PATIENTS predominate, CCU02 Surgical adult PATIENTS (unspecified specialty), CCU06 Cardiac surgical adult PATIENTS predominate, CCU07 Thoracic surgical adult PATIENTS predominate; for XC06Z–XC07Z, Adult Critical Care, 0–1 organs supported.
Intensive care day – cardiac specialty	2269	NHS Reference Costs 2021–2.[41] Critical Care. CCU06, Cardiac surgical adult PATIENTS predominate. Weighted average of XC01Z – XC05Z, Adult Critical Care, 2–6 or more organs supported.
Intensive care day – thoracic/abdominal specialties	2531	NHS Reference Costs 2021–2.[41] Critical Care. Weighted average of CCU01 Non-specific, general adult critical care PATIENTS predominate, CCU02 Surgical adult PATIENTS (unspecified specialty), CCU06 Cardiac surgical adult PATIENTS predominate, CCU07 Thoracic surgical adult PATIENTS predominate; for XC01Z – XC05Z, Adult Critical Care, 2–6 or more organs supported.
Ward day at another hospital	378	NHS Reference Costs 2017–8.[43] Weighted average of elective and non-elective inpatient excess bed-day costs across all activities.

TABLE 26 Unit costs for analgesia and local anaesthetics

Drug name	Route	Dose	Dose cost (£)	Source
Alfentanil	IV	1 mg/2 ml	0.35	eMIT
Alfentanil	IV	5 mg/1 ml	1.06	eMIT
Amitriptyline	Oral	10 mg	0.01	eMIT
Amitriptyline	Oral	20 mg	0.02	eMIT
Aspirin	Oral	75 mg	0.01	eMIT
Aspirin	Oral	150 mg	0.02	eMIT
Aspirin	Oral	300 mg	0.03	eMIT
Aspirin	Rectal	150 mg	2.31	PCA
Aspirin	Rectal	300 mg	4.26	PCA
Buprenorphine	Patch	5 mcg/hour for 7 days	1.16	eMIT
Buprenorphine	Patch	10 mcg/hour for 7 days	1.84	eMIT
Buprenorphine	Patch	35 mcg/hour for 72 hours	1.75	eMIT
Buprenorphine	IV	300 mcg/1 ml	0.49	PCA
Bupivacaine 0.25%	IV	25 mg/10 ml	0.84	eMIT
Bupivacaine 0.5%	IV	50 mg/10 ml	0.70	eMIT
Caffeine citrate	Oral	20 mg/5 ml	4.32	PCA
Caffeine citrate	Oral	50 mg/5 ml	5.20	PCA
Celecoxib	Oral	100 mg	0.02	eMIT
Celecoxib	Oral	200 mg	0.05	eMIT
Celecoxib	Oral	100 mg	0.02	eMIT
Celecoxib	Oral	200 mg	0.05	eMIT
Codeine	Oral	30 mg	0.02	eMIT
Codeine	Oral	60 mg	0.03	eMIT
Codeine phosphate	Oral	15 mg/5 ml	0.01	PCA
Colchicine	Oral	500 mcg	0.63	PCA
Clonidine	Oral	100 mcg	0.08	PCA
Clonidine	Oral	25 mcg	0.08	PCA
Clonidine	IV	150 mcg	0.42	PCA

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 26 Unit costs for analgesia and local anaesthetics (*continued*)

Drug name	Route	Dose	Dose cost (£)	Source
Co-codamol	Oral	8 mg/500 mg	0.01	eMIT
Co-codamol	Oral	30 mg/500 mg	0.02	eMIT
Codydramol	Oral	10 mg/500 mg	0.02	eMIT
Dexmedetomidine	IV	200 mcg/2 ml	9.88	eMIT
Diclofenac	Oral	50 mg	0.04	PCA
Diclofenac	Oral	75 mg	0.23	PCA
Diclofenac	Oral	100 mg	0.35	PCA
Diclofenac	IV	75 mg	0.99	PCA
Diclofenac	Patch	100 mg	0.27	eMIT
Diclofenac	Rectal	100 mg	0.27	eMIT
Dihydrocodeine	Oral	30 mg	0.02	eMIT
Diamorphine	IV	5 mg	2.56	PCA
Diamorphine	IV	10 mg	3.35	PCA
Diamorphine	IV	30 mg	3.37	PCA
Diamorphine	IV	100 mg	8.48	PCA
Diamorphine	IV	500 mg	37.54	PCA
Diamorphine	Oral	2.5 mg/5 ml	0.54	PCA
Diamorphine	Oral	2 mg/5 ml	0.56	PCA
Diamorphine	Oral	100 mg/5 ml	0.33	PCA
Fentanyl	IV	100 mcg/2 ml	0.16	eMIT
Fentanyl	IV	500 mcg/10 ml	0.35	eMIT
Fentanyl	Patch (8 hours)	12 mcg/hour	1.79	PCA
Fentanyl	Patch (8 hours)	25 mcg/hour	2.56	PCA
Fentanyl	Patch	50 mcg/hour	6.73	PCA
Fentanyl	Patch	75 mcg/hour	9.40	PCA
Fentanyl	Patch	100 mcg/hour	11.6	PCA
Gabapentin	Oral	300 mg	0.01	eMIT
Gabapentin	Oral	1200 mg	0.07	eMIT
Heavy bupivacaine 0.5%	IV	20 mg/4 ml	1.45	PCA

TABLE 26 Unit costs for analgesia and local anaesthetics (*continued*)

Drug name	Route	Dose	Dose cost (£)	Source
Hyoscine butylbromide	IV	20 mg/ml	0.27	eMIT
Ibuprofen	Oral	100 mg	0.27	PCA
Ibuprofen	Oral	400 mg	0.04	eMIT
Ibuprofen	Oral	800 mg	0.04	eMIT
Ibuprofen 5% gel	Topical	50 g	0.42	eMIT
Ibuprofen 10% gel	Topical	1 g	0.05	PCA
Indometacin	Oral	25 mg	0.02	eMIT
Indometacin	Oral	50 mg	0.02	eMIT
Ketamine	IV	50 mg/5 ml	7.27	PCA
Ketamine	IV	200 mg/20 ml	5.06	PCA
Ketamine	IV	500 mg/10 ml	2.64	PCA
Ketorolac	IV	30 mg	0.37	eMIT
Levobupivacaine 0.125%	IV	125 mg/100 ml	4.55	eMIT
Levobupivacaine 0.125%	IV	250 mg/200 ml	8.72	eMIT
Levobupivacaine 0.25%	IV	25 mg/10 ml	1.08	eMIT
Levobupivacaine 0.5%	IV	50 mg/10 ml	1.19	eMIT
Levobupivacaine 0.75%	IV	75 mg/10 ml	1.66	eMIT
Lidocaine 0.5%	IV	10 ml	0.90	eMIT
Lidocaine 1%	IV	2 ml	0.12	eMIT
Lidocaine 1%	IV	5 ml	0.16	eMIT
Lidocaine 1%	IV	10 ml	0.23	eMIT
Lidocaine 1%	IV	20 ml	0.50	eMIT
Lidocaine 2%	IV	2 ml	0.17	eMIT
Lidocaine 2%	IV	5 ml	0.16	eMIT
Lidocaine 2%	IV	10 ml	0.38	eMIT
Lidocaine 2%	IV	20 ml	0.59	eMIT
Lidocaine 5%	Patch	700 mg	2.28	PCA
Lidocaine 5%	Topical	1 g	0.55	PCA

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DOI: 10.3310/PLMH9787

TABLE 26 Unit costs for analgesia and local anaesthetics (*continued*)

Drug name	Route	Dose	Dose cost (£)	Source
Magnesium	Oral	243 mg/10 mmol	0.69	PCA
Magnesium sulphate 50% (magnesium 2 mmol/ml)	IV	2 ml	0.40	eMIT
Magnesium sulphate 50% (magnesium 2 mmol/ml)	IV	5 ml	2.41	eMIT
Magnesium sulphate 50% (magnesium 2 mmol/ml)	IV	10 ml	0.34	eMIT
Magnesium sulphate 50% (magnesium 2 mmol/ml)	IV	20 ml	4.83	eMIT
Meloxicam	Oral	7.5 mg	0.05	eMIT
Meloxicam	Oral	15 mg	0.15	eMIT
Morphine	Oral	5 mg	0.05	PCA
Morphine	Oral	10 mg	0.09	eMIT
Morphine	Oral	15 mg	0.15	PCA
Morphine	Oral	20 mg	0.18	eMIT
Morphine	Oral	50 mg	0.52	eMIT
Morphine	IV	10 mg/1 ml	0.18	eMIT
Morphine	IV	15 mg/1 ml	0.24	eMIT
Morphine	IV	30 mg/1 ml	0.34	eMIT
Morphine	IV	60 mg/2 ml	1.55	eMIT
Morphine (prolonged release)	Oral	10 mg	0.06	PCA
Naproxen	Oral	500 mg	0.03	eMIT
Nortriptyline	Oral	10 mg	0.02	PCA
Oxycodone	Oral	5 mg	0.06	eMIT
Oxycodone	Oral	10 mg	0.07	eMIT
Oxycodone	Oral	15 mg	0.12	eMIT
Oxycodone	Oral	20 mg	0.12	eMIT
Oxycodone	IV	10 mg/1 ml	0.49	eMIT
Oxycodone	IV	20 mg/2 ml	0.73	eMIT
Oxycodone (prolonged release)	Oral	5 mg	0.20	PCA

DOI: 10.3310/PLMH9787

TABLE 26 Unit costs for analgesia and local anaesthetics (*continued*)

Drug name	Route	Dose	Dose cost (£)	Source
Oxycodone (prolonged release)	Oral	20 mg	0.82	PCA
Paracetamol	Oral	1 g	0.01	eMIT
Paracetamol	Oral	1.5 g	0.01	eMIT
Paracetamol	Oral	2 g	0.02	eMIT
Paracetamol	Oral	2.5 g	0.02	eMIT
Paracetamol	Oral	3 g	0.03	eMIT
Paracetamol	Oral	4 g	0.04	eMIT
Paracetamol/caffeine	Oral	500 mg/65 mg	0.13	PCA
Paracetamol	IV	500 mg/50 ml	0.70	eMIT
Paracetamol	IV	1 g/100 ml	0.50	eMIT
Paracetamol	Rectal	1 g	5.95	PCA
Parecoxib	IV	40 mg	3.74	eMIT
Pethidine	IV	100 mg/2 ml	0.26	eMIT
Pethidine	IV	50 mg/1 ml	0.20	eMIT
Pregabalin	Oral	25 mg	0.06	PCA
Pregabalin	Oral	50 mg	0.06	PCA
Pregabalin	Oral	75 mg	0.08	PCA
Pregabalin	Oral	100mg	0.07	PCA
Pregabalin	Oral	150 mg	0.07	PCA
Pregabalin	Oral	200 mg	0.08	PCA
Pregabalin	Oral	300 mg	0.10	PCA
Sumatriptan	Oral	100 mg	1.93	eMIT
Temazepam	Oral	20 mg	0.05	eMIT
Tramadol	Oral	50 mg	0.01	eMIT
Tramadol	IV	100 mg/2 ml	0.28	eMIT

i.v., intravenous.
PCA, prescription cost analysis.

Note

These are all sourced from the eMIT,[39] which provides the reduced prices paid for generic drugs in hospital, or from PCA.[40]

TABLE 27 Resource use assumed for complications and total costs

Complication	Treatment/action	Cost (£)	Assumptions
Cardiac complications			
Myocardial infarction	No additional treatment	0	Captured in increased LoS
Cardiac arrest (requiring resuscitation involving ventricular defibrillation/direct current shock)	Cardiac arrest treatment	774	
Cardiac arrest (requiring external/internal cardiac massage)	Cardiac arrest treatment	774	
Congestive heart failure (requiring treatment)		0	
Pericarditis requiring treatment		0	
Bleeding (needing reoperation or not)	Chest X-ray, and blood transfusion – assume 1 unit of red blood cells if abdominal/thoracic. For cardiac assume two-thirds have 2 units of red blood cells, 1 platelet, 2 fresh-frozen plasma, 1 cryoprecipitate, and a third have 1 unit of red blood cells.	Cardiac: £620.97 Thoracic/abdominal: £183.99	Reoperations already captured
Blood clots	Duplex scan, IV heparin (initial 5000 units, then 15,000 units every 12 hours for 5 days) then apixaban (5 mg 2× day oral)	253.39	Assumed that the patients took apixaban for 2.5 months
Haematoma	No additional treatment	0	Reoperations already captured
Deep vein thrombosis	Duplex scan, IV heparin (initial 5000 units, then 15,000 units every 12 hours for 5 days)	116.59	
Pulmonary embolus	Transthoracic echo, CT chest, IV heparin for 5 days (initial 5000 units, then 15,000 units every 12 hours for 5 days)	249.59	
Pericardial effusion	No additional treatment	0	Reoperation already captured
Pacing	No additional treatment	0	
Arrhythmias/palpitations (including supraventricular tachycardia/atrial fibrillation/atrial flutter/ventricular tachycardia)	No additional treatment	0	LoS
Respiratory/thoracic/mediastinal complications			
Intubation/re-intubation and ventilation	Cardiac participants get transthoracic echo; thoracic/abdominal – no additional treatment	128 cardiac only	Captured in ICU admission
Tracheostomy	No additional treatment	0	Captured in ICU admission

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Initiation of CPAP or non-invasive ventilation	No additional treatment	0	Captured in ICU admission
Acute respiratory distress syndrome	No additional treatment	0	Captured in ICU admission
Pneumothorax	Chest X-ray, chest drain	850	
Acute respiratory failure	No additional treatment	0	Captured in intensive care and ward LoS
Atelectasis/pulmonary collapse	No additional treatment	0	LoS
Surgical emphysema (requiring intervention)	Chest X-ray, chest drain reinsertion	850	
Bronchopleural fistula	No additional treatment	0	Captured in return to theatre
Prolonged air leak	Chest X-ray	38	
Chylothorax	Chest X-ray, chest drain	850	Captured in return to theatre or increased LoS
Pleural effusion	Chest X-ray, 30% have chest drain	281.6	
Dyspnoea	No additional treatment	0	
Cough	No additional treatment	0	
Intrathoracic collection/abscess (requiring drainage or not)	Chest X-ray, 50% have chest drain	444	
Respiratory depression	No additional treatment	0	
Gastrointestinal complications			
Gastrointestinal bleed	Endoscopy, blood – 2 units of red blood cells	849.98	Reoperations captured separately
Perforation	No additional treatment	0	Reoperations captured separately
Diagnostic laparotomy/laparoscopy	Laparoscopy (unless laparotomy captured in reoperations)	952	Reoperations captured separately – checked for laparotomy to avoid double counting
Leak from anastomosis, staple line, or localised conduit necrosis	Result in reoperation	0	Reoperations captured separately
Conduit necrosis/failure	Result in reoperation	0	Reoperations captured separately
Intestinal ischaemia	CT scan	90	Reoperations captured separately
Ileus (small bowel dysfunction preventing/delaying enteral feeding)	25% have a CT scan	22.5	Reoperations captured separately
Intestinal obstruction	CT scan	90	Reoperations captured separately

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Delayed gastric emptying (requiring intervention or delaying discharge or requiring maintenance of nasogastric drainage > 7 days post-op)		0	LoS
Ascites	Ultrasound scan	58	
Vomiting	No additional treatment	0	
Nausea	No additional treatment	0	
Diarrhoea	IV fluids	2.66	
Abdominal pain	No additional treatment	0	
Dyspepsia	No additional treatment	0	
Constipation	No additional treatment	0	
Dry mouth/throat	No additional treatment	0	
Flatulence	No additional treatment	0	
Pancreatitis	CT scan, parenteral nutrition for 5 days, IV fluids (1500 ml)	325	Reoperations captured separately, LoS
Intra-abdominal collection/abscess (requiring drainage or not)	CT scan, 50% have chest drain	496	
Dysphagia	Speech and language therapy review, nasendoscopy, oropharyngeal fluoroscopy	446	
Dental abnormalities	No additional treatment	0	
Renal/urinary complications			
Urinary retention (requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter)		0	LoS
Acute renal failure		0	Captured in intensive care unit admission/LoS
Incontinence		0	
Psychiatric complications			
Acute delirium (including hostility/confusion/emotional lability)	No additional treatment	0	LoS
Depression	No additional treatment	0	LoS

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Anxiety	No additional treatment	0	LoS
Thinking abnormal	No additional treatment	0	LoS
Agitation	No additional treatment	0	LoS
Hallucinations	No additional treatment	0	LoS
Surgical/medical procedure complications			
Reoperation due to any cause	Reoperations individually costed – see *Table 29*	Various	Reoperations captured separately
Bronchoscopy (any cause)	Diagnostic/therapeutic bronchoscopy	955	
Injury/poisoning/procedural complications			
Recurrent laryngeal nerve damage	Review by ENT for vocal cord medialisation procedure after hospital discharge	155	
Wound dehiscence	Minor treatment (dressing rather than negative pressure wound therapy)	198	Reoperations captured separately
Incisional hernia	No additional treatment	0	Reoperations captured separately
Conversion from minimal access surgery to open surgery	No additional treatment	0	
Genital/renal tract injury	No additional treatment	0	
Chyle leak/chylous ascites	Chest X-ray, chest drain	850	Captured in return to theatre or increased LoS
Surgical complications (including anatomical/surgical damage)		0	
Abrasion	No additional treatment	0	
Fall	No additional treatment	0	
Infection complications			
Pneumonia	Antibiotics – piperacillin/tazobactam 4.5 g IV 3x day for 5 days, chest X-ray, CT scan 20%	82.65	
Respiratory infection	Antibiotics – co-amoxiclav, chest X-ray	64.85	
Urinary tract infection	Antibiotics – piperacillin/tazobactam, urine test	26.65	
Sepsis	CT scan, antibiotics (piperacillin/tazobactam)	116.65	Captured in intensive care unit admission

continued

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Wound infection	CT scan, antibiotics (piperacillin/tazobactam)	116.65	
Central venous line infection (requiring removal or antibiotics)	Antibiotics (piperacillin/tazobactam)	26.65	
Infection (other, with/without antibiotics)	50% get antibiotics (co-amoxiclav)	13.43	
Vascular complications			
Hypertension/haemodynamic control (use of vasodilators)	No additional treatment	0	
Vasodilatation/haemodynamic support (any inotropes)	Noradrenaline 1 mg/hour for 5 days	30.18	ICU
Haemodynamic support (IABP)	Intra-aortic balloon pump	3191	
Haemodynamic support (pulmonary artery catheter)	No additional treatment	0	ICU
Blood/lymphatic complications			
Thrombocytopenia	No additional treatment	0	
Leucopenia	No additional treatment	0	
Anaemia		0	LoS already captured
Immune system complications			
Allergic reactions (e.g. urticarial)	No additional treatment	0	
Metabolism complications			
Anorexia	No additional treatment	0	
Hyperglycaemia (observed mostly in diabetic patients)	No additional treatment	0	
Hypoglycaemia (observed mostly in diabetic patients)	No additional treatment	0	
Hyponatraemia	No additional treatment	0	
Neurological complications			
Permanent stroke	Rehabilitation, CT scan, MRI 50%	650	
TIA	CT scan, echo, carotid ultrasound scan, chest X-ray, ECG	495	

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Recurrent laryngeal nerve damage	Review by ENT for vocal cord medialisation procedure after hospital discharge	155	
Other neurological injury	No additional treatment	0	
Somnolence	No additional treatment	0	
Dizziness	No additional treatment	0	
Insomnia	No additional treatment	0	
Mental impairment	No additional treatment	0	
Convulsions	CT scan	90	LoS
Hyperkinesia	No additional treatment	0	
Dysarthria	CT scan	90	
Tremor	No additional treatment	0	
Headache	No additional treatment	0	
Sensations (e.g. paraesthesia, hypaesthesia, co-ordination abnormal, nystagmus, increased/decreased/absent reflex)	No additional treatment	0	
Loss of consciousness	No additional treatment	0	
Other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)	No additional treatment	0	
Eye complications			
Visual disturbances (e.g. amblyopia, diplopia)	Review by ophthalmologist 50%	71	
Hepatobiliary complications			
Hepatitis	No additional treatment	0	LoS
Jaundice	No additional treatment	0	LoS
Skin/subcutaneous tissue complications			
Facial oedema	No additional treatment	0	
Purpura (e.g. trauma bruises)	No additional treatment	0	
Rash	No additional treatment	0	
Pruritus	No additional treatment	0	

continued

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 27 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Musculoskeletal complications			
Arthralgia	No additional treatment	0	
Myalgia	No additional treatment	0	
Back pain	No additional treatment	0	
Elevated alkaline phosphatase	No additional treatment	0	
General disorder complications			
Fatigue	No additional treatment	0	
Fever	No additional treatment	0	
Peripheral oedema	No additional treatment	0	
Pain	No additional treatment	0	
Generalised oedema	No additional treatment	0	
Chest pain	No additional treatment	0	
Asthenia	No additional treatment	0	
Malaise	No additional treatment	0	
Investigation			
White blood cell count decreased	No additional treatment	0	
Weight gain	No additional treatment	0	
Elevated liver function tests	No additional treatment	0	
Malignancy complications			
Disease recurrence/progression (*local, regional, distant*)	Specific treatments captured and cost in hospital admissions and visits as occurred	0	
New primary and secondary cancers	Specific treatments captured and costed in hospital admissions and visits as occurred	0	

CPAP, continuous positive airway pressure; CT, computerised tomography; ECG, electrocardiogram; ENT, ear, nose, and throat doctor; IABP, intra-aortic balloon pump; ICU, intensive care unit; i.v., intravenous; MRI, magnetic resonance imaging; TIA, transient ischaemic attack.

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TABLE 28 Unit costs of treatments/actions associated with complications and other complications or SAEs

Treatment/action	Unit cost (£)	Reference
Antibiotics – co-amoxiclav – 1.2 g IV 3x day for 5 days	26.85	eMIT[39]
Antibiotics – piperacillin/tazobactam 4.5 g IV 3x day for 5 days	26.65	eMIT[39]
Antibiotics – flucloxacillin – 1 g IV 4x day for 5 days	12.40	eMIT[39]
Apixaban – 5 mg 2x day oral	1.80 daily	PCA[40]
Cardiac arrest	774	NHS Reference Costs 2021–2.[41] Non-elective Short Stay. EB05C Cardiac Arrest with CC Score 0–4
Cardioversion	425	NHS Reference Costs 2021–2.[41] Non-Elective Inpatient – Short Stay. EB07E, Arrhythmia or Conduction Disorders, with CC Score 0–3
Chest drain	812	NHS Reference Costs 2017–8.[43] Average of the costs of two codes: Non-elective long stay. DZ16N Pleural Effusion with Single Intervention, with CC Score 0–5, with costs associated with the average LoS reported subtracted at the corresponding excess bed-day cost. Non-elective long stay. DZ26L Pneumothorax or Intrathoracic Injuries, with Single Intervention, with CC Score 0–2, with costs associated with the average LoS reported subtracted at the corresponding excess bed-day cost
Chest X-ray	38	NHS Reference Costs 2021–2.[41] Directly Accessed Diagnostic Services. DAPF. Direct Access Plain Film.
Computerised tomography scan	90	NHS Reference Costs 2021–2.[41] Diagnostic Imaging – Direct Access. RD20A Computerised Tomography Scan of One Area, without Contrast, 19 years and over
Bronchoscopy	955	NHS Reference Costs 2021–2.[41] Outpatient procedure. DZ69A Diagnostic Bronchoscopy, 19 years and over
Duplex scan	85	NHS Reference Costs 2021–2.[41] Diagnostic Imaging – Direct Access. RD47Z, Vascular Ultrasound Scan
Electrocardiogram	181	NHS Reference Costs 2021–2.[41] Outpatient procedures. EY51Z Electrocardiogram Monitoring or Stress Testing
Endoscopy	558	NHS Reference Costs 2021–2.[41] Outpatient procedure. FE22Z Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over for 301 Gastroenterology Service
Insertion of implantable cardioverter defibrillator	3189	NHS Reference Costs 2021–2.[41] Admitted Patient Care. Daycase. EY02B, Implantation of Cardioverter Defibrillator with CC Score 0–8
Intra-aortic balloon pump	3191	NICE Medical technology guidance 8[82]
IV fluids (1500 ml)	2.66	PCA[40]
IV heparin for 5 days (initial 5000 units, then 15,000 units every 12 hours for 5 days)	31.59	PCA[40]
Laparoscopy	952	NHS Reference Costs 2021–2.[41] Admitted Patient Care. Daycase. FF53A Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over

continued

TABLE 28 Unit costs of treatments/actions associated with complications and other complications or SAEs (*continued*)

Treatment/action	Unit cost (£)	Reference
Lung biopsy	937	NHS Reference Costs 2021–2.[41] Day case. YD03Z Percutaneous Biopsy of Lesion of, Lung or Mediastinum
Minor treatment for wound dehiscence	198	NHS Reference Costs 2021–2.[41] Outpatient Procedures. 330 Dermatology Service. JC43C Minor Skin Procedures, 19 years and over
Magnetic resonance imaging scan	156	NHS Reference Costs 2021–2.[41] Imaging: Direct Access. RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
Noradrenaline 1 mg/hour for 5 days	30.18	eMIT[40]
Parenteral nutrition for 5 days	232	NICE,[83] Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition costing report.
Rehabilitation for stroke/hemiparesis	482	NHS Reference Costs 2021–2.[41] Rehabilitation. REHABL3. Non-specialist rehabilitation services level 3. Admitted patient care. VC04Z. Rehabilitation for Stroke
Review by ear, nose and throat doctor for vocal cord medialisation procedure after hospital discharge	155	NHS Reference Costs 2021–2.[41] Total Outpatient Attendance for 120, Ear Nose and Throat Service
Review by ophthalmologist	142	NHS Reference Costs 2021–2.[41] Total Outpatient Attendance for 130, Ophthalmology Service
Speech and language therapy review	188	NHS Reference Costs 2021–2.[41] Total Outpatient Attendance for 652, Speech and Language Therapy Service
Suprapubic catheter	197	NHS Reference Costs 2021–2.[41] Outpatient Procedures. LB15E, Minor Bladder Procedures, 19 years and over.
Oropharyngeal fluoroscopy	129	NHS Reference Costs 2021–2.[41] Diagnostic Imaging – Direct Access. RD30Z Contrast Fluoroscopy Procedures with duration of < 20 minutes
Transthoracic echocardiogram	128	NHS Reference Costs 2021–2.[41] Diagnostic Imaging – Direct Access. RD51A Simple Echocardiogram, 19 years and over
Ultrasound scan	58	NHS Reference Costs 2021–2.[41] Diagnostic Imaging – Direct Access. RD40Z Ultrasound Scan with duration of < 20 minutes, without Contrast
Urine test	9	NHS Reference Costs 2021–2.[41] Directly accessed pathology services. DAPS07 Microbiology
Blood products		
Red blood cells	145.99	NHSBT Price List 2021–2[84]
Platelets	222.94	NHSBT Price List 2021–2[84]
Fresh-frozen plasma	36.70	NHSBT Price List 2021–2[84]
Cryoprecipitate	213.14	NHSBT Price List 2021–2[84]

ENT, ear, nose and throat doctor; IAPB, intra-aortic balloon pump; i.v., intravenous; MRI, magnetic resonance imaging.
PCA, prescription cost analysis.

TABLE 29 Unit costs for reoperations and further surgery in the index admission

Resource	Unit cost (£)	Reference
Reopening for bleeding – cardiac	4305	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ63C, Major Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Reopening for bleeding – thoracic	2570	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ64C, Intermediate Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Completion pneumonectomy	4277	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ02K, Complex Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Laparotomy	3023	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF51E, Major General Abdominal Procedures, 19 years and over, with CC Score 0, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Laparotomy and ileostomy	3074	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF34C, Major Large Intestine Procedures, 19 years and over, with CC Score 0, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Refashioning of ileostomy	495	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF36Z, Intermediate Large Intestine Procedures, 19 years and over, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Reoperation for stoma refashioning	495	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF36Z, Intermediate Large Intestine Procedures, 19 years and over, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Subtotal colectomy	3074	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF34C, Major Large Intestine Procedures, 19 years and over, with CC Score 0, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Reoperation for anastomotic leak	4917	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF31D, Complex Large Intestine Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Reoperation for washout of haemothorax	2570	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ64C, Intermediate Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Reoperation to close chest	4305	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ63C, Major Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Sternal wound debridement	1280	NHS Reference Costs 2017–8.[43] Non-elective long stay. JC42C, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Video-assisted thoracoscopic surgery wash out and ligation of thoracic duct	2570	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ64C, Intermediate Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Reoperation for intestinal obstruction	2132	NHS Reference Costs 2021–2.[41] Admitted Patient Care. Daycase. FF52C, Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with CC Score 0
Reoperation, cardiac arrest	4305	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ63C, Major Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost

DOI: 10.3310/PLMH9787

TABLE 30 Unit costs for reattending hospital in follow-up, and further operations in follow-up

Resource	Unit cost (£)	Reference
Reattending hospital		
Ward day for re-admissions	378	NHS Reference Costs 2017–8.[43] Weighted average of elective and non-elective inpatient excess bed-day costs across all activities.
Intensive care day for re-admissions	2174	NHS Reference Costs 2021–2.[41] Critical Care. Weighted average of CCU01 Non-specific, general adult critical care PATIENTS predominate, CCU02 Surgical adult PATIENTS (unspecified specialty), CCU03 Medical adult PATIENTS (unspecified specialty), CCU06 Cardiac surgical adult PATIENTS predominate, CCU07 Thoracic surgical adult PATIENTS predominate; for XC01Z – XC07Z, Adult Critical Care, 0–6 or more organs supported.
Emergency department attendance	261	NHS Reference Costs 2021–2.[41] Emergency Care. Weighted average of all codes
Further operations		
Liver resection (elective)	3269	NHS Reference Costs 2017–8.[43] Elective inpatient. GA05D, Very Major, Hepatobiliary or Pancreatic Procedures, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Pelvic exenteration	15,473	NHS Reference Costs 2017–8.[43] Non-elective long stay. LB71Z, Total Pelvic Exenteration, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Right hemicolectomy	4177	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF32C, Proximal Colon Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Anterior resection	4918	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF31D, Complex Large Intestine Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Endosponge insertion	495	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF36Z, Intermediate Large Intestine Procedures, 19 years and over, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Reversal of stoma	495	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF36Z, Intermediate Large Intestine Procedures, 19 years and over, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Removal of rectal polyp (colorectal)	495	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF36Z, Intermediate Large Intestine Procedures, 19 years and over, with cost of average LoS reported subtracted at the average non-elective excess bed-day cost (corresponding excess bed-day cost not available)
Completion lobectomy	4472	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ02K, Complex Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Right side surgery; video-assisted thoracoscopic surgery and bullectomy	4472	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ02K, Complex Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Left upper vats wedge resection	4472	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ02K, Complex Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Drainage and debridement of continued collection	4918	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF31D, Complex Large Intestine Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Colorectal surgery and formation of stoma	4918	NHS Reference Costs 2017–8.[43] Non-elective long stay. FF31D, Complex Large Intestine Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Drainage of pericardial effusion	2505	NHS Reference Costs 2017–8.[43] Non-elective long stay. ED31C, Standard, Other Operations on Heart or Pericardium, with CC Score 0–4, with cost of average LoS reported subtracted at the corresponding excess bed-day cost

TABLE 30 Unit costs for reattending hospital in follow-up, and further operations in follow-up (*continued*)

Resource	Unit cost (£)	Reference
Hepatectomy radical bile duct excision and Roux-en-Y hepaticojejunostomy (elective)	3269	NHS Reference Costs 2017–8.[43] Elective inpatient. GA05D, Very Major, Hepatobiliary or Pancreatic Procedures, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Hepatectomy radical bile duct excision and Roux-en-Y hepaticojejunostomy (elective)	3269	NHS Reference Costs 2017–8.[43] Elective inpatient. GA05D, Very Major, Hepatobiliary or Pancreatic Procedures, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Abdominal aortic aneurysm repair (elective)	5624	NHS Reference Costs 2017–8.[43] Elective inpatient. YQ09C, Standard Open Repair of Abdominal Aortic Aneurysm with CC Score 0–3, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Prostate operation	2518	NHS Reference Costs 2017–8.[43] Non-elective long stay. LB25F, Transurethral Prostate Resection Procedures with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Right thyroid lobectomy (elective)	3641	NHS Reference Costs 2017–8.[43] Elective inpatient. KA09E, Thyroid Procedures with CC Score 0–1, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Removal of bladder stones	1454	NHS Reference Costs 2021–2.[41] Admitted Patient Care. Daycase. LB14Z, Intermediate Endoscopic Bladder Procedures
Transcatheter aortic valve implantation	4645	NHS Reference Costs 2017–8.[43] Non-elective long stay. EY21B, Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 0–7, with cost of average LoS reported subtracted at the corresponding excess bed-day cost
Bronchopleural fistula	2570	NHS Reference Costs 2017–8.[43] Non-elective long stay. DZ64C, Intermediate Thoracic Procedures, 19 years and over, with CC Score 0–2, with cost of average LoS reported subtracted at the corresponding excess bed-day cost

VATS, video-assisted thoracoscopic surgery.

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 31 Unit costs for outpatient appointments

Specialty	Service code	Unit cost (£)[a]
General surgery	100	161
Urology	101	138
Breast surgery	103	197
Colorectal surgery	104	130
Upper gastrointestinal surgery	106	170
Vascular surgery	107	207
Trauma and orthopaedics	110	159
Ear, nose and throat	120	155
Ophthalmology	130	142
Neurosurgery	150	217
Cardiothoracic surgery	170	401
Cardiac surgery	172	332
Thoracic surgery	173	242
Anaesthetics	190	118
Pain management	191	204
Intensive care medicine	192	198
Gastroenterology	301	149
Endocrinology	302	198
Clinical haematology	303	194
Hepatology	306	192
Clinical genetics	311	530
Cardiac rehabilitation	327	134
Specialist rehabilitation	345	161
Cardiology	320	169
Anticoagulant service	324	68
Stroke medicine	328	302
Dermatology	330	152
Respiratory medicine	340	185
Respiratory physiology	341	145
Sleep medicine	347	355
Medical oncology	370	206
Neurology	400	214
Clinical neurophysiology	401	309
Rheumatology	410	165
Dental medicine	450	191
Gynaecology	502	181

TABLE 31 Unit costs for outpatient appointments (*continued*)

Specialty	Service code	Unit cost (£)[a]
Gynaecological oncology	503	165
Physiotherapy	650	100
Occupational therapy	651	106
Speech and language therapy	652	188
Dietetics service	654	105
Clinical psychology	656	253
Adult mental health	710	295
Interventional radiology	811	194
Audiology	840	126

a These are all sourced from NHS Reference Costs 2021–2.[41] They are all average costs for each specialty (from the Total Outpatient Attendances page, Total activity).

TABLE 32 Unit costs for chemotherapy and radiotherapy

Resource	Unit cost (£)	Reference
Chemotherapy		
First chemotherapy administration	381	NHS Reference Costs 2021–2.[41] Chemotherapy. Day Case. SB13Z, Deliver more Complex Parenteral Chemotherapy at First Attendance
Subsequent chemotherapy administration	384	NHS Reference Costs 2021–2.[41] Chemotherapy. Day Case. SB15Z, Deliver Subsequent Elements of a Chemotherapy Cycle
Radiotherapy		
Define volume for radiation therapy	407	NHS Reference Costs 2021–2.[41] Radiotherapy. Outpatient. SC47Z Preparation for Simple Radiotherapy with Imaging and Simple Calculation
First radiotherapy administration	194	NHS Reference Costs 2021–2.[41] Radiotherapy. Outpatient. SC23Z Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Subsequent radiotherapy administration	175	NHS Reference Costs 2021–2.[41] Radiotherapy. Outpatient. SC22Z Deliver a Fraction of Treatment on a Megavoltage Machine

TABLE 33 Unit costs associated with follow-up outpatient visits and other free-text events

Treatment/action	Unit cost (£)	Reference
Day case unit	1038	NHS Reference Costs 2021–2.[41] Total HRGs. Average across all day case activity
Colonoscopy	745	NHS Reference Costs 2021–2.[41] Day Case. FE32Z Diagnostic Colonoscopy, 19 years and over
Colonoscopy with biopsy	900	NHS Reference Costs 2021–2.[41] Day Case. FE31Z Diagnostic Colonoscopy with Biopsy, 19 years and over
Positron emission tomography scan	665	NHS Reference Costs 2021–2.[41] Total HRGs. RNO07A Positron Emission Tomography (PET), 19 years and over
Emergency medicine	242	NHS Reference Costs 2021–2.[41] Total HRGs. VB01Z–VB99Z weighted average cost of all Emergency Medicine categories
Dexa scan	85	NHS Reference Costs 2021–2.[41] Diagnostic Imaging. Direct Access, RD50Z. Dexa Scan

TABLE 34 Unit costs for post-discharge community health and social care contacts

Resource	Unit cost (£)	Reference
GP or out-of-hours GP at surgery or walk-in centre	32	Unit Costs of Health and Social Care 2022.[42] 9.4, GP – unit costs. Per surgery consultation contact lasting 9.22 minutes. Excluding qualification costs and direct care staff costs
GP at home	56	Unit Costs of Health and Social Care 2022.[42] 9.4, GP – unit costs. Assumes 9.22 minutes of patient contact, and 12 minutes of travel time. Excluding qualification costs and direct care staff costs
GP by telephone	32	Unit Costs of Health and Social Care 2022.[42] 10.3b, GP – unit costs. Assumes 9.22 minutes of patient contact. Excluding qualification costs and direct care staff costs
Nurse at GP surgery or walk-in centre	15	Unit Costs of Health and Social Care 2022.[42] 9.3, Nurse (GP practice). £46 per hour, excluding qualification costs. (Assumes average contact 15.5 minutes, and ratio of direct:indirect time 1 : 0.3, from previous edition.)
Nurse at home	54	NHS Reference Costs 2021–2.[41] Community Health Services. N02AF District Nurse, Adult, Face to face
Healthcare assistant	11	Unit Costs of Health and Social Care 2022.[42] 11.2. Hospital-based nurses. Band 4. Cost per working hour £33. (Assumes average contact 15.5 minutes, and ratio of direct:indirect time 1 : 0.3, as nurse above.)
Respiratory nurse	110	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing N08AF Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Face to face
Cardiac clinical nurse specialist by telephone	89	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing. N11AN Specialist Nursing, Cardiac Nursing/Liaison, Adult, Non face to face
Clinical nurse specialist by telephone	67.7	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing N29AN Other Specialist Nursing, Adult, Non face to face
Clinical nurse specialist	75.6	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing N29AF Other Specialist Nursing, Adult, Face to face
Tissue viability nurse	95	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing N25AF Specialist Nursing, Tissue Viability Nursing/Liaison, Adult, Face to face
Breast care nurse specialist	89	NHS Reference Costs 2021–2.[41] Community Health Services. Nursing N09AF Specialist Nursing, Breast Care Nursing/Liaison, Adult, Face to face
Doctor at a community hospital	189	NHS Reference Costs 2021–2.[41] Non consultant led. WF01A/B Non-Admitted Face-to-Face Attendance, Weighted average of First and Follow-up for all service codes except those for Paediatrics
Hospital doctor by telephone	140	NHS Reference Costs 2021–2.[41] Non consultant led. WF01C/D Non-Admitted Non-Face-to-Face Attendance, Weighted average of First and Follow-up for all service codes except those for Paediatrics
Dietitian	77	NHS Reference Costs 2021–2.[41] Community Health Services. Allied Health Professionals. A03 Dietitian
Occupational therapy	99	NHS Reference Costs 2021–2.[41] Community Health Services. Allied Health Professionals. A06A1 Occupational Therapist, Adult, One to One
Physiotherapist	73	NHS Reference Costs 2021–2.[41] Community Health Services. Allied Health Professionals. A08A1 Physiotherapist, Adult, One to One

TABLE 34 Unit costs for post-discharge community health and social care contacts (*continued*)

Resource	Unit cost (£)	Reference
Speech and language therapist	128	NHS Reference Costs 2021–2.[41] Community Health Services. Allied Health Professionals. A13A1 Speech and Language Therapist, Adult, One to One
Pharmacist	18	Unit Costs of Health and Social Care 2022.[42] 8. Scientific and professional staff. Band 6. Cost per working hour £55. Assume 20 minutes
Paramedic	268	NHS Reference Costs 2021–2.[41] Ambulance ASS01 See and treat or refer
Call to 111	14	Pope *et al.*[44]
Community Rehabilitation Teams	131	NHS Reference Costs 2021–2.[41] Community Health Services. Community Rehabilitation Teams OSCCRT Other single condition community rehabilitation teams.

GP, general practitioner.

TABLE 35 Sensitivity analyses performed around unit costs

Sensitivity analysis	Resource	Unit costs used in base-case analysis	Alternative strategy for sensitivity analysis
1	Time in theatre	£1356 per hour	± 50%
2	Intensive care and high-dependency bed-days in index admission	Cardiac: £2269 for ICU and £1246 for HDU Thoracic/abdominal: £2531 for ICU and £1664 for HDU	± 50%
3	Intensive care and high-dependency bed-days in index admission	Cardiac: £2269 for ICU and £1246 for HDU Thoracic/abdominal: £2531 for ICU and £1664 for HDU	All at the thoracic/abdominal costs
4	Intensive care and high-dependency bed-days in index admission	£1445 for intensive care and £917 for high dependency	All at the cardiac costs
5	Ward bed-days in index admission	£471	± 50%

HDU, high-dependency unit; ICU, intensive care unit.

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Health Technology Assessment 2026 Vol. 30 No. 9

Appendix 2 Additional tables and figures

TABLE 36 Reasons why screened patients were excluded

	Cardiac	Thoracic	Abdominal	Total
Excluded				
Ineligible	**229**	**163**	**141**	**533**
Aged < 18 years		2/163 (1.2%)		2
Not undergoing non-emergency surgery		3/163 (1.8%)	1/141 (0.7%)	4
Not expected to stay 2 days or more		17/163 (10.4%)	1/141 (0.7%)	18
Not expected to be able to swallow	16/229 (7.0%)	8/163 (4.9%)	2/141 (1.4%)	26
Taking anti-epileptic medications	27/229 (11.8%)	4/163 (2.5%)	8/141 (5.7%)	39
Allergy to gabapentin	8/229 (3.5%)	8/163 (4.9%)	8/141 (5.7%)	24
Already taking gabapentin or gabapentinoids	35/229 (15.3%)	24/163 (14.7%)	20/141 (14.2%)	79
Rare hereditary problems of galactose intolerance	4/229 (1.7%)	1/163 (0.6%)	5/141 (3.5%)	10
Planned epidural analgesia		4/163 (2.5%)	12/141 (8.5%)	16
Intended use of gabapentinoids in perioperative analgesia	5/229 (2.2%)		3/141 (2.1%)	8
Known renal impairment	18/229 (7.9%)	5/163 (3.1%)	2/141 (1.4%)	25
Weight < 50 kg	13/229 (5.7%)	25/163 (15.3%)	20/141 (14.2%)	58
Inability to provide written informed consent	9/229 (3.9%)	3/163 (1.8%)	7/141 (5.0%)	19
Unwilling to participate in follow-up	30/229 (13.1%)	22/163 (13.5%)	11/141 (7.8%)	63
Prisoner	1/229 (0.4%)			1
Currently taking an IMP as part of other trial	4/229 (1.7%)	1/163 (0.6%)	2/141 (1.4%)	7
Co-enrolment not permitted by other trial	7/229 (3.1%)	8/163 (4.9%)	12/141 (8.5%)	27
Co-enrolment would result in too much participant burden	10/229 (4.4%)	2/163 (1.2%)	2/141 (1.4%)	14
Multiple reasons for ineligibility	19/229 (8.3%)	20/163 (12.3%)	24/141 (17.0%)	63
Screening log not completed	23 (10%)	6 (3.7%)	1 (0.7%)	30
Not given participant information	**308**	**157**	**150**	**615**
Not interested	182/308 (59%)	95/157 (61%)	51/150 (34%)	328
Staff unavailable	56/308 (18%)	15/157 (9.6%)	51/150 (34%)	122
Not enough time	53/308 (17%)	5/157 (3.2%)	13/150 (8.7%)	71

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 36 Reasons why screened patients were excluded (*continued*)

	Cardiac	Thoracic	Abdominal	Total
Clinician decision	2/308 (0.6%)	30/157 (19%)	12/150 (8.0%)	44
Surgery no longer required		2/157 (1.3%)	3/150 (2.0%)	5
Ineligible	6/308 (1.9%)	3/157 (1.9%)	7/150 (4.7%)	16
Translation services unavailable	2/308 (0.6%)		5/150 (3.3%)	7
Administrative error	2/308 (0.6%)		5/150 (3.3%)	7
Other or not stated	5/308 (1.6%)	7/157 (4.5%)	3/150 (2.0%)	15
Not approached	**61**	**36**	**64**	**161**
Not interested	14/61 (23%)	8/36 (22%)	11/64 (17%)	33
Staff unavailable	8/61 (13%)	9/36 (25%)	20/64 (31%)	37
Insufficient time	13/61 (21%)	6/36 (17%)	4/64 (6.3%)	23
Ineligible	8/61 (13%)	1/36 (2.8%)	2/64 (3.1%)	11
PIL not received	5/61 (8.2%)		1/64 (1.6%)	6
Surgery cancelled or no longer required	4/61 (6.6%)	5/36 (139%)	12/64 (18.8%)	21
Clinician choice	3/61 (4.9%)		2/64 (3.1%)	5
Administrative error		1/36 (2.8%)	2/64 (3.1%)	3
Recruitment paused or closed	1/61 (1.6%)	4/36 (11%)	8/64 (13%)	13
Other	5/61 (8.2%)	2/36 (5.6%)	2/64 (3.1%)	9
Not consented	**412**	**216**	**178**	**806**
Not interested	167/412 (41%)	50/216 (23%)	49/178 (28%)	266
Wants standard care	73/412 (18%)	47/216 (22%)	44/178 (25%)	164
Personal reasons	90/412 (22%)	23/216 (11%)	40/178 (22%)	153
No reason given	22/412 (5.3%)	35/216 (16%)	24/178 (13%)	81
Not enough time to consider	30/412 (7.3%)	12/216 (5.6%)	14/178 (7.9%)	56
Patient missed by research team	7/412 (1.7%)	22/216 (10%)	2/178 (1.1%)	31
Surgery no longer required or moved to another hospital	13/412 (3.2%)	10/216 (4.6%)		23
Ineligible	4/412 (1.0%)	3/216 (1.4%)	1/178 (0.6%)	8
Did not feel they would benefit	2/412 (0.5%)	5/216 (2.3%)	1/178 (0.6%)	8

TABLE 36 Reasons why screened patients were excluded (*continued*)

	Cardiac	Thoracic	Abdominal	Total
Unable to agree to consent questions		2/216 (0.9%)		2
Language difficulties		1/216 (0.5%)		1
Insurance invalidated	1/412 (0.2%)			1
Other or not stated	3/412 (0.7%)	6/216 (2.8%)	3/178 (1.7%)	12
Not randomised	**20**	**38**	**36**	**94**
Patient changed their mind about study	3/20 (15.0%)	2/38 (5.3%)	4/36 (11.1%)	9
Patient does not wish to take study medication		1/38 (2.6%)	1/36 (2.8%)	2
Patient no longer wants surgery			2/36 (5.6%)	2
Surgery no longer appropriate	1/20 (5.0%)	7/38 (18.4%)	7/36 (19.4%)	15
Patient no longer eligible	1/20 (5.0%)	5/38 (13.2%)	2/36 (5.6%)	8
Clinician not willing to administer study medication	2/20 (10.0%)		1/36 (2.8%)	3
Patient died		1/38 (2.6%)	2/36 (5.6%)	3
Study paused/closed	2/20 (10.0%)	13/38 (34.2%)	7/36 (19.4%)	22
Surgery cancelled/rescheduled	4/20 (20.0%)	2/38 (5.3%)	4/36 (11.1%)	10
Staffing issue	2/20 (10.0%)	2/38 (5.3%)	1/36 (2.8%)	5
Patient moved elsewhere		3/38 (7.9%)	1/36 (2.8%)	4
Logistic issue		1/38 (2.6%)	1/36 (2.8%)	2
Other or not stated	5/20 (25.0%)	2/38 (5.3%)	2/36 (5.6%)	9

IMP, investigational medicinal product; PIL, patient information leaflet.

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 37 Eligibility, approach and consent rates

	Cardiac	Thoracic	Abdominal	Total
Screened	1530	956	919	3405
Eligible (% of screened)	1301 (85.0%)	793 (82.9%)	778 (84.7%)	2872 (84.3%)
Approached (% of eligible)	932 (71.6%)	600 (75.7%)	564 (72.5%)	2096 (73.0%)
Consented (% of approached)	520 (55.8%)	384 (64.0%)	386 (68.4%)	1290 (61.5%)
Randomised (% of approached)	500 (96.2%)	346 (90.1%)	350 (90.7%)	1196 (92.7%)

TABLE 38 Randomisations by centre

	Total randomised			Randomisation rate per month		
Study site	Cardiac	Thoracic	Abdominal	Cardiac	Thoracic	Abdominal
Bristol	346	206	205	11.5	4.4	4.3
Southampton	123	130	29	5.1	3.0	0.7
Taunton	–	–	90	–	–	2.7
Basildon	–	–	6	–	–	0.2
Blackpool	31	10	–	2.4	0.3	–
Bath	–	–	10	–	–	0.3
Liverpool	–	–	10	–	–	2.0
Total	**500**	**346**	**350**	**7.5**	**2.8**	**1.9**

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 39 Age of non-randomised patients and trial participants

Characteristic	Cardiac	Thoracic	Abdominal	Total
Ineligible	**229**	**163**	**141**	**533**
Age (years)[a]	70.0 (60.5–76.5)	70.0 (63.0–76.0)	68.0 (59.0–76.0)	69.0 (61.0–76.0)
Not approached	**369**	**193**	**214**	**776**
Age (years)[a]	70.0 (59.0–75.0)	71.0 (62.0–76.0)	69.0 (56.0–76.0)	70.0 (59.0–76.0)
Did not consent	**412**	**216**	**178**	**806**
Age (years)[a]	70.5 (63.0–77.0)	70.0 (63.0–77.0)	71.0 (62.0–76.0)	71.0 (63.0–77.0)
Consented but not randomised	**20**	**38**	**36**	**94**
Age (years)[a]	67.0 (61.0–73.5)	67.5 (59.0–73.0)	70.5 (64.5–74.5)	69.0 (61.0–74.0)
Randomised	**499**[b]	**346**	**350**	**1195**
Age (years)[a]	70.0 (62.0–75.0)	68.0 (60.0–75.0)	66.0 (57.0–73.0)	68.0 (60.0–74.0)

a Three patients with missing data (two ineligible, one randomised).
b One participant withdrew their consent to use their data.

Note
Data are presented as median (IQR).

TABLE 40 Reasons for the participant Bang Blinding assessment not being done

Reason (where given)	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo	Randomised to gabapentin	Randomised to placebo	Randomised to gabapentin	Randomised to placebo	Randomised to gabapentin	Randomised to placebo	Randomised to gabapentin
Discharge	***10***	***14***	***5***	***9***	***6***	***6***	***21***	***29***
Participant unwell	–	–	–	–	–	1/3 (33.3%)	–	1/10 (10.0%)
Participant upset	1/8 (12.5%)	–	–	–	–	–	1/13 (7.7%)	–
Inconvenient	0/8 (0.0%)	–	–	–	–	1/3 (33.3%)	–	1/10 (10.0%)
Discharged earlier than anticipated	3/8 (37.5%)	1/2 (50.0%)	1/1 (100%)	2/5 (40.0%)	1/4 (25.0%)	–	5/13 (38.5%)	3/10 (30.0%)
Other	4/8 (50.0%)	1/2 (50.0%)	–	3/5 (60.0%)	3/4 (75.0%)	1/3 (33.3%)	7/13 (53.8%)	5/10 (50.0%)
Four-month follow-up	***12***	***15***	***21***	***23***	***9***	***13***	***42***	***51***
Participant refused	1/6 (16.7%)	–	1/9 (0.0%)	–	–	–	2/21 (9.5%)	–
Participant unwell	–	–	1/9 (11.1%)	–	–	–	1/21 (4.8%)	–
Patient upset	–	–	1/9 (0.0%)	–	1/6 (16.7%)	–	2/21 (9.5%)	–
Discharged earlier than anticipated	–	1/2 (50.0%)	1/9 (0.0%)	–	–	–	1/21 (4.8%)	1/8 (25.0%)
Unable to contact patient	1/6 (16.7%)	–	3/9 (33.3%)	1/2 (50.0%)	4/6 (66.7%)	2/4 (50.0%)	8/21 (38.1%)	3/8 (37.5%)
Administrative error	3/6 (50.0%)	–	2/9 (22.2%)	1/2 (50.0%)	–	–	5/21 (23.8%)	1/8 (25.0%)
Other	1/6 (16.7%)	1/2 (50.0%)	3/9 (33.3%)	–	1/6 (16.7%)	2/4 (50.0%)	5/21 (23.8%)	3/8 (37.5%)

Note
Data are *n*/*N* (%).

DOI: 10.3310/PLMH9787

TABLE 41 Medication at baseline

Medication	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo[a,b] (*n* = 249)	Randomised to gabapentin[b] (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
On analgesia	***120/248 (48.4%)***	***132/249 (53.0%)***	***65/172 (37.8%)***	***70/174 (40.2%)***	***65/175 (37.1%)***	***45/175 (25.7%)***	***250/595 (42.0%)***	***247/598 (41.3%)***
Paracetamol	44/120 (36.7%)	54/132 (40.9%)	52/65 (80.0%)	44/70 (62.9%)	49/65 (75.4%)	36/45 (80.0%)	145/250 (58.0%)	134/247 (54.3%)
Mean (median, IQR) in mg	2022.7 (2000, 2000–2000)	2235.8 (2000, 2000–2000)	2509.6 (2000, 2000–4000)	2056.8 (2000, 2000–2000)	2265.3 (2000, 2000–2500)	2027.8 (2000, 2000–2000)	2279.3 (2000, 2000–3000)	2120.3 (2000, 2000–2000)
Aspirin	88/120 (73.3%)	98/132 (74.2%)	12/65 (18.5%)	18/70 (25.7%)	11/65 (16.9%)	8/45 (17.8%)	111/250 (44.4%)	124/247 (50.2%)
Mean (median, IQR) in mg	75 (75, 75–75)	74.2 (75, 75–75)	75.0 (75, 75–75)	106.9 (75, 75–75)	75.0 (75, 75–75)	93.8 (75, 75–75)	75.0 (75, 75–75)	80.2 (75, 75–75)
Ibuprofen	6/120 (5.0%)	9/132 (6.8%)	8/65 (12.3%)	14/70 (20.0%)	10/65 (15.4%)	4/45 (8.9%)	24/250 (9.6%)	27/247 (10.9%)
Mean (median, IQR) in mg	566.7 (600, 600–600)	588.9 (600, 400–600)	600 (600, 600–600)	557.1 (600, 400–600)	630 (600, 400–800)	475 (500, 350–600)	604.2 (600, 600–600)	555.6 (600, 400–600)
Opioid use[c]	12/120 (10.0%)	20/132 (15.2%)	34/65 (52.3%)	25/70 (35.7%)	21/65 (32.3%)	16/45 (35.6%)	67/250 (26.8%)	61/247 (24.7%)
Mean (median, IQR) in morphine equivalents	5.2 (3.6, 2.0–5.6)	4.0 (3.3, 2.0–5.0)	3.7 (2.7, 2.0–4.0)	5.4 (4.0, 2.0–5.3)	5.9 (4.0, 2.0–7.9)	3.7 (3.4, 2.0–5.0)	4.7 (3.3, 2.0–5.9)	4.5 (3.4, 2.0–5.3)
On anti-depressants	***29/248 (11.7%)***	***26/249 (10.4%)***	***20/172 (11.6%)***	***34/174 (19.5%)***	***19/175 (10.9%)***	***19/175 (10.9%)***	***68/595 (11.4%)***	***79/598 (13.2%)***
Amitriptyline	11/29 (37.9%)	9/26 (34.6%)	6/20 (30.0%)	13/34 (38.2%)	6/19 (31.6%)	6/19 (31.6%)	23/68 (33.8%)	28/79 (35.4%)
Mean (median, IQR) in mg	23.6 (25, 20–25)	25.0 (25, 20–25)	24.2 (22.5, 20–30)	28.5 (10, 10–20)	13.3 (10, 10–20)	16.7 (15, 10–25)	21.1 (20, 10–25)	24.8 (20, 10–25)
Nortriptyline[d]	–	–	–	–	2/19 (10.5%)[c]	–	2/68 (2.9%)	–
Selective serotonin reuptake inhibitors (SSRIs)	8/29 (27.6%)	11/26 (42.3%)	11/20 (55.0%)	14/34 (41.2%)	7/19 (36.8%)	11/19 (57.9%)	26/68 (38.2%)	36/79 (45.6%)
Mean (median, IQR) in mg	27.5 (20, 15–20)	30.6 (20, 10–50)	34.3 (20, 20–40)	62.1 (40, 20–100)	69.3 (100, 25–100)	36.4 (40, 20–50)	41.6 (20, 20–50)	44.6 (40, 20–50)
Benzodiazepines[e]	2/29 (6.9%)	–	–	1/34 (2.9%)	2/19 (10.5%)	1/19 (5.3%)	4/68 (5.9%)	2/79 (2.5%)
Duloxetine[f]	3/29 (10.3%)	–	–	2/34 (5.9%)	2/19 (10.5%)	–	5/68 (7.4%)	2/79 (2.5%)

continued

TABLE 41 Medication at baseline (*continued*)

Medication	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo[a,b] (*n* = 249)	Randomised to gabapentin[b] (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Flupentixol[g]	1/29 (3.4%)	–	–	–	–	–	1/68 (1.5%)	–
Mirtazapine[h]	5/29 (17.2%)	2/26 (7.7%)	1/20 (5.0%)	2/34 (5.9%)	2/19 (10.5%)	1/19 (5.3%)	8/68 (11.8%)	5/79 (6.3%)
Mean (median, IQR) in mg	27.0 (30, 15–30)	–	–	–	–	–	30.0 (30, 15–45)	22.5 (15, 15–22.5)
Venlafaxine[i]	2/29 (6.9%)	1/26 (3.8%)	–	–	3/19 (15.8%)	1/19 (5.3%)	5/68 (7.4%)	2/79 (2.5%)

a One participant was taking 600 mg/day of pregabalin.
b One participant withdrew after randomisation as the surgery was cancelled.
c Includes codeine, tramadol, fentanyl, morphine (short acting and prolonged release), oxycodone (short acting and prolonged release), dihydrocodeine and buprenorphine.
d Doses were 50 mg and 10 mg/day, respectively.
e Doses (mg/day) were (placebo, gabapentin) cardiac (5, –), thoracic (–, 2), abdominal (2 and 5, 2).
f Doses (mg/day) were cardiac (30, 30 and 80), thoracic (60 and 120), abdominal (120 and 120), respectively.
g Dose was 30 mg/day.
h Doses (mg/day) were (placebo, gabapentin) (–, 15), thoracic (45, 22.5 and 45), abdominal (15 and 45, 15).
i Doses (mg) were (placebo, gabapentin) cardiac (112.5 and 150, 112.5), abdominal (75 and 225 and 225, 75).

TABLE 42 Surgical details

Surgical details	Randomised to placebo	Randomised to gabapentin	Total
Cardiac	***247***	***248***	***499***
Isolated valve	104/247 (42.1%)	101/248 (40.7%)	205/495 (41.4%)
Isolated coronary artery bypass	77/247 (31.2%)	87/248 (35.1%)	164/495 (33.1%)
Coronary artery bypass and valve replacement/repair	40/247 (16.2%)	37/248 (14.9%)	77/495 (15.6%)
Replacement of thoracic aorta	15/247 (6.1%)	12/248 (4.8%)	27/495 (5.5%)
Two or more valves replaced/repaired	10/247 (4.0%)	10/248 (4.0%)	20/495 (4.0%)
Other cardiac procedure	1/247 (0.4%)	1/248 (0.4%)	2/495 (0.4%)
Time from randomisation to the start of surgery (hours)	1.8 (1.5, 2.5)	1.8 (1.4, 2.7)	
Remain mechanically ventilated at the end of surgery	246/247 (99.6%)	248/248 (100%)	494/495 (99.8%)
Duration of initial ventilation (hours)	7.7 (5.9, 10.3)	7.7 (5.6, 11.2)	
Re-intubated after first extubation	2/247 (0.8%)	10/248 (4.0%)	12/495 (2.4%)
Duration of reventilation (hours)	66.0 (9.5, 88.0)	69.0 (15.6, 262.3)	
Thoracic	***169***	***173***	***342***
Lung lobectomy	115/169 (68.0%)	105/173 (60.7%)	220/342 (64.3%)
Segment/lesion resection of the lung	27/169 (16.0%)	34/173 (19.7%)	61/342 (17.8%)
Pleural surgery	6/169 (3.6%)	9/173 (5.2%)	15/342 (4.4%)
Mediastinal surgery	2/169 (1.2%)	8/173 (4.6%)	10/342 (2.9%)
Resection of thymus	7/169 (4.1%)	3/173 (1.7%)	10/342 (2.9%)
Pneumonectomy	3/169 (1.8%)	5/173 (2.9%)	8/342 (2.3%)
Chest wall surgery	1/169 (0.6%)	4/173 (2.3%)	5/342 (1.5%)
Lung volume reduction	1/169 (0.6%)	2/173 (1.2%)	3/342 (0.9%)
Other thoracic procedure	7/169 (4.1%)	3/173 (1.7%)	10/342 (2.9%)
Time from randomisation to the start of surgery (hours)	1.5 (1.9, 2.4)	1.6 (1.1, 2.4)	
Remain mechanically ventilated at the end of surgery	1/169 (0.6%)	2/173 (1.2%)	3/342 (0.7%)
Duration of initial ventilation (hours)	14.9	0.02 and 0.3	
Re-intubated after first extubation	3/169 (1.8%)	5/173 (2.9%)	8/342 (1.9%)
Duration of reventilation (hours)	2.2 (1.1, 2.5)	77.1 (36.9, 543.1)	

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 42 Surgical details (*continued*)

Surgical details	Randomised to placebo	Randomised to gabapentin	Total
Abdominal	***173***	***174***	**347**
Resection of intestine without artificial stoma	87/173 (50.3%)	81/174 (46.6%)	168/347 (48.4%)
Resection of liver	33/173 (19.1%)	34/174 (19.5%)	67/347 (19.3%)
Resection of intestine with artificial stoma	30/173 (17.3%)	31/174 (17.8%)	61/347 (17.6%)
Closure/revision fistula (e.g. ileostomy)	4/173 (2.3%)	6/174 (3.4%)	10/347 (2.9%)
Resection of stomach	3/173 (1.7%)	7/174 (4.0%)	10/347 (2.9%)
Resection of the urinary tract	6/173 (3.5%)	2/174 (3.5%)	8/347 (2.3%)
Resection of the pancreas	4/173 (2.3%)	3/174 (1.7%)	7/347 (2.0%)
Gynaecological resection	1/173 (0.6%)	4/174 (2.3%)	5/347 (1.4%)
Peritoneal surgery	2/173 (1.2%)	2/174 (1.1%)	4/347 (1.2%)
Gall bladder surgery	2/173 (1.2%)	2/174 (1.1%)	4/347 (1.2%)
Other abdominal procedure	1/173 (0.6%)	2/174 (1.1%)	3/347 (0.9%)
Time from randomisation to the start of surgery (hours)	1.9 (1.5, 2.7)	1.8 (1.5, 2.4)	
Remain mechanically ventilated at the end of surgery	3/173 (1.7%)	3/174 (1.7%)	6/347 (1.7%)
Duration of initial ventilation (hours)	80.1 (0.2, 160.0)	15.0 (0.4, 46.2)	
Re-intubated after first extubation	3/173 (1.7%)	4/174 (2.3%)	7/347 (2.0%)
Duration of reventilation (hours)	5.0 (2.0, 14.0)	2.2 (1.8, 39.4)	

Note
Data are presented or *n*/*N* (%) or median (IQR).

TABLE 43 Reasons for delayed discharge from hospital by specialty and randomised group

	Cardiac		Thoracic		Abdominal		
Reason	**Placebo**	**Gabapentin**	**Placebo**	**Gabapentin**	**Placebo**	**Gabapentin**	**Total**
Discharged to rehabilitation/other hospital care	1	5	0	0	0	0	6
Pharmacy	2	3	0	0	0	1	6
Living arrangements	0	1	1	1	1	1	5
Transport	3	0	1	0	0	0	4
Other	3	2	1	2	0	1	9
Total	9	11	3	3	1	3	30

TABLE 44 Sensitivity analyses – primary outcome: time to discharge from hospital after surgery

	Excluding ineligible participants (n = 20)		Excluding participants from site with data quality concerns (n = 10)	
Time from surgery to hospital discharge (days)	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
All participants	1.06 (0.95–1.20)	0.30	1.07 (0.96–1.21)	0.24
Cardiac	1.06 (0.89–1.27)	0.52	1.07 (0.90–1.28)	0.44
Thoracic	1.09 (0.88–1.36)	0.42	1.09 (0.88–1.36)	0.42
Abdominal	1.03 (0.84–1.29)	0.73	1.05 (0.85–1.31)	0.64
Treatment by specialty interaction		0.95		0.97

Note
Hazard ratio (gabapentin: placebo).

TABLE 45 Surgical access

	Cardiac (n = 499)		Thoracic (n = 346)		Abdominal (n = 350)		Overall (n = 1195)[a]	
Surgical access	**Randomised to placebo (n = 249)**	**Randomised to gabapentin (n = 250)**	**Randomised to placebo (n = 172)**	**Randomised to gabapentin (n = 174)**	**Randomised to placebo (n = 175)**	**Randomised to gabapentin (n = 175)**	**Randomised to placebo (n = 596)**	**Randomised to gabapentin (n = 599)**
Open	247/247 (100%)	248/248 (100%)	64/169 (37.9%)	60/173 (34.7%)	93/173 (53.8%)	101/174 (58.0%)	404/589 (68.6%)	409/595 (68.7%)
Minimal access			105/169 (62.1%)	113/173 (65.3%)	80/173 (46.2%)	73/174 (42.0%)	185/589 (31.4%)	186/595 (31.3%)

a Participants who did not undergo surgery are excluded.

Note
Data are n/N (%).

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TABLE 46 Hazard ratios for hospital discharge by subgroup

Subgroup	HR (95% CI)	*p*-value	Subgroup	HR (95% CI)	*p*-value	Subgroup	HR (95% CI)	*p*-value
All participants			All participants			All participants		
Minimal access	1.05 (0.85–1.30)		Female	1.19 (0.98–1.46)		Pre COVID-19	1.08 (0.94–1.24)	
Open surgery	1.07 (0.93–1.23)		Male	1.01 (0.88–1.17)		Post COVID-19	1.04 (0.84–1.28)	
Cardiac			Cardiac			Cardiac		
Minimal access	–		Female	1.12 (0.77–1.64)		Pre COVID-19	1.08 (0.90–1.29)	
Open surgery	0.71 (0.49–1.01)		Male	1.17 (0.86–1.57)		Post COVID-19	0.97 (0.58–1.62)	
Thoracic			Thoracic			Thoracic		
Minimal access	1.13 (0.86–1.48)		Female	1.04 (0.76–1.44)		Pre COVID-19	1.14 (0.87–1.49)	
Open surgery	0.81 (0.56–1.18)		Male	0.89 (0.65–1.21)		Post COVID-19	0.23 (0.89–1.70)	
Abdominal			Abdominal			Abdominal		
Minimal access	0.96 (0.69–1.32)		Female	1.48 (1.04–2.12)		Pre COVID-19	1.01 (0.73–1.40)	
Open surgery	0.73 (0.54–1.00)		Male	0.99 (0.73–1.34)		Post COVID-19	1.12 (0.81–1.54)	
Treatment by specialty by surgery type interaction		0.42	Treatment by specialty by sex interaction		0.13	Treatment by specialty by COVID-19 interaction		0.88
Treatment by specialty interaction		0.96	Treatment by specialty interaction		0.97	Treatment by specialty interaction		0.96
Treatment by surgery type interaction		0.88	Treatment by sex interaction		0.19	Treatment by COVID-19 interaction		0.79
Surgery type by specialty interaction		0.71	Sex by specialty interaction		0.21	COVID-19 by specialty interaction		0.63

TABLE 47 Surgery relative to the start of the COVID-19 pandemic

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)[a]	
COVID-19	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Pre COVID-19	234/249 (94.0%)	234/250 (93.6%)	110/172 (64.0%)	111/174 (63.8%)	76/175 (43.4%)	76/175 (43.4%)	420/596 (70.5%)	421/599 (70.3%)
Post COVID-19	15/249 (6.0%)	16/250 (6.4%)	62/172 (36.0%)	63/174 (36.2%)	99/175 (56.6%)	99/175 (56.6%)	176/596 (29.5%)	178/599 (29.7%)

a Participants who did not undergo surgery are excluded.

Note
Data are *n*/*N* (%).

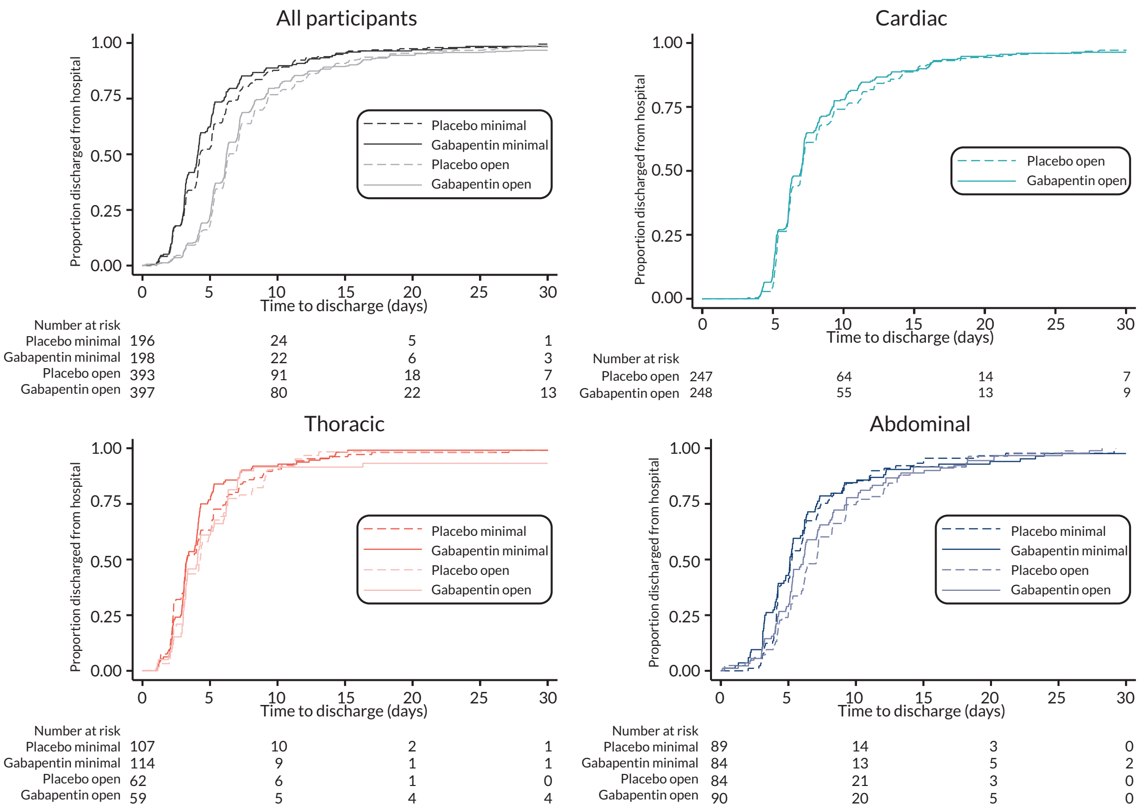

FIGURE 21 Time to discharge in open surgery and minimal access surgery subgroups.

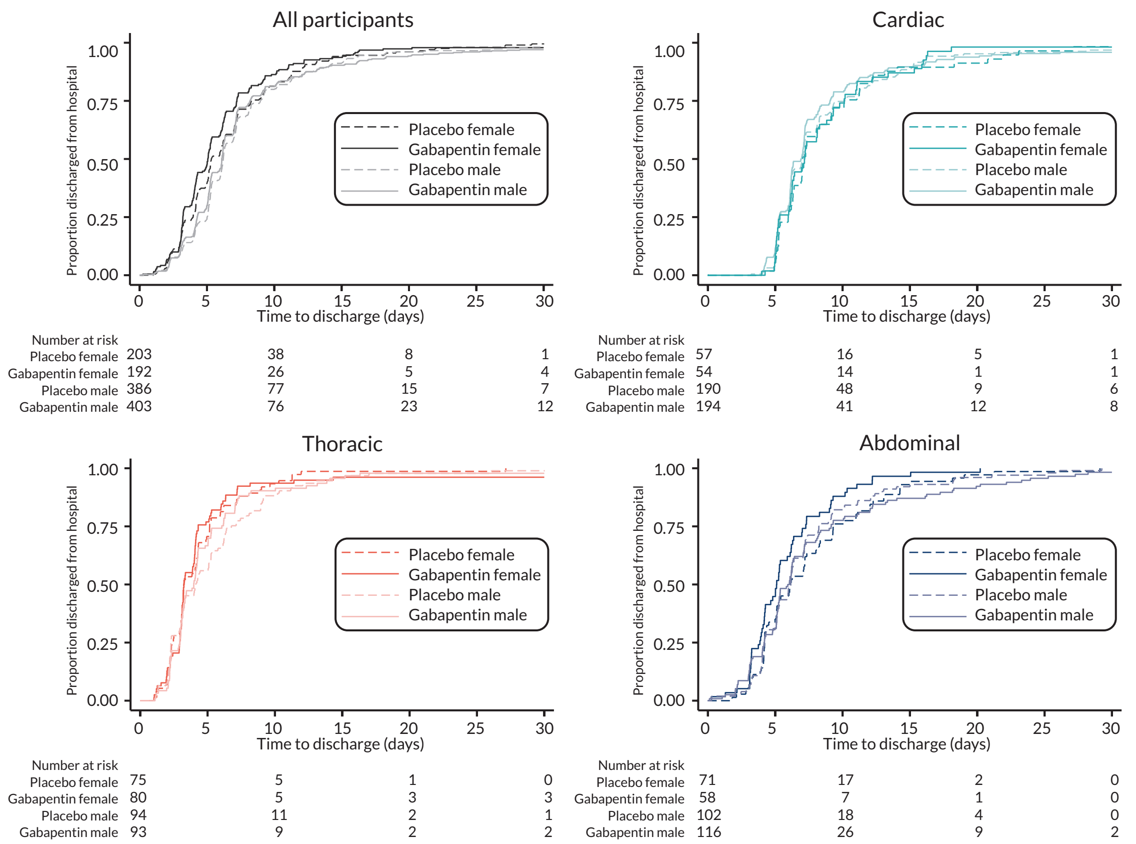

FIGURE 22 Time to discharge in male and female subgroups.

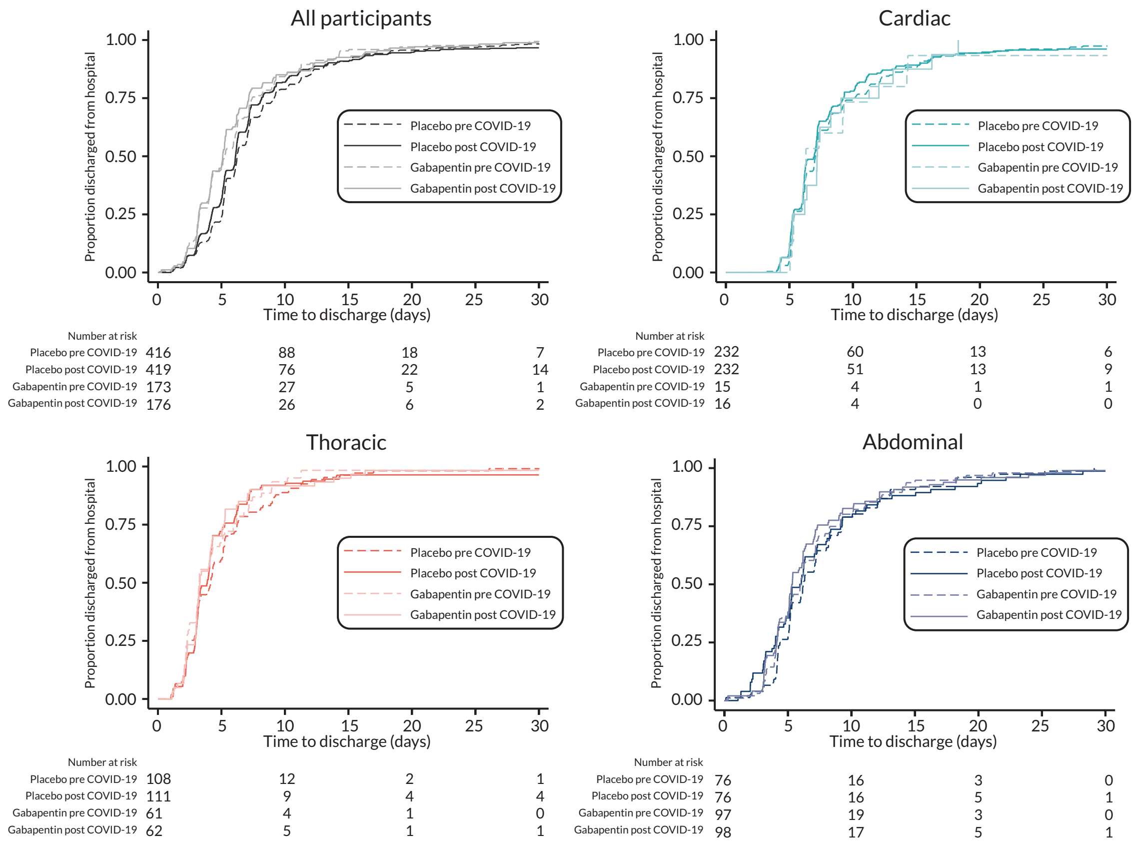

FIGURE 23 Time to discharge in pre- and post-COVID subgroups.

TABLE 48 Analgesia and adjuvants received during trial participation

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Placebo (*n* = 249)	Gabapentin (*n* = 250)	Placebo (*n* = 172)	Gabapentin (*n* = 174)	Placebo (*n* = 175)	Gabapentin (*n* = 175)	Placebo (*n* = 596)	Gabapentin (*n* = 599)
Per day in hospital								
Paracetamol (mg)								
n/*N* (%)	246/247 (99.6%)	249/249 (100.0%)	167/168 (99.4%)	171/171 (100.0%)	173/173 (100.0%)	173/174 (99.4%)	586/588 (99.7%)	593/594 (99.8%)
Mean (median, IQR)	4552.8 (4654.8, 4000.0–5159.1)	4712.6 (4733.3, 4166.7–5250.0)	3857.8 (3750.0, 3333.3–4333.3)	3808.0 (3833.3, 3333.3–4300.0)	4240.4 (4300.0, 3600.0–4916.7)	4177.1 (4300.0, 3500.0–4909.1)	4262.5 (4285.7, 3611.1–4900.0)	4295.5 (4321.4, 3625.0–5000.0)
Aspirin (mg)								
n/*N* (%)	191/247 (77.3%)	203/249 (81.5%)	23/168 (13.7%)	29/171 (17.0%)	17/173 (9.8%)	14/174 (8.0%)	231/588 (39.3%)	246/594 (41.4%)
Mean (median, IQR)	99.4 (75.0, 75.0–107.1)	97.1 (75.0, 75.0–107.1)	127.2 (75.0, 75.0–75.0)	83.1 (75.0, 75.0–75.0)	89.2 (75.0, 75.0–75.0)	101.8 (75.0, 75.0–75.0)	101.4 (75.0, 75.0–107.1)	95.7 (75.0, 75.0–107.1)
Ibuprofen (mg)								
n/*N* (%)	6/247 (2.4%)	5/249 (2.0%)	41/168 (24.4%)	54/171 (31.6%)	17/173 (9.8%)	12/174 (6.9%)	64/588 (10.9%)	71/594 (12.0%)
Mean (median, IQR)	714.4 (766.7, 400.0–933.3)	573.3 (600.0, 400.0–933.3)	727.6 (800.0, 400.0–914.3)	806.0 (900.0, 600.0–1000.0)	781.3 (945.5, 400.0–1000.0)	733.9 (800.0, 400.0–920.0)	740.6 (800.0, 400.0–965.7)	777.4 (800.0, 600.0–1000.0)
Codine (mg)								
n/*N* (%)	45/247 (18.2%)	46/249 (18.5%)	29/168 (17.3%)	26/171 (15.2%)	22/173 (12.7%)	20/174 (11.5%)	96/588 (16.3%)	92/594 (15.5%)
Mean (median, IQR)	89.6 (77.1, 60.0–120.0)	86.1 (90.0, 60.0–108.0)	113.4 (100.0, 60.0–165.0)	94.6 (100.0, 60.0–120.0)	111.1 (93.8, 60.0–172.5)	94.6 (78.8, 56.3–120.0)	101.7 (90.0, 60.0–150.0)	90.3 (90.0, 60.0–120.0)
Dihydrocodeine (mg)								
n/*N* (%)	53/247 (21.5%)	48/249 (19.3%)	53/168 (31.5%)	51/171 (29.8%)	9/173 (5.2%)	8/174 (4.6%)	115/588 (19.6%)	107/594 (18.0%)
Mean (median, IQR)	58.8 (60.0, 47.1–70.0)	60.6 (58.9, 40.0–76.3)	71.6 (75.0, 60.0–90.0)	69.0 (70.0, 45.0–90.0)	64.6 (70.0, 51.0–75.0)	56.3 (60.0, 40.0–65.0)	65.2 (60.0, 50.0–80.0)	64.3 (60.0, 45.0–84.0)
Alfentanil (mg)								
n/*N* (%)	40/247 (16.2%)	54/249 (21.7%)	3/168 (1.8%)	1/171 (0.6%)	7/173 (4.0%)	9/174 (5.2%)	50/588 (8.5%)	64/594 (10.8%)
Mean (median, IQR)	9.2 (5.0, 2.6–14.0)	7.8 (6.8, 3.3–10.7)	9.2 (8.0, 6.5–13.0)	14.9	9.4 (1.0, 0.8–9.3)	10.7 (12.0, 1.0–17.0)	9.2 (5.0, 2.0–13.5)	8.3 (7.1, 3.0–12.0)
Tramadol (oral and IV) (mg)								
n/*N* (%)	98/247 (39.7%)	112/249 (45.0%)	97/168 (57.7%)	99/171 (57.9%)	108/173 (62.4%)	100/174 (57.5%)	303/588 (51.5%)	311/594 (52.4%)
Mean (median, IQR)	133.8 (100.0, 59.1–183.3)	127.8 (100.0, 75.0–175.0)	264.5 (250.0, 150.0–337.5)	238.8 (200.0, 125.0–350.0)	261.7 (243.2, 150.0–379.2)	252.9 (250.0, 150.0–339.1)	221.2 (200.0, 100.0–310.0)	203.3 (175.0, 100.0–287.5)

continued

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Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 48 Analgesia and adjuvants received during trial participation (*continued*)

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Placebo (*n* = 249)	Gabapentin (*n* = 250)	Placebo (*n* = 172)	Gabapentin (*n* = 174)	Placebo (*n* = 175)	Gabapentin (*n* = 175)	Placebo (*n* = 596)	Gabapentin (*n* = 599)
Fentanyl (IV, intrathecal and epidural) (mg)								
n/N (%)	229/247 (92.7%)	217/249 (87.1%)	126/168 (75.0%)	134/171 (78.4%)	126/173 (72.8%)	132/174 (75.9%)	481/588 (81.8%)	483/594 (81.3%)
Mean (median, IQR)	1.3 (1.0, 0.8–1.5)	1.3 (1.3, 0.8–1.5)	0.4 (0.4, 0.3–0.5)	0.4 (0.4, 0.3–0.4)	1.1 (0.3, 0.2–0.5)	0.3 (0.3, 0.2–0.4)	1.0 (0.5, 0.3–1.0)	0.7 (0.5, 0.3–1.0)
Diamorphine (IV and intrathecal) (mg)								
n/N (%)	3/247 (1.2%)	3/249 (1.2%)	0/168 (0.0%)	1/171 (0.6%)	12/173 (6.9%)	13/174 (7.5%)	15/588 (2.6%)	17/594 (2.9%)
Mean (median, IQR)	17.8 (2.5, 1.0–50.0)	5.0 (2.5, 2.5–10.0)	–	4.0	0.5 (0.5, 0.5–0.5)	1.0 (0.5, 0.4–0.5)	3.9 (0.5, 0.5–0.7)	1.9 (0.5, 0.5–2.5)
Morphine (oral and IV) (mg)								
n/N (%)	234/247 (94.7%)	239/249 (96.0%)	144/168 (85.7%)	136/171 (79.5%)	134/173 (77.5%)	127/174 (73.0%)	512/588 (87.1%)	502/594 (84.5%)
Mean (median, IQR)	23.2 (18.0, 10.0–31.0)	21.0 (16.7, 10.0–30.0)	34.1 (29.5, 16.0–45.3)	29.7 (23.1, 15.0–39.7)	32.4 (23.0, 13.3–42.5)	25.8 (23.0, 11.0–33.8)	28.7 (22.0, 11.0–37.5)	24.6 (20.0, 11.0–33.3)
Oxycodone (oral and IV) (mg)								
n/N (%)	40/247 (16.2%)	36/249 (14.5%)	69/168 (41.1%)	69/171 (40.4%)	66/173 (38.2%)	66/174 (37.9%)	175/588 (29.8%)	171/594 (28.8%)
Mean (median, IQR)	19.8 (15.0, 7.3–23.5)	13.8 (10.0, 5.0–20.0)	16.6 (10.0, 6.0–15.0)	16.6 (10.0, 7.5–16.0)	25.1 (17.0, 10.0–33.3)	20.6 (17.0, 10.0–26.5)	20.5 (12.5, 7.5–25.5)	17.6 (10.5, 8.3–21.3)
Buprenorphine (sublingual and patch) (mg)								
n/N (%)	1/247 (0.4%)	1/249 (0.4%)	0/168 (0.0%)	0/171 (0.0%)	3/173 (1.7%)	0/174 (0.0%)	4/588 (0.7%)	1/594 (0.2%)
Mean (median, IQR)	N/A	73.6	–	–	301.7 (240.0, 210.0–455.0)		226.3 (225.0, 105.0–347.5)	73.6
Pethidine (mg)								
n/N (%)	4/247 (1.6%)	1/249 (0.4%)	0/168 (0.0%)	0/171 (0.0%)	0/173 (0.0%)	1/174 (0.6%)	4/588 (0.7%)	2/594 (0.3%)
Mean (median, IQR)	43.8 (37.5, 25.0–62.5)	25	–	–	–	25	43.8 (37.5, 25.0–62.5)	25
Per day during follow-up								
Paracetamol (mg)								
n/N (%)	239/246 (97.2%)	236/246 (95.9%)	166/169 (98.2%)	161/169 (95.3%)	153/172 (89.0%)	154/174 (88.5%)	558/587 (95.1%)	551/589 (93.5%)
Mean (median, IQR)	2678.1 (2026.7, 2000.0–4000.0)	2569.8 (2000.0, 2000.0–4000.0)	3084.7 (3603.3, 2026.7–4000.0)	3316.3 (4000.0, 2373.3–4000.0)	3121.5 (4000.0, 2000.0–4000.0)	3083.4 (4000.0, 2000.0–4000.0)	2919.0 (2617.9, 2000.0–4000.0)	2922.5 (2560.0, 2000.0–4000.0)
Aspirin (mg)								

TABLE 48 Analgesia and adjuvants received during trial participation (*continued*)

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Placebo (*n* = 249)	Gabapentin (*n* = 250)	Placebo (*n* = 172)	Gabapentin (*n* = 174)	Placebo (*n* = 175)	Gabapentin (*n* = 175)	Placebo (*n* = 596)	Gabapentin (*n* = 599)
n/N (%)	180/246 (73.2%)	190/246 (77.2%)	21/169 (12.4%)	32/169 (18.9%)	15/172 (8.7%)	14/174 (8.0%)	216/587 (36.8%)	236/589 (40.1%)
Mean (median, IQR)	79.5 (75.0, 75.0–75.0)	81.9 (75.0, 75.0–75.0)	75.0 (75.0, 75.0–75.0)	75.0 (75.0, 75.0–75.0)	75.0 (75.0, 75.0–75.0)	86.5 (75.0, 75.0–75.0)	78.8 (75.0, 75.0–75.0)	81.3 (75.0, 75.0–75.0)
Ibuprofen (mg)								
n/N (%)	5/246 (2.0%)	7/246 (2.8%)	35/169 (20.7%)	47/169 (27.8%)	21/172 (12.2%)	13/174 (7.5%)	61/587 (10.4%)	67/589 (11.4%)
Mean (median, IQR)	992.8 (1200.0, 800.0–1200.0)	857.1 (800.0, 600.0–1200.0)	943.0 (1200.0, 600.0–1200.0)	1028.8 (1200.0, 848.0–1200.0)	720.1 (600.0, 600.0–1200.0)	1008.3 (1200.0, 600.0–1200.0)	872.0 (800.0, 600.0–1200.0)	1004.7 (1200.0, 604.0–1200.0)
Codeine (mg)								
n/N (%)	71/246 (28.9%)	76/246 (30.9%)	45/169 (26.6%)	49/169 (29.0%)	29/172 (16.9%)	31/174 (17.8%)	145/587 (24.7%)	156/589 (26.5%)
Mean (median, IQR)	119.4 (120.0, 60.0–120.0)	105.5 (120.0, 60.0–120.0)	93.3 (70.0, 50.2–120.0)	77.2 (60.0, 32.0–120.0)	78.7 (60.0, 60.0–113.1)	87.8 (60.0, 30.0–120.0)	103.0 (97.7, 60.0–120.0)	93.8 (101.2, 60.0–120.0)
Dihydrocodeine (mg)								
n/N (%)	39/246 (15.9%)	39/246 (15.9%)	57/169 (33.7%)	49/169 (29.0%)	7/172 (4.1%)	8/174 (4.6%)	103/587 (17.5%)	96/589 (16.3%)
Mean (median, IQR)	89.1 (60.0, 60.0–120.0)	85.7 (60.0, 60.0–120.0)	112.2 (120.0, 120.0–120.0)	113.3 (120.0, 120.0–120.0)	105.1 (120.0, 90.2–120.0)	143.6 (90.0, 60.0–227.3)	103.0 (120.0, 60.0–120.0)	104.1 (120.0, 60.0–120.0)
Alfentanil								
n/N (%)	1/246 (0.4%)	0/246 (0.0%)	0/169 (0.0%)	0/169 (0.0%)	0/172 (0.0%)	0/174 (0.0%)	1/587 (0.2%)	0/589 (0.0%)
Tramadol (mg)								
n/N (%)	26/246 (10.6%)	23/246 (9.3%)	59/169 (34.9%)	51/169 (30.2%)	47/172 (27.3%)	48/174 (27.6%)	132/587 (22.5%)	122/589 (20.7%)
Mean (median, IQR)	179.6 (200.0, 100.0–200.0)	153.6 (200.0, 100.0–200.0)	173.2 (198.7, 100.0–200.0)	203.3 (200.0, 109.0–200.0)	160.1 (100.0, 100.0–200.0)	161.9 (100.0, 100.0–200.0)	169.8 (150.0, 100.0–200.0)	177.5 (200.0, 100.0–200.0)
Fentanyl (mg)								
n/N (%)	1/246 (0.4%)	1/246 (0.4%)	0/169 (0.0%)	1/169 (0.6%)	2/172 (1.2%)	0/174 (0.0%)	3/587 (0.5%)	2/589 (0.3%)
Doses	0.06	1.4	–	0.3	0.001, 0.001		0.18 (0.06–0.30)	0.001 (0.001–1.4)
Morphine (short acting) (mg)								
n/N (%)	10/246 (4.1%)	3/246 (1.2%)	34/169 (20.1%)	27/169 (16.0%)	11/172 (6.4%)	12/174 (6.9%)	55/587 (9.4%)	42/589 (7.1%)
Mean (median, IQR)	14.5 (12.5, 5.0–20.0)	30.0 (30.0, 20.0–40.0)	29.3 (20.0, 20.0–40.0)	34.3 (20.0, 20.0–40.0)	16.7 (10.0, 10.0–20.0)	18.0 (20.0, 20.0–20.0)	24.2 (20.0, 10.0–40.0)	31.3 (20.0, 20.0–40.0)

continued

TABLE 48 Analgesia and adjuvants received during trial participation (*continued*)

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Placebo (*n* = 249)	Gabapentin (*n* = 250)	Placebo (*n* = 172)	Gabapentin (*n* = 174)	Placebo (*n* = 175)	Gabapentin (*n* = 175)	Placebo (*n* = 596)	Gabapentin (*n* = 599)
Morphine (prolonged release) (mg)								
n/N (%)	0/246 (0.0%)	1/246 (0.4%)	2/169 (1.2%)	0/169 (0.0%)	3/172 (1.7%)	0/174 (0.0%)	5/587 (0.9%)	1/589 (0.2%)
Doses	–	20.0	5.6, 58.0	–	30.0 (20.0, 10.0–60.0)	–	30.7 (20.0, 10.0–58.0)	20.0
Oxycodone (short acting) (mg)								
n/N (%)	2/246 (0.8%)	1/246 (0.4%)	6/169 (3.6%)	9/169 (5.3%)	6/172 (3.5%)	3/174 (1.7%)	14/587 (2.4%)	13/589 (2.2%)
Mean (median, IQR)	2.5 and 10.0	30.0	25.0 (30.0, 15.0–30.0)	21.3 (15.0, 9.0–30.0)	46.7 (24.2, 18.5–75.0)	15.0, 30.0, N/A	30.5 (18.5, 15.0–30.0)	20.9 (15.0, 9.0–30.0)
Oxycodone (prolonged release) (mg)								
n/N (%)	1/246 (0.4%)	0/246 (0.0%)	3/169 (1.8%)	4/169 (2.4%)	1/172 (0.6%)	1/174 (0.6%)	5/587 (0.9%)	5/589 (0.8%)
Mean (median, IQR)	5.0	–	10.0 (10.0, 10.0–10.0)	13.3 (10.0, 10.0–20.0)	20.0	12.1	11.3 (10.0, 7.5–15.0)	13.0 (11.0, 10.0–16.0)
Buprenorphine (mg)								
n/N (%)	1/246 (0.4%)	1/246 (0.4%)	1/169 (0.6%)	0/169 (0.0%)	3/172 (1.7%)	0/174 (0.0%)	5/587 (0.9%)	1/589 (0.2%)
Mean (median, IQR)	0.48	0.24	0.03	–	0.4 (0.2, 0.2–0.8)	–	0.4 (0.2, 0.2–0.5)	0.24
Pregabalin (mg)								
n/N (%)	1/246 (0.4%)	1/246 (0.4%)	5/169 (3.0%)	2/169 (1.2%)	1/172 (0.6%)	1/174 (0.6%)	7/587 (1.2%)	4/589 (0.7%)
Mean (median, IQR)	300	568.8	187.6 (100.0, 75.0–150.0)	150.0, 300.0	100.0	300.0	191.1 (100.0, 75.0–300.0)	329.7 (300.0, 225.0–434.4)
Gabapentin (mg)								
n/N (%)	6/246 (2.4%)	1/246 (0.4%)	7/169 (4.1%)	9/169 (5.3%)	3/172 (1.7%)	1/174 (0.6%)	16/587 (2.7%)	11/589 (1.9%)
Mean (median, IQR)	498.3 (450.0, 300.0–650.0)	566.1	418.8 (300.0, 300.0–600.0)	605.3 (721.3, 300.0–900.0)	2859.1 (600.0, 450.0–7527.3)	2700	975.8 (525.0, 300.0–628.2)	810.9 (721.3, 300.0–900.0)

i.v., intravenous.
a Dose 48 mcg.

TABLE 49 Magnesium use following surgery

Magnesium use	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)[a]	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Given magnesium	103/247 (41.4%)	111/249 (44.4%)	13/168 (7.6%)	10/171 (5.8%)	19/173 (10.9%)	20/174 (11.4%)	135/588 (22.7%)	141/594 (23.5%)
Amount received	2778.3 (0, 0–5000)	2904.6 (0, 0–5000)	345.2 (0, 0–0)	787.9 (0, 0–0)	666.2 (0, 0–0)	659.4 (0, 0–0)	1461.7 (0, 0–0)	1637.6 (0, 0–0)

a Participants who did not undergo surgery are excluded.

Note
Data are *n*/*N* (%) and mean (median, IQR).

TABLE 50 Results when imputing missing outcome data for EQ-5D and SF-12

	Without imputation		Imputing missing outcome data	
	Mean difference	*p*-value	Mean difference	*p*-value
EQ-5D utility score				
All participants	−0.014 (−0.033 to + 0.005)	0.16	−0.015 (−0.034 to + 0.004)	0.12
Cardiac	−0.015 (−0.043 to + 0.014)	0.31	−0.013 (−0.041 to + 0.015)	0.35
Thoracic	−0.024 (−0.060 to + 0.012)	0.19	−0.024 (−0.061 to + 0.013)	0.20
Abdominal	−0.009 (−0.044 to + 0.026)	0.63	−0.009 (−0.044 to + 0.026)	0.62
Treatment by time by specialty interaction		0.35		0.95
Treatment by time interaction		0.39		0.56
Treatment by specialty interaction		0.83		0.54
Time by specialty interaction		< 0.001		< 0.001
SF-12 PCS				
All participants	−0.87 (−1.71 to −0.04)	0.04	−0.883 (−1.72 to −0.05)	0.04
Cardiac	−0.63 (−1.89 to + 0.63)	0.33	−0.634 (−1.89 to + 0.63)	0.32
Thoracic	−1.73 (−3.33 to −0.12)	0.035	−1.61 (−3.17 to −0.059)	0.04
Abdominal	−0.30 (−1.86 to + 1.26)	0.38	−0.51 (−2.08 to + 1.05)	0.52

continued

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Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 50 Results when imputing missing outcome data for EQ-5D and SF-12 (*continued*)

	Without imputation		Imputing missing outcome data	
	Mean difference	*p*-value	Mean difference	*p*-value
Treatment by time by specialty interaction		0.98		0.95
Treatment by time interaction		0.53		0.56
Treatment by specialty interaction		0.47		0.54
Time by specialty interaction		< 0.001		< 0.001
SF-12 MCS				
All participants				
4 weeks	0.74 (−0.39 to 1.87)	0.20	0.78 (−0.33 to 1.89)	0.17
4 months	−0.55 (−1.61 to 0.51)	0.31	−0.60 (−1.68 to 0.47)	0.27
Cardiac				
4 weeks	−0.0006 (−1.51 to 1.51)	1.00	0.20 (−1.28 to 1.68)	0.79
4 months	−1.28 (−2.72 to 0.16)	0.08	−1.18 (−2.62 to 0.25)	0.11
Thoracic				
4 weeks	1.45 (−0.37 to 3.28)	0.12	1.43 (−0.34 to 3.21)	0.11
4 months	0.17 (−1.61 to 1.96)	0.85	0.05 (−1.73 to 1.84)	0.95
Abdominal				
4 weeks	1.18 (−0.60 to 2.95)	0.19	0.95 (−0.76 to 2.66)	0.28
4 months	−0.10 (−1.83 to 1.62)	0.91	−0.43 (−2.1 to 1.24)	0.61
Treatment by time by specialty interaction		0.20		0.34
Treatment by time interaction		0.056		0.03
Treatment by specialty interaction		0.35		0.49
Time by specialty interaction		0.07		0.09

TABLE 51 Results when imputing missing outcome data for BPI

BPI	Without imputation		Imputing missing outcome data	
Pain severity index				
Pain present	**Odds ratio**	***p*-value**	**Odds ratio**	***p*-value**
All participants	1.42 (1.15–1.75)	0.001	1.39 (1.13–1.70)	0.002
Cardiac	1.35 (0.98–1.86)	0.07	1.33 (0.97–1.82)	0.078
Thoracic	1.63 (1.10–2.42)	0.014	1.58 (1.04–2.39)	0.031
Abdominal	1.34 (0.91–1.97)	0.14	1.30 (0.90–1.89)	0.166
Pain severity (where present)	**Geometric mean ratio**	***p*-value**	**Geometric mean ratio**	***p*-value**
All participants	0.99 (0.90–1.08)	0.77	1.00 (0.91–1.10)	0.98
Cardiac	0.98 (0.86–1.12)	0.78	0.99 (0.87–1.13)	0.91
Thoracic	1.08 (0.93–1.26)	0.33	1.08 (0.92–1.26)	0.33
Abdominal	0.90 (0.73–1.10)	0.29	0.93 (0.77–1.12)	0.44
Treatment by time by specialty interaction		0.34		0.62
Treatment by time interaction		0.77		0.73
Treatment by specialty interaction		0.24		0.38
Time by specialty interaction		0.003		0.002
Pain interference index				
Pain present	**Odds ratio**	***p*-value**	**Odds ratio**	***p*-value**
All participants	1.38 (1.12–1.70)	0.003	1.36 (1.10–1.68)	0.004
Cardiac	1.31 (0.94–1.82)	0.11	1.32 (0.95–1.83)	0.10
Thoracic	1.70 (1.15–2.51)	0.008	1.65 (1.11–2.45)	0.013
Abdominal	1.22 (0.84–1.76)	0.30	1.17 (0.81–1.69)	0.39
Pain interference (where present)	**Geometric mean ratio**	***p*-value**	**Geometric mean ratio**	***p*-value**
All participants	1.07 (0.94–1.22)	0.30	1.06 (0.94–1.20)	0.35
Cardiac	1.14 (0.93–1.39)	0.21	1.12 (0.92–1.37)	0.24
Thoracic	1.14 (0.93–1.40)	0.21	1.12 (0.91–1.38)	0.28

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DOI: 10.3310/PLMH9787 Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 51 Results when imputing missing outcome data for BPI (*continued*)

BPI	Without imputation		Imputing missing outcome data	
Abdominal	0.90 (0.69–1.16)	0.41	0.91 (0.71–1.16)	0.45
Treatment by time by specialty interaction		0.44		0.56
Treatment by time interaction		0.92		0.80
Treatment by specialty interaction		0.28		0.35
Time by specialty interaction		0.002		0.004

GMR, geometric mean ratio.

TABLE 52 Adverse events by MedDRA system organ class

	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
AE	**Randomised to placebo (*n* = 249)**	**Randomised to gabapentin (*n* = 250)**	**Randomised to placebo (*n* = 172)**	**Randomised to gabapentin (*n* = 174)**	**Randomised to placebo (*n* = 175)**	**Randomised to gabapentin (*n* = 175)**	**Randomised to placebo (*n* = 596)**	**Randomised to gabapentin (*n* = 599)**
Total events (events/participants)	1082/243 (97.6%)	1135/245 (97.7%)	164/91 (53%)	133/75 (43.2%)	207/99 (56.6%)	220/100 (57.2%)	1453/433 (72.2%)	1488/420 (70.0%)
Blood and lymphatic system disorders	**14/14 (5.6%)**	**6/6 (2.4%)**	**1/1 (0.6%)**	**1/1 (0.6%)**	**4/4 (2.3%)**	**3/3 (1.7%)**	**19/19 (3.2%)**	**10/10 (1.7%)**
Anaemia	4/4 (1.6%)		1/1 (0.6%)	1/1 (0.6%)	4/4 (2.3%)	1/1 (0.6%)	9/9 (1.5%)	2/2 (0.3%)
Thrombocytopenia	10/10 (4.0%)	6/6 (2.4%)				2/2 (1.1%)	10/10 (1.7%)	8/8 (1.3%)
Cardiac disorders	**149/131 (52.6%)**	**139/116 (46.2%)**	**19/19 (11.0%)**	**2/2 (1.1%)**	**3/3 (1.7%)**	**6/6 (3.4%)**	**171/153 (25.7%)**	**147/124 (20.7%)**
Arrhythmia	17/16 (6.4%)	19/19 (7.6%)	8/8 (4.7%)		1/1 (0.6%)	4/4 (2.3%)	26/25 (4.2%)	23/23 (3.8%)
Atrial fibrillation	80/80 (32.1%)	74/74 (29.5%)	10/10 (5.8%)	2/2 (1.1%)	2/2 (1.1%)		92/92 (15.4%)	76/76 (12.7%)
Atrial flutter	2/2 (0.8%)	3/3 (1.2%)				2/2 (1.1%)	2/2 (0.3%)	5/5 (0.8%)
Atrioventricular block		2/2 (0.8%)						2/2 (0.3%)
Atrioventricular block complete		1/1 (0.4%)						1/1 (0.2%)
Atrioventricular block first degree	4/4 (1.6%)	1/1 (0.4%)					4/4 (0.7%)	1/1 (0.2%)
Bradycardia	1/1 (0.4%)	1/1 (0.4%)					1/1 (0.2%)	1/1 (0.2%)
Bundle branch block left	4/4 (1.6%)	6/6 (2.4%)					4/4 (0.7%)	6/6 (1.0%)
Bundle branch block right	2/2 (0.8%)						2/2 (0.3%)	0/0 (.)
Cardiac failure congestive	3/3 (1.2%)						3/3 (0.5%)	0/0 (.)
Myocardial infarction		1/1 (0.4%)						1/1 (0.2%)
Nodal rhythm	2/2 (0.8%)	2/2 (0.8%)					2/2 (0.3%)	2/2 (0.3%)

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Pericardial effusion	20/20 (8.0%)	14/14 (5.6%)					20/20 (3.4%)	14/14 (2.3%)
Pericarditis	1/1 (0.4%)						1/1 (0.2%)	0/0 (.)
Sinus bradycardia	2/2 (0.8%)	3/3 (1.2%)					2/2 (0.3%)	3/3 (0.5%)
Tachycardia	6/6 (2.4%)	7/7 (2.8%)	1/1 (0.6%)				7/7 (1.2%)	7/7 (1.2%)
Ventricular fibrillation	2/2 (0.8%)	0/0 (.)					2/2 (0.3%)	0/0 (.)
Ventricular tachycardia	3/3 (1.2%)	5/5 (2.0%)					3/3 (0.5%)	5/5 (0.8%)
Ear and labyrinth disorders	**1/1 (0.4%)**						**1/1 (0.2%)**	
Deafness	1/1 (0.4%)						1/1 (0.2%)	
Eye disorders	**9/9 (3.6%)**	**9/9 (3.6%)**		**1/1 (0.6%)**	**1/1 (0.6%)**		**10/10 (1.7%)**	**10/10 (1.7%)**
Diplopia	8/8 (3.2%)	9/9 (3.6%)		1/1 (0.6%)	1/1 (0.6%)		9/9 (1.5%)	10/10 (1.7%)
Eye oedema	1/1 (0.4%)						1/1 (0.2%)	
Gastrointestinal disorders	**82/59 (23.7%)**	**90/64 (25.5%)**	**28/22 (12.8%)**	**27/22 (12.6%)**	**98/62 (35.4%)**	**102/62 (35.4%)**	**208/143 (24.0%)**	**219/148 (24.7%)**
Abdominal pain	4/4 (1.6%)	2/2 (0.8%)			8/8 (4.6%)	5/5 (2.9%)	12/12 (2.0%)	7/7 (1.2%)
Ascites					1/1 (0.6%)		1/1 (0.2%)	
Constipation	16/16 (6.4%)	26/26 (10.4%)	8/8 (4.7%)	10/10 (5.7%)	4/4 (2.3%)	3/3 (1.7%)	28/28 (4.7%)	39/39 (6.5%)
Diarrhoea	8/8 (3.2%)	9/9 (3.6%)	0/0 (.)	1/1 (0.6%)	2/2 (1.1%)	4/4 (2.3%)	10/10 (1.7%)	14/14 (2.3%)
Dry mouth	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)		1/1 (0.6%)		3/3 (0.5%)	1/1 (0.2%)
Dyspepsia	1/1 (0.4%)	1/1 (0.4%)				1/1 (0.6%)	1/1 (0.2%)	2/2 (0.3%)
Dysphagia	2/2 (0.8%)	4/4 (1.6%)					2/2 (0.3%)	4/4 (0.7%)
Flatulence	1/1 (0.4%)	1/1 (0.4%)			1/1 (0.6%)		2/2 (0.3%)	1/1 (0.2%)
Gastrointestinal haemorrhage	1/1 (0.4%)	2/2 (0.8%)				1/1 (0.6%)	1/1 (0.2%)	3/3 (0.5%)
Ileus	1/1 (0.4%)	3/3 (1.2%)			15/15 (8.6%)	13/13 (7.4%)	16/16 (2.7%)	16/16 (2.7%)
Nausea	27/26 (10.4%)	20/20 (8.0%)	12/12 (7.0%)	13/13 (7.5%)	35/35 (20.0%)	36/36 (20.6%)	74/73 (12.2%)	69/69 (11.5%)
Tooth injury			1/1 (0.6%)				1/1 (0.2%)	
Vomiting	20/20 (8.0%)	21/21 (8.4%)	6/6 (3.5%)	3/3 (1.7%)	29/29 (16.6%)	39/38 (21.7%)	55/55 (9.2%)	63/62 (10.3%)
Gastrointestinal obstruction					1/1 (0.6%)		1/1 (0.2%)	

continued

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Intra-abdominal fluid collection					1/1 (0.6%)		1/1 (0.2%)	
General disorders and administration site conditions	**69/59 (23.7%)**	**85/72 (28.7%)**	**10/10 (5.8%)**	**10/9 (5.2%)**	**15/15 (8.6%)**	**15/14 (8.0%)**	**94/84 (14.1%)**	**110/95 (15.8%)**
Asthenia		2/2 (0.8%)						2/2 (0.3%)
Chest pain	2/2 (0.8%)	2/2 (0.8%)	1/1 (0.6%)	3/3 (1.7%)	1/1 (0.6%)		4/4 (0.7%)	5/5 (0.8%)
Fatigue		1/1 (0.4%)	1/1 (0.6%)				1/1 (0.2%)	1/1 (0.2%)
Generalised oedema	5/5 (2.0%)	7/7 (2.8%)			1/1 (0.6%)	1/1 (0.6%)	6/6 (1.0%)	8/8 (1.3%)
Malaise						1/1 (0.6%)		1/1 (0.2%)
Oedema	1/1 (0.4%)						1/1 (0.2%)	
Oedema peripheral	12/12 (4.8%)	13/13 (5.2%)	1/1 (0.6%)	1/1 (0.6%)	1/1 (0.6%)	1/1 (0.6%)	14/14 (2.3%)	15/15 (2.5%)
Pain	14/14 (5.6%)	14/14 (5.6%)	6/6 (3.5%)	6/6 (3.4%)	10/10 (5.7%)	7/7 (4.0%)	30/30 (5.0%)	27/27 (4.5%)
Peripheral swelling	1/1 (0.4%)						1/1 (0.2%)	
Post-procedural fever	34/31 (12.4%)	46/46 (18.3%)	1/1 (0.6%)		2/2 (1.1%)	5/5 (2.9%)	37/34 (5.7%)	51/51 (8.5%)
Hepatobiliary disorders						**1/1 (0.6%)**		**1/1 (0.2%)**
Hepatitis						1/1 (0.6%)		1/1 (0.2%)
Immune system disorders		**1/1 (0.4%)**						**1/1 (0.2%)**
Urticaria		1/1 (0.4%)						1/1 (0.2%)
Infections and infestations	**47/41 (16.5%)**	**58/52 (20.7%)**	**9/8 (4.7%)**	**10/9 (5.2%)**	**10/9 (5.1%)**	**19/15 (8.6%)**	**66/58 (9.7%)**	**87/76 (12.7%)**
Endocarditis		1/1 (0.4%)						1/1 (0.2%)
Infection	3/3 (1.2%)	9/9 (3.6%)	1/1 (0.6%)		2/2 (1.1%)	5/5 (2.9%)	6/6 (1.0%)	14/14 (2.3%)
Lower respiratory tract infection		1/1 (0.4%)						1/1 (0.2%)
Mediastinitis	1/1 (0.4%)						1/1 (0.2%)	
Pneumonia	6/6 (2.4%)	15/15 (6.0%)	2/2 (1.2%)	5/5 (2.9%)	1/1 (0.6%)	4/4 (2.3%)	9/9 (1.5%)	24/24 (4.0%)
Sepsis	2/2 (0.8%)	1/1 (0.4%)		1/1 (0.6%)	1/1 (0.6%)	3/3 (1.7%)	3/3 (0.5%)	5/5 (0.8%)
Sinusitis			1/1 (0.6%)				1/1 (0.2%)	
Urinary tract infection	6/6 (2.4%)	5/5 (2.0%)	1/1 (0.6%)		1/1 (0.6%)	1/1 (0.6%)	8/8 (1.3%)	6/6 (1.0%)
Arteriovenous graft site infection		1/1 (0.4%)						1/1 (0.2%)

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Wound abscess	1/1 (0.4%)						1/1 (0.2%)	
Respiratory tract infection	28/28 (11.2%)	24/24 (9.6%)	4/4 (2.3%)	4/4 (2.3%)	4/4 (2.3%)	5/5 (2.9%)	36/36 (6.0%)	33/33 (5.5%)
Candida infection		1/1 (0.4%)						1/1 (0.2%)
Medical device site infection					1/1 (0.6%)	1/1 (0.6%)	1/1 (0.2%)	1/1 (0.2%)
Injury, poisoning and procedural complications	**82/67 (26.9%)**	**73/60 (23.9%)**	**14/14 (8.1%)**	**7/7 (4.0%)**	**12/11 (6.3%)**	**12/12 (6.9%)**	**108/92 (15.4%)**	**92/79 (13.2%)**
Fall	1/1 (0.4%)	2/2 (0.8%)	3/3 (1.7%)		2/2 (1.1%)	2/2 (1.1%)	6/6 (1.0%)	4/4 (0.7%)
Haematuria traumatic		2/2 (0.8%)						2/2 (0.3%)
Paralysis recurrent laryngeal nerve				1/1 (0.6%)				1/1 (0.2%)
Subcutaneous emphysema	3/3 (1.2%)	2/2 (0.8%)	7/7 (4.1%)	4/4 (2.3%)	1/1 (0.6%)		11/11 (1.8%)	6/6 (1.0%)
Surgical procedure repeated	2/2 (0.8%)	2/2 (0.8%)	2/2 (1.2%)		1/1 (0.6%)	1/1 (0.6%)	5/5 (0.8%)	3/3 (0.5%)
Wound dehiscence	1/1 (0.4%)				1/1 (0.6%)		2/2 (0.3%)	
Wound infection	5/5 (2.0%)	5/5 (2.0%)			5/5 (2.9%)	4/4 (2.3%)	10/10 (1.7%)	9/9 (1.5%)
Post-procedural haemorrhage	69/62 (24.9%)	55/47 (18.7%)	1/1 (0.6%)		1/1 (0.6%)	1/1 (0.6%)	71/64 (10.7%)	56/48 (8.0%)
Post-procedural bile leak					1/1 (0.6%)		1/1 (0.2%)	
Procedural complication	1/1 (0.4%)	4/4 (1.6%)		1/1 (0.6%)		1/1 (0.6%)	1/1 (0.2%)	6/6 (1.0%)
Renal injury		1/1 (0.4%)						1/1 (0.2%)
Injection-related reaction						1/1 (0.6%)		1/1 (0.2%)
Conversion from minimal access to open surgery			1/1 (0.6%)	1/1 (0.6%)		2/2 (1.1%)	1/1 (0.2%)	3/3 (0.5%)
Investigations	**48/46 (18.5%)**	**46/44 (17.5%)**	**2/2 (1.2%)**	**1/1 (0.6%)**	**2/2 (1.1%)**	**6/6 (3.4%)**	**52/50 (8.4%)**	**53/51 (8.5%)**
Bronchoscopy			2/2 (1.2%)				2/2 (0.3%)	
C-reactive protein increased	1/1 (0.4%)						1/1 (0.2%)	
Electrocardiogram ST segment elevation	1/1 (0.4%)						1/1 (0.2%)	
Weight increased	39/39 (15.7%)	32/32 (12.7%)					39/39 (6.5%)	32/32 (5.3%)
White blood cell count decreased						1/1 (0.6%)		1/1 (0.2%)

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Liver function test increased	7/5 (2.0%)	14/13 (5.2%)		1/1 (0.6%)	2/2 (1.1%)	5/5 (2.9%)	9/7 (1.2%)	20/19 (3.2%)
Metabolism and nutrition disorders	**37/35 (14.1%)**	**31/31 (12.4%)**	**3/3 (1.7%)**	**5/5 (2.9%)**	**4/4 (2.3%)**	**1/1 (0.6%)**	**44/42 (7.0%)**	**37/37 (6.2%)**
Gout	1/1 (0.4%)						1/1 (0.2%)	
Hyperglycaemia	22/22 (8.8%)	24/24 (9.6%)			2/2 (1.1%)		24/24 (4.0%)	24/24 (4.0%)
Hyperkalaemia	1/1 (0.4%)						1/1 (0.2%)	
Hypernatraemia	1/1 (0.4%)	1/1 (0.4%)					1/1 (0.2%)	1/1 (0.2%)
Hyponatraemia	9/9 (3.6%)	6/6 (2.4%)	3/3 (1.7%)	5/5 (2.9%)	2/2 (1.1%)	1/1 (0.6%)	14/14 (2.3%)	12/12 (2.0%)
Decreased appetite	3/3 (1.2%)						3/3 (0.5%)	
Musculoskeletal and connective tissue disorders	**3/3 (1.2%)**	**2/2 (0.8%)**					**3/3 (0.5%)**	**2/2 (0.3%)**
Arthralgia	1/1 (0.4%)						1/1 (0.2%)	
Back pain	2/2 (0.8%)	2/2 (0.8%)					2/2 (0.3%)	2/2 (0.3%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)				**2/2 (1.1%)**	**1/1 (0.6%)**		**1/1 (0.2%)**	**2/2 (0.3%)**
Neoplasm recurrence				2/2 (1.1%)	1/1 (0.6%)		1/1 (0.2%)	2/2 (0.3%)
Nervous system disorders	**30/25 (10.0%)**	**32/27 (10.8%)**	**8/7 (4.1%)**	**10/10 (5.7%)**	**12/12 (6.9%)**	**16/14 (8.0%)**	**50/44 (7.4%)**	**58/51 (8.5%)**
Co-ordination abnormal		1/1 (0.4%)						1/1 (0.2%)
Dizziness	9/9 (3.6%)	10/10 (4.0%)	3/3 (1.7%)	7/7 (4.0%)	8/8 (4.6%)	7/7 (4.0%)	20/20 (3.4%)	24/24 (4.0%)
Dysarthria	2/2 (0.8%)	1/1 (0.4%)			2/2 (1.1%)		4/4 (0.7%)	1/1 (0.2%)
Dyskinesia	1/1 (0.4%)						1/1 (0.2%)	
Extrapyramidal disorder		1/1 (0.4%)						1/1 (0.2%)
Headache		2/2 (0.8%)				1/1 (0.6%)		3/3 (0.5%)
Hemiparesis	1/1 (0.4%)						1/1 (0.2%)	
Hemiplegic migraine	1/1 (0.4%)						1/1 (0.2%)	
Hyperkinesia			1/1 (0.6%)				1/1 (0.2%)	
Hypoaesthesia	2/2 (0.8%)	1/1 (0.4%)					2/2 (0.3%)	1/1 (0.2%)
Insomnia	3/3 (1.2%)					2/2 (1.1%)	3/3 (0.5%)	2/2 (0.3%)

DOI: 10.3310/PLMH9787

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Loss of consciousness	3/3 (1.2%)		2/2 (1.2%)		2/2 (1.1%)		7/7 (1.2%)	
Mental impairment		4/4 (1.6%)	1/1 (0.6%)			1/1 (0.6%)	1/1 (0.2%)	5/5 (0.8%)
Migraine	1/1 (0.4%)						1/1 (0.2%)	
Muscular weakness	2/1 (0.4%)						2/1 (0.2%)	
Myoclonus		1/1 (0.4%)						1/1 (0.2%)
Paraesthesia						1/1 (0.6%)		1/1 (0.2%)
Seizure		1/1 (0.4%)						1/1 (0.2%)
Sensory disturbance						1/1 (0.6%)		1/1 (0.2%)
Somnolence	3/3 (1.2%)	7/7 (2.8%)	1/1 (0.6%)	2/2 (1.1%)		2/2 (1.1%)	4/4 (0.7%)	11/11 (1.8%)
Transient ischaemic attack	2/2 (0.8%)	1/1 (0.4%)					2/2 (0.3%)	1/1 (0.2%)
Tremor		2/2 (0.8%)		1/1 (0.6%)				3/3 (0.5%)
Anal incontinence						1/1 (0.6%)		1/1 (0.2%)
Psychiatric disorders	**29/26 (10.4%)**	**27/25 (10.0%)**	**8/6 (3.5%)**	**9/8 (4.6%)**	**12/10 (5.7%)**	**9/9 (5.1%)**	**49/42 (7.0%)**	**45/42 (7.0%)**
Agitation	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)	1/1 (0.6%)	1/1 (0.6%)	1/1 (0.6%)	3/3 (0.5%)	3/3 (0.5%)
Anxiety	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)			1/1 (0.6%)	2/2 (0.3%)	2/2 (0.3%)
Delirium	13/13 (5.2%)	7/7 (2.8%)	1/1 (0.6%)		3/3 (1.7%)	1/1 (0.6%)	17/17 (2.9%)	8/8 (1.3%)
Depression		2/2 (0.8%)	1/1 (0.6%)			3/3 (1.7%)	1/1 (0.2%)	5/5 (0.8%)
Hallucination	5/5 (2.0%)	9/9 (3.6%)	2/2 (1.2%)	3/3 (1.7%)	7/7 (4.0%)	3/3 (1.7%)	14/14 (2.3%)	15/15 (2.5%)
Thinking abnormal	2/2 (0.8%)						2/2 (0.3%)	
Confusion postoperative	7/7 (2.8%)	7/7 (2.8%)	2/2 (1.2%)	5/5 (2.9%)	1/1 (0.6%)		10/10 (1.7%)	12/12 (2.0%)
Renal and urinary disorders	**22/22 (8.8%)**	**35/31 (12.4%)**	**17/15 (8.7%)**	**22/21 (12.1%)**	**12/12 (6.9%)**	**9/9 (5.1%)**	**51/49 (8.2%)**	**66/61 (10.2%)**
Incontinence					2/2 (1.1%)		2/2 (0.3%)	
Urinary retention	5/5 (2.0%)	10/10 (4.0%)	14/13 (7.6%)	21/21 (12.1%)	8/8 (4.6%)	6/6 (3.4%)	27/26 (4.4%)	37/37 (6.2%)
Acute kidney injury	17/17 (6.8%)	25/25 (10.0%)	3/3 (1.7%)	1/1 (0.6%)	2/2 (1.1%)	3/3 (1.7%)	22/22 (3.7%)	29/29 (4.8%)
Reproductive system and breast disorders					**1/1 (0.6%)**		**1/1 (0.2%)**	

continued

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Vaginal discharge					1/1 (0.6%)		1/1 (0.2%)	
Respiratory, thoracic and mediastinal disorders	**106/85 (34.1%)**	**105/89 (35.5%)**	**38/35 (20.3%)**	**22/20 (11.5%)**	**8/7 (4.0%)**	**12/12 (6.9%)**	**152/127 (21.3%)**	**139/121 (20.2%)**
Acute respiratory failure	2/2 (0.8%)	1/1 (0.4%)			1/1 (0.6%)		3/3 (0.5%)	1/1 (0.2%)
Atelectasis	34/34 (13.7%)	33/33 (13.1%)	2/2 (1.2%)	1/1 (0.6%)	4/4 (2.3%)	4/4 (2.3%)	40/40 (6.7%)	38/38 (6.3%)
Cough		2/2 (0.8%)				2/2 (1.1%)		4/4 (0.7%)
Dyspnoea		1/1 (0.4%)	4/4 (2.3%)		1/1 (0.6%)	1/1 (0.6%)	5/5 (0.8%)	2/2 (0.3%)
Lung abscess		1/1 (0.4%)				1/1 (0.6%)		2/2 (0.3%)
Pleural effusion	50/50 (20.1%)	63/62 (24.7%)	3/3 (1.7%)	3/3 (1.7%)	2/2 (1.1%)	2/2 (1.1%)	55/55 (9.2%)	68/67 (11.2%)
Pneumothorax	15/14 (5.6%)	2/2 (0.8%)	13/13 (7.6%)	8/8 (4.6%)		1/1 (0.6%)	28/27 (4.5%)	11/11 (1.8%)
Pulmonary oedema	1/1 (0.4%)						1/1 (0.2%)	
Respiratory depression		1/1 (0.4%)	1/1 (0.6%)			1/1 (0.6%)	1/1 (0.2%)	2/2 (0.3%)
Bronchopleural fistula	3/3 (1.2%)	1/1 (0.4%)	15/15 (8.7%)	9/9 (5.2%)			18/18 (3.0%)	10/10 (1.7%)
Bronchial secretion retention				1/1 (0.6%)				1/1 (0.2%)
Acute lung injury	1/1 (0.4%)						1/1 (0.2%)	
Skin and subcutaneous tissue disorders	**4/4 (1.6%)**	**6/6 (2.4%)**	**1/1 (0.6%)**	**1/1 (0.6%)**	**4/4 (2.3%)**	**6/6 (3.4%)**	**9/9 (1.5%)**	**13/13 (2.2%)**
Blister		3/3 (1.2%)						3/3 (0.5%)
Decubitus ulcer		1/1 (0.4%)						1/1 (0.2%)
Face oedema	1/1 (0.4%)					1/1 (0.6%)	1/1 (0.2%)	1/1 (0.2%)
Pruritus	1/1 (0.4%)		1/1 (0.6%)	1/1 (0.6%)	3/3 (1.7%)	2/2 (1.1%)	5/5 (0.8%)	3/3 (0.5%)
Purpura	1/1 (0.4%)						1/1 (0.2%)	
Rash		2/2 (0.8%)			1/1 (0.6%)	2/2 (1.1%)	1/1 (0.2%)	4/4 (0.7%)
Skin erosion	1/1 (0.4%)					1/1 (0.6%)	1/1 (0.2%)	1/1 (0.2%)
Surgical and medical procedures	**126/117 (47.0%)**	**126/112 (44.6%)**	**3/3 (1.7%)**		**2/2 (1.1%)**		**131/122 (20.5%)**	**126/112 (18.7%)**
Cardioversion		1/1 (0.4%)						1/1 (0.2%)
Tracheostomy			2/2 (1.2%)				2/2 (0.3%)	
Implantable defibrillator insertion		1/1 (0.4%)						1/1 (0.2%)

DOI: 10.3310/PLMH9787

TABLE 52 Adverse events by MedDRA system organ class (*continued*)

AE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Continuous positive airway pressure	20/17 (6.8%)	18/18 (7.2%)			1/1 (0.6%)		21/18 (3.0%)	18/18 (3.0%)
Gastrointestinal tube insertion		1/1 (0.4%)						1/1 (0.2%)
Pacemaker-generated rhythm	104/103 (41.4%)	100/99 (39.4%)					104/103 (17.3%)	100/99 (16.5%)
Endotracheal intubation	1/1 (0.4%)	3/3 (1.2%)	1/1 (0.6%)		1/1 (0.6%)		3/3 (0.5%)	3/3 (0.5%)
Vascular catheterisation	1/1 (0.4%)	2/2 (0.8%)					1/1 (0.2%)	2/2 (0.3%)
Vascular disorders	**224/186 (74.7%)**	**264/201 (80.1%)**	**3/3 (1.7%)**	**3/3 (1.7%)**	**6/4 (2.3%)**	**3/3 (1.7%)**	**233/193 (32.4%)**	**270/207 (34.5%)**
Cerebral infarction	1/1 (0.4%)	1/1 (0.4%)			2/1 (0.6%)		3/2 (0.3%)	1/1 (0.2%)
Haematuria		1/1 (0.4%)		1/1 (0.6%)				2/2 (0.3%)
Hypertension	64/61 (24.5%)	59/56 (22.3%)					64/61 (10.2%)	59/56 (9.3%)
Hypotension		1/1 (0.4%)	1/1 (0.6%)	1/1 (0.6%)	1/1 (0.6%)		2/2 (0.3%)	2/2 (0.3%)
Vasodilatation	155/141 (56.6%)	201/178 (70.9%)	1/1 (0.6%)	1/1 (0.6%)	2/2 (1.1%)	3/3 (1.7%)	158/144 (24.2%)	205/182 (30.3%)
Venous thrombosis	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)		1/1 (0.6%)		3/3 (0.5%)	1/1 (0.2%)
Haemodynamic instability	3/3 (1.2%)						3/3 (0.5%)	

Note
Data are number of events/number of participants (% of total participants), for example 10/7 denotes 10 events in 7 participants.

TABLE 53 Serious adverse events by MedDRA system organ class

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Total events (events/participants)	187/78 (31.3%)	216/82 (32.7%)	83/44 (25.6%)	111/55 (31.6%)	144/67 (38.3%)	178/58 (33.1%)	414/189 (31.7%)	505/195 (32.5%)
Blood and lymphatic system disorders	2/1 (0.4%)	1/1 (0.4%)		1/1 (0.6%)	1/1 (0.6%)	2/1 (0.6%)	3/2 (0.3%)	4/3 (0.5%)
Anaemia	2/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)	2/1 (0.6%)			3/2 (0.3%)	3/2 (0.3%)
Leucopenia						1/1 (0.6%)		1/1 (0.2%)
Cardiac disorders	43/33 (13.3%)	40/30 (12.0%)	2/2 (1.2%)	2/2 (1.1%)	2/2 (1.1%)	7/6 (3.4%)	47/37 (6.2%)	49/38 (6.3%)
Arrhythmia	6/5 (2.0%)	4/3 (1.2%)	1/1 (0.6%)	3/3 (1.7%)			7/6 (1.0%)	7/6 (1.0%)
Atrial fibrillation	10/10 (4.0%)	12/11 (4.4%)		3/3 (1.7%)			10/10 (1.7%)	15/14 (2.3%)
Atrial flutter	3/3 (1.2%)	1/1 (0.4%)					3/3 (0.5%)	1/1 (0.2%)
Atrioventricular block					1/1 (0.6%)		1/1 (0.2%)	
Bundle branch block left		1/1 (0.4%)						1/1 (0.2%)
Bundle branch block right	1/1 (0.4%)						1/1 (0.2%)	
Cardiac arrest	1/1 (0.4%)	1/1 (0.4%)		1/1 (0.6%)			1/1 (0.2%)	2/2 (0.3%)
Cardiac failure congestive	5/4 (1.6%)	7/5 (2.0%)					5/4 (0.7%)	7/5 (0.8%)
Myocardial infarction					1/1 (0.6%)	2/2 (1.1%)	1/1 (0.2%)	2/2 (0.3%)
Pericardial effusion	16/15 (6.0%)	10/8 (3.2%)	1/1 (0.6%)				17/16 (2.7%)	10/8 (1.3%)
Supraventricular tachycardia		1/1 (0.4%)						1/1 (0.2%)
Tachycardia		3/3 (1.2%)						3/3 (0.5%)
Ventricular tachycardia	1/1 (0.4%)						1/1 (0.2%)	
Endocrine disorders			**1/1 (0.6%)**				**1/1 (0.2%)**	
Steroid withdrawal syndrome					1/1 (0.6%)		1/1 (0.2%)	
Eye disorders	1/1 (0.4%)						1/1 (0.2%)	
Diplopia	1/1 (0.4%)						1/1 (0.2%)	
Gastrointestinal disorders	11/8 (3.2%)	12/11 (4.4%)	3/3 (1.7%)	6/6 (3.4%)	43/30 (17.1%)	79/42 (24.0%)	57/41 (6.9%)	97/59 (9.8%)
Abdominal pain		2/2 (0.8%)	3/3 (1.7%)	5/5 (2.9%)	1/1 (0.6%)	1/1 (0.6%)	4/4 (0.7%)	8/8 (1.3%)

TABLE 53 Serious adverse events by MedDRA system organ class (*continued*)

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Abdominal pain upper			1/1 (0.6%)				1/1 (0.2%)	
Colitis				1/1 (0.6%)				1/1 (0.2%)
Constipation	2/2 (0.8%)		2/2 (1.1%)	1/1 (0.6%)			4/4 (0.7%)	1/1 (0.2%)
Diarrhoea	1/1 (0.4%)	5/5 (2.0%)	7/6 (3.4%)	12/10 (5.7%)		1/1 (0.6%)	8/7 (1.2%)	18/16 (2.7%)
Dry mouth		1/1 (0.4%)						1/1 (0.2%)
Dysphagia	1/1 (0.4%)	2/2 (0.8%)					1/1 (0.2%)	2/2 (0.3%)
Gastrointestinal haemorrhage	2/2 (0.8%)	1/1 (0.4%)	1/1 (0.6%)			1/1 (0.6%)	3/3 (0.5%)	2/2 (0.3%)
Gastrointestinal necrosis				1/1 (0.6%)				1/1 (0.2%)
Ileus	1/1 (0.4%)		11/10 (5.7%)	20/20 (11.4%)	2/2 (1.2%)		14/13 (2.2%)	20/20 (3.3%)
Large intestine perforation						1/1 (0.6%)		1/1 (0.2%)
Nausea	1/1 (0.4%)		2/2 (1.1%)	8/8 (4.6%)			3/3 (0.5%)	8/8 (1.3%)
Oesophagitis				1/1 (0.6%)				1/1 (0.2%)
Pancreatitis	1/1 (0.4%)						1/1 (0.2%)	
Vomiting	1/1 (0.4%)		4/4 (2.3%)	12/12 (6.9%)		1/1 (0.6%)	5/5 (0.8%)	13/13 (2.2%)
Gastrointestinal ischaemia	1/1 (0.4%)					1/1 (0.6%)	1/1 (0.2%)	1/1 (0.2%)
Gastrointestinal obstruction		1/1 (0.4%)	3/3 (1.7%)	3/3 (1.7%)			3/3 (0.5%)	4/4 (0.7%)
Gastrointestinal anastomotic leak			2/2 (1.1%)	7/7 (4.0%)			2/2 (0.3%)	7/7 (1.2%)
Intra-abdominal fluid collection			7/7 (4.0%)	8/8 (4.6%)			7/7 (1.2%)	8/8 (1.3%)
Abdominal pain		2/2 (0.8%)	3/3 (1.7%)	5/5 (2.9%)	1/1 (0.6%)	1/1 (0.6%)	4/4 (0.7%)	8/8 (1.3%)
General disorders and administration site conditions	7/7 (2.8%)	8/6 (2.4%)	2/1 (0.6%)	5/5 (2.9%)	14/13 (7.4%)	4/4 (2.3%)	23/21 (3.5%)	17/15 (2.5%)
Chest pain	3/3 (1.2%)	1/1 (0.4%)	1/1 (0.6%)	1/1 (0.6%)	2/1 (0.6%)		6/5 (0.8%)	2/2 (0.3%)
Fatigue			1/1 (0.6%)			1/1 (0.6%)	1/1 (0.2%)	1/1 (0.2%)
Oedema peripheral	1/1 (0.4%)	1/1 (0.4%)		2/2 (1.1%)			1/1 (0.2%)	3/3 (0.5%)
Pain	2/2 (0.8%)		8/7 (4.0%)	1/1 (0.6%)		4/4 (2.3%)	10/9 (1.5%)	5/5 (0.8%)

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 53 Serious adverse events by MedDRA system organ class (*continued*)

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Multiple organ dysfunction syndrome		1/1 (0.4%)						1/1 (0.2%)
Post-procedural fever	1/1 (0.4%)	5/3 (1.2%)	4/4 (2.3%)				5/5 (0.8%)	5/3 (0.5%)
Hepatobiliary disorders		2/2 (0.8%)						2/2 (0.3%)
Cholecystitis		1/1 (0.4%)						1/1 (0.2%)
Jaundice		1/1 (0.4%)						1/1 (0.2%)
Infections and infestations	36/25 (10.0%)	35/27 (10.8%)	27/18 (10.5%)	15/14 (8.0%)	24/21 (12.0%)	22/20 (11.4%)	87/64 (10.7%)	72/61 (10.2%)
Empyema						1/1 (0.6%)		1/1 (0.2%)
Endocarditis	1/1 (0.4%)						1/1 (0.2%)	
Gastroenteritis		1/1 (0.4%)						1/1 (0.2%)
Infection	6/5 (2.0%)	3/3 (1.2%)	10/10 (5.7%)	7/7 (4.0%)	3/2 (1.2%)	3/3 (1.7%)	19/17 (2.9%)	13/13 (2.2%)
Mediastinitis	4/3 (1.2%)	3/3 (1.2%)					4/3 (0.5%)	3/3 (0.5%)
Osteomyelitis		1/1 (0.4%)						1/1 (0.2%)
Pneumonia	6/5 (2.0%)	5/5 (2.0%)	1/1 (0.6%)	6/6 (3.4%)	11/11 (6.4%)	5/5 (2.9%)	18/17 (2.9%)	16/16 (2.7%)
Sepsis	2/2 (0.8%)	4/4 (1.6%)	3/2 (1.1%)	7/7 (4.0%)	4/4 (2.3%)	2/2 (1.1%)	9/8 (1.3%)	13/13 (2.2%)
Urinary tract infection	1/1 (0.4%)	1/1 (0.4%)	5/5 (2.9%)	1/1 (0.6%)		1/1 (0.6%)	6/6 (1.0%)	3/3 (0.5%)
Cardiac infection	1/1 (0.4%)						1/1 (0.2%)	
Wound abscess		1/1 (0.4%)						1/1 (0.2%)
Respiratory tract infection	14/13 (5.2%)	16/14 (5.6%)	2/2 (1.1%)	1/1 (0.6%)	8/6 (3.5%)	3/2 (1.1%)	24/21 (3.5%)	20/17 (2.8%)
Candida infection			1/1 (0.6%)				1/1 (0.2%)	
Medical device site infection	1/1 (0.4%)		2/2 (1.1%)		1/1 (0.6%)		4/4 (0.7%)	
Injury, poisoning and procedural complications	10/7 (2.8%)	20/13 (5.2%)	18/14 (8.1%)	16/13 (7.5%)	40/30 (17.1%)	34/21 (12.0%)	68/51 (8.6%)	70/47 (7.8%)
Fall	1/1 (0.4%)		1/1 (0.6%)			1/1 (0.6%)	2/2 (0.3%)	1/1 (0.2%)
Incisional hernia			1/1 (0.6%)				1/1 (0.2%)	
Intentional overdose					1/1 (0.6%)		1/1 (0.2%)	

TABLE 53 Serious adverse events by MedDRA system organ class (*continued*)

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Subcutaneous emphysema					2/2 (1.2%)	4/4 (2.3%)	2/2 (0.3%)	4/4 (0.7%)
Surgical procedure repeated	2/2 (0.8%)	4/4 (1.6%)	11/11 (6.3%)	22/14 (8.0%)	9/9 (5.2%)	8/7 (4.0%)	22/22 (3.7%)	34/25 (4.2%)
Wound dehiscence	1/1 (0.4%)	4/3 (1.2%)	4/4 (2.3%)	5/5 (2.9%)	1/1 (0.6%)	1/1 (0.6%)	6/6 (1.0%)	10/9 (1.5%)
Wound infection	2/2 (0.8%)	8/6 (2.4%)	11/10 (5.7%)	5/5 (2.9%)	3/2 (1.2%)	2/2 (1.1%)	16/14 (2.3%)	15/13 (2.2%)
Post-procedural haemorrhage	1/1 (0.4%)	3/2 (0.8%)	7/7 (4.0%)	2/2 (1.1%)			8/8 (1.3%)	5/4 (0.7%)
Chylothorax					2/2 (1.2%)		2/2 (0.3%)	
Procedural complication	3/3 (1.2%)	1/1 (0.4%)	4/4 (2.3%)				7/7 (1.2%)	1/1 (0.2%)
Renal injury					1/1 (0.6%)		1/1 (0.2%)	
Conversion from minimal access to open surgery			1/1 (0.6%)					
Investigations	4/3 (1.2%)	4/4 (1.6%)		2/2 (1.1%)	1/1 (0.6%)	2/1 (0.6%)	5/4 (0.7%)	8/7 (1.2%)
Bronchoscopy						2/2 (1.1%)		2/2 (0.3%)
Weight increased	1/1 (0.4%)						1/1 (0.2%)	
White blood cell count decreased				1/1 (0.6%)				1/1 (0.2%)
Liver function test increased	3/2 (0.8%)	4/4 (1.6%)	1/1 (0.6%)	1/1 (0.6%)			4/3 (0.5%)	5/5 (0.8%)
Metabolism and nutrition disorders	3/3 (1.2%)	5/4 (1.6%)		1/1 (0.6%)	1/1 (0.6%)		4/4 (0.7%)	6/5 (0.8%)
Hyperglycaemia			1/1 (0.6%)				1/1 (0.2%)	
Hypoglycaemia	1/1 (0.4%)	1/1 (0.4%)					1/1 (0.2%)	1/1 (0.2%)
Hypomagnesaemia		1/1 (0.4%)						1/1 (0.2%)
Hyponatraemia	2/2 (0.8%)	2/1 (0.4%)					2/2 (0.3%)	2/1 (0.2%)
Decreased appetite		1/1 (0.4%)				1/1 (0.6%)		2/2 (0.3%)
Musculoskeletal and connective tissue disorders	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)			2/1 (0.6%)	2/2 (0.3%)	3/2 (0.3%)
Arthralgia					1/1 (0.6%)		1/1 (0.2%)	
Back pain		1/1 (0.4%)						1/1 (0.2%)

continued

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 53 Serious adverse events by MedDRA system organ class (*continued*)

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Myalgia	1/1 (0.4%)						1/1 (0.2%)	
Blood alkaline phosphatase increased				2/1 (0.6%)				2/1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		1/1 (0.4%)	8/7 (4.1%)	6/5 (2.9%)			8/7 (1.2%)	7/6 (1.0%)
Neoplasm		1/1 (0.4%)			1/1 (0.6%)	1/1 (0.6%)	1/1 (0.2%)	2/2 (0.3%)
Neoplasm recurrence					7/6 (3.5%)	5/4 (2.3%)	7/6 (1.0%)	5/4 (0.7%)
Nervous system disorders	6/6 (2.4%)	5/5 (2.0%)	1/1 (0.6%)	5/5 (2.9%)		5/5 (2.9%)	7/7 (1.2%)	15/15 (2.5%)
Cerebral infarction	3/3 (1.2%)	5/4 (1.6%)					5/5 (0.8%)	7/5 (0.8%)
Dizziness	1/1 (0.4%)	2/2 (0.8%)					1/1 (0.2%)	2/2 (0.3%)
Dysarthria				1/1 (0.6%)				1/1 (0.2%)
Hemiparesis				1/1 (0.6%)				1/1 (0.2%)
Hemiplegic migraine	1/1 (0.4%)						1/1 (0.2%)	
Insomnia				1/1 (0.6%)				1/1 (0.2%)
Loss of consciousness	1/1 (0.4%)	1/1 (0.4%)				1/1 (0.6%)	1/1 (0.2%)	2/2 (0.3%)
Mental impairment				2/2 (1.1%)	1/1 (0.6%)		1/1 (0.2%)	2/2 (0.3%)
Neuralgia						2/2 (1.1%)		2/2 (0.3%)
Seizure	1/1 (0.4%)						1/1 (0.2%)	
Transient ischaemic attack	1/1 (0.4%)					2/2 (1.1%)	1/1 (0.2%)	2/2 (0.3%)
Neurological symptom		1/1 (0.4%)						1/1 (0.2%)
Psychiatric disorders	4/4 (1.6%)	9/7 (2.8%)	3/1 (0.6%)	3/2 (1.1%)		1/1 (0.6%)	7/5 (0.8%)	13/10 (1.7%)
Anxiety					1/1 (0.6%)		1/1 (0.2%)	
Delirium		6/5 (2.0%)		1/1 (0.6%)		2/2 (1.1%)		9/8 (1.3%)
Depression					2/1 (0.6%)		2/1 (0.2%)	
Hallucination						1/1 (0.6%)		1/1 (0.2%)

TABLE 53 Serious adverse events by MedDRA system organ class (*continued*)

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Thinking abnormal		2/1 (0.4%)						2/1 (0.2%)
Confusion postoperative	4/4 (1.6%)	1/1 (0.4%)					4/4 (0.7%)	1/1 (0.2%)
Renal and urinary disorders	8/6 (2.4%)	5/5 (2.0%)	1/1 (0.6%)		6/6 (3.4%)	6/6 (3.4%)	15/13 (2.2%)	11/11 (1.8%)
Urinary retention	2/2 (0.8%)	1/1 (0.4%)	6/6 (3.4%)	3/3 (1.7%)			8/8 (1.3%)	4/4 (0.7%)
Acute kidney injury	6/4 (1.6%)	4/4 (1.6%)		3/3 (1.7%)	1/1 (0.6%)		7/5 (0.8%)	7/7 (1.2%)
Respiratory, thoracic and mediastinal disorders	24/15 (6.0%)	31/22 (8.8%)	11/10 (5.8%)	33/23 (13.2%)	7/5 (2.9%)	7/5 (2.9%)	42/30 (5.0%)	71/50 (8.3%)
Acute respiratory distress syndrome	1/1 (0.4%)	1/1 (0.4%)		2/1 (0.6%)			1/1 (0.2%)	3/2 (0.3%)
Acute respiratory failure	1/1 (0.4%)	4/4 (1.6%)				4/4 (2.3%)	1/1 (0.2%)	8/8 (1.3%)
Atelectasis	3/3 (1.2%)	4/4 (1.6%)	1/1 (0.6%)		1/1 (0.6%)		5/5 (0.8%)	4/4 (0.7%)
Cough	1/1 (0.4%)	1/1 (0.4%)	1/1 (0.6%)			1/1 (0.6%)	2/2 (0.3%)	2/2 (0.3%)
Dyspnoea	1/1 (0.4%)	1/1 (0.4%)		2/2 (1.1%)	2/2 (1.2%)	2/2 (1.1%)	3/3 (0.5%)	5/5 (0.8%)
Lung abscess						5/3 (1.7%)		5/3 (0.5%)
Pharyngitis		1/1 (0.4%)						1/1 (0.2%)
Pleural effusion	17/12 (4.8%)	18/16 (6.4%)	3/2 (1.1%)	3/3 (1.7%)	1/1 (0.6%)	3/3 (1.7%)	21/15 (2.5%)	24/22 (3.7%)
Pneumothorax			1/1 (0.6%)		4/4 (2.3%)	8/7 (4.0%)	5/5 (0.8%)	8/7 (1.2%)
Pulmonary oedema			1/1 (0.6%)				1/1 (0.2%)	
Respiratory depression		1/1 (0.4%)						1/1 (0.2%)
Chylothorax					2/2 (1.2%)		2/2 (0.3%)	
Bronchopleural fistula					2/2 (1.2%)	10/9 (5.2%)	2/2 (0.3%)	10/9 (1.5%)
Surgical and medical procedures	18/11 (4.4%)	24/18 (7.2%)	1/1 (0.6%)	9/5 (2.9%)	1/1 (0.6%)	5/5 (2.9%)	20/13 (2.2%)	38/28 (4.7%)
Tracheostomy	3/2 (0.8%)	3/3 (1.2%)				1/1 (0.6%)	3/2 (0.3%)	4/4 (0.7%)
Continuous positive airway pressure	2/2 (0.8%)	1/1 (0.4%)				2/2 (1.1%)	2/2 (0.3%)	3/3 (0.5%)
Abdominal exploration			1/1 (0.6%)	2/2 (1.1%)			1/1 (0.2%)	2/2 (0.3%)
Pacemaker-generated rhythm	8/8 (3.2%)	10/10 (4.0%)					8/8 (1.3%)	10/10 (1.7%)

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DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 53 Serious adverse events by MedDRA system organ class *(continued)*

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
Endotracheal intubation	5/2 (0.8%)	10/8 (3.2%)		3/3 (1.7%)	1/1 (0.6%)	6/5 (2.9%)	6/3 (0.5%)	19/16 (2.7%)
Vascular disorders	9/7 (2.8%)	13/10 (4.0%)	4/4 (2.3%)	7/5 (2.9%)	4/4 (2.3%)	2/1 (0.6%)	17/15 (2.5%)	22/16 (2.7%)
Cerebral infarction	3/3 (1.2%)	5/4 (1.6%)	1/1 (0.6%)		1/1 (0.6%)	2/1 (0.6%)	5/5 (0.8%)	7/5 (0.8%)
Intestinal infarction						1/1 (0.6%)		1/1 (0.2%)
Pulmonary embolism		2/2 (0.8%)	2/2 (1.1%)	1/1 (0.6%)	2/2 (1.2%)	2/2 (1.1%)	4/4 (0.7%)	5/5 (0.8%)
Vasodilatation	4/4 (1.6%)	5/4 (1.6%)		1/1 (0.6%)		1/1 (0.6%)	4/4 (0.7%)	7/6 (1.0%)
Venous thrombosis	2/1 (0.4%)	2/2 (0.8%)	1/1 (0.6%)		1/1 (0.6%)	1/1 (0.6%)	4/3 (0.5%)	3/3 (0.5%)
Haemodynamic instability	1/1 (0.4%)						1/1 (0.2%)	
Deaths	1/249	3/250	7/172	5/174	0/175	2/175	8/596	10/599

Note
Data are number of events/number of participants (% of total participants), for example 10/7 denotes 10 events in 7 participants.

DOI: 10.3310/PLMH9787

TABLE 54 Expectedness, relatedness and intensity of SAEs

SAE	Cardiac (*n* = 499)		Thoracic (*n* = 346)		Abdominal (*n* = 350)		Overall (*n* = 1195)	
	Randomised to placebo (*n* = 249)	Randomised to gabapentin (*n* = 250)	Randomised to placebo (*n* = 172)	Randomised to gabapentin (*n* = 174)	Randomised to placebo (*n* = 175)	Randomised to gabapentin (*n* = 175)	Randomised to placebo (*n* = 596)	Randomised to gabapentin (*n* = 599)
SAE	**187**	**216**	**83**	**111**	**144**	**178**	**414**	**505**
Expectedness								
Anticipated after surgery	73/187 (39.0%)	85/216 (39.4%)	34/83 (41.0%)	64/111 (57.7%)	63/144 (43.8%)	79/178 (44.4%)	170/414 (41.1%)	228/505 (45.1%)
Expected from gabapentin	100/187 (53.5%)	117/216 (54.2%)	39/83 (47.0%)	41/111 (36.9%)	79/144 (54.9%)	92/178 (51.7%)	218/414 (52.7%)	250/505 (49.5%)
Anticipated surgery and expected from gabapentin	9/187 (4.8%)	8/216 (3.7%)	2/83 (2.4%)	1/111 (0.9%)	1/144 (0.7%)	2/178 (1.1%)	12/414 (2.9%)	11/505 (2.2%)
Unexpected	5/187 (2.7%)	6/216 (2.8%)	8/83 (9.6%)	5/111 (4.5%)	1/144 (0.7%)	5/178 (2.8%)	14/414 (3.4%)	16/505 (3.2%)
Relatedness								
Not related	48/186 (25.8%)	44/216 (20.4%)	79/83 (95.2%)	110/111 (99.1%)	128/144 (88.9%)	156/178 (87.6%)	255/413 (61.7%)	310/505 (61.4%)
Unlikely to be related	138/186 (74.2%)	170/216 (78.7%)	4/83 (4.8%)	1/111 (0.9%)	16/144 (11.1%)	21/178 (11.8%)	158/413 (38.3%)	192/505 (38.0%)
Possibly related[a]		2/216 (0.9%)				1/178 (0.6%)		3/505 (0.6%)
Intensity (where recorded)								
Mild	3/39 (7.7%)	1/35 (2.9%)	4/19 (21.1%)		1/10 (10.0%)	1/10 (10.0%)	8/68 (11.8%)	2/54 (3.7%)
Moderate	21/39 (53.8%)	15/35 (42.9%)	6/19 (31.6%)	1/9 (11.1%)	7/10 (70.0%)	5/10 (50.0%)	34/68 (50.0%)	21/54 (38.9%)
Severe	15/39 (38.5%)	19/35 (54.3%)	9/19 (47.4%)	8/9 (88.9%)	2/10 (20.0%)	4/10 (40.0%)	26/68 (38.2%)	31/54 (57.4%)

a The events were: cardiac – loss of consciousness and respiratory depression each lasting 1 day before resolving both were classified as life-threatening, and abdominal – vomiting lasting 3 days before resolving which prolonged the hospital stay.

Note
Data are *n*/*N* (%).

TABLE 55 Number of participants with complete data for health economic analyses

Category	Randomised to placebo (*n* = 589) *n* (%)	Randomised to gabapentin (*n* = 595) *n* (%)
Resource use		
Index admission		
Time in theatre	589 (100)	595 (100)
Intensive care unit stay	587 (100)	593 (100)
High-dependency unit stay	587 (100)	593 (100)
Ward stay	587 (100)	592 (99)
Ward stay at another hospital	586 (99)	593 (100)
In-hospital complications and SAEs	552 (94)	558 (94)
Analgesia	578 (98)	580 (97)
Index admission total	544 (92)	547 (92)
Primary and secondary care post-hospital discharge		
Hospital discharge to 4 weeks	512 (87)	520 (87)
4 weeks to 4 months	534 (91)	533 (90)
All	438 (74)	442 (74)
Outcomes		
EQ-5D at baseline	577 (98)	583 (98)
EQ-5D at 4 weeks	523 (89)	521 (88)
EQ-5D at 4 months	511 (87)	494 (83)
QALYs	468 (79)	456 (77)
All costs and QALYs	356 (60)	347 (58)

DOI: 10.3310/PLMH9787

Health Technology Assessment 2026 Vol. 30 No. 9

TABLE 56 Results of sensitivity analyses around unit costs

SA	Randomised to placebo (*n* = 589) Mean cost (£) (SE)	Randomised to gabapentin (*n* = 595) Mean cost (£) (SE)	Gabapentin vs. placebo Mean cost (£) difference (95% CI)
Base case	12,634 (422)	13,011 (423)	+ 377 (−797 to + 1550)
SA1 (theatre)			
+ 50%	14,933 (443)	15,258 (443)	+ 325 (−904 to + 1554)
−50%	10,335 (406)	10,763 (407)	+ 428 (−699 to + 1556)
SA2 (critical care)			
+ 50%	14,445 (560)	15,027 (560)	+ 582 (−972 to + 213)
−50%	10,823 (300)	10,994 (303)	+ 171 (−667 to + 1009)
SA3 (critical care)			
All at thoracic/abdominal costs	13,265 (454)	13,636 (455)	+ 371 (−889 to + 1632)
SA4 (critical care)			
All at cardiac costs	12,426 (410)	12,794 (411)	+ 367 (−772 to + 1507)
SA5 (ward stay)			
+ 50%	13,791 (434)	14,114 (435)	+ 322 (−885 to + 1530)
−50%	11,477 (413)	11,908 (415)	+ 431 (−718 to + 1580)

SA, sensitivity analysis.

TABLE 57 Costs, QALYs and cost-effectiveness results by surgical specialty and surgical access type

Specialty	Surgical access		Randomised to placebo Mean (SE)	Randomised to gabapentin Mean (SE)	Gabapentin vs. placebo Mean difference (95% CI)	ICER (Cost/QALY)
All participants	Open	*n*	404	409		Placebo dominant (−£68,291)
		Total cost (£)	14,136 (499)	14,417 (500)	+ 281 (−1106 to + 1668)	
		QALYs	0.245 (0.003)	0.240 (0.003)	−0.004 (−0.012 to + 0.004)	
	Minimal access	*n*	185	186		Placebo dominant (−£360,812)
		Total cost (£)	9354 (737)	9919 (743)	+ 565 (−1487 to + 2617)	
		QALYs	0.251 (0.004)	0.249 (0.004)	−0.002 (−0.014 to + 0.011)	
Cardiac	Open		247	248		£30,314
		Total cost (£)	15,493 (630)	15,302 (629)	−190 (−1938 to + 1557)	
		QALYs	0.246 (0.004)	0.239 (0.004)	−0.006 (−0.017 to + 0.004)	
	Minimal access	*n*	0	0		
Thoracic	Open	*n*	64	60		Placebo dominant (−£173,901)
		Total cost (£)	9435 (1239)	12,432 (1328)	+ 2996 (−563 to + 6556)	
		QALYs	0.237 (0.008)	0.220 (0.008)	−0.017 (−0.038 to + 0.004)	
	Minimal access	*n*	105	113		Placebo dominant (−£9207)
		Total cost (£)	8468 (968)	8405 (949)	−63 (−2724 to + 2597)	
		QALYs	0.239 (0.006)	0.246 (0.006)	+ 0.007 (−0.009 to + 0.023)	
Abdominal	Open	*n*	93	101		Placebo dominant (−£40,641)
		Total cost (£)	13,768 (1029)	13,421 (991)	−347 (−3148 to + 2455)	
		QALYs	0.247 (0.006)	0.255 (0.006)	+ 0.009 (−0.008 to + 0.026)	
	Minimal access	*n*	80	73		Placebo dominant (−£146,776)
		Total cost (£)	10,517 (1108)	12,262 (1160)	+ 1745 (−1403 to + 4893)	
		QALYs	0.266 (0.007)	0.254 (0.007)	−0.012 (−0.031 to + 0.007)d	

EME
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