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Clinical Investigation

CLINICAL INVESTIGATION

Utility of the SmartPilot® View advisory screen to improve anaesthetic drug titration and postoperative outcomes in clinical practice: a two-centre prospective observational trial

Merel H. Kuizenga[1,*], Hugo E. M. Vereecke[1,2], Anthony R. Absalom[1], Christian H. Bucher[3,†], Laura N. Hannivoort[1], Johannes P. van den Berg[1], Livia Schmalz[3], Michel M. R. F. Struys[1] and Martin Luginbühl[3]

[1]Department of Anaesthesiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [2]Department of Anaesthesia and Reanimation, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium and [3]Department of Anaesthesia, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

*Corresponding author. E-mail: m.h.kuizenga@umcg.nl
†Present address: Julius Wolff Institut, Charité—Universitätsmedizin Berlin, Berlin, Germany

Abstract

Background: The advisory system SmartPilot® View (Drägerwerk AG, Lübeck, Germany) provides real-time, demographically adjusted pharmacodynamic information throughout anaesthesia, including time course of effect-site concentrations of administered drugs and a measure of potency of the combined drug effect termed the '"Noxious Stimulation Response Index' (NSRI). This dual-centre, prospective, observational study assesses whether the availability of SmartPilot® View alters the behaviour of anaesthetic drug titration of anaesthetists and improves the Anaesthesia Quality Score (AQS; percentage of time spent with MAP 60–80 mm Hg and Bispectral Index [BIS] 40–60 [blinded]).
Methods: We recruited 493 patients scheduled for elective surgery in two university centres. A control group (CONTROL; n=170) was enrolled to observe drug titration in current practice. Thereafter, an intervention group was enrolled, for which SmartPilot® View was made available to optimise drug titration (SPV; n=188). The AQS, haemodynamic and hypnotic effects, recovery times, pain scores, and other parameters were compared between groups.
Results: There were 358 patients eligible for analysis. Anaesthesia quality score was similar between CONTROL and SPV (median AQS [Q1–Q3]) 25.3% [7.4–41.5%] and 22.2% [8.0–44.4%], respectively; P=0.898). Compared with CONTROL, SPV patients had less severe hypotension and hypertension, less BIS <40, faster tracheal extubation, and lower early postoperative pain scores.
Conclusions: Adding SmartPilot® View information did not affect average drug titration behaviour. However, small improvements in control of MAP and BIS and early recovery suggest improved titration for some patients without increasing the risk of overdosing or underdosing.
Clinical trial registration. NCT01467167.

Keywords: drug interaction; drug titration; general anaesthesia; intraoperative monitoring; pharmacodynamics

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Editor's key points

- Computer-assisted drug dosing has the potential to improve safe and effective personalised delivery of anaesthesia.
- A software program and display that provide real-time information on the time course of individualised effect-site concentrations of propofol, volatile anaesthetics, opioids, and neuromuscular blocking drugs were assessed in a two-centre observational study.
- A composite primary endpoint of quality of anaesthesia was not improved by SmartPilot® View, but secondary endpoints in the monitor group included reductions in hypotension, hypertension, low Bispectral Index values, early postoperative pain scores, and faster tracheal extubation.
- Whether these small improvements in healthy patients will have more marked effects in higher-risk patients requires further study.

Optimal quality of anaesthesia during surgery is characterised by homeostasis in vital organ systems in combination with adequate depth of anaesthesia. Variability in the management of arterial BP and depth of anaesthesia, both between anaesthetists and between different anaesthetic techniques prevalent in various centres, could result in suboptimal control and negative outcomes.[1,2] Real-time data advisory displays might improve standardisation of anaesthetic management and optimise drug titration in surgical patients.[3–5] SmartPilot® View (Drägerwerk AG, Lübeck, Germany) (Fig 1) is a software program and display that provides real-time information on the time course of individualised effect-site concentrations of propofol, volatile anaesthetics, opioids, and neuromuscular blockers. The displayed time course of effect-site concentration (Ce) for administered drugs allows the user to estimate expected onset and elimination of clinical effects accurately. Additionally, effect-site concentrations serve as inputs for response surface interaction models[6–9] that calculate combined drug effects in terms of probability of tolerance (absence of motor response) to shake and shout (P_{TOSS}) and laryngoscopy (P_{TOL}). An inverse derivative of P_{TOL}, the Noxious Stimulation Response Index (NSRI), is plotted *vs* time as a measure of potency of the combined anaesthetic drugs. The NSRI scales between 100 and 0, where 100 reflects a minimal and 0 a maximal probability of tolerance of laryngoscopy. The NSRI values of 80, 50, and 20 correspond to P_{TOL} of 0.1, 0.5, and 0.9, respectively.[10] Use of SmartPilot® View might reveal differences in anaesthetic management related to drug titration, both between anaesthetists and between different departments.

The primary purpose of this two-centre, prospective, observational study was to assess whether the availability of information provided by SmartPilot® View changes drug titration behaviour compared with common practice, thereby improving the quality of anaesthesia.

Methods

This prospective, observational study was performed in two university hospital anaesthesia departments (University Hospital Bern, Bern, Switzerland and University Medical Center Groningen, Groningen, The Netherlands). After institutional ethical committee approval (Medisch Ethische Toetsingscommissie 2011.163), clinical trial registration (ClinicalTrials.gov: NCT01467167), and written informed consent in both participating centres, 493 patients with ASA physical status 1–3, 18–90 yr old, and scheduled for elective surgery under general anaesthesia were enrolled in both centres, half of them before and half of them after the introduction of SmartPilot® View. Exclusion criteria included BMI >35 kg m^{-2}, neurological disorders, recent use of psychoactive drugs, alcohol abuse, hepatic disease (Child–Pugh B or higher), contraindications or allergies to the drugs used in the study, combined regional and general anaesthesia, surgery with an expected duration <30 min, and use of cardiopulmonary bypass.

The study was conducted in two consecutive phases. In the first phase, patients were included in the control group (CONTROL), in which anaesthesia was performed using standard monitoring and drug titration practice at the discretion of the attending anaesthetists. Clinical events, drug delivery data, and haemodynamic and electroencephalographic measurements were monitored and recorded in a time-synchronised fashion using data collection software (RUGLOOP II; Demed, Temse, Belgium). After completing enrolment of the control group in both centres, the SmartPilot® View system was introduced and patients were included in the intervention group (SPV). Anaesthesia in the SPV group was conducted using standard monitoring, comparable with CONTROL, but in addition, SmartPilot® View (version 2.0) was made available throughout each case (Fig 1). Drug delivery data and haemodynamic and electroencephalographic measurements were recorded by SmartPilot® View in time-synchronised fashion, and data were exported on a USB memory device at the end of surgery. Clinical events during SPV cases were recorded with a time-synchronised event logger, developed by CHB, using Visual Basic® for Applications within Microsoft® Excel (Microsoft, Redmond, WA, USA). Throughout the SPV recruitment phase, consecutively involved research fellows and clinical staff were trained in the use and interpretation of the SmartPilot® View system.

During the CONTROL and SPV phases, anaesthetic drug administration was at the discretion of the anaesthetist, but in SPV, the anaesthetist was advised to integrate the population-based pharmacodynamic information provided by SmartPilot® View into their titration decisions, in an attempt to avoid excessive drug dosing during maintenance as much as possible. The target range of P_{TOL} or NSRI was left at the discretion of the anaesthetist. A research fellow attended each case for event registration and assistance. Enrolment was completed in two consecutive recruitment phases to minimise the risk for learning bias evoked by the use of SmartPilot® View, which may affect drug titration habits in randomly recruited CONTROL patients.

Anaesthetic management

Premedication and monitoring

Premedication was administered at the discretion of the anaesthetist and according to current departmental practice. Standard patient monitoring (Philips IntelliVue MX800; Philips Healthcare, Eindhoven, the Netherlands) included electrocardiography, pulse oximetry, and intermittent noninvasive BP measurements. The electroencephalogram was acquired and analysed using a Bispectral Index™ (BIS) module (Medtronic, Dublin, Ireland), for the Philips monitor, and a BIS™ Quatro

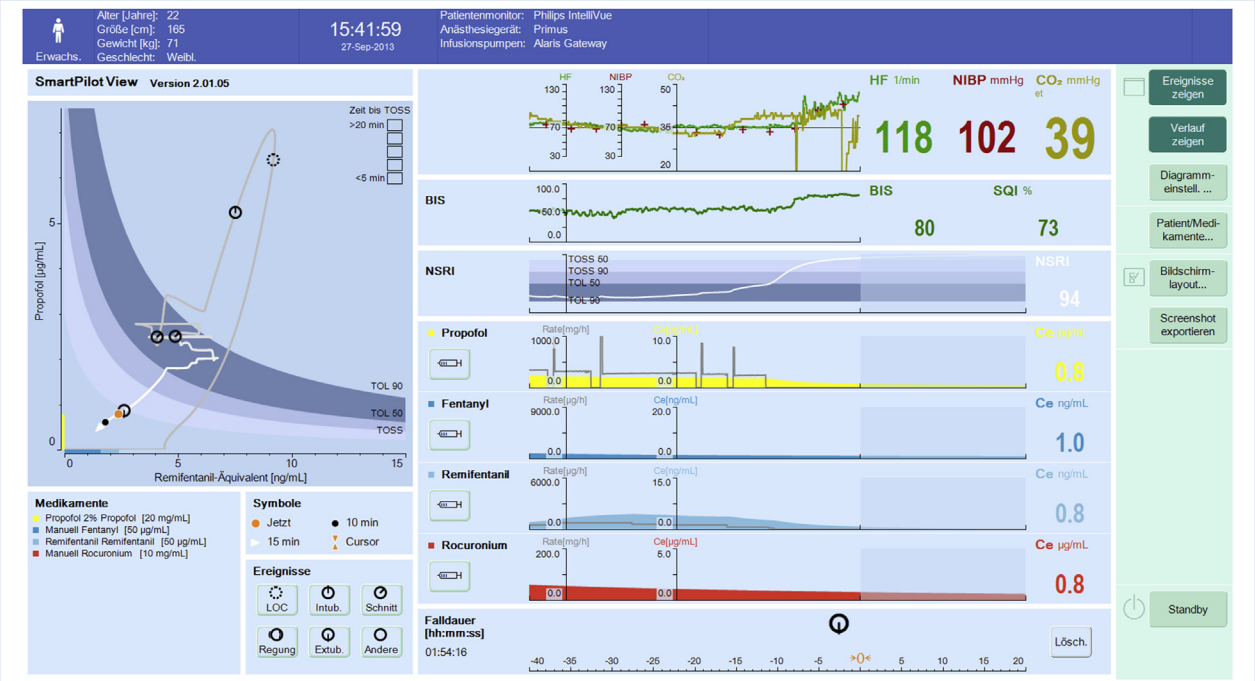

Fig 1. SmartPilot® View screenshot. Image (software version 2) from a 22-yr-old patient undergoing laparoscopy for endometriosis at Bern University Hospital. Propofol (target-controlled infusion), remifentanil, fentanyl, and rocuronium were used. The left side shows the P_{TOL} trajectory of the complete case in relation to isoboles of equipotent effect with event marks for loss of consciousness, tracheal intubation, incision, closure, and tracheal extubation. The x-axis shows total opioid dose in remifentanil equivalents, with the fentanyl component in dark and the remifentanil component in light blue. The y-axis shows the effect-site propofol concentration. Tolerance of shake and shout (TOSS) 90% and 50% and tolerance of laryngoscopy (TOL) 90% and 50% are the upper and lower margins of the light and dark grey zones, respectively. A prediction of the trajectory over the following 15 min based on the current dosing rates is displayed (orange circle, present; black circle, x+10 min; white circle, x+15 min). The upper right part shows HR, MAP, end-tidal CO_2, and Bispectral Index with Signal Quality Index. The lower right part shows the time course of the effect-site concentrations for each administered drug (calculated from either manually or automatically recorded dosing history), including a prediction of the next 20 min. The Noxious Stimulus Response Index (NSRI) (right middle part) is an inverse derivative from P_{TOL}, plotted *vs* time to serve as a measure of changing potency attributable to shifts in anaesthetic drug combinations. Maintaining a constant NSRI despite changing drug concentrations ensures equipotency for P_{TOL}.

sensor (Medtronic). The smoothing time interval was set to 15 s. In both study phases, anaesthesia teams were blinded to BIS. Anti-emetic prophylaxis was given according to department standards.

Induction and maintenance of anaesthesia

In the CONTROL and in the SPV phase, anaesthesia was induced with propofol, either as an i.v. bolus or a fixed-rate or target-controlled infusion using an Alaris™ PK infusion pump (BD Medical, Franklin Lakes, NJ, USA). Opioids were administered at the discretion of the anaesthetist. Neuromuscular block was used if required. The study protocol allowed the use of both i.v. (propofol) or volatile agents for maintenance of anaesthesia.

In both phases, the anaesthetist was asked to dose drugs to maintain haemodynamic stability, avoid awareness and recall, and achieve a rapid emergence with optimal early postoperative analgesia. In case of hypotension (MAP <60 mm Hg), a bolus of crystalloids or treatment with norepinephrine, phenylephrine, or ephedrine was administered whenever deemed necessary by the attending anaesthetist.

In the SPV phase, the pharmacodynamic information provided by SmartPilot® View, including P_{TOL} and NSRI, was available to assist in titration decisions; no mandatory thresholds for NSRI were defined. Otherwise, anaesthetic management was identical to the CONTROL phase.

Emergence

The anaesthetist was asked to ensure emergence from anaesthesia as soon as possible after skin closure. If needed, neuromuscular blocking drugs were antagonised. During emergence, the patients were instructed to open their eyes every 30 s. Time to extubation and Aldrete score 5 min after extubation were recorded. At the end of the procedure, the anaesthetist, trainee anaesthetist, or anaesthetic nurse registered the NASA Task Load Index questionnaire (Supplementary Fig. S1), which rates perceived workload for managing anaesthesia.

Postoperative management

Nurses in the PACU recorded the Numerical Rating Scale (NRS) for pain (from 0, indicating no pain, to 10, indicating very

severe pain); modified Aldrete score (Supplementary Table S1); presence of nausea or vomiting; and all analgesic and anti-emetic drugs given at arrival in the PACU and at 30, 60, 90, 120, 150, and 180 min after arrival. Subjects were transferred to the ward according to PACU criteria.

Outcome measures

Inspired by the work of Gurman,[11] we used as primary outcome the Anaesthesia Quality Score (AQS), a composite metric for quality of anaesthesia incorporating MAP and BIS. The AQS was calculated as follows: MAP was recorded every 5 min during maintenance of anaesthesia (from incision to skin closure). For invasive BP measurements, MAP was recorded every 10 s and averaged for each 5 min epoch. The desired target range for MAP was 60–80 mm Hg. BIS was recorded every 5 s, and median filtered BIS values for each 60-s epoch were used for analysis to handle distortions and artifacts. The target range for BIS was 40–60. The MAP and BIS values were paired for each 5 min during maintenance. A single pair of a corresponding MAP and BIS was defined as one anaesthesia quality data point. The number of data points within the target range of both MAP and BIS divided by the total number of data points yielded the AQS (in %). AQS is a measure for simultaneous haemodynamic stability and adequate hypnotic drug effects over time during maintenance of anaesthesia.

Secondary intraoperative outcomes during maintenance were:

(i) Percentage of time for MAP or BIS within, above, or below the desired targets
(ii) Area under the curve (AUC) for deviations above or below threshold of MAP (in mm Hg · min) and BIS (in BIS units · s)
(iii) Median NSRI values calculated *post hoc* in CONTROL and derived real time in SPV
(iv) Mean effect-site concentrations for each administered drug
(v) Effect-site concentrations of hypnotic drugs and opioids at 10 and 5 min before the end of surgery, at the end of skin closure, and at tracheal extubation
(vi) Recovery time between end of surgery and tracheal extubation (in min)

Secondary postoperative outcomes were:

(i) Number of non-opioid analgesics administered intraoperatively and in PACU
(ii) Time between tracheal extubation and first opioid administration in the PACU (in min)
(iii) Pain scores (NRS)
(iv) Modified Aldrete scores (Supplementary Table S1)
(v) Number of events and incidence of nausea or vomiting and anti-emetic drugs used
(vi) NASA Task Load Index questionnaire (Supplementary Fig. S1)

Interdepartmental differences were also considered as secondary outcomes.

Doses of different opioids used in CONTROL were compared by converting the effect-site concentrations of fentanyl[12,13] and sufentanil[14,15] *post hoc* to remifentanil equivalent effect-site concentration (Ce_{REMIeq}) using identical conversion factors as applied in SmartPilot® View software.[12–17]

Statistical analysis

Sample size was calculated based on a pilot study that included 40 patients (unpublished data) who were anaesthetised with propofol and alfentanil during orthopaedic surgery with a protocolised anaesthetic regimen. Based on the intraoperative AQS of 24 (standard deviation [SD] 26), we postulated that with an expected SD of 30, power of 0.8, and α <0.05, 143 subjects per group would suffice to detect a difference in mean AQS of 10 or more. With a planned recruitment of 400 patients, the power would be 0.914 (for *t*-test).

Statistical significance was set at $P<0.05$. Data from both centres were analysed in a pooled approach to detect differences between CONTROL and SPV. Interdepartmental differences were also assessed. Categorical variables are expressed as incidence (%) and continuous data as mean (SD) or median [25th–75th percentiles]. Categorical variables were compared with χ^2 and numerical variables with (independent) Student's *t*-test or non-parametric test, as appropriate. Analyses and graphs of AQS, MAP, BIS, NSRI, and drug concentrations were plotted in SigmaPlot version 14 (Systat Software, Inc., San Jose, CA, USA). Analyses on recovery and postoperative outcomes were performed in SPSS version 23 (IBM SPSS Statistics, Chicago, IL, USA).

Results

Data were collected from 2011 to 2017, with analysis and paper preparation from 2018 to 2021 (Supplementary Fig. S2). Of 493 patients screened for eligibility, 387 could be analysed: 189 and 198 in the CONTROL and SPV groups, respectively (Fig 2). *Post hoc*, it was evident that volatile agents were used in only 29 subjects in Groningen and none in Bern, leading to an imbalanced data set for comparing NSRI and other endpoints between centres. These subjects were therefore excluded from analysis. In total, 170 and 188 subjects were analysed in the CONTROL and SPV groups, respectively.

Baseline characteristics

Subject characteristics and baseline haemodynamic variables were comparable between the CONTROL and SPV groups, except for sex ($P=0.004$), ASA physical status ($P=0.011$), and type of surgery ($P=0.008$) (Table 1). These differences were small and of minimal clinical impact, so no adaptations in statistical methods were deemed necessary. We observed limited variability in age, height, weight, and BMI. Most procedures involved gynaecological surgery, and therefore, most patients were female.

Primary outcome

The AQS was 25.3 [7.4–41.5]% in the CONTROL and 22.2 [8.0–44.4]% SPV groups, without statistical significance ($P=0.898$; Table 2).

Secondary outcomes

Fig. 3 shows the raw data for MAP (Panel A) and BIS (Panel C) for both groups. Panel B and D respectively show the associated mean and 95% confidence interval (CI) for MAP and BIS in one-minute intervals. The blue and red colours are data from respectively the CONTROL and SPV group.

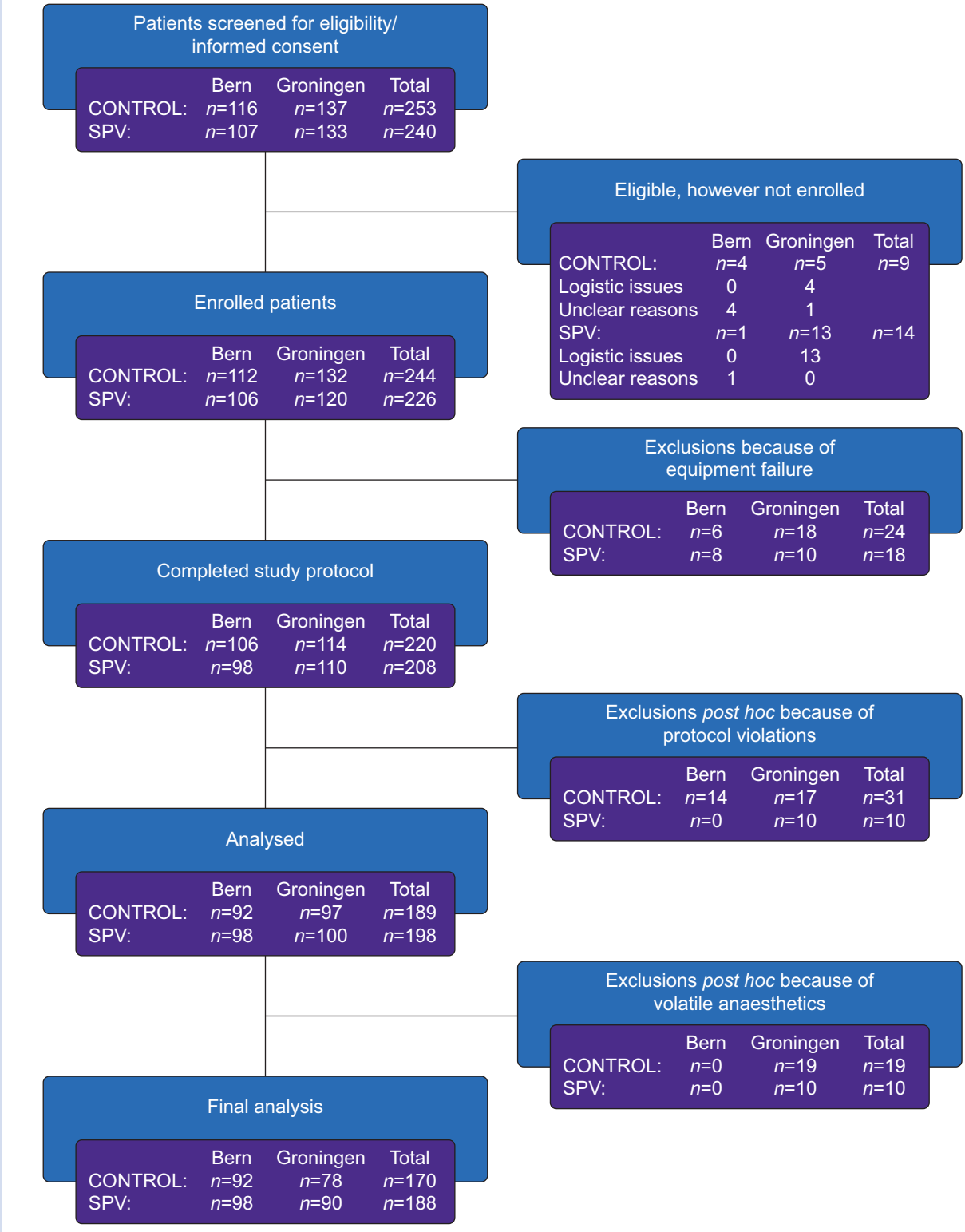

Fig 2. Modified Consolidated Standards of Reporting Trials diagram of the study conduct.

Table 1 Subject characteristics and preoperative baseline measurements. Baseline characteristics for the control (CONTROL) and SmartPilot® View (SPV) groups in Bern and Groningen. Data presented as mean (standard deviation) or number (%). DBP, diastolic BP; SBP, systolic BP. *P*-value compares pooled data between the CONTROL and SPV groups using Mann–Whitney *U*-test for age, height, weight, BMI, systolic BP, diastolic BP, MAP, and HR, and a χ^2 test for sex and ASA physical status. $P<0.05$ is considered statistically significant.

	Control			SPV			*P*-value
	Bern	Groningen	Total	Bern	Groningen	Total	
Number of subjects	92	78	170	98	90	188	
Sex, *n* (%)							
Male	0 (0)	0 (0)	0 (0)	0 (0)	9 (10)	9 (5)	0.004
Female	92 (100)	78 (100)	170 (100)	98 (100)	81 (90)	179 (95)	
Age (yr)	44 (16)	47 (15)	46 (16)	43 (15)	53 (18)	48 (17)	0.504
Range	19–87	19–80	19–87	20–83	20–88	20–88	
Height (m)	1.66 (0.06)	1.68 (0.07)	1.67 (0.07)	1.66 (0.06)	1.70 (0.09)	1.68 (0.08)	0.471
Weight (kg)	67 (13)	72 (12)	69 (13)	67 (12)	74 (13)	71 (13)	0.367
BMI (kg m^{-2})	24.1 (4.2)	25.5 (4.0)	24.8 (4.2)	24.4 (4.1)	25.9 (4.1)	25.1 (4.1)	0.579
ASA physical status, *n* (%)							0.011
1	50 (55)	41 (53)	91 (53)	35 (36)	36 (40)	71 (38)	
2	37 (40)	36 (46)	73 (43)	62 (63)	46 (51)	108 (57)	
3	5 (5)	1 (1)	6 (4)	1 (1)	8 (9)	9 (5)	
Surgery type, *n* (%)							0.008
Gynaecological	80 (87)	78 (100)	158 (93)	82 (84)	80 (89)	162 (86)	
Breast	12 (13)	0 (0)	12 (7)	16 (16)	0 (0)	16 (9)	
Other	0 (0)	0 (0)	0 (0)	0 (0)	10 (11)	10 (5)	
SBP (mm Hg)	126 (14)	132 (18)	129 (16)	126 (16)	133 (18)	130 (18)	0.749
DBP (mm Hg)	75 (10)	75 (10)	75 (10)	75 (11)	75 (11)	75 (11)	0.825
MAP (mm Hg)	92 (10)	94 (12)	93 (11)	92 (11)	94 (11)	93 (11)	0.945
HR (beats min^{-1})	78 (11)	75 (12)	76 (12)	78 (12)	76 (14)	77 (13)	0.918

The percentage of time that MAP was within the 60–80 mm Hg target range was not statistically different between groups (56.9 [30.5–72.3]% in CONTROL and 50 [25.9–75]% in SPV [$P=0.495$]). The percentage of time that BIS was within the 40–60 target range was also not statistically different (56.8 [26.8–81.9]% in CONTROL and 63.5 [31.6–82.8]% in SPV [$P=0.287$; Table 2]).

The percentages of MAP recordings above 80 mm Hg or below 60 mm Hg were also similar between groups ($P=0.265$ and $P=0.114$, respectively). However, the AUC of MAP >80 mm Hg (11.1 *vs* 2.4 mm Hg min [$P=0.001$]) or <60 mm Hg (0.6 *vs* 0.1 mm Hg min [$P=0.003$]) were both significantly higher in CONTROL compared with SPV. This indicates more severe hypotensive and hypertensive events, despite similar durations of the deviations (Table 2).

For BIS, both the percentage of time above 60 (0.0 *vs* 1.4% in CONTROL and SPV, respectively [$P=0.001$]) and the corresponding AUC (0.0 *vs* 0.1 BIS units s [$P=0.005$]) were slightly but significantly lower in CONTROL compared with SPV. The number of BIS records <40 (35.9% *vs* 25.5% in CONTROL and SPV, respectively [$P=0.013$]) and the corresponding AUC (8 *vs* 1 BIS unit s [$P=0.001$]) were significantly higher in CONTROL compared with SPV (Table 2). This shows reduced duration and severity of BIS below threshold in the SPV group.

The NSRI before incision was higher in CONTROL compared with SPV (27 [13–40] *vs* 23 [15–30]; $P=0.015$), but it was not different between groups thereafter (Table 2).

Effect-site concentration of propofol (Ce_{PROP}) was higher in CONTROL compared with SPV at incision, during surgery, and at emergence (10, 5, and 0 min, respectively, before the end of surgery) (Table 2). Ce_{PROP} at tracheal extubation was similar in CONTROL and SPV (0.97 [0.81–1.24] μg ml^{-1} *vs* 0.98 [0.77–1.28] μg ml^{-1}; $P=0.928$). In contrast, Ce_{REMIeq} was lower in CONTROL compared with SPV at incision (4.33 *vs* 4.9 ng ml^{-1}; $P=0.004$), during surgery (4.79 *vs* 4.96 ng ml^{-1}; $P=0.044$), and at tracheal extubation (2.18 *vs* 2.86 ng ml^{-1}; $P<0.001$). At skin closure, no difference in opioid concentration was observed (Table 2).

The time from skin closure to tracheal extubation was significantly longer in CONTROL (7.2 [4.3–12.6] min) compared with SPV (5.1 [2.2–10.0] min; $P<0.001$).

Table 3 shows the postoperative results. A shift in clinical practice (not related to the study) was seen regarding the number of non-opioid analgesic drugs (e.g. paracetamol or NSAIDs) given intraoperatively with a mean of 0.76 (0.79) dosages given in CONTROL *vs* 1.12 (1.17) in SPV ($P=0.001$). The numbers of non-opioid analgesic drugs given in the PACU were similar between groups ($P=0.676$), as was the time between tracheal extubation and the first postoperative opioid analgesic administration (CONTROL 31.5 [35.8] min; SPV 26.3 [35.7] min; $P=0.205$). The initial NRS pain scores at arrival in the PACU were higher in CONTROL (2.96 [2.86]) compared with SPV (1.97 [2.28]) ($P=0.001$). Thereafter, no differences were found in NRS scores at 30, 60, and 90 min postoperatively. After 120 min, NRS scores were slightly lower in CONTROL compared with SPV. Modified Aldrete scores in the PACU showed only small differences that were deemed clinically irrelevant. The frequency of postoperative nausea and vomiting events and the number of anti-emetic drugs given did not differ between groups. Duration of PACU stay also did not differ (CONTROL 168 [54] min; SPV 167 [61] min; $P=0.869$).

Table 2 Intraoperative measurements. Data presented as median [Q1–Q3] unless stated otherwise. AQS, anaesthesia quality score, defined as percentage of time spent within the range of 60–80 mm Hg for MAP and 40–60 for BIS; AUC, area under the curve; BIS, bispectral index; Ce_{PROP}, propofol effect-site concentration; Ce_{REMIeq}, combined opioid effect-site concentration, as remifentanil equivalents; NSRI, noxious stimulation response index. The presented *P*-value is the result of the comparison between the control (CONTROL) and SmartPilot® View (SPV) groups of pooled results. $P<0.05$ is considered statistically significant. *Significant difference between study sites in CONTROL group. †Significant difference between study sites in the SPV group. ‡Significant difference between the CONTROL and SPV groups in the same centre.

	Control			SPV			*P*-value pooled data
	Bern	Groningen	Pooled	Bern	Groningen	Pooled	
AQS (%), during surgery							
Median	28.5 [12–46.8]	20.0 [4.6–37.5]	25.3 [7.4–41.5]	25 [12.5–50]	17.3 [5.7–34.5]	22.2 [8.0–44.4]	0.898
MAP (mm Hg), during surgery							
Above range (%)	26.1 [5.9–53.1]	31.5 [7.2–64.1]	27.9 [6.5–60.0]	22.3 [4.0–62.1]	43.8 [11.1–71.6]†	34.2 [7.9–66.8]	0.265
In range (%)	56.3 [31.4–67.4]	59.2 [29.2–78.5]	56.9 [30.5–72.3]	50.0 [25.9–75]	50.0 [25.8–73.3]	50.0 [25.9–75.0]	0.495
Below range (%)	12.5 [2.1–23.9]	0.0 [0.0–9.9]*	4.2 [0.0–18.6]	8.3 [0.0–21.1]	0.0 [0.0–5.6]†	2.2 [0.0–13.7]	0.114
AUC above upper limit	9.3 [1.6–24.3]	11.6 [1.8–35.8]	11.1 [1.8–29.9]	6.5 [0.4–23.1]	1.8 [0.4–5.6]†‡	2.4 [0.4–11.7]	0.001
AUC below lower limit	2.7 [0.2–7.2]	0.0 [0.0–1.0]*	0.6 [0.0–4.8]	1.1 [0.0–5.5]	0.0 [0.0–0.1]†	0.1 [0.0–1.3]	0.003
BIS, during surgery							
Above range (%)	0.0 [0.0–1.8]	0.0 [0.0–1.1]	0.0 [0.0–1.6]	3.4 [0.0–9.2]‡	0.0 [0.0–5.0]†	1.4 [0.0–6.3]	0.001
In range (%)	70.3 [38.8–84.9]	43.1 [12.7–72.8]*	56.8 [26.8–81.9]	70.9 [51.6–84.9]	49.4 [20.4–78.8]†	63.5 [31.6–82.2]	0.287
Below range (%)	26.7 [8.9–60.5]	54.1 [14.3–86.7]*	35.9 [11.5–73.2]	15.7 [1.7–36.6]	45.6 [9.0–79.6]†	25.5 [5.2–65.9]	0.013
AUC above upper limit	0.0 [0.0–0.3]	0.0 [0.0–0.2]	0.0 [0.0–0.2]	0.2 [0.0–0.5]‡	0.0 [0.0–0.4]	0.1 [0.0–0.5]	0.005
AUC below lower limit	5.7 [1.2–14.9]	16.3 [1.9–40.9]*	8.0 [1.5–28.3]	0.4 [0.0–1.9]‡	2.7 [0.4–7.3]†‡	1.0 [0.1–4.8]	0.001
NSRI							
Before incision	37 [29–45]	13 [8–21]*	27 [13–40]	27 [22–35]‡	16 [10–24]†	23 [15–30]	0.015
At incision	33 [22–50]	16 [10–26]*	25 [15–39]	29 [25–34]	20 [12–27]†	25 [18–32]	0.370
During surgery	28 [20–38]	23 [14–36]	26 [17–38]	29 [25–36]	22 [16–30]†	27 [19–33]	0.840
Ce_{PROP} (μg ml^{-1})							
At incision	2.79 [2.50–2.99]	3.29 [2.95–3.94]*	2.99 [2.51–3.40]	2.49 [2.36–2.68]‡	3.00 [2.96–3.83]†	2.75 [2.49–3.02]	0.021
During surgery	2.59 [2.38–2.86]	3.16 [2.79–3.54]*	2.81 [2.51–3.19]	2.36 [2.18–2.53]‡	3.04 [2.74–3.50]†	2.61 [2.34–3.00]	0.005
10 min to closure	2.50 [2.21–2.79]	2.99 [2.72–3.50]*	2.70 [2.39–3.05]	2.25 [1.96–2.50]‡	3.00 [2.51–3.15]†	2.50 [2.10–3.00]	0.004
5 min to closure	2.31 [1.95–2.58]	2.80 [2.36–3.09]*	2.49 [2.03–2.88]	1.85 [1.56–2.20]‡	2.79 [2.39–3.00]†	2.26 [1.78–2.80]	0.002
At closure	1.68 [1.27–2.19]	2.11 [1.64–2.64]*	1.91 [1.48–2.46]	1.22 [1.03–1.71]‡	2.11 [1.61–2.71]†	1.62 [1.17–2.21]	0.001
At tracheal extubation	0.92 [0.78–1.18]	1.04 [0.84–1.29]	0.97 [0.81–1.24]	0.91 [0.76–1.11]	1.08 [0.79–1.46]†	0.98 [0.77–1.28]	0.928
Ce_{REMIeq} (ng ml^{-1})							
At incision	3.92 [2.96–4.97]	4.97 [3.96–6.42]*	4.33 [3.31–5.38]	4.74 [4.07–5.52]‡	4.94 [4.00–5.47]	4.90 [4.01–5.49]	0.004
During surgery	4.93 [3.84–6.08]	4.54 [3.43–5.76]	4.79 [2.80–5.88]	5.41 [4.76–6.06]	4.69 [4.04–5.65]†	4.96 [4.33–5.81]	0.044
10 min to closure	5.06 [3.27–6.34]	4.04 [2.57–5.24]*	4.57 [3.15–5.91]	5.24 [4.40–5.96]	3.83 [3.26–5.58]†	4.63 [3.61–5.85]	0.151
5 min to closure	4.96 [3.23–5.82]	3.69 [2.32–4.77]*	4.26 [3.08–5.43]	4.76 [3.96–5.78]	3.58 [3.05–5.16]†	4.33 [3.37–5.60]	0.189
At closure	3.81 [2.92–4.90]	3.19 [2.05–4.18]*	3.43 [2.45–4.53]	3.74 [3.14–5.16]	3.26 [2.76–4.41]	3.53 [2.92–5.04]	0.079
At tracheal extubation	2.06 [1.58–2.73]	2.41 [1.55–3.07]	2.18 [1.56–2.83]	3.07 [2.65–4.09]‡	2.57 [2.12–3.31]†	2.86 [2.41–3.64]	<0.001
Recovery parameters (min)							
Skin closure to tracheal extubation	6.7 [4.0–12.3]	7.9 [5.4–13.5]	7.2 [4.3–12.6]	3.1 [1.5–7.1]‡	8.7 [4.3–12.2]†	5.1 [2.2–10.0]	<0.001

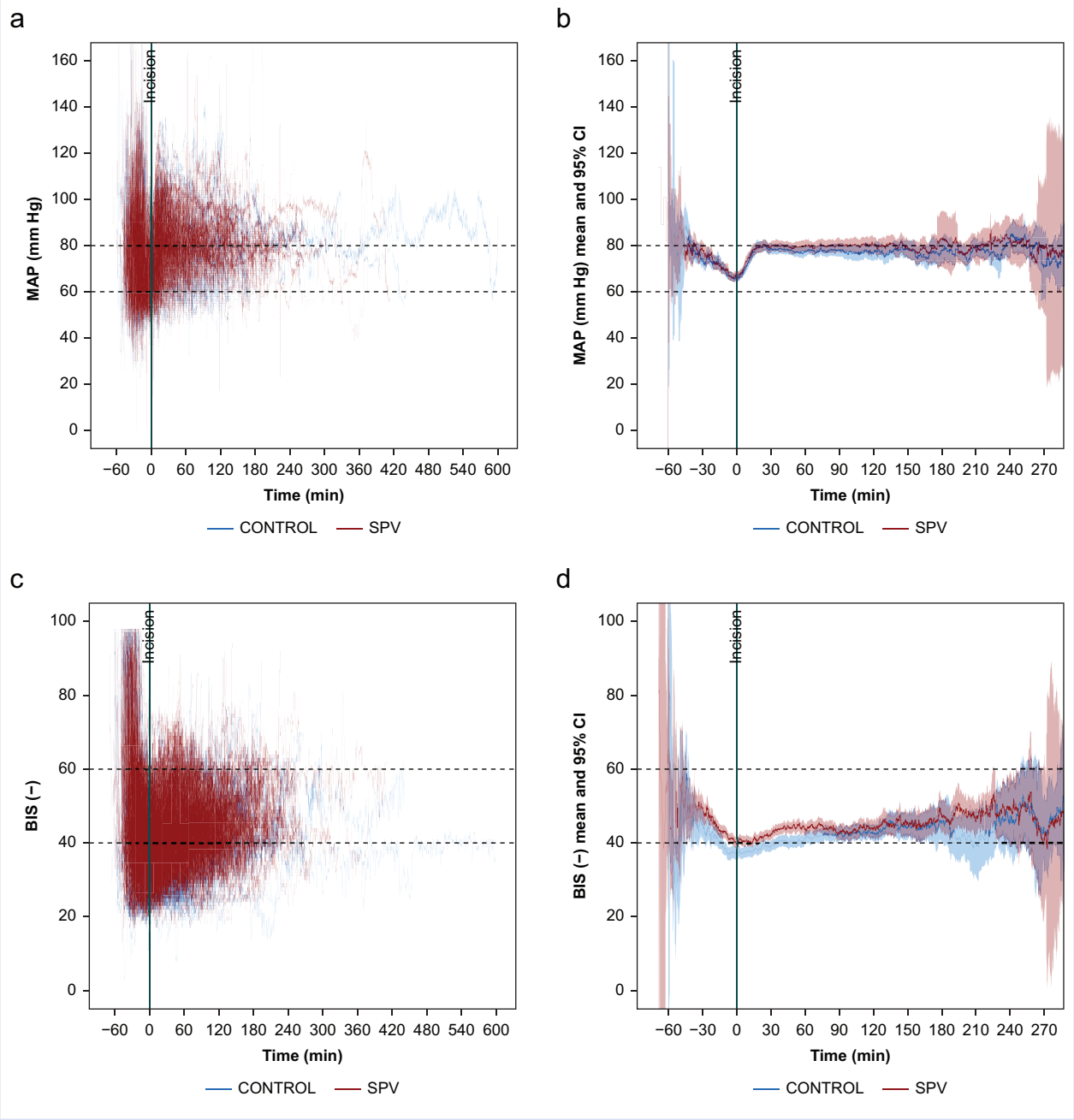

Fig 3. Raw data and associated means and confidence intervals over time for MAP and Bispectral Index (BIS). (a) and (c) The MAP and BIS data for the control (CONTROL; blue) and SmartPilot® View (SPV; red) groups. Data are synchronised to time of incision (green line). Dashed lines are the desired thresholds for MAP (60–80 mm Hg) and BIS (40–60). Each red or blue line represents the time course of individual measurements between start of drug infusion and 600 min of case time. (b and d) Mean MAP and mean BIS in 1 min intervals, respectively, with corresponding 95% confidence intervals (CIs), between start of drug infusion and 270 min of case time. Less than five cases were observed in one of the groups after 270 min, making further CI calculations irrelevant.

The NASA Task Load Index questionnaire showed low scores overall but lower scores in favour of the SPV group for the mental, physical, and temporal demands and effort required by the anaesthetist to manage the case. Personal performance and level of frustration were similar between CONTROL and SPV.

Interdepartmental differences

Multiple subtle differences were found in intraoperative and postoperative measurements between the two centres (Tables 2 and 3; Supplementary Figs S3–S9), without clinical relevance. The Ce_{PROP} in Bern was lower than in Groningen,

Table 3 Postoperative outcome data. Data presented as mean (standard deviation) or number (%). NRS, numerical rating scale (NRS; 0–10); PONV, postoperative nausea and vomiting; NASA Task Load Index, perceived workload (scores range between 0 [low demand] and 20 [very high demand]). The 'P-value pooled data' are the results of the comparison between the control (CONTROL) and SmartPilot® View (SPV) groups of the pooled results. $P<0.05$ is considered statistically significant. *Significant difference between the CONTROL and SPV groups in Bern. †Significant difference between the CONTROL and SPV groups in Groningen.

	Control			SPV			P-value pooled data
	Bern	Groningen	Pooled	Bern	Groningen	Pooled	
Number of different non-opioid analgesics administered intraoperatively	1.08 (0.85)	0.38 (0.52)	0.76 (0.79)	2.01 (0.92)*	0.16 (0.36)†	1.12 (1.17)	0.001
Number of different non-opioid analgesics administered in the PACU	1.10 (0.75)	0.77 (0.76)	0.95 (0.77)	0.76 (0.73)*	1.07 (0.97)†	0.91 (0.87)	0.676
Time between extubation and first administration of opioid analgesics (min)	44.4 (37.6)	22.3 (31.6)	31.5 (35.8)	28.9 (42.3)*	23.4 (26.9)	26.3 (35.7)	0.205
NRS							
At arrival in PACU	2.5 (2.7)	3.4 (3.0)	3.0 (2.9)	1.9 (2.4)	2.1 (2.2)†	2.0 (2.3)	0.001
After 30 min	2.9 (2.3)	4.3 (2.7)	3.6 (2.6)	2.6 (2.1)	3.6 (2.5)	3.0 (2.3)	0.057
After 60 min	2.3 (1.8)	3.4 (1.9)	2.8 (1.9)	2.5 (1.8)	3.3 (2.1)	2.9 (2.0)	0.828
After 90 min	2.0 (1.5)	3.2 (1.7)	2.4 (1.7)	2.1 (1.5)	3.0 (1.8)	2.5 (1.6)	0.805
After 120 min	1.9 (1.5)	2.4 (1.0)	2.0 (1.4)	2.1 (1.3)	3.2 (1.6)†	2.5 (1.5)	0.026
After 150 min	1.7 (1.4)	2.1 (1.0)	1.8 (1.3)	2.1 (1.2)	3.2 (1.4)†	2.4 (1.3)	0.002
After 180 min	1.5 (1.3)	2.8 (1.9)	1.7 (1.5)	1.9 (1.2)	3.3 (1.1)	2.2 (1.3)	0.046
Modified Aldrete score							
5 min after extubation		7.7 (1.7)	7.7 (1.7)		8.4 (1.3)†	8.4 (1.3)	0.004
At arrival in PACU	9.1 (0.9)	8.3 (1.6)	8.8 (1.3)	8.7 (1.0)*	8.6 (1.2)	8.6 (1.1)	0.354
After 15 min	9.1 (0.9)	8.8 (1.3)	9.0 (1.1)	8.8 (0.9)*	8.8 (1.2)	8.8 (1.0)	0.121
After 30 min	9.2 (0.7)	9.0 (1.1)	9.1 (0.9)	8.9 (0.8)*	9.1 (0.9)	9.0 (0.9)	0.190
After 45 min	9.2 (0.7)	9.1 (1.1)	9.2 (0.9)	9.0 (0.9)*	9.2 (0.9)	9.1 (0.9)	0.332
After 60 min	9.3 (0.7)	9.3 (0.9)	9.3 (0.8)	9.0 (0.8)*	9.3 (0.8)	9.2 (0.8)	0.052
After 120 min	9.5 (0.7)	9.6 (0.6)	9.5 (0.6)	9.2 (0.8)*	9.3 (0.8)	9.3 (0.8)	0.004
After 180 min	9.7 (0.5)	9.3 (0.9)	9.6 (0.6)	9.5 (0.8)	9.0 (0.7)	9.4 (0.8)	0.009
At discharge	9.8 (0.4)	9.6 (0.7)	9.7 (0.6)	9.7 (0.5)	9.6 (0.5)	9.7 (0.5)	0.822
PONV							
Incidence of nausea	0.27 (0.45)	0.21 (0.41)	0.24 (0.43)	0.21 (0.41)	0.18 (0.38)	0.20 (0.40)	0.367
Incidence of vomiting	0.02 (0.15)	0.04 (0.21)	0.04 (0.19)	0.05 (0.22)	0.00 (0.00)	0.02 (0.15)	0.545
Number of anti-emetics given	0.31 (0.57)	0.31 (0.63)	0.31 (0.60)	0.29 (0.61)	0.21 (0.49)	0.25 (0.55)	0.317
Length of PACU stay (min)	191.5 (42.0)	141.0 (54.6)	168.1 (54.4)	176.4 (40.7)*	156.8 (75.5)	167.0 (60.6)	0.869
NASA Task Load Index							
Mental demand	9.6 (3.9)	7.3 (3.8)	8.6 (4.0)	7.9 (3.8)*	7.2 (3.9)	7.6 (3.8)	0.019
Physical demand	5.6 (3.2)	5.6 (3.4)	5.6 (3.3)	3.8 (2.6)*	5.5 (3.4)	4.6 (3.1)	0.005
Temporal demand	9.0 (4.1)	5.7 (3.0)	7.5 (4.0)	7.5 (4.1)*	5.6 (3.0)	6.5 (3.7)	0.023
Performance	6.6 (3.3)	6.9 (4.0)	6.7 (3.6)	6.6 (3.5)	6.5 (4.0)	6.6 (3.7)	0.698
Effort	8.8 (3.7)	7.5 (3.8)	8.2 (3.8)	7.4 (3.4)*	7.3 (3.9)	7.3 (3.6)	0.031
Frustration	5.3 (4.1)	5.2 (3.7)	5.2 (3.9)	5.7 (4.3)	4.9 (3.6)	5.3 (4.0)	0.803

which was reflected by fewer BIS measurements <40 in Bern. The main difference was stricter adherence in Bern compared with Groningen in reducing Ce_{PROP} towards the end of the procedure in the SPV group, and a further reduction in median time from closure to tracheal extubation from 6.7 in the CONTROL group to 3.1 min in the SPV group ($P<0.001$).

No adverse events, including awareness under anaesthesia, were reported during the study.

Discussion

Introduction of the real-time anaesthesia monitoring software program SmartPilot® View into clinical practice did not change AQS compared with standard drug titration practice in two academic medical centres. Overall, no clinically important changes in drug dosing were observed when SmartPilot® View was used. However, the severity of hypotension and hypertension during surgery, the number and duration of BIS values below 40, and the time to tracheal extubation were lower in the SPV compared with the CONTROL group.

The AQS is a multiplex metric for the ability of the anaesthetist to maintain MAP and BIS values simultaneously within the desired ranges. Our target range for MAP (60–80 mm Hg) was arbitrarily defined. Table 2 reveals that MAP values >80 mm Hg were tolerated in a substantial number of subjects in both groups, probably because this corresponds to standard practice. Together with the fact that only BIS readings were blinded, an improvement in AQS with the additional information provided by SmartPilot® View was too ambitious. For MAP and BIS, the percentage of time within and outside thresholds (except for BIS >60) was not different between CONTROL and SPV, and therefore did not affect the AQS.

The AUC calculations of the deviations of MAP and BIS outside the predefined limits add quantification of the severity of the deviation into the comparison. The AUC of MAP >80 and <60 mm Hg was lower in SPV, which indicates a significant reduction in severity of hypertensive and hypotensive events compared with CONTROL.

The AUC of BIS <40 was significantly lower in SPV compared with CONTROL, indicating a decrease in excessive hypnotic effect as measured by BIS. This positive effect on BIS was accompanied by a small but significant increase in the percentage of time (1.4% *vs* 0%) and AUC (0.1 *vs* 0 BIS units s) of BIS >60; however, this has only limited clinical relevance. Furthermore, no explicit awareness was reported postoperatively. Nonetheless, in clinical practice, it might be advisable to combine the population-derived pharmacodynamic information provided by SmartPilot® View with a monitor of hypnotic depth, especially for i.v. anaesthesia, to avoid unintended underdosing in individual patients.

The raw data for MAP and BIS *vs* time show a wider population variability for MAP and BIS in CONTROL compared with SPV. It is likely that this larger population variability contributed to the statistical differences found in AUC for MAP and BIS between groups. Mean MAP values were similar between groups, but for (the blinded) BIS, confidence intervals do not overlap during the first 60 min, suggesting a significantly lower mean BIS in CONTROL *vs* SPV in the first phase of anaesthesia maintenance.

Our results are similar to those of LeBlanc and colleagues,[5] who included only older patients undergoing hip fracture surgery under general anaesthesia with *volatile agents*, and found also no significant difference in time spent in the 'appropriate anaesthesia zone' defined as BIS of 45–60 and *systolic* arterial pressure of 80–140 mm Hg between control group (31% [4–60]) and SmartPilot® View (23% [2–74]) groups. LeBlanc and colleagues[5] similarly found a shorter cumulative time of low *systolic* arterial pressure (<80 mm Hg) in the SmartPilot® View group, but they did not find significant differences in intraoperative duration of low BIS (<45). In contrast, Cirillo and colleagues[18] found comparable haemodynamic conditions, higher BIS, and lower end-tidal sevoflurane concentrations in a SmartPilot® View-guided group compared with common practice. However, the latter study only included 15 patients per group and might therefore be underpowered.

A limitation of AQS as an effect measure is that only BIS (and not MAP) could ethically be blinded to the attending anaesthetist for this study. To detect a change in titration habits, we therefore also compared predicted propofol and opioid concentrations and the net anaesthetic potency as represented by NSRI during surgery at several time points.

Introduction of SmartPilot® View only evoked subtle shifts in the balance between Ce_{PROP} and Ce_{REMIeq} and the resulting NSRI. However, a lower Ce_{PROP} was selected in the SPV group during surgery and towards skin closure, a result that was mainly attributable to the data from Bern. The Ce_{PROP} at tracheal extubation was similar within and between the centres in both phases and corresponds closely with tracheal extubation values of ~1.0 [0.8–1.7] $\mu g\,ml^{-1}$, as found by Lee and colleagues.[19] The improved effort to anticipate recovery in the SPV group led to a reduction in time to tracheal extubation of 2.1 min. This result was also most pronounced in Bern. These institutional differences suggest that greater adherence to the information provided by SmartPilot® View might result in a greater effect on recovery times, as seen in Bern compared with Groningen. Our findings suggest that a more active reduction of Ce_{PROP} towards the end of surgery is an effective way to improve tracheal extubation times. This is in contrast with the findings of LeBlanc and colleagues,[5] who observed no impact on the mean time to tracheal extubation of 10 min when using SmartPilot® View compared with their control group.

Despite differences in drug titration, drug choices, and balance between hypnotic and analgesic drugs between centres, no difference was found in NSRI at incision or during surgery. Both study centres maintained a consistent P_{TOL} during the process. This is a relevant finding, as both NSRI, the position on the P_{TOL} isobole, and Ce_{REMIeq} make dosing habits of different departments transparent and could provide targets for standardised titration protocols to improve reproducibility in outcomes.

The postoperative results show that initial pain scores were slightly better in the PACU in the SPV compared with the CONTROL group, possibly as a result of more deliberate titration of opioids at the end of surgery in anticipation of postoperative pain. However, the effect on pain score deteriorated over time, with even a slightly higher NRS after 120 min in the SPV group. As NRS scores remained below 3, these findings are minimally relevant because overall pain control was deemed sufficient. No differences in number of non-opioid analgesic drugs given in the PACU were found between CONTROL and SPV, nor in the time between tracheal extubation and the first need for postoperative opioids. A clear causal relationship between this observation and the use of SmartPilot® View therefore remains speculative. Modified Aldrete scores were comparable in the CONTROL and SPV groups, suggesting that use of higher targets for Ce_{REMIeq} towards the end of surgery did not evoke residual sedation. No differences were seen in the number of postoperative nausea and vomiting events and treatment, and

the length of PACU stay did not differ between the CONTROL and SPV groups, which is in concordance with the findings by LeBlanc and colleagues.[5] We conclude that the use of SmartPilot® View did not evoke clinically relevant differences in postoperative outcomes in the PACU.

Total workload as perceived by anaesthetists was positively rated according to the NASA questionnaire. Introduction of SmartPilot® View did not add cognitive burden or distraction during anaesthesia. This is a promising result, considering the utility of SmartPilot® View as an educational tool in clinical practice.

Our study has some limitations. For organisational reasons, the majority of subjects underwent gynaecological surgery in both centres. The population therefore showed little variety in sex or age, and few older or frail patients were included. Another limitation is that only TIVA could be investigated despite that the choice of hypnotic was at the discretion of the anaesthetist. Total intravenous anaesthesia with propofol was by far the preferred hypnotic in both departments, and the number of volatile anaesthetics delivered did not allow a meaningful analysis. The accuracy of data recording in our study was high because a research fellow was present for every case to assist data input in SmartPilot® View, if required. Calculations of total anaesthetic potency in terms of NSRI or P_{TOL} would be affected by inaccurate input of drug administration that could misguide the anaesthetist. The risk of such erroneous input of data might be higher in clinical practice compared with our study setting.

In conclusion, use of SmartPilot® View did not result in a significant difference in AQS or a significant shift in drug titration behaviour of anaesthetists. However, it significantly reduced the severity of hypotension and hypertension during maintenance of anaesthesia and excessive depth of anaesthesia, and it produced small differences in early recovery parameters. These results suggest that some patients benefit from the use of SmartPilot® View without increases in adverse events and without increasing perceived anaesthetist workload.

Authors' contributions

Study conception: ARA, MMRFS, ML.
Study design: MHK, HEMV, ARA, MMRFS, ML.
Data acquisition: MHK, HEMV, LNH, JPvdB, CHB.
Data analysis: MHK, HEMV, CHB, LS, ARA, MMRFS, ML.
Data interpretation: MHK, HEMV, LS, ARA, MMRFS, ML.
Preparation of paper: MHK, HEMV.
Revision of paper: LNH, JPvdB, CHB, LS, ARA, MMRFS, ML.
Final approval of paper: all authors
Agreement to be accountable for all aspects of the work: all authors.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.02.033.

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