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Total Intravenous vs Volatile Inhalational Anesthesia for Major Noncardiac Surgery
A Randomized Clinical Trial

Shaman Jhanji, PhD; Katie Booth, MSc; Louise Hiller, PhD; John Braun; Janet Dunn, PhD; Lucy Eggleston; Llewellyn Fenton-May, MBChB; Sam Frempong, PhD; Katie Gilchrist, MSc; Claire Jacques, MMedSci; Monica Jefford, MBA; Rebecca Kandiyali, PhD; Dalbir Kaur, BSc; James Mason, DPhil; S. Ramani Moonesinghe, MD(Res); Rupert Pearse, MD(Res); Ravishankar Rao Baikady, MBBS; Toby Reynolds, MBBS; Ben Shelley, MD; Rhona C. F. Sinclair, MPhil; Thomas Teare, MBChB; Cecilia Vindrola-Padros, PhD; Joyce Yeung, PhD; for the VITAL Trial Team

IMPORTANCE Older adults undergoing major noncardiac surgery experience substantial postoperative morbidity and health care use. The comparative effectiveness of total intravenous anesthesia (TIVA) vs volatile-based inhalational anesthesia on recovery and safety remains uncertain.

OBJECTIVES To determine whether TIVA improves days alive and at home at 30 days compared with inhalational anesthesia and to evaluate differences in patient-centered outcomes and recovery.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, multicenter, open-label randomized clinical trial conducted in 49 UK National Health Service hospitals from January 2022 to April 2024 (final follow-up, October 2024) among patients aged 50 years or older scheduled for elective major noncardiac surgery.

INTERVENTIONS Participants were randomized 1:1 to receive maintenance of general anesthesia with either TIVA (propofol infusion) (n = 1254) or volatile-based inhalational agents (n = 1254). All other perioperative care was at clinician discretion.

MAIN OUTCOMES AND MEASURES The primary outcome was days alive and at home at 30 days. Secondary outcomes included days alive and at home at 90 days; mortality at 30 days, 90 days, and 6 months; Quality of Recovery–15 score at day 3; patient satisfaction (Bauer Patient Satisfaction Questionnaire) at day 1; delirium (4 As Test [4AT]) at day 3; unintentional awareness under anesthesia; and major postoperative complications within 30 days.

RESULTS Among the 2508 randomized participants, the mean age was 67 (SD, 8.9) years, and 55% were male. Characteristics were balanced across randomized groups. Days alive and at home at 30 days were similar between groups (mean, 22.5 [SD, 6.8] days vs 22.4 [SD, 6.6] days for TIVA vs inhalational anesthesia, respectively; incidence rate ratio, 1.00; 95% CI, 0.99-1.02; adjusted *P* = .68). There were no differences in days alive and at home at 90 days; mortality at 30 days, 90 days, or 6 months; or Quality of Recovery–15 score at day 3. Lower rates of thirst, hoarseness, and nausea and vomiting were reported in the TIVA group. Levels of delirium were similar between groups, with the majority (87.6%) having no delirium at day 3. Major complications occurred in 12.4% of patients overall, with no significant between-group differences. Two cases of certain or probable unintentional awareness under anesthesia were reported, both in the TIVA group.

CONCLUSIONS AND RELEVANCE Among older adults undergoing major noncardiac surgery, TIVA did not improve days alive and at home at 30 days compared with inhalational anesthesia.

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Visual Abstract
Research Summary
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of the VITAL Trial Team appears in Supplement 4.

Corresponding Author: Joyce Yeung, PhD, Warwick Medical School, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, United Kingdom (j.yeung.4@warwick.ac.uk).

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More than 300 million major surgical procedures are performed worldwide each year, including a variety of procedures from cancer resections to orthopedic, vascular, and abdominal surgery.[1,2] High-quality general anesthesia is central to ensuring patient safety during these operations, providing hemodynamic stability, preventing intraoperative awareness, and supporting safe postoperative recovery. General anesthesia is typically maintained with an inhaled volatile agent such as sevoflurane or isoflurane.[3] An established alternative approach is total intravenous anesthesia (TIVA), which involves continuous infusion of intravenous propofol. Although both approaches achieve unconsciousness, they differ significantly in their pharmacological profiles, intraoperative physiological effects, and perioperative safety profiles.[4] Despite its relatively short intraoperative duration, anesthetic technique may influence inflammatory, hemodynamic, and immune responses that contribute to postoperative complications and patient recovery.

Over the last 20 years, use of TIVA has expanded substantially. This change has been driven by hypothesized links between anesthetic technique and long-term cancer outcomes[5-8] and by growing concerns regarding the environmental impact of volatile gases.[9] While these proposed benefits are debated, the increasing adoption of TIVA has far outpaced the generation of high-quality data on patient outcomes and safety. Among patients undergoing cardiac surgery, anesthesia with a volatile agent did not result in significantly fewer deaths at 1 year than TIVA.[10,11] However, there is no robust evidence base for the far larger population undergoing noncardiac surgery, leaving a key unanswered question about the comparative safety of 2 techniques used in millions of patients globally every day. This evidence gap has important patient safety implications. Intravenous anesthesia may suppress proinflammatory mediators, potentially moderating the surgical stress response,[12,13] while inhalational agents have been suggested to confer cardioprotective effects in preclinical and observational studies.[14,15] Yet in real-world practice, the degree to which these physiological differences translate into meaningful improvements—or harms—for patients undergoing noncardiac surgery remains unknown.[16,17]

Anesthetic choice may also influence postoperative safety outcomes, including recovery trajectories, complications, and the risk of unintentional awareness under anesthesia. Despite advances such as processed electroencephalography, unintentional awareness with TIVA remains a recognized clinical concern.[3] Systematic reviews in specific surgical populations have found that TIVA can facilitate faster emergence, reduce postoperative nausea and vomiting, and lessen early postoperative pain.[18-24] These early effects may support mobilization, rehabilitation, and earlier recovery and limit deconditioning, especially in older or frail patients, although their impact on longer-term outcomes remain uncertain. A recent meta-analysis of randomized clinical trials suggested a small increase in mortality associated with propofol across heterogeneous perioperative and critical care populations; however, these findings were not consistently observed in individual trials and should be interpreted cautiously.[16]

Key Points

Question Among patients aged 50 years or older undergoing major elective noncardiac surgery, does maintaining general anesthesia with total intravenous anesthesia improve outcomes compared with volatile inhalational anesthesia?

Findings In this pragmatic randomized clinical trial across 49 UK hospitals (n = 2508), days alive and at home at 30 days did not differ between total intravenous anesthesia and volatile anesthesia (22.5 days vs 22.4 days for TIVA vs inhalational anesthesia, respectively).

Meaning Total intravenous anesthesia did not improve days alive and at home at 30 days compared with inhalational anesthesia.

Against this backdrop of widespread clinical adoption, divergent physiological mechanisms, and a striking lack of large-scale safety data in noncardiac surgery, there is an urgent need for high-quality randomized evidence regarding TIVA. The Volatile vs Total Intravenous Anesthesia for Major Non-Cardiac Surgery (VITAL) trial was designed to meet this need. Embedded within the UK's national Perioperative Quality Improvement Programme (PQIP), VITAL provides a pragmatic, real-world evaluation of whether TIVA leads to improved patient-centered recovery and safety outcomes compared with inhalational anesthesia in the diverse surgical populations in whom it is now commonly used. We hypothesized that TIVA would be superior to inhalational anesthesia with respect to patient outcomes.

Methods

Trial Design and Oversight

VITAL was a multicenter, pragmatic, open-label randomized clinical trial conducted across 49 UK National Health Service (NHS) hospitals between January 2022 and April 2024. Patient and public research partners contributed at every stage of the VITAL trial, including its design, ongoing management, and oversight. Trial data were collected through the PQIP, a national prospective cohort study, using standardized definitions and electronic case report forms completed by trained clinical teams.[25] Core outcomes, including mortality, patient-reported outcomes, complications, and length of stay, were derived from the PQIP dataset. Data quality is supported through predefined variable definitions, structured data collection, central monitoring processes, and linkage to electronic health records for key outcomes such as mortality and readmissions.[26] Leveraging this existing platform enabled VITAL to use preexisting data flows and follow-up mechanisms, substantially reducing research burden for both patients and local research teams. The embedded design also ensured consistent data quality and improved efficiency in recruitment and follow-up.

A trial steering committee provided independent oversight of the trial. An independent data monitoring committee reviewed all available data alongside anonymized reports of serious adverse events experienced by participants annually.

The trial protocol and all amendments received UK Health Research Authority approval (Integrated Research Application System [IRAS] project ID 297034; Research Ethics Committee reference 21/YH/0162). The protocol has been published previously and is available in Supplement 1.[26] The statistical analysis plan is available in Supplement 2. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

VITAL was embedded within the PQIP, which was already actively recruiting in 168 hospitals in the UK.[25,27] Eligible patients were identified from preoperative assessment clinics and operating theater lists and were approached by trained research staff prior to surgery. Patients were eligible if they were aged 50 years or older and scheduled for elective major noncardiac surgery under general anesthesia. If patients had any known contradiction to either TIVA or inhalational anesthesia or were not expected to survive for 30 days post surgery, they were not eligible for inclusion. Written informed consent was obtained from all participants prior to randomization.

Randomization and Masking

Patients were randomized 1:1 to receive either TIVA or inhalational anesthesia for maintenance of anesthesia on the day of surgery. Randomization was performed on the day of surgery using a computerized minimization algorithm to ensure balance in treatment allocation across surgical specialty (musculoskeletal, intra-abdominal, thoracic, vascular, or other), expected duration of surgery (<2 hours vs ≥2 hours), surgery type (cancer or noncancer), and preoperative Rockwood Clinical Frailty Scale score (well, vulnerable, or frail).[28] Given the nature of the interventions, blinding of clinicians was not feasible; patients were not explicitly informed of allocation.

Interventions and Perioperative Care

Anesthetic technique was defined by the intended primary mode of maintenance (intravenous propofol vs volatile agent) according to local guidelines. No minimum dose thresholds were specified. All other perioperative management, including induction agents, airway management, analgesia strategies, and monitoring, was at the discretion of treating anesthesiologists.

Outcomes

The primary outcome was days alive and at home 30 days after surgery.[29] Days alive and at home at 30 days is a validated composite outcome incorporating mortality, postoperative complications, and health care utilization and has been shown to be strongly associated with adverse events after surgery.[30] It therefore reflects both patient-centered recovery and key dimensions of perioperative safety. Days alive and at home at 30 days are calculated as discrete numbers between 0 and 30, reflecting the total number of days that a patient spends alive and at home within 30 days after surgery.[31] In this definition, *home* reflects any place other than the hospital. If a patient dies within those 30 days, their value is set to 0. Days alive and at home at 30 days were calculated using complete days in the hospital; for example, if a patient was admitted on Monday and discharged that week on Wednesday, it would count as 2 days in the hospital.

Secondary outcomes were (1) days alive and at home at 90 days; (2) 30-day, 90-day, and 6-month mortality; (3) the Quality of Recovery-15 (QoR-15)[32] score at day 3 after surgery; and (4) patient satisfaction with anesthesia (Bauer Patient Satisfaction Questionnaire)[33] at day 1 after surgery. Adverse and serious adverse events were collected until day 30. Other safety outcomes included delirium (measured by the 4 As Test [4AT][34] at day 3), unintentional awareness under anesthesia (modified Brice Questionnaire)[35] at day 3 and day 30 after surgery, and major postoperative complications (Clavien-Dindo grade ≥II)[36] within 30 days after surgery. Any reports of potential unintentional awareness were followed up and assessed by site teams to determine whether it was true awareness and were managed in line with local protocols. Definitions of trial outcomes are provided in eTable 1 in Supplement 3.

Data on intraoperative management, drugs administered, and analgesic techniques were collected for all patients.

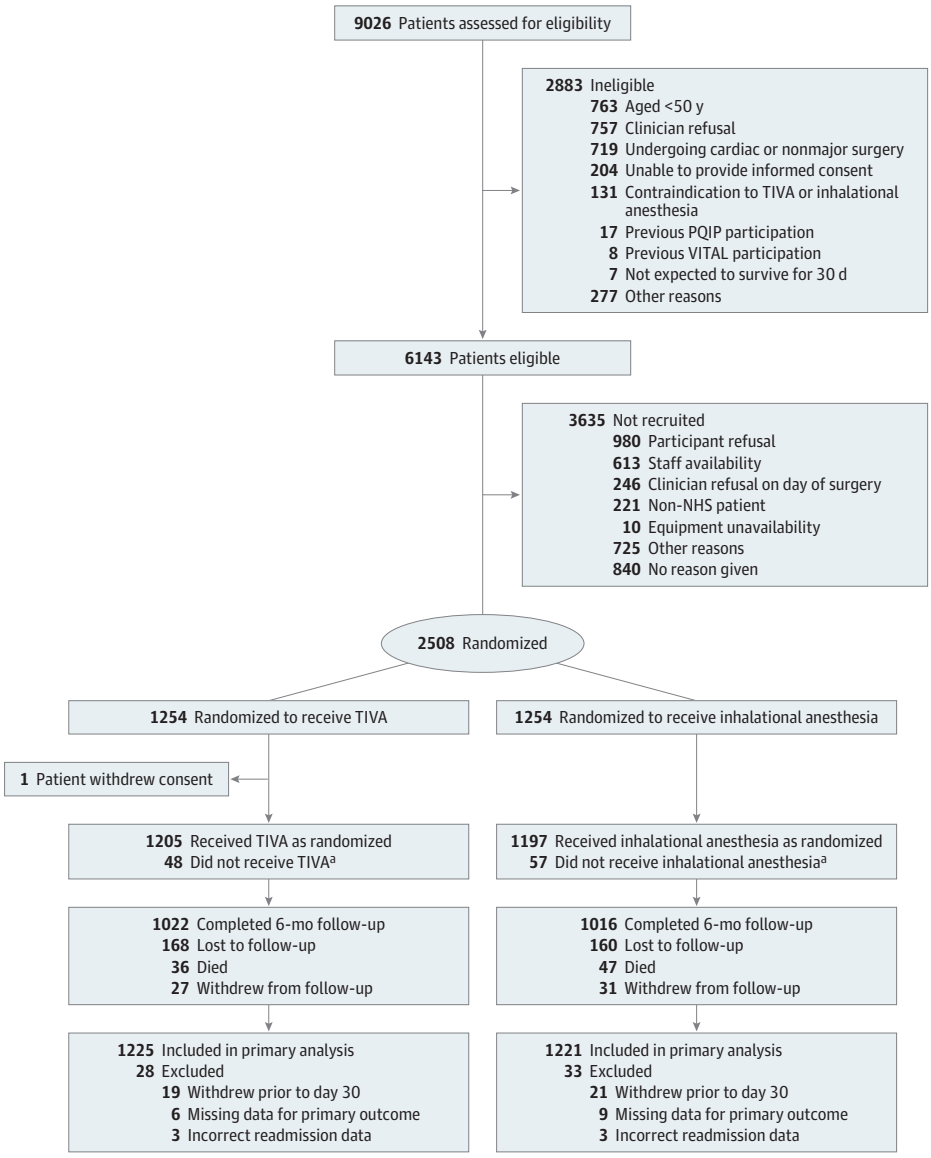
Sample Size

We estimated a mean number of days alive and at home at 30 days of 25 (SD, 7.5) days based on a conservative estimate of previous studies with similar cohorts of patients undergoing major surgery.[29,30] Consequently, 2500 patients were required to enable detection of a 1-day difference in days alive and at home at 30 days between randomized groups, with $\alpha = .05$ 2-sided significance and 90% power, allowing for 5% loss to follow-up. Applying the VITAL trial inclusion and exclusion criteria to pilot NHS data, the mean days alive and at home at 30 days was 72.9 (SD, 21.3) days and the 90-day mortality rate was 3.8%. This sample size also allowed detection of a 3-day difference in days alive and at home at 90 days with 90% power, or a 4-day difference with greater than 95% power. For a safety noninferiority analysis of 90-day mortality, assuming there is truly no difference between modes of anesthesia (3.8% mortality), a 2500-patient sample would provide 80% power for a 1-sided 95% confidence interval to exclude a 1.9% increase in mortality due to TIVA (a relative risk of 1.5). A 1-sided 97.5% confidence interval would exclude an increase due to TIVA of 2.2% (a relative risk of 1.6).

Statistical Analysis

Due to the primary outcome, days alive and at home at 30 days, being overdispersed and zero-inflated, the primary analysis was performed using a zero-inflated negative binomial regression model and adjusted for by stratification variables. All patients with available data were included in the intention-to-treat analysis. The secondary outcome of days alive and at home at 90 days was analyzed using a negative binomial model, the continuous secondary outcomes were modeled using linear regression, and the categorical outcomes were modeled using logistic regression. All secondary outcome analyses were adjusted for stratification variables, reported using point estimates and 95% confidence intervals, and no adjustments

Figure. Flow Diagram of Participants in the VITAL Study



NHS indicates National Health Service; PQIP, Perioperative Quality Improvement Programme; TIVA, total intravenous anesthesia; and VITAL, Volatile vs Total Intravenous Anesthesia for Major Non-Cardiac Surgery.

[a]See eTable 3 in Supplement 3 for reasons.

were made for multiple comparisons. A per-protocol analysis was also performed for the primary outcome including only patients who received their allocated treatment, using the same modeling and adjustments as the primary analysis. Data completeness was high; therefore, no sensitivity analysis of missing data was required.

Subgroup analyses investigated subgroups of interest as defined using the stratification variables. An additional subgroup of interest was the proportion of TIVA used in hospitals prior to involvement in the VITAL trial. Analyses were carried out using Stata software, version 18.0 (StataCorp).

Results

Across 49 hospitals, 9026 patients were screened and 6143 were eligible. Between January 12, 2022, and April 10, 2024, 2508 patients were randomized, with 1254 in each intervention group (**Figure**). After randomization, 1 patient withdrew consent and was completely removed from the trial; no data are available for this patient. Pretrial use of TIVA varied across participating sites, with 27 sites (55%) predominantly using inhalational anesthesia and 21 (43%) favoring TIVA (eTable 20 in Supplement 3). The mean age of participants was 67 (SD, 8.9) years, with randomized groups balanced across patient characteristics. Cancer was the most common indication for surgery (75.4%), the majority of surgeries were intra-abdominal (72.1%), and most surgeries were expected to last longer than 2 hours (98.1%) (**Table 1**).

Adherence to randomized interventions was high (95.8% [2402/2507]) and balanced across groups (**Table 2**; eTable 3 in Supplement 3). In most surgeries (78.3%), additional regional analgesic technique was also used, with the

most common technique being subarachnoid block (50.3% [987/1962]) (eTable 5 in Supplement 3).

In the primary intention-to-treat analysis, 1221 (97.4%) of 1254 inhalational anesthesia group patients and 1225 (97.8%) of 1253 TIVA group patients had calculable data for days alive and at home at 30 days. There was no difference between the 2 groups in the number of days alive and at home at 30 days (mean, 22.5 days vs 22.4 days for TIVA vs inhalational anesthesia, respectively; incidence rate ratio, 1.00; 95% CI, 0.99-1.02; adjusted P = .68) (**Table 3**). As anticipated, the distribution of days alive and at home at 30 days was skewed, with 86 patients (3.5%) scoring zero: 72 patients (2.9%) spent all 30 days in the hospital and 14 (0.6%) died within 30 days (eTables 6 and 7 and eFigure 1 in Supplement 3). A per-protocol analysis including only patients who received their allocated trial drug showed similar results (incidence rate ratio, 1.00; 95% CI, 0.99-1.02; P = .54) (eTables 8-10 in Supplement 3).

No significant differences were detected between randomized groups in days alive and at home at 90 days; mortality rates at 30 days, 90 days, or 6 months; or QoR-15 scores at day 3 (Table 3). Exploratory analyses of the Bauer Patient Satisfaction Questionnaire at day 1 suggested modest differences in early postoperative symptoms, with lower reported rates of thirst (74% vs 78%), hoarseness (48% vs 54%), and nausea and vomiting (27% vs 36%) in the TIVA group compared with the inhalational anesthesia group (Table 3).

A total of 312 participants (12.4%) developed a postoperative complication (Clavien-Dindo grade ≥II) within 30 days after surgery; 158 in the inhalational anesthesia group and 154 in the TIVA group (Table 3). No differences were found in rates of prospectively captured complications (cardiac events, acute kidney injury, infectious complications, postoperative pulmonary complications, and stroke). The 14 additional postoperative complication events reported were incidences of bleeding, ileus, bowel perforation, and ischemic bowel (10 events in the inhalational anesthesia group and 4 events in the TIVA group). The proportion of patients with delirium detected by the 4AT on postoperative day 3 was similar between groups, with most patients (87.6%) having no evidence of delirium. There were 2 cases of certain or probable unintentional awareness under anesthesia, both in the TIVA group (eTables 12-14 in Supplement 3). There were 14 additional serious adverse events by day 30 (eTable 17 in Supplement 3), 10 in the inhalational anesthesia group and 4 in the TIVA group.

There were no apparent differences in any subgroup analyses of the primary and secondary outcomes (eFigure 4 in Supplement 3).

Table 1. Baseline Participant Characteristics

Characteristics	No. (%)	
	Total intravenous anesthesia (n = 1253)	Inhalational anesthesia (n = 1254)
Age at randomization, y	n = 1253	n = 1253
50 to <60	295 (24)	305 (24)
60 to <70	458 (37)	440 (35)
70 to <80	398 (32)	420 (34)
≥80	102 (8)	88 (7)
Sex	n = 1243	n = 1251
Female	568 (46)	546 (44)
Male	675 (54)	705 (56)
Ethnic group[a]	n = 1216	n = 1221
Arab	1 (0.1)	1 (0.1)
Asian/Asian British	60 (5)	51 (4)
Black/African/Caribbean/Black British	46 (4)	44 (4)
White British	1045 (86)	1075 (88)
Other White background	47 (4)	36 (3)
Other ethnic group	10 (1)	7 (1)
Multiple ethnic groups	7 (1)	7 (1)
Surgical procedure details		
Surgical specialty[b]		
Intra-abdominal	903 (72)	904 (72)
Thoracic	111 (9)	110 (9)
Musculoskeletal	68 (5)	70 (6)
Vascular	27 (2)	28 (2)
Other	144 (11)	142 (11)
Expected duration of surgery ≥2 h[b]	1229 (98)	1231 (98)
Cancer surgery[b]	943 (75)	947 (76)
Mode of procedure[c]	n = 1240	n = 1249
Open	560 (45)	539 (43)
Minimally invasive	542 (44)	553 (44)
Robotic	254 (20)	266 (21)
Participant health status		
Preoperative frailty (Rockwood Clinical Frailty Scale score)[b,d]		
Well (1-3)	1006 (80)	1010 (81)
Vulnerable (4-6)	201 (16)	198 (16)
Frail (7-9)	46 (4)	46 (4)
EQ-5D utility score, mean (SD)[e]	0.76 (0.24) [n = 1207]	0.76 (0.25) [n = 1212]

[a] Ethnicity was self-reported; full options are listed in eTable 2 in Supplement 3. "Other" was a category participants could choose from.

[b] Stratification variables at randomization.

[c] Multiple responses allowed. Minimally invasive includes laparoscopic and thoracoscopic procedures.

[d] The Rockwood Clinical Frailty Scale score ranges from 1 to 9, with higher scores indicating worse clinical frailty.

[e] The EuroQol 5-Dimension (EQ-5D) utility score ranges from less than 0 to 1, with higher scores indicating better quality of life.

Discussion

In this large, pragmatic, multicenter randomized clinical trial, no significant difference was found between TIVA and volatile-based inhalational anesthesia in the primary outcome of days alive and at home at 30 days following major noncardiac surgery in patients aged 50 years or older. Secondary outcomes (days alive and at home at 90 days; mortality at 30 days, 90 days, and 6 months; quality of recovery; and incidence of postoperative complications) were also similar between the 2 groups.

Table 2. Intraoperative Management and Postsurgery Destination

Parameters	No. (%)	
	Total intravenous anesthesia (n = 1253)	Inhalational anesthesia (n = 1254)
Adhered to randomized intervention[a]	1205 (96.2)	1197 (95.5)
Maintenance agents administered[b]		
Propofol infusion	1207 (96.3)	38 (3.0)
Opioid infusion[c,d]	1048 (83.6)	562 (44.8)
Inhalational anesthesia[e]	27 (2.2)	1200 (95.7)
Nitrous oxide[c]	20 (1.6)	35 (2.8)
Dexmedetomidine infusion[c]	10 (0.8)	12 (1.0)
No maintenance anesthetics reported	21 (1.7)	17 (1.4)
Induction agents administered		
Propofol	1196 (95)	1182 (94.3)
Sevoflurane	31 (2.5)	279 (22.3)
Other intravenous agents[f]	11 (0.9)	15 (1.2)
Other inhalational agents[g]	4 (0.3)	3 (0.2)
No induction agents reported	18 (1.4)	12 (1.0)
Intraoperative management		
Muscle relaxant given	1172 (93.5)	1189 (94.8)
Depth of anesthesia monitoring used	1135 (90.6)	621 (49.5)
Intravenous dexamethasone given	975 (77.8)	976 (77.8)
Regional anesthesia technique used	980 (78.2)	982 (78.3)
Reversal for neuromuscular blockade given	819 (65.4)	823 (65.6)
Timing		
Time between start of anesthesia and start of surgery (knife to skin), median (IQR), min	50 (35-70) [n = 1234]	50 (33-68) [n = 1238]
Total duration of anesthesia, median (IQR), h[h]	4.3 (3.3-5.9) [n = 1235]	4.3 (3.2-6.1) [n = 1237]
Postsurgery destination[i]		
Ward care	1214 (96.9)	1213 (96.7)
Post-anesthetic care unit	106 (8.5)	121 (9.6)
High-dependency unit	370 (29.5)	364 (29.0)
Intensive care unit	62 (4.9)	73 (5.8)

[a] Further details on adherence can be found in eTable 3 in Supplement 3.

[b] Participants could receive infusions of multiple drugs; therefore, total maintenance agents do not equal total participants.

[c] These drugs did not count toward intervention adherence.

[d] Includes infusion of remifentanil or alfentanil.

[e] Includes administration of sevoflurane, isoflurane, desflurane, or other undefined inhalational anesthesia.

[f] Includes ketamine, midazolam, etomidate, and combinations of these agents.

[g] Includes desflurane.

[h] For graphical distribution of duration, see eFigure 5 in Supplement 3. Further details on investigation of expected duration of surgery are in eTable 4 and eFigure 6 in Supplement 3.

[i] Postsurgery destination refers to locations patients were admitted after leaving the recovery area of the operating theater. Patients could spend time in multiple units. The post-anesthetic care unit provides additional monitoring of vital signs with ward care staffing. The high-dependency unit provides invasive monitoring and single organ support with a 1:2 nursing ratio. The intensive care unit provides advanced organ support with a 1:1 nursing ratio. Additional information on discharge destination is in eTable 19 in Supplement 3.

These findings align with evidence from a recent meta-analysis of 317 randomized clinical trials (>51 000 patients), which demonstrated no difference between TIVA and inhalational anesthesia in mortality or major organ-specific morbidity, while reporting advantages of TIVA in patient-centered outcomes such as postoperative nausea and vomiting, early recovery, and emergence delirium.[17] The findings of VITAL reinforce this pattern and suggest that symptomatic benefits of TIVA may be particularly relevant in older or more vulnerable patients.

The findings of VITAL have several important implications for clinical practice. First, they provide strong reassurance that both TIVA and volatile anesthesia can be safely used for major noncardiac surgery in older adults. Given the rapid rise in TIVA use, often ahead of robust evidence, these results fill a long-standing evidence gap and confirm that choosing TIVA does not compromise core safety outcomes such as survival, complication rates, or recovery at home. Second, the improved early postoperative comfort associated with TIVA, including reductions in nausea, vomiting, thirst, and hoarseness, should be incorporated into shared decision-making. These benefits may be particularly meaningful in enhanced recovery pathways and ambulatory surgery and for patients who prioritize immediate postoperative recovery. Third, although unintentional awareness under anesthesia was rare, both cases occurred in the TIVA group, underscoring the continued importance of appropriate depth-of-anesthesia monitoring, especially in patients with altered pharmacokinetics, high-risk procedures, or clinical scenarios requiring rapid sequence induction. Fourth, the equivalence of major outcomes allows anesthesiologists to consider environmental factors, including the carbon footprint of volatile agents, when selecting anesthetic maintenance strategies. Importantly, such considerations can now be weighed without compromising patient safety. Taken together, these findings support that anesthetic choice should be individualized—guided by patient preference, predicted tolerance of postoperative symptoms, clinician expertise, and environmental considerations. In patients undergoing major noncardiac surgery, there was no

Table 3. Outcomes by Intervention Group

Outcomes	Total intravenous anesthesia (n = 1253)	Inhalational anesthesia (n = 1254)	Absolute difference, mean or % (95% CI)	Adjusted estimate (95% CI)[a]	*P* value
Primary outcome					
Days alive and at home at 30 d[b]					
Mean (SD)	22.5 (6.8) [n = 1225]	22.4 (6.6) [n = 1221]	0.01 (−0.52 to 0.54)	IRR: 1.00 (0.99 to 1.02)	.68[c]
Median (IQR)	24 (21-27) [n = 1225]	24 (21-27) [n = 1221]			
Secondary outcomes					
Days alive and at home at 90 d[d]					
Mean (SD)	80.8 (13.1) [n = 1220]	80.2 (14.6) [n = 1217]	0.62 (−0.48 to 1.73)	IRR: 1.01 (0.99 to 1.03)	.42[e]
Median (IQR)	84 (81-87) [n = 1220]	84 (80-87) [n = 1217]			
Deceased at 30 d, No./total (%)	9/1227 (0.7)	5/1227 (0.4)	0.30 (−0.27 to 0.92)	OR: 1.81 (0.60 to 5.42)	.29[f]
Deceased at 90 d, No./total (%)[g]	14/1220 (1.1)	19/1221 (1.6)	0.40 (−1.32 to 0.51)	OR: 0.74 (0.37 to 1.48)	.39[f]
Deceased at 6 mo, No./total (%)[h]	36/1211 (3.0)	47/1213 (3.9)	0.90 (−2.35 to 0.55)	OR: 0.76 (0.49 to 1.18)	.23[f]
QoR-15 score at day 3, mean (SD)[i]	103.8 (23.6) [n = 1097]	103.6 (23.7) [n = 1120]	0.20 (−1.77 to 2.18)	MD: 0.15 (−1.80 to 2.09)	.88[j]
Bauer Patient Satisfaction Questionnaire, response of "yes," No./total (%)[k]					
Thirst	849/1151 (73.8)	896/1146 (78.2)			
Pain at the site or surgery	837/1151 (72.7)	842/1148 (73.3)			
Drowsiness	760/1152 (66.0)	799/1147 (69.7)			
Hoarseness	547/1150 (47.6)	622/1147 (54.2)			
Sore throat	453/1152 (39.3)	490/1147 (42.7)			
Nausea or vomiting	308/1151 (26.8)	414/1148 (36.1)			
Feeling cold	240/1151 (20.9)	227/1147 (19.8)			
Confusion or disorientation	194/1150 (16.9)	218/1147 (19.0)			
Pain at the site of anesthetic injection	146/1149 (12.7)	155/1146 (13.5)			
Shivering	127/1151 (11.0)	134/1146 (11.7)			
Additional outcomes					
Delirium (4AT score at day 3), No. (%)	n = 1080	n = 1068			
No delirium (0)	946 (87.6)	936 (87.6)			
Cognitive impairment, no delirium (1-3)	65 (6.0)	60 (5.6)			
Delirium (≥4)	69 (6.4)	72 (6.7)			

(continued)

Table 3. Outcomes by Intervention Group (continued)

Outcomes	Total intravenous anesthesia (n = 1253)	Inhalational anesthesia (n = 1254)	Absolute difference, mean or % (95% CI)	Adjusted estimate (95% CI)[a]	*P* value
Postoperative complications within 30 d, No./total (%)[l]					
≥1 Complication	154/1253 (12.3)	158/1254 (12.6)			
Infectious complications	118/1220 (9.7)	124/1226 (10.1)			
Postoperative pulmonary complications	39/1220 (3.2)	35/1226 (2.9)			
Cardiac events	17/1220 (1.4)	18/1225 (1.5)			
Acute kidney injury (KDIGO stage 3)	7/1220 (0.6)	8/1225 (0.7)			
Stroke	2/1220 (0.2)	0			

Abbreviations: 4AT, 4 As Test; IRR, incidence rate ratio; MD, mean difference; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio.

[a] Adjusted for surgical specialty (musculoskeletal, intra-abdominal, thoracic, vascular, or other), expected duration of surgery (<2 hours vs ≥2 hours), type of surgery (cancer or noncancer), and Rockwood Clinical Frailty Scale score (well, vulnerable, or frail).

[b] Days alive and at home at 30 days is a continuous measure from 0 to 30 that reflects the total number of days that a patient spent alive and at home within 30 days after surgery. The minimum clinically important difference is 3 days.

[c] Modeled using a zero-inflated negative binomial model. The IRR provided is from the count equation part of the model. The results of the zero-inflation half of the model are in eTable 7 in Supplement 3. See eTables 6 and 7 in Supplement 3 for detailed model output.

[d] Days alive and at home at 90 days is a continuous measure from 0 to 90 that reflects the total number of days that a patient spent alive and at home within 90 days after surgery.

[e] Modeled using a negative binomial model (used instead of a zero-inflated model due to convergence not being achieved). See eTable 11 in Supplement 3 for information on scores of 0.

[f] Modeled using logistic regression.

[g] Additional results of the noninferiority analysis for 90-day mortality are in eTable 16 in Supplement 3.

[h] Causes of death are in eTable 18 in Supplement 3.

[i] The Quality of Recovery–15 (QoR-15) score, measured at day 3, is a 15-question instrument with scores ranging from 0 to 150, with higher scores indicating better quality of recovery. The minimum clinically important difference is 6.0.

[j] Modeled using linear regression (or appropriate regression after assessing distribution).

[k] "Yes" categories include "mild," "moderate," and "severe." For visual representation of full responses, see eFigure 2 in Supplement 3. For responses to the satisfaction section of the Bauer Patient Satisfaction Questionnaire, see eTable 15 and eFigure 3 in Supplement 3.

[l] Postoperative complications include prospectively captured complications (cardiac event, acute kidney injury, infectious complications, pulmonary complications, and stroke) and individually reported complications (bleeding, ileus, bowel perforation, and ischemic bowel).

meaningful difference between TIVA and inhalational anesthesia in patient-centered recovery at 30 days or longer-term outcomes, although differences in early postoperative recovery were observed; results from exploratory analyses should be interpreted with caution.

VITAL used days alive and at home at 30 days as a validated, patient-centered primary outcome that integrates survival, hospital stay, and recovery at home. This measure was chosen by the study's patient partners as the outcome that best reflects real-world recovery and is particularly relevant for older, frail patients, who represent a growing proportion of the surgical population. Importantly, participants in VITAL were broadly representative of the contemporary UK major surgical population captured within PQIP, including age distribution, frailty profile, and surgical case mix, enhancing generalizability. High protocol adherence and balanced baseline characteristics strengthen the internal validity of the trial.

Although exploratory analyses showed that TIVA improved patient comfort in the immediate postoperative period, these benefits did not translate into differences in complication rates or broader recovery. Postoperative complication rates vary depending on definitions but are generally estimated between 7% and 17%.[37-39] In the VITAL trial, 12.4% of patients experienced postoperative complications, which is consistent with the lower rates typically observed in elective surgical cohorts. The trial was not powered to detect differences in individual postoperative complications, and these findings should therefore be interpreted cautiously. Delivering anesthesia safely remains critical, as postoperative complications carry significant consequences for both patients and health care systems.[40] The incidence of unintentional awareness under anesthesia was low, but the small number of events limits definitive conclusions. This study's findings are consistent with other studies in cardiac and oncology surgery. The MYRIAD study (n = 5400)[10] found no difference in 1-year mortality between volatile anesthesia and TIVA, and a contemporary multicenter randomized clinical trial in China (modified intention to treat; n = 3083)[11] showed no difference in major complications or 30-day mortality. In oncological populations, large randomized clinical trials—including a major cancer surgery trial in older adults (modified intention to treat; n = 1195)[41] and the CAN Study (n = 1764)[42]—have not demonstrated a difference in long-term survival outcomes between anesthetic techniques. However, other analyses, including pooled and per-protocol datasets, have reported signals suggesting potential differences in mortality with propofol-based anesthesia, although these findings are inconsistent and not observed across all studies. Taken together, the current evidence does not support a definitive effect of anesthetic maintenance technique on long-term oncological outcomes.

Environmental considerations have increasingly influenced anesthetic choice as magnitude of environmental impact remains debated; the clinical equivalence demonstrated in VITAL means environmental factors can now be incorporated into practice and policy decisions with greater confidence. The study also directly addresses the long-standing lack of high-quality evidence in the large noncardiac surgical population, an area in which TIVA use has expanded most rapidly.

Limitations

This study has limitations. First, given the nature of the intervention and the pragmatic context of the study, blinding was not feasible. The unblinded design may have influenced subjective patient-reported outcomes, although patients were not informed of their allocation and there is no evidence to suggest they held any preference or bias toward either technique. Objective outcomes were not susceptible to this limitation, and the study design reflects real-world clinical practice. Second, the definition of *home* as any location other than an acute hospital introduces important limitations. The intent of this definition is to capture the time patients spend outside acute institutional care, regardless of their baseline residential situation. However, it is possible that variations in local rehabilitation pathways may influence days alive and at home. Third, while the trial included a large proportion of patients undergoing cancer surgery, it did not investigate longer-term oncological outcomes such as cancer recurrence or disease-free survival.

Fourth, the low incidence of unintentional awareness events limits the ability to draw firm conclusions about the comparative safety of anesthetic techniques. Planned individual patient data meta-analysis with the THRIVE study (Trajectories of Recovery After Intravenous Propofol vs Inhaled Volatile Anesthesia; NCT05991453) may provide more definitive insights. Fifth, the VITAL trial was conducted within the UK NHS, and findings may not be generalizable to health care systems with different perioperative practices or patient populations. Sixth, VITAL recruited only patients undergoing elective surgery, with the majority of patients deemed as well (80.5% with a Rockwood Clinical Frailty Scale score of 1-3) and undergoing intra-abdominal surgery (72.1%). Generalizability to emergency surgery or non-UK settings is uncertain, and further research is needed in frail, cognitively impaired, and urgent surgery populations. Seventh, the use of regional anesthesia was high in both groups (78.2% in the TIVA group and 78.3% in the inhalational anesthesia group). While this reflects contemporary practice within the UK, patterns of regional anesthesia use may differ across other health care systems, which should be considered when interpreting the generalizability of these findings. Eighth, further investigation into the cost-effectiveness of TIVA, particularly in relation to recovery pathways and resource utilization, is warranted.

Conclusions

This study's findings show no evidence of a meaningful difference between TIVA and inhalational anesthesia in patient-centered recovery or major clinical outcomes, including days alive and at home at 30 days and mortality. Although exploratory analyses suggested improved early postoperative comfort with TIVA, these findings did not translate into differences in complication rates or longer-term recovery.

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Author Affiliations: Department of Anesthesia, Perioperative Medicine and Critical Care, Royal Marsden NHS Foundation Trust, London, United Kingdom (Jhanji, Rao Baikady); Division of Radiotherapy and Imaging, Institute of Cancer Research, London, United Kingdom (Jhanji); Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom (Booth, Hiller, Braun, Dunn, Eggleston, Jacques, Jefford, Kaur, Yeung); Cardiff and Vale University Health Board, Cardiff, United Kingdom (Fenton-May); Centre for Health Economics at Warwick, University of Warwick, Coventry, United Kingdom (Frempong, Kandiyali, Mason); University College London, London, United Kingdom (Gilchrist, Moonesinghe, Vindrola-Padros); Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom (Pearse); Royal London Hospital, London, United Kingdom (Reynolds); University of Glasgow, Glasgow, United Kingdom (Shelley); Royal Victoria Infirmary, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle Upon Tyne, United Kingdom (Sinclair); Somerset NHS Foundation Trust, Somerset, United Kingdom (Teare); University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom (Yeung).

Author Contributions: Ms Booth and Drs Hiller and Yeung had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jhanji, Hiller, Braun, Dunn, Eggleston, Jefford, Kaur, Mason, Moonesinghe, Pearse, Shelley, Vindrola-Padros, Yeung.
Acquisition, analysis, or interpretation of data: Jhanji, Booth, Hiller, Dunn, Eggleston, Fenton-May, Frempong, Gilchrist, Jacques, Kandiyali, Kaur, Mason, Moonesinghe, Pearse, Rao Baikady, Reynolds, Shelley, Sinclair, Teare, Vindrola-Padros, Yeung.
Drafting of the manuscript: Jhanji, Booth, Hiller, Eggleston, Frempong, Gilchrist, Kaur, Pearse, Shelley, Vindrola-Padros, Yeung.
Critical review of the manuscript for important intellectual content: Jhanji, Braun, Dunn, Fenton-May, Jacques, Jefford, Kandiyali, Mason, Moonesinghe, Pearse, Rao Baikady, Reynolds, Shelley, Sinclair, Teare, Vindrola-Padros, Yeung.
Statistical analysis: Booth, Hiller, Dunn, Yeung.
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Supervision: Jhanji, Hiller, Dunn, Eggleston, Kandiyali, Kaur, Mason, Moonesinghe, Pearse, Rao Baikady, Vindrola-Padros.

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