The Use of Propofol Target-Controlled Sedation in Emergency Department Procedural Sedation

Dr Fiona Marie Burton

MBChB, MRCS, FRCEM

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Abstract

Background

Procedural sedation (PS) is commonly required in the Emergency Department (ED). Propofol is a drug commonly used for this. It is administered as an intravenous bolus and adverse events can occur. Target-controlled infusion (TCI) is another way of administering Propofol and may produce less adverse events as the concentration is targeted to be within the therapeutic window. TCI is not currently used in the ED. I assessed the feasibility of running an RCT comparing Propofol TCI vs bolus administration in the ED.

Methods

I assessed feasibility of a future RCT by; conducting a survey to describe current local PS practice, a time to set up TCI study, a systematic review of rate of adverse events for Propofol TCI vs bolus in PS and a multicentre single arm feasibility study on Propofol TCI in ED sedation.

Results

112 respondents completed the survey; most respondents experienced a complication during PS and 79% of respondents were comfortable using Propofol. The difference in median set up time of TCI vs bolus was 143 seconds, approximately half of what participants felt was acceptable. There is a paucity of studies involving TCI in the ED. Twenty-five patients were recruited to the study and results suggests a trend towards fewer respiratory and hypotensive events with Propofol TCI versus other methods of administration. No adverse events were recorded. TCI was deemed acceptable by patients and staff.

Conclusion

Although results indicate that an RCT to compare the incidence of adverse events in ED procedural sedation would be technically feasible, there may be more efficient approaches to achieving a safe change in practice.

Table of Contents

List of Tables

List of Figures

Preface

“You are never too old to set another goal or to dream a new dream.”

C.S.Lewis

Sponsorship Declaration

Many thanks go to Carefusion BD for their generous support by providing TCI pumps to each of the four Emergency Departments involved. Carefusion BD had no input to the research design nor contributed to the final manuscript. They received a copy of the results and published article when available.

Contributions

Chapter 1

Dr Fiona M Burton wrote the Chapter. Dr Malcolm Watson & Professor Malcolm Sim reviewed and suggested corrections.

Chapter 2

Dr Fiona M Burton wrote the Chapter. Dr Malcolm Watson & Professor Malcolm Sim reviewed and suggested corrections.

Chapter 3

Dr Fiona M Burton wrote the Chapter. Dr Malcolm Watson & Professor Malcolm Sim reviewed and suggested corrections.

Chapter 4

Dr Fiona M Burton conceived the idea, designed and tested the survey, collected the data, performed the analysis and wrote the Chapter. Dr Malcolm Watson & Professor Malcolm Sim reviewed and suggested corrections. Higher specialist trainees assisted with distribution and collection of the survey.

Chapter 5

Dr Fiona M Burton conceived the idea, designed and conducted the study, collected the data, performed the analysis, wrote the paper and wrote the Chapter. Professor Malcom Sim provided the educational sessions. Dr Malcolm Watson & Professor Malcolm Sim reviewed both the paper and Chapter suggesting corrections.

Chapter 6

Dr Fiona M Burton conceived the idea, designed and conducted the systematic review, collected the data, performed the analysis, wrote the paper and wrote the Chapter. Professor David Lowe was the second reviewer. Professor Malcolm Sim was the third reviewer if a conflict arose. Dr Malcolm Watson & Professor Malcolm Sim reviewed both the systematic review and Chapter suggesting corrections. Martin Shaw offered statistical advice.

Chapter 7

Professor David Lowe and Dr Jonathan Millar conceived the initial study idea. Dr Fiona M Burton developed the idea, wrote the protocol, obtained ethical approval, set up the study on each site, collected the data, performed the analysis, wrote the paper and wrote the Chapter. Dr Malcolm Watson & Professor Malcolm Sim reviewed the protocol, the paper and Chapter suggesting corrections. Martin Shaw offered statistical advice.

Publications & Presentations

Publications

Burton, F.M. 2015. *Propofol target-controlled infusion versus bolus administration for sedation, does it reduce the incidence and severity of adverse events?* [Online]. Available: https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015026067&ID=CRD42015026067 [Accessed 15th December 2022].

Burton, F.M., Coady, G. and Sim, M.A.B. 2019a. Is there time for target-controlled infusion in the Emergency Department? *European Journal of Emergency Medicine*. **26**(4), pp.309-310.

Burton, F.M., Lowe, D.J., Millar, J., Corfield, A.R. and Sim, M.A.B. 2019b. A study protocol for a feasibility study: Propofol Target-Controlled Infusion in Emergency Department Sedation (ProTEDS)—a multi-centre feasibility study protocol. *Pilot and feasibility studies*. **5**(1), pp.1-8.

Burton, F.M., Lowe, D.J., Millar, J., Corfield, A.R., Watson, M.J. and Sim, M.A.B. 2021. Propofol target-controlled infusion in emergency department sedation (ProTEDS): a multicentre, single-arm feasibility study. *Emergency Medicine Journal*. **38**(3), pp.205-210.

Burton, F.M., Lowe, D.J., Millar, J.E., Corfield, A.R., Watson, M.J., Shaw, M. and Sim, M.A.B. 2020. Effect of target-controlled Propofol infusion to reduce the incidence of adverse events for procedural sedation in the emergency department: a systematic review. *European Journal of Emergency Medicine*. **27**(4), pp.253-259.

Presentations

Burton FM, Lowe DJ, Millar J, Corfield AR, Watson MJ, Sim MAB. Propofol Target-Controlled Infusion in Emergency Department Sedation (ProTEDS): a multicentre, single-arm feasibility study. University of Glasgow, School of Medicine, Dentistry and Nursing, Postgraduate Research Day, May 2021.

O'Mailley P, Kinsey A, Sim M, Kane R, **Burton FM**. A survey of Emergency Department procedural sedation in the West of Scotland; is there a role for using target-controlled infusion of Propofol to minimise complications? RCEM Scottish clinical meeting, 2019.

Burton FM – Upping the game: TCI sedation in the ED. European Society for Emergency Medicine conference, Glasgow, September 2018. Invited Speaker.

Burton FM, Coady G, Henderson S, Sim M. Time to set up Target-Controlled Infusion. Scottish RCEM meeting, Edinburgh, May 2017.

Burton FM. Propofol Target-controlled infusion in Emergency Department Sedation (ProTEDS). RCEM Clinical Studies Group Meeting, January 2016, Birmingham.

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Author's declaration

I declare that, except where explicit reference is made to the contribution of others, that this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature

Printed Name: Dr Fiona Marie Burton

Abbreviations

AAGA	Accidental Awareness during General Anaesthesia
ASA	American Society of Anesthesiologists
ACCS	Acute Care Common Stem
BIS	Bispectral Index
BMA	British Medical Association
BMI	Body Mass Index
BMJ	British Medical Journal
CCT	Certificate of Completion of Training
CESR	Certificate of Eligibility for Specialist Registration
C_{et}	Effect Site Concentration
CPD	Continuing professional development
C_{pt}	Plasma Site Concentration
DOA	Depth of Anaesthesia
DRE-EM	Defined Route of Entry into Emergency Medicine
ED	Emergency Department
EEG	Electroencephalographic
EM	Emergency Medicine
FRCEM	Fellow of the Royal College of Emergency Medicine
GMC	General Medical Council
IBW	Ideal Body Weight
ICM	Intensive Care Medicine
ICU	Intensive Care Unit
IHI	Institute for Healthcare Improvement
IQR	Interquartile Range
ISTF	International Sedation Task Force
LBM	Lean Body Mass
LMA	Laryngeal Mask Airway
MAP	Mean Arterial Pressure
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale
MRC	Medical Research Council
MRCEM	Member of the Royal College of Emergency Medicine
MVLS	Medical, Veterinary & Life Sciences
NIBP	Non-invasive blood pressure
NIHR	National Institute for Health and Care Research
OAA/S	Observer's Assessment of Alertness/Sedation Scale
OSCE	Objective Structured Clinical Environment
PD	Pharmacodynamics
PEM	Paediatric Emergency Medicine
PHEM	Pre-Hospital Emergency Medicine
PK	Pharmacokinetics
PMA	Post Menstrual Age
PPI	Patient and Public Involvement

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
ProTEDS	Propofol TCI in Emergency Department Sedation
PS	Procedural Sedation
PSA	Procedural Sedation and Analgesia
RCEM	Royal College of Emergency Medicine
RCT	Randomised Control Trial
RSS	Ramsay Sedation Scale
SBA	Single Best Answer
SBP	Systolic Blood Pressure
SIVA	Society for Intravenous Anaesthesia
SKIRC	Safety, Skills, and Improvement Research Collaborative
SLO	Specialty Learning Outcome
TBW	Total Body Weight
TCI	Target-controlled infusion
VAS	Visual Analogue Scale
GRIPP	Guidance for Reporting Involvement of Patients and the Public
HFNO	High Flow Nasal Oxygen

Chapter 1 Procedural Sedation in the Emergency Department

1.1 History of Emergency Medicine in the UK

In 2015 the Royal College of Emergency Medicine (RCEM) was permitted to use the word Royal in its title, seven years after being granted a Royal Charter. Compared to the Royal College of Physicians of London which was granted a Royal Charter from King Henry VIII in 1518, the RCEM is a relatively new medical college as is the specialty of Emergency Medicine (EM).

Emergency Departments had existed for many years before the establishment of the NHS in 1948 but with the introduction of the NHS, they were more commonly known as Casualty departments (Guly, 2005). Until the publication of the Sir Harry Platt report in 1962, there had been no consistency in the organisation of Emergency Departments nor consideration of future development. The Platt report also recommended that departments were renamed from 'Casualty' to Accident and Emergency (Standing Medical Advisory Committee, 1962). The recommendations included an increase in consultant staffing to three consultant surgeons and the recommendation that at least two of these should be Orthopaedic surgeons. The majority of the workload at that point was within the skillset of an Orthopaedic surgeon. In 1962 there was one recognised consultant in Casualty, Dr Maurice Ellis who had been appointed in 1952. On his retiral in 1969 he was replaced by an Orthopaedic consultant as outlined in the Platt report.

Unfortunately, during the subsequent years after the Platt report the standards in the Accident & Emergency (A&E) departments did not improve as they had trouble with staffing and "absentee Orthopaedic landlords" (Ellis, 1972). Medical recruitment was difficult as it was widely viewed as an appointment for a 'failed surgeon'. The majority of the medical staffing was provided by surgical trainees who were

mandated to complete a period of working in the A&E to satisfy requirements for the Fellowship of the Royal College of Surgeons (FRCS) (Collins, 1972).

In the 1970's it was appreciated that the task given to the Orthopaedic surgeons of managing and developing the A&E departments had failed. Discussions began about the correct medical staffing model for A&E departments. The majority view for the post holders was that there should be dedicated A&E consultants and that the individual's background was of no consequence (Garden, 1965).

At the end of 1971, members of the British Medical Association (BMA) convened and outlined what they saw as the future of A&E. They recommended the appointment of A&E consultants to manage the departments. Their background training should be reflective of the diversity of presentations at the A&E departments (Bainbridge, 1972). The importance of teaching junior doctors was also recognised. Based on the BMA's recommendations the proposal was ratified by both the government and the NHS and 32 consultant posts were created on a pilot basis to be monitored over a five-year period (Bruce, 1971).

1.1.1 Emergency Medicine Curriculum

At the 1971 BMA meeting, the appointment of A&E consultants was judged a success and the need for increased recruitment to the specialty was acknowledged (Lewin, 1978). It was realised that specialty A&E trainees had to be trained to become the A&E consultants of the future. A curriculum was developed despite opposition from the Royal College of Surgeons and in 1978 the first senior registrar was appointed (Guly, 2005). In 1981 the Royal College of Surgeons of Edinburgh (RCSEd) announced the first professional exam for A&E with the first candidates sitting the examination in 1982.

The following 40 years have seen a significant expansion in consultant numbers with some of the larger departments having more than twenty consultants (Smith et al., 2018). Trainees in the specialty no longer universally have a surgical background and are entering their higher specialist training years with more varied backgrounds of Medicine, Anaesthesia and Intensive Care Medicine (ICM) (Nazir et al., 2011).

Entry into Emergency Medicine training in 2023 is possible via a few routes following an initial successful two-year period as a Foundation Year doctor (RCEM, 2023). The Acute Common Care Stem (ACCS) describes a 24-month period where a trainee will rotate between Emergency Medicine, Anaesthesia, ICM or Acute Medicine with 12 of those months being in EM. There is also the Defined Route of Entry into Emergency Medicine (DRE-EM). This is possible for trainees who have completed two years of a UK core surgical training programme and obtained their MRCS. Successful completion of these programmes will give the participants the Certificate of Completion of Training (CCT) which allows them to enter the General Medical Council's (GMC) specialist register and be eligible for consultant positions. It is also possible for a doctor to join the specialist register via the Certificate of Eligibility for Specialist Registration (CESR). CESR is for doctors who have acquired the necessary skill sets and examinations but not in recognised training positions. It requires submission of evidence to the RCEM. It is also now possible for trainees to accredit for the specialty register with dual accreditation in another specialty; Paediatric Emergency Medicine (PEM), Pre-Hospital Emergency Medicine (PHEM) and ICM.

The EM curriculum has evolved as have the examinations to ensure that trainees understand the various breadth and complexity of the clinical scenarios they may encounter (Driscoll et al., 1988, Johnson et al., 1997, Boyle et al., 2021). A trainee doctor must successfully achieve their Membership of the Royal College of Emergency Medicine (MRCEM) and Fellowship of the Royal College of Emergency Medicine

(FRCEM) exams (RCEM, 2021) to progress in EM training. These exams have been designed to test the knowledges and skills required to be an EM consultant.

The MRCEM must be satisfactorily completed before a trainee can embark upon higher training in EM. There are three component parts, two Single Best Answer (SBA) multiple choice papers and an Objective Structured Clinical Examination (OSCE). The FRCEM is completed during a trainees higher training to indicate readiness to become a consultant. The FRCEM currently consists of a SBA paper and an OSCE.

1.2 Procedural Sedation

Procedural sedation is an essential skill for Emergency Physicians to allow painful, anxiety inducing procedures to be undertaken within the ED. It too has evolved over the years and there are now numerous options available for patients. The skill of the clinician is developed through their years of experience as they rotate through various specialities and EM. Emergency physicians choose the most appropriate method depending upon various factors including the procedure to be undertaken, patient choice and patient physiology.

Procedural sedation in the ED is required for a variety of procedures. These procedures can include chest drain insertion, joint reduction, fracture manipulation and cardioversion. Each patient and procedure combination is unique requiring a bespoke approach to their sedation.

In line with the curriculum, the skillsets of teams delivering emergency patient care have grown and the ability to provide safe, effective procedural sedation is one of the key skills necessary (Royal College of Emergency Medicine, 2022). Today's Emergency Physicians are trained to deliver procedural sedation in contrast to the past when

procedural sedation was delivered by either the General Surgeon, Anaesthetist, Orthopaedic surgeon, and junior medical or surgical doctors working in the 'Casualty' (Guly, 2005). It is recognised in the 2021 Curriculum (RCEM) as Specialty Learning Outcome (SLO) 6, deliver key procedural skills.

1.2.1 Defining Procedural Sedation

Clinicians providing procedural sedation recognise the American Society of Anesthesiologists (2019) (ASA) description of a sedation continuum. It ranges from mild to deep sedation/general anaesthesia (Table 1-1). However, when it comes to defining the term procedural sedation, there is a lack of consensus. Clinicians will be biased towards including the elements of procedural sedation which are most important to them (Williams et al., 2017).

Table 1-1 ASA Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (2019)

	Minimal Sedation (Anxiolysis)	Moderate Sedation/ Analgesia	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation*	Unresponsive, even with painful stimuli
Airway patency	Unaffected	No intervention needed	May require intervention	Intervention often required
Spontaneous breathing	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

*Reflex withdrawal from a painful stimulus does not represent a purposeful response

The International Committee for the Advancement of Procedural Sedation (ICAPS) recognised the lack of consensus on the definition of procedural sedation. ICAPS noted that the definitions of procedural sedation would often describe the continuum or be so non-specific that they could be describing general anaesthesia. Green et al. (2021), published the results of a Delphi exercise undertaken over an 11-month period with input from clinicians from various specialities that undertake procedural sedation, not just Emergency Medicine. They defined procedural sedation as,

> *'.....the administration of one or more pharmacological agents to facilitate a diagnostic or therapeutic procedure while targeting a state during which airway patency, spontaneous respiration, protective airway reflexes, and haemodynamic stability are preserved while alleviating anxiety and pain.'*

1.2.2 Training in procedural sedation

Training in procedural sedation in the ED is provided following national guidance from the Royal College of Emergency Medicine (2022), Table 1-2.

Table 1-2 RCEM procedural sedation training requirements for clinicians, Level 1 = minimal sedation & Level 2 = moderate/deep sedation (RCEM 2022). Reproduced with the permission of the RCEM.

Level 1 Sedation Training Requirements	Level 2 Sedation Training Requirements
ASA grading	As per level 1
Pre procedural assessment including prediction of difficult airway	Drug selection with emphasis on potential alternative strategies and/or lighter sedation
Pre procedural fasting and risk benefit assessment	Monitoring complications (e.g., hypoxia, hypotension) and rescue strategies
Consent and documentation	Safe use of Propofol
Drug selection and preparation: benzodiazepine/opioid combinations; increments and reversal	Safe use of ketamine
Monitoring, complications (e.g., hypoxia and hypotension) and rescue strategies	Governance and audit
Governance and audit	

By the end of the Acute Common Care Stem (ACCS) training, trainees will have shown competency in providing procedural sedation for ASA Grade I & II patients to level 2b on the RCEM entrustment scale (Table 1-3). ASA Grade I is defined as a normal healthy patient and Grade II is a patient with mild systemic disease that poses no functional limitation, and the disease is well-controlled. Level 2b correlates to having 'supervision within the hospital for queries, able to provide prompts and

direction or assistance and the trainee knows reliably when to ask for help'. On completion of the certificate of training, a trainee will be competent at Level 4 which implies they 'will be able to manage procedural sedation with no supervisor involvement'.

To evidence this training and progression, they will submit the following to their Annual Review of Competence Progression; initial assessment of competence certificate, logbook, holistic assessment of learning objectives, multi-source feedback, multiple consultant report, exam success and training courses attended.

Table 1-3 RCEM Entrustment Scale where the entrustment score is a 'judgement based assessment' decided by trainers who understands the area being assessed (RCEM, 2021). Reproduced with the permission of the RCEM.

1	Direct supervisor observation/involvement, able to provide immediate direction/assistance
2a	Supervisor on the 'shop-floor' (e.g., ED, theatres, AMU, ICU), monitoring at regular intervals
2b	Supervisor within hospital for queries, able to provide prompt direction or assistance and trainee knows reliably when to ask for help
3	Supervisor 'on call' from home for queries, able to provide directions via phone and able to attend the bedside if required to provide direct supervision
4	Would be able to manage with no supervisor involvement (all trainees practice with a consultant taking overall clinical responsibility)

1.2.3 Planning for procedural sedation

The first decision for a trained provider of procedural sedation is having the situational awareness to decide firstly whether the procedural sedation should be undertaken in the ED or if it should be undertaken in a theatre environment. Patients that are likely to benefit from the theatre procedure are those that are physiologically unstable with a higher ASA or a procedure unlikely to be successful in the ED. The second decision is which level of sedation is required (Royal College of Emergency Medicine, 2022).

The four categories of sedation that comprise the continuum of sedation as described by the ASA are well known and accepted by the medical community (Table 1-1). Whilst not described by the ASA, there is an accepted fifth category describing dissociative (Domino and Warner, 2010, Corssen and Domino, 1966) sedation. Dissociative sedation describes a state of profound sedation and analgesia but with maintenance of breathing and protective airway reflexes. This is unlike the sedation continuum where these gradually disappear as general anaesthesia is reached. The clinician must have the appropriate skill set and training to keep the patient safe if the patient enters the next level on the sedation continuum.

1.2.4 Procedural sedation guidelines

In 2012, the RCEM and the Royal College of Anaesthetists published, 'Safe Sedation of Adults in the Emergency Department'(2012). This publication outlined the essential monitoring for each of the sedation levels in addition to guidance on fasting and discharge of patients post sedation. Implementation of the guidelines and safe sedation has been the topic of the RCEM national audits in both 2016 and 2018.

Guidelines for ED procedural sedation in the UK developed by the working party recommend that Oxygen should be given to patients undergoing procedural sedation from the start of the encounter(2012). The use of capnography (Whitaker and Benson, 2016, Burton, 2012) is recommended for moderate sedation and stated as mandatory for stages beyond this including dissociative sedation. Continuous monitoring with ECG, non-invasive blood pressure (NIBP) and pulse oximetry is recommended for moderate sedation and the subsequent stages including dissociative sedation. These guidelines were released in 2012 and have recently been reviewed as an RCEM Best Practice Guideline (2022), Table 1-4.

Table 1-4 RCEM Requirements for monitoring, minimum staffing, competencies and location for adult procedural sedation (RCEM, 2022). Reproduced with the permission of the RCEM.

	Moderate Sedation "Conscious sedation"	Deep Sedation	Dissociative Sedation
Example	Benzodiazepines	Propofol	Ketamine
Monitoring	Pulse Oximetry Capnography ECG NIBP	Pulse Oximetry Capnography ECG NIBP	Pulse Oximetry Capnography ECG NIBP
Minimum Staffing	Nurse Sedationist Proceduralist	Nurse Sedationist Proceduralist	Nurse Sedationist Proceduralist
Competencies	ILS/ALS Level 1 sedation Training local sign-off	RCoA initial assessment of competencies Level 2 sedation training local sign-off	RCoA initial assessment of competencies Level 2 sedation training local sign-off
Location	Resus Room facilities	Resus Room facilities	Resus Room facilities

1.3 Pharmacological Principals

Pharmacokinetics (PK) describes the concentration of a drug as it is absorbed, distributed, metabolised, and excreted by the body. Pharmacodynamics (PD) describes the physiological effects of a medication.

1.3.1 Volume of Distribution (V_D)

The V_D of a drug describes the extent that the drug is distributed to the rest of the body compared to the plasma:

$$V_D = \frac{\text{Amount of drug in body}}{\text{Plasma concentration}}$$

If the drug largely remains in the plasma, the denominator will be larger with a resultant small V_D. This would indicate that the drug is not redistributed to the rest of the body. If, however, the drug is redistributed to the rest of the body, the denominator will be smaller with a resultant larger V_D. The V_D is the theoretical volume of distribution (Øie, 1986).

1.3.2 Steady-state concentration (C_{ss})

A steady-state concentration (C_{ss}) is achieved when there is no net flux of drug between the compartments, the compartments have achieved a state of equilibrium where all movements are equal. The concentration of the drug in the body is now consistent.

1.3.3 Volume of Distribution in a steady-state (V_{ss})

The V_{ss} describes the V_D when the C_{ss} has been achieved.

1.3.4 Context-sensitive half time

Context-sensitive half time is used to describe the offset times of a drug when used in an infusion with the underlying principle that the longer the infusion time the longer the offset time (Bailey, 2002).

1.3.5 pKa

The pKa of a drug is the pH at which it is completely balanced between its lipophilic, lipid soluble, unionised form and its ionised, water-soluble form. Propofol has a pKa of 11 which means that at a physiological pH of 7.4, most of this weak acid is unionised, active and fat-soluble (Smith et al., 2015).

1.3.6 Time to Peak Effect (TTPE)

The TTPE is the time taken for a drug to achieve the maximum clinical effect after a dose.

1.4 Analgesics

Opioids are the most used analgesics used to aid procedural sedation of which morphine and fentanyl are used most often.

1.4.1 Morphine

Morphine is commonly used in the ED to alleviate pain in patients. The analgesic pharmacodynamic properties of morphine are mainly achieved by binding to the μ-opioid receptors in the peripheral and central nervous system. Binding to μ-opioid receptors has the effect of decreasing pain transmission by activating inhibitory pathways in the CNS and inhibiting peripheral nociceptors. The side effects of morphine include respiratory depression, reduced conscious level, nausea, vomiting and hypotension. It is normally administered at a dose of 0.1-0.2mg/kg of body weight and titrated to effect. It's time to peak effect is approximately 20 minutes (Aubrun et al., 2012) and has a duration of action of approximately 3-4 hours.

1.4.2 Fentanyl

Fentanyl acts in a similar pharmacodynamic manner to Morphine by binding to μ-opioid receptors but has a faster onset with a time to peak effect of 4 minutes and is 100 times more potent than morphine. Fentanyl is lipophilic compared to the relatively hydrophilic Morphine which means that it can cross the blood-brain barrier more rapidly. The lipophilic properties explain its reduced duration of action of 30-60 minutes of analgesia as the fentanyl is redistributed rapidly from the effect compartment. It is normally administered 1-1.5mcg/kg of body weight titrated to effect. Fentanyl has a similar side effect profile to morphine.

1.4.3 Alfentanil

Alfentanil is a Fentanyl derivative which mainly acts by binding to μ-opioid receptors. It has a time to peak effect of approximately 90 seconds, is less potent than Fentanyl but it has a faster onset and shorter duration of action. Alfentanil is less lipophilic than Fentanyl but its lower pKa means that a greater proportion is available to cross the lipid membranes at a pH of 7.4 and it has a similar side effect profile to other opioids.

1.4.4 Remifentanil

Remifentanil is an opioid that became available in the late 1990's (Rosow, 1999). It is an ultra-short-acting opioid. Remifentanil is a μ-opioid receptor agonist with less affinity for the δ- and κ-receptors (Rosow, 1999, Glass et al., 1999). Non-specific esterases in blood and other tissue metabolise Remifentanil by acting at its ester linkage. Its metabolite is dependent on renal excretion, but it is of such low potency that it is unlikely to reach clinically significant concentrations in clinical practice (Hoke et al., 1997). Remifentanil has a time-to-peak drug effect after a bolus of 1.5

min and a rapid offset with a context-sensitive half-time of 3-5 min regardless of the duration of the infusion.

Dose dependent respiratory depression is one of the main side effects (Glass et al., 1993) of Remifentanil but given its ultra-short duration of action these effects are short lived and if needed can be reversed by Naloxone. An increased incidence of muscle rigidity has also been noted when compared with Fentanyl.

1.4.5 Nitrous Oxide

One of the earliest analgesic agents used was Nitrous Oxide (N_2O). In most departments, it can be delivered via an anaesthetic machine allowing the clinician to vary the ration of N_2O:O_2 or via cannisters of Entonox which is a 50:50 mixture of 50% N_2O and 50% O_2. N_2O is inhaled via a mouthpiece or delivered via a facemask, no intravenous access is required. It provides a degree of amnesia, with no sedative effect in normobarbic conditions and is primarily an analgesic agent.

Nitrous oxide is relatively insoluble in blood with an associated rapid onset of effect of 30-60 seconds as the alveolar concentration rises rapidly. When it has been stopped it also has a fast offset as it is rapidly cleared from the lungs. If it is administered via an anaesthetic machine, there is a safety system in place (Royal College of Anaesthetists, 2001, Saunders and Meek, 2001) to ensure that the % of N_2O can never rise above 70% and that the mix always contains a minimum of 30% O_2 to avoid hypoxaemia. It has shown to be clinically safe with very few side effects. These include nausea, dizziness, and euphoria. Despite it being relatively safe the relative solubility of N_2O in comparison to nitrogen means that N_2O moves faster into closed gas cavities than nitrogen is removed. This will result in an increase in the cavity's volume or pressure. Certain cavities can increase their volume and they are known as compliant cavities such as the pleural space, lung, or bowel. Others result

in a pressure increase as they are non-compliant cavities such as head injuries, eye injuries, pneumothorax, bowel obstruction and severe COPD emphysematous bullae.

Whilst nitrous oxide has been shown to be clinically safe with very few side effects, there are concerns about its contribution to environmental toxicity (Muret et al., 2019) Figure 1-1. In 2013, the NHS Sustainable Development Unit reported that the total emissions for anaesthetic gases represented 2.5% of the UK footprint with more than 50% attributable to Nitrous Oxide (2013). In the 'Delivering a 'Net Zero' National Health Service (2022), NHS England has committed to decreasing Nitrous Oxide wastage which may see a decrease in its availability over the coming years.

1.5 Sedating Agents

Currently there is no ideal sedating agent if we consider what would constitute the ideal (Dundee, 1980). These properties can be considered as the agent's pharmaceutical, pharmacokinetic (PK) and pharmacodynamic (PD) properties.

The perfect sedating agent would be water soluble and chemically stable. Ideally it would have a rapid onset, offset, could be administered in a variety of routes, would have no deleterious impact on the patient's cardiovascular or respiratory system and there would be no interindividual variation in dose. This does not currently exist though the common sedating agents will display some of the properties.

A clinician's choice of sedating agent is based upon their understanding of the drug, the patient, and the procedure being undertaken. Clinical experience with sedative drugs will often be a key part of this decision-making. Sedating agents are co-administered with analgesics as most sedative agents have no analgesic properties. It is important for the clinician to be familiar with the analgesia being used as this will

impact the pharmacodynamics of the sedating agent. Clinicians need to be mindful of the time to peak effect (TTPE) to ensure that the synergistic relationship between the analgesia and sedating agent occurs to the benefit of the patient to achieve adequate sedation safely.

1.5.1 Emergency Department Choice

The National RCEM audit of ED procedural sedation in 2017/18 (2018) showed that the most frequently used agents were opioids, benzodiazepines, ketamine and Propofol. The National RCEM audit noted a rise in the use of Propofol and ketamine from the last national audit in 2015/16 of 45% to 50% and 9% to 12% respectively (Royal College of Emergency Medicine, 2016). It also showed that the two most common combinations used were opioid/benzodiazepines and opioids/Propofol at 32% and 23% respectively.

1.5.2 Midazolam

Midazolam is a commonly used benzodiazepine in procedural sedation. It has no analgesic properties and requires co-administration of a suitable analgesic but is a potent retrograde amnesic at a relatively non-sedating dose. Midazolam works as an agonist at benzodiazepine receptors which are coupled to GABA type A receptors. Stimulation of this leads to an increased frequency of opening of the GABAA Chloride ion channel leading to an influx of Chloride ions into the cell. This causes membrane hyperpolarisation and inhibits neurotransmission.

Midazolam is a lipophilic drug with a time to peak effect of 15 minutes. It has a duration of 60-90 minutes. Dosing of midazolam for sedation varies between 0.02-0.1mg/kg and can be titrated to effect. Care must be taken when opioids have been co-administered as combined there is a synergistic effect that may lead to

undesirable respiratory depression. It is also recommended to start at the lower end of the dosing scale in elderly patients as the desired effects (Sun et al., 2008) occur with a significantly lower dose.

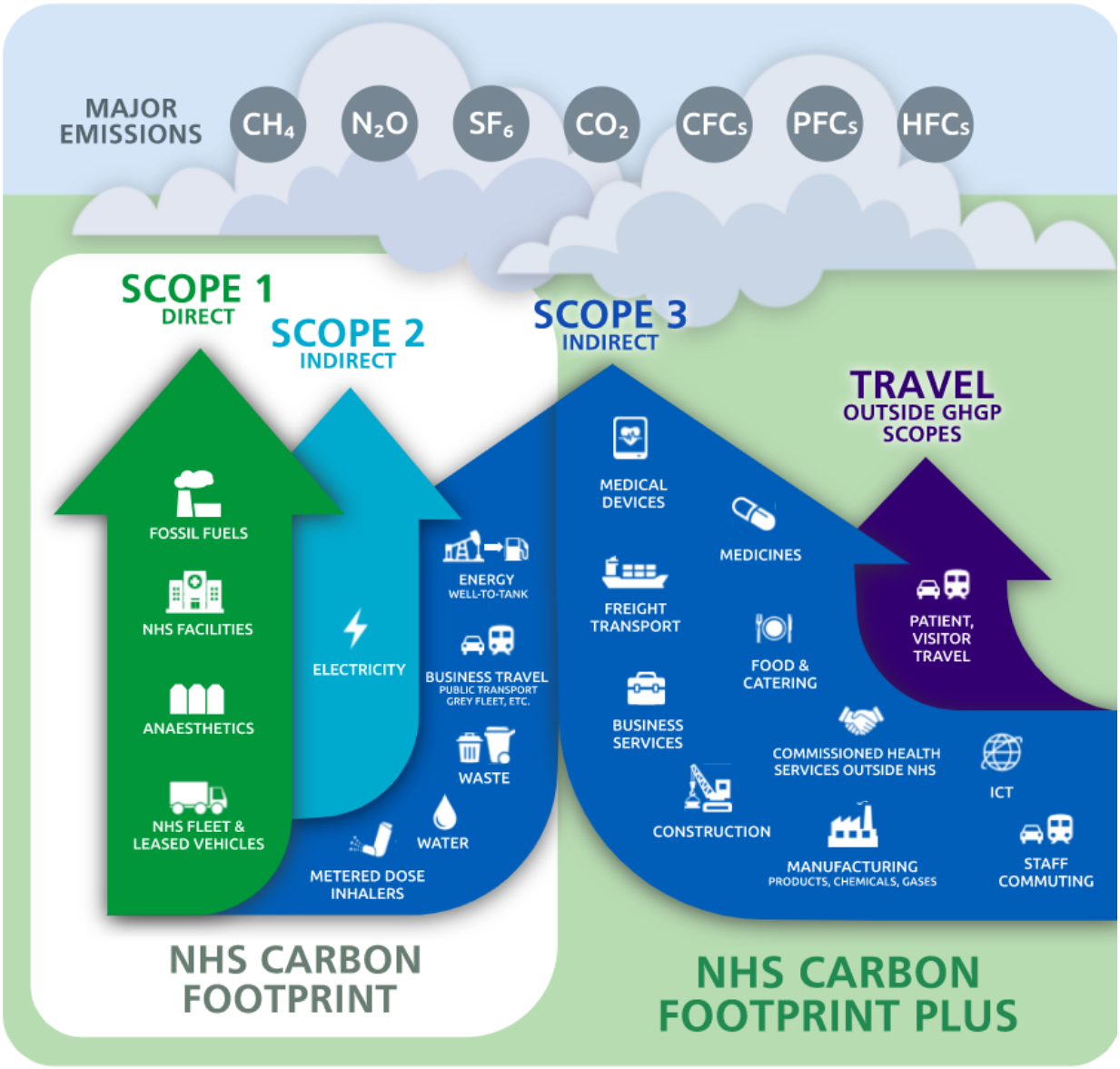


Figure 1-1 Greenhouse Gas Emissions From The National Health Service (NHS). NHS Carbon Footprint = emissions controlled directly by the NHS. NHS Carbon Footpring Plus = emissions we can influence. Image reproduced from the Delivering a 'Net Zero' National Health Service report (2022). Contains public sector information licensed under the Open Government Licence v3.0.

1.5.3 Ketamine

Ketamine is a dissociative agent that is popular for procedural sedation in the ED (Pai and Heining, 2007, Morton, 2004). It produces a dissociative state where the patient appears detached from the external environment entering a trance like state with

their eyes open and desensitised to pain. Ketamine has many different mechanisms of action but the main one is by acting as an NMDA receptor antagonist. By blocking the NMDA receptors, it prevents Glutamate, an excitatory neurotransmitter from binding and inhibits the transmission of an action potential.

Ketamine is lipophilic with a rapid onset and a time to peak effect of 1-5 minutes. It has a duration of action of 10-20 minutes. Dosing of ketamine is recommended at 1-2mg/kg of body weight administered over 1-2 minutes. Ketamine preserves protective airway reflexes and is felt to be haemodynamically stable secondary to its sympathomimetic properties. Common side effects associated with the use of Ketamine are hypersalivation and dysphoric auditory and visual hallucinatory emergence reactions. Ketamine should be avoided in patients with schizophrenia as it may potentially trigger a psychotic reaction.

1.5.4 Etomidate

Etomidate was traditionally used as an induction agent but at times also used for procedural sedation in the ED (Vinson and Bradbury, 2002). It has a brief duration of sedation with no analgesic effects. It exhibits very little cardiorespiratory upset but can cause myoclonic movements and is painful on injection. Despite it having little analgesic effect it was felt to be a safe and effective choice of drug as it caused relatively little cardiovascular instability. However, it was shown to cause adrenal suppression in those receiving infusions for sedation in Intensive Care Units (ICU) (Ledingham and Watt, 1983) but this was not evidenced after a single bolus (Thompson Bastin et al., 2014). Despite a lack of clinical evidence, etomidate remains an unpopular choice for procedural sedation and anaesthesia in the UK.

1.6 Propofol

Today Propofol (2,6-diisopropylphenol, Figure 1-2) is commonly used for the intravenous (IV) induction and maintenance of general anaesthesia as well as procedural sedation. It is a rapid acting IV sedative-hypnotic agent that exhibits rapid recovery with additional anti-emetic (Borgeat et al., 1992) and amnesic properties. It has no analgesic properties.

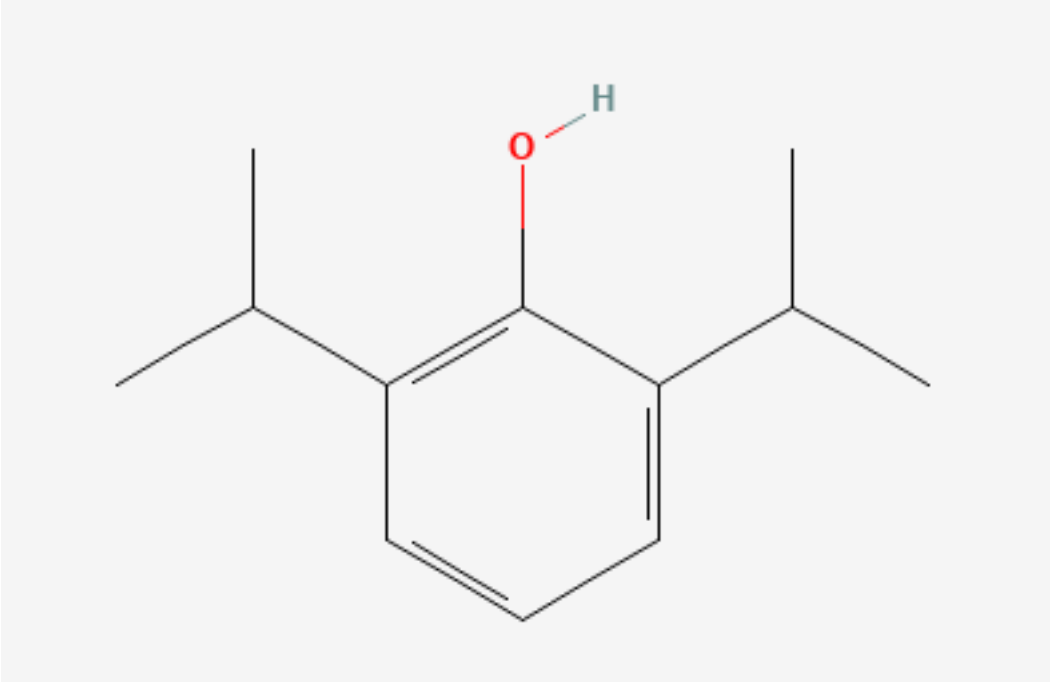


Figure 1-2 Chemical Structure of Propofol. Image used with permission from Pub Chem Propofol Compound Summary (https://pubchem.ncbi.nlm.nih.gov).

1.6.1 Development of Propofol

Propofol was developed by a team of researchers from the Imperial Chemical Industries (ICI) who gathered to look for and evaluate novel anaesthetic agents. They wanted to identify compounds that could be administered intravenously and provide a rapid recovery regardless of repeated doses in contrast to Sodium Thiopentone which exhibited delayed recovery when administered in repeated doses. They also sought to maintain the positive attributes of Sodium Thiopentone with its ability to provide a

rapid, smooth induction. Other compounds being evaluated at that time were often found to produce unwanted excitatory effects often manifesting as myoclonic movements.

Dr John B Glen, a veterinarian from the West of Scotland, led this multi-disciplinary group on their journey to develop Propofol to the solution that we are familiar with today. In their quest to discover novel anaesthetic agents, the ICI team had discovered a group of phenolic compounds that existed as oils at room temperature (James and Glen, 1980). Given that the solubility of these compounds in water was poor, this prohibited them from investigating further until a suitable carrier vehicle was identified.

Cremophor EL, a polyethoxylated castor oil derivate was identified as that suitable carrier vehicle and allowed the team to revisit that group of compounds. Dr Glen first noted the anaesthetic activity of Propofol or as it was referred to then, ICI 35 868, in the animal population on the 23rd May, 1973 (Glen, 2019). In 1980 Dr Glen presented the results of animal studies looking at the anaesthetic activity of Propofol in the British Journal of Anaesthesia (Glen, 1980), reporting the positive attributes that they had been seeking.

As clinical trials continued using the Cremophor EL, it become apparent that some of the trial participants experienced anaphylactoid reactions in response to the Cremophor EL (Baker et al., 2005, Briggs et al., 1982, Glen and Hunter, 1984). Trials using this preparation were halted as Dr Glen and his team at ICI looked for an alternative. Working with the ICI pharmaceutical department they identified the soybean emulsion formulation that we are familiar with today. This allowed the research to continue in the human population with the first patient receiving this formulation in July 1983 in a dose confirmation study (Cummings et al., 1984).

1.6.2 Propofol Pharmacokinetics

Propofol crosses the blood brain rapidly owing to its highly lipophilic nature. This enables it to exert it's sedative and hypnotic effects in less than a minute. Propofol is a γ-aminobutyric acid (GABA) receptor agonist acting by decreasing the dissociation of the GABA from the receptor, keeping the GABA-mediated chloride channels open for longer with hyperpolarisation of the cell membrane. This leads to inhibition of nerve conduction as it increases the threshold for an action potential to be conducted by hyperpolarising the cell membrane.

Propofol emulsion appears white to the eye and is available in 1% or 2% preparations. It is administered intravenously owing to low bioavailability because of high first-pass metabolism if given orally (Raoof et al., 1996). Propofol is extensively protein bound in the order of 97-98% and has a high volume of distribution (V_D), approximately $4L.kg^{-1}$.

When considering Propofol we use a multi-compartment model to predict its absorption, distribution, and elimination. All compartmental modelling is theoretical with the compartments themselves not equating to actual anatomical spaces but instead reflecting mathematical constructs that allows us to predict the pharmacokinetics of a drug.

A single compartment model assumes that the drug administered will stay within that compartment with equal distribution throughout that volume. We know that this is not the case for Propofol given its lipophilic nature hence why the three-compartment model is used (Figure 1-3). Our three compartments can be thought of as a central (V1) compartment, a well-perfused (V2) compartment, and a poorly perfused (V3) compartment.

Movement of Propofol between compartments is concentration dependent. The rate at which this equilibration occurs is known as the k_{e0}, a first order rate constant. The larger the k_{e0}, the faster the predicted equilibrium between the plasma and effect site.

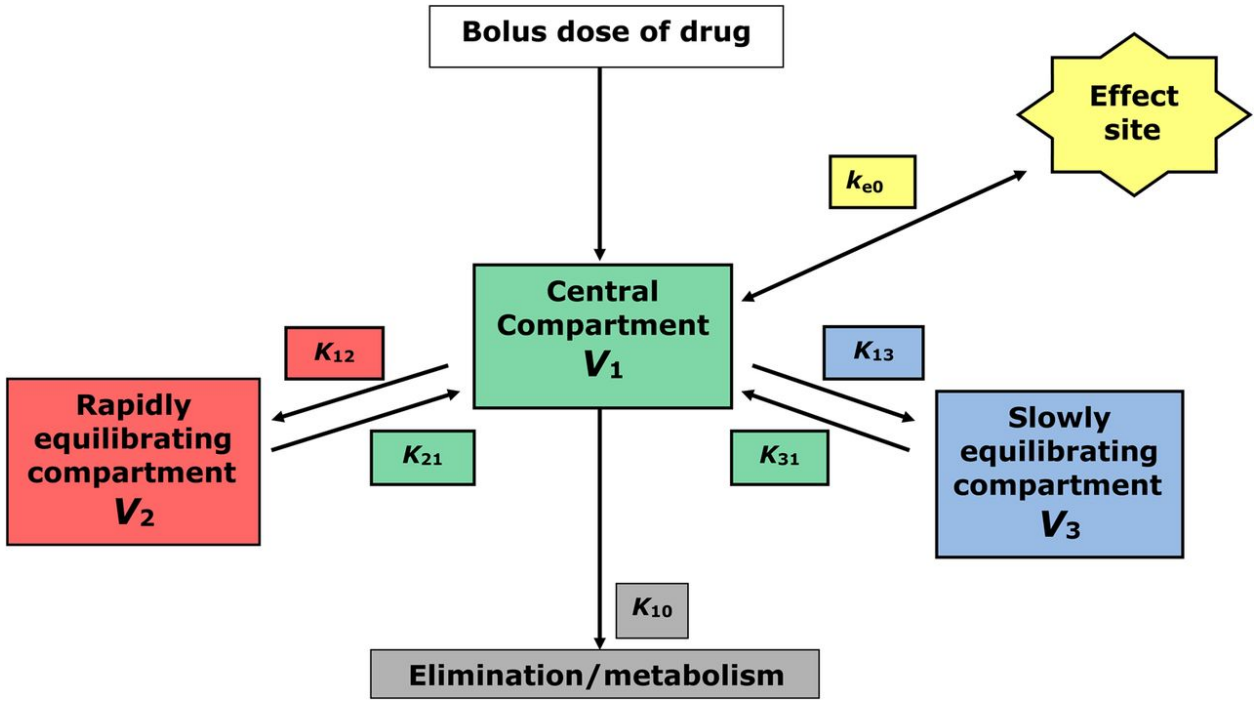


Figure 1-3 Three-compartment model outlining the different compartments and associated rate constants. a.$V_1/V_2/V_3$ = volumes of respective compartments b. K_{12} = rate constant between V_1 and V_2 c.K_{12} = rate constant between V_2 and V_1 d. K_{13} = rate constant between V_1 and V_3 e. K_{31} = rate constant between V_3 and V_1 f. K_{10} = rate constant for elimination of drug from the central compartment g. k_e0 = rate constant for equilibration between plasma and effect-site concentrations (Al-Rifai and Mulvey, 2016). Image reproduced with the permission of Elsevier.

A bolus dose of Propofol rapidly moves from the plasma (V1) into the peripheral compartments, this is known as the initial, distribution phase (Figure 1-3). The time taken for the plasma concentration to fall by 50% is known as the distribution half-life (t 1/2 (α)) and for Propofol this is 2-8 minutes, reflecting its fast offset (Khan et al., 2014). After the distribution phase is the elimination phase where concentrations of Propofol declines in all compartments. This is followed by the terminal phase.

During the terminal phase, stored Propofol is redistributed from the poorly perfused compartment into the central compartment. This is the most prolonged of all the phases.

When Propofol is administered as an infusion, the concentration in the compartments move towards achieving a steady state equilibrium which equates to the volume of distribution. Over time, as the concentration of the drug steadily increases with the infusion, the three compartments achieve a V_D known as steady state (V_{SS}). Steady state is achieved when there is no net flux between the compartments, the compartments have achieved a state of equilibrium where all movements are equal.

When considering Propofol infusions we must consider half-life times, the time for the concentration to fall to half its original value. Context-sensitive half-life time is used to describe the offset times of Propofol when used in an infusion with the underlying principle that the longer the infusion time the longer the offset time (Bailey, 2002). Propofol has been shown to decrease its plasma concentration by 50% within 5 minutes of stopping a short infusion. When an infusion is longer, >8 hour, the context-sensitive half-life time will increase significantly, upwards of forty minutes (Sahinovic, Struys, and Absalom, 2018). This is not a concern in the Emergency Department where an infusion for procedural would be short lasting.

Propofol is mainly metabolised by the liver with other sites being the kidneys, small intestine with some believing that the lungs are also potential sites (Dawidowicz et al, 2000). Metabolites of Propofol do not exhibit any hypnotic activity. Eighty eight percent of Propofol is excreted in the urine within five days occasionally turning it green.

1.6.3 Propofol Pharmacodynamics

Propofol has obvious clinical effects on numerous systems; respiratory, cardiovascular, and central nervous system.

Positive effects of Propofol during procedural sedation are its ability to create a hypnotic effect on the patient altering their consciousness as they move through the continuum of sedation with an eventual state of unconsciousness as they enter general anaesthesia. It also induces amnesia and anxiolysis.

The main negative effect of Propofol is that it is a potent respiratory depressant at sedative doses. The respiratory depression becomes more pronounced as the dose increases, reducing responses to hypercapnia and hypoxia eventually leading to apnoea. There is also loss of upper airway reflexes with upper airway relaxation which is good for induction of anaesthesia and airway instrumentation but undesirable in procedural sedation when maintenance of ventilatory effort and respiratory protection is required.

Propofol administration causes a fall in the systemic vascular resistance with a resultant fall in blood pressure. This has been shown to be more pronounced in frail, elderly and particularly in blood volume depleted, cardiovascularly unstable patients.

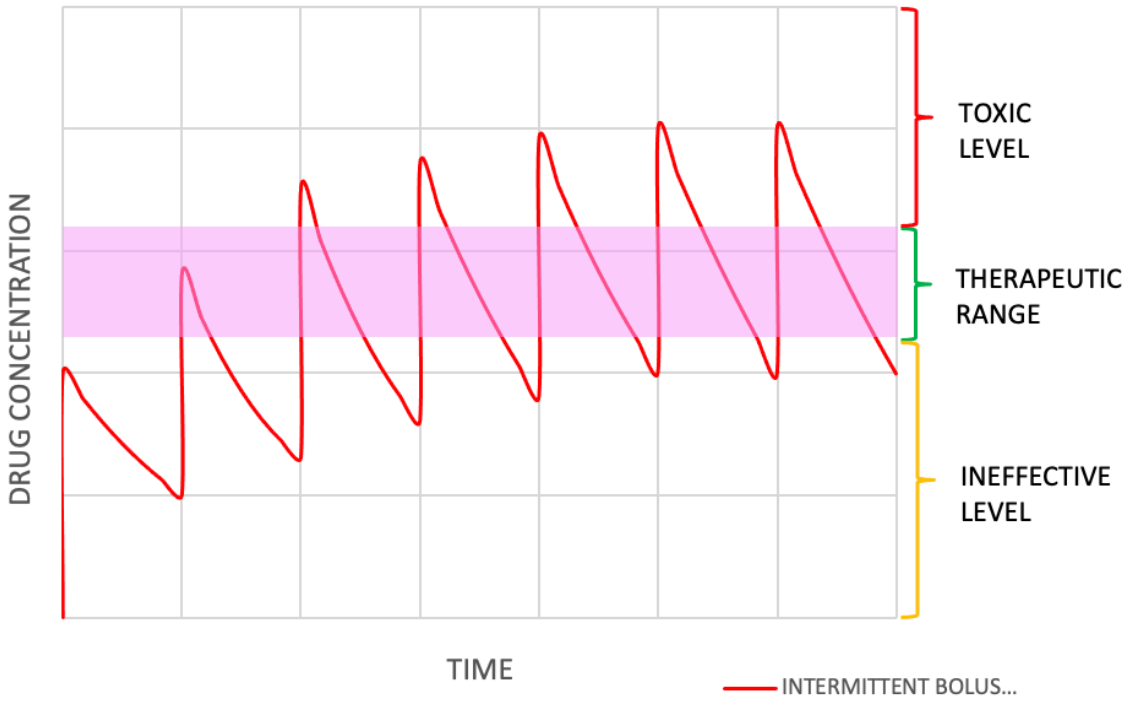


Figure 1-4 Plasma concentration of Propofol after successive bolusing showing the relationship between this and the resultant clinical effects. Successive bolusing leads to plasma concentrations that overshoot the therapeutic range resulting in unwanted clinical effects like apnoea or hypotension.

Concerns highlighting the use of Propofol by non-anaesthetists are not uncommon (Wade, 2014, Lamb and Harper, 2014, Green et al., 2016). In response to an article (Davison and Stewart, 2009) describing Propofol sedation for reduction of hip dislocations in the ED, a group of anaesthetists (Anderson et al., 2010) from Glasgow felt the results demonstrated that it represented unsafe clinical practice.

The initial reporting in the article did not present the incidence of adverse events with confidence intervals (CI) but the authors of the letter did. They reported that the rate of airway/respiratory events equated to 80/1000 but potentially could be anywhere between 26 and 134/1000 patients. They compared unfavourably to the adverse incidence rate of 0.3 (95% CI – 0.3 to 0.9)/1000 patients in a group of 3000 patients undergoing conscious sedation for oocyte retrieval (Edwards et al., 2010).

Review of the oocyte retrieval article (Edwards et al., 2010) showed that the way in which the Propofol was delivered was different to our standard bolus administration in the ED and was delivered using a target-controlled infusion (TCI) system. The ability to target a concentration and smooth out the variability inherent with bolus dosing (Figure 1-4 & 1-5) may be a safer option in the ED (Green and Krauss, 2016).

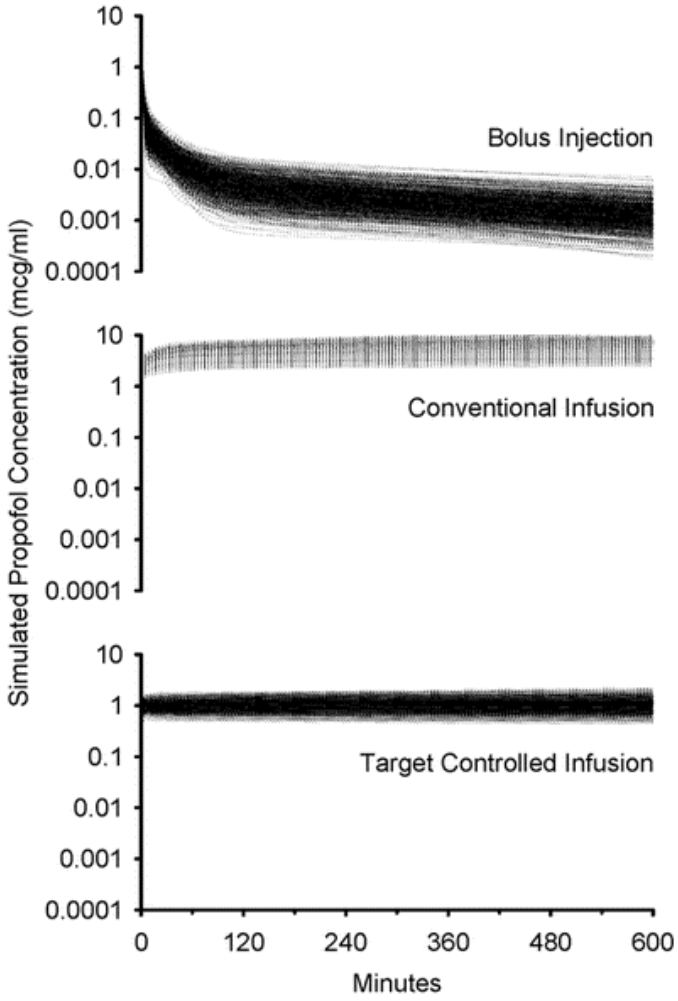


Figure 1-5 Simulated Propofol Concentration; Bolus, Infusion & TCI
Simulation of 1,000 patients receiving either a 10-mg bolus of Propofol (top graph), a Propofol infusion at 10 mg/minT1-5016 (middle graph), or a target-controlled infusion of Propofol at a target plasma concentration of 1 µg/ml (bottom graph). The log scale permits visual assessment of the coefficient of variation for the three drug delivery paradigms. The coefficient of variation is greater with bolus injection. (Hu et al., 2005) Reproduced with permission from Wolters Kluwer.

1.7 Summary

Emergency Medicine has evolved over the years and continues to do so. Patient safety has been at the heart of all the developments made within the field. Procedural sedation is commonly undertaken by trained clinicians in line with current guidance in a safe environment with monitoring. Adverse events do still happen

despite this, and these are often cardio-respiratory in nature with the potential to cause morbidity or mortality.

There is an increased frequency in the use of Propofol for procedural sedation in the Emergency Department. Propofol has the potential to have negative impacts on the cardio-respiratory system and cause harm to the patient if dosing and tissue concentrations are in excess of the therapeutic window.

Normal practice in the ED is to administer Propofol in intermittent boluses which results in peaks and troughs in the drug concentration. TCI provides the ability to choose a target concentration within the therapeutic window eliminating the peaks and troughs in propofol concentration.

Chapter 2 Target-Controlled Infusion

TCI is used extensively outside of the ED and is no longer considered a 'new' technology in these areas (Edwards et al., 2010). It is used in dentistry (Oei-Lim et al., 1998), for alleviation of anxiety in MRI imaging (Haberman and Oliver, 2013), to supplement local/regional anaesthesia (Arslan and Sezen, 2020, De Castro et al., 2003), sedation for bronchoscopy (Caron et al., 2015, Lee, 2004) and for endoscopy (García Guzzo et al., 2020). What could be taken from other areas into the ED to develop procedural sedation with improved safety?

2.1 What is a Target-Controlled Infusion?

A Target-Controlled Infusion (TCI) system consists of a user interface, microprocessor(s) with PK software, infusion pump and audio-visual safety alarm systems. When a target concentration is entered, along with the patient covariates, the system will calculate a bolus dose and subsequent infusion rate to achieve and maintain that target concentration. Infusion rates are adjusted in accordance with the calculations being continuously updated. Combined with the expertise of the operator who has pre-existing knowledge of the drug being used, PK models and real time clinical information from the patient, TCI is delivered (Figure).

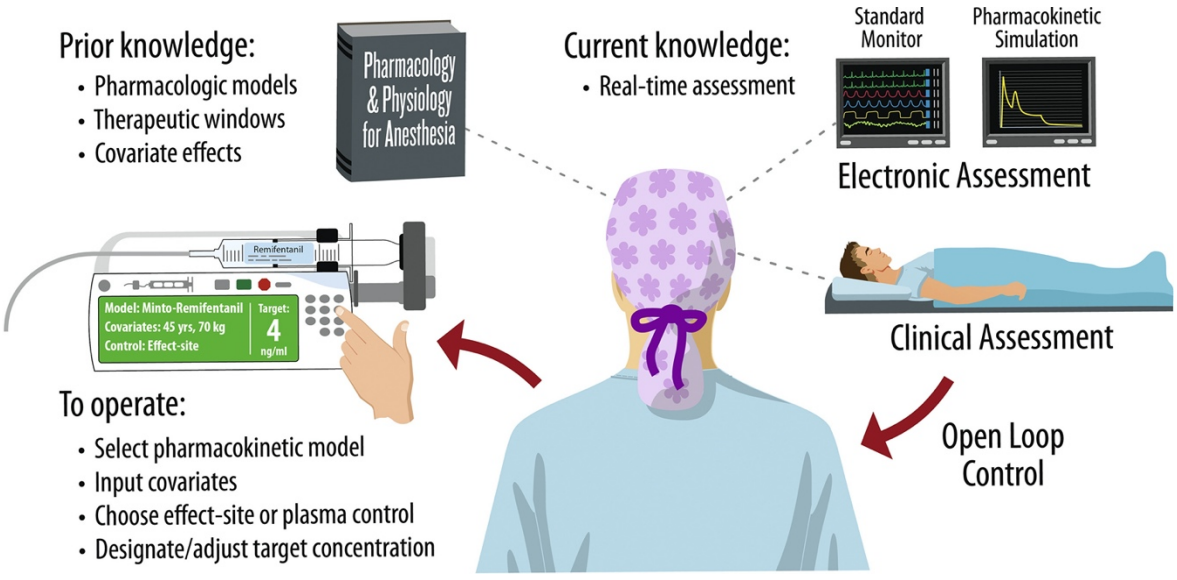


Figure 2-1 Operating a Target-Controlled Infusion (TCI) pump.
A schematic layout of selected elements of the knowledge base and clinical assessment required to operate a TCI pump. No element can work independently of the other and administration of TCI requires the human and machine based interactions. Reproduced from Egan et al. (2020) with permission.

The target concentration can be either the plasma concentration (C_{pt}) or the effect site concentration (C_{et}). Effect site TCI is referring to the concentration at the brain. If a target concentration is increased, an additional bolus is given, and the infusion rate is adjusted to achieve the higher target concentration. If the target concentration is decreased, the infusion is stopped until the target concentration is reached and then the infusion is restarted at a rate to maintain the lower target concentration.

This is displayed in Figure 2-2 where the C_{pt} has initially been set at 3 µg/ml. A bolus is administered with the infusion returning to a steady state as the concentration at the effect site rises (C_{et}). The operator then chooses to increase the C_{pt} to 6 µg so another bolus is given with an associated peak in the concentration and a subsequent reduction to a steady state at a higher concentration. The C_{et} continues to rise. At ten minutes the operator reduces the C_{pt} to 3 µg/ml. The infusion stops for a period

of time as dictated by the model and then resumes at a lower rate to allow the C_{et} to decrease.

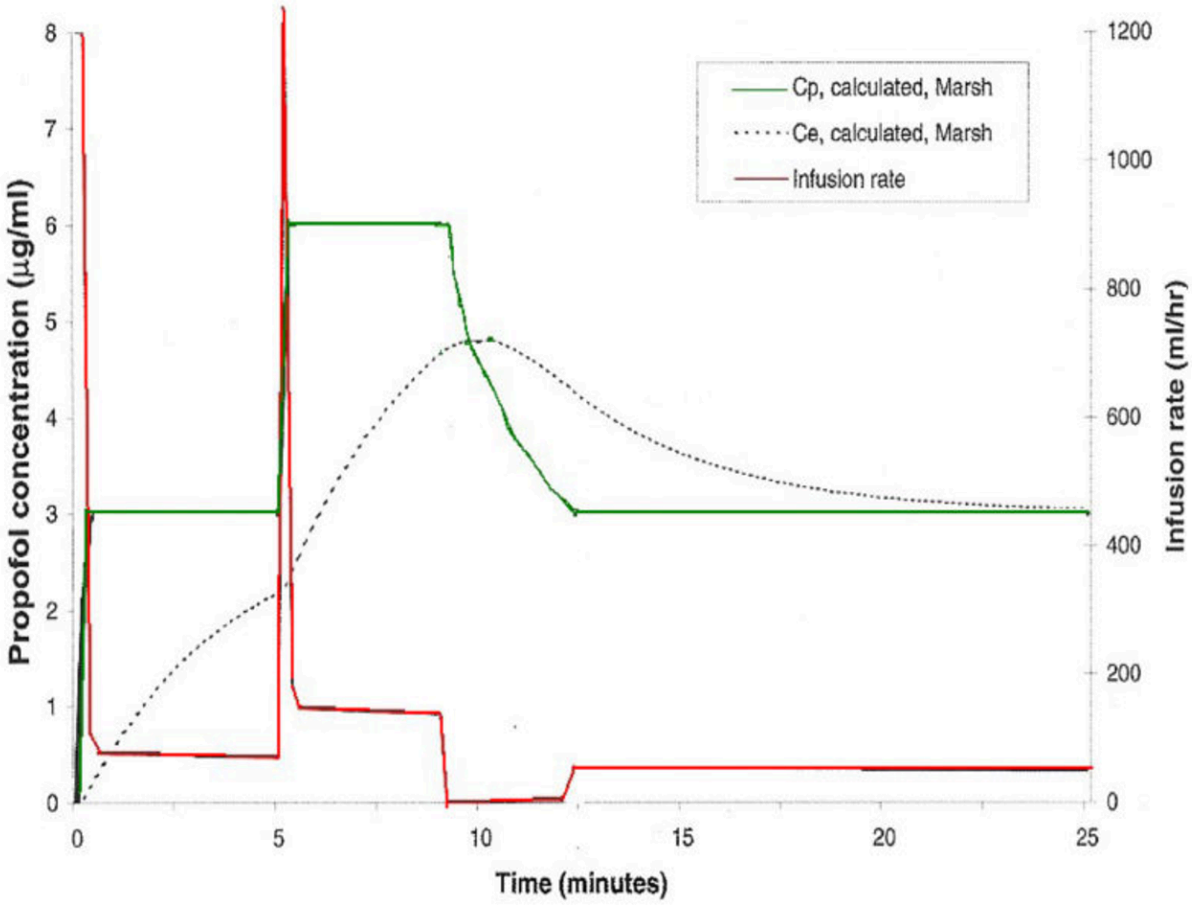


Figure 2-2 C_{pt} and C_{et} concentrations during a Propofol TCI using the Marsh model. Changes in both concentrations when the target concentrations is adjusted are shown. Phases shown are the initial target concentration set followed by an increase in the target concentration and then a reduction in the target concentration. Reproduced with permission from the World Federation of Societies of Anaesthesiologists (https://resources.wfsahq.org/atotw/target-controlled-infusions-in-anaesthetic-practice-anaesthesia-tutorial-of-the-week-75/).

2.2 History of TCI

Prior to the launch of the first commercial target-controlled infusion (TCI) system in 1996, TCI systems had been developed and used in research settings. TCI systems used various Pharmacokinetic (PK) models with some based on two compartment and

some three compartments. Various systems existed with differing PK models meaning there was no standardisation. Huge variation was noted across the studies whereby TCI systems using the same target Propofol concentration (Vuyk et al., 1992) but different PK models, led to very different measured Propofol concentrations and clinical outcomes.

In 1992, ICI collaborated with the TCI community to develop a TCI system to administer Propofol for the maintenance of anaesthesia considering safety, efficacy, and expert opinion. ICI chose to develop the Diprifusor module. The Diprifusor TCI system was the first commercially available in 1996.

2.2.1 Nomenclature

In 1997, a group of experts in the TCI field collectively agreed the nomenclature (Glass et al., 1997) for these devices. TCI was defined by the group as 'all such systems that require a microprocessor-controlled infusion pump programmed with infusion rate control algorithms linked to a PK simulation programme. The program includes a PK model and a specific set of PK parameters for the drug to be infused. Target-controlled infusion (TCI) now replaced; computer-assisted total intravenous anesthesia (CATIA), titration of intravenous agents by computer (TIAC), computer-assisted continuous infusion (CACI) and computer-controlled infusion pump (CCIP) (Figure 2-3). The removal of computer from the nomenclature, highlighted that a clinician was adjusting the targets to maintain the desired clinical effects. The group also outlined the terminology that should be used to denote the target site concentration.

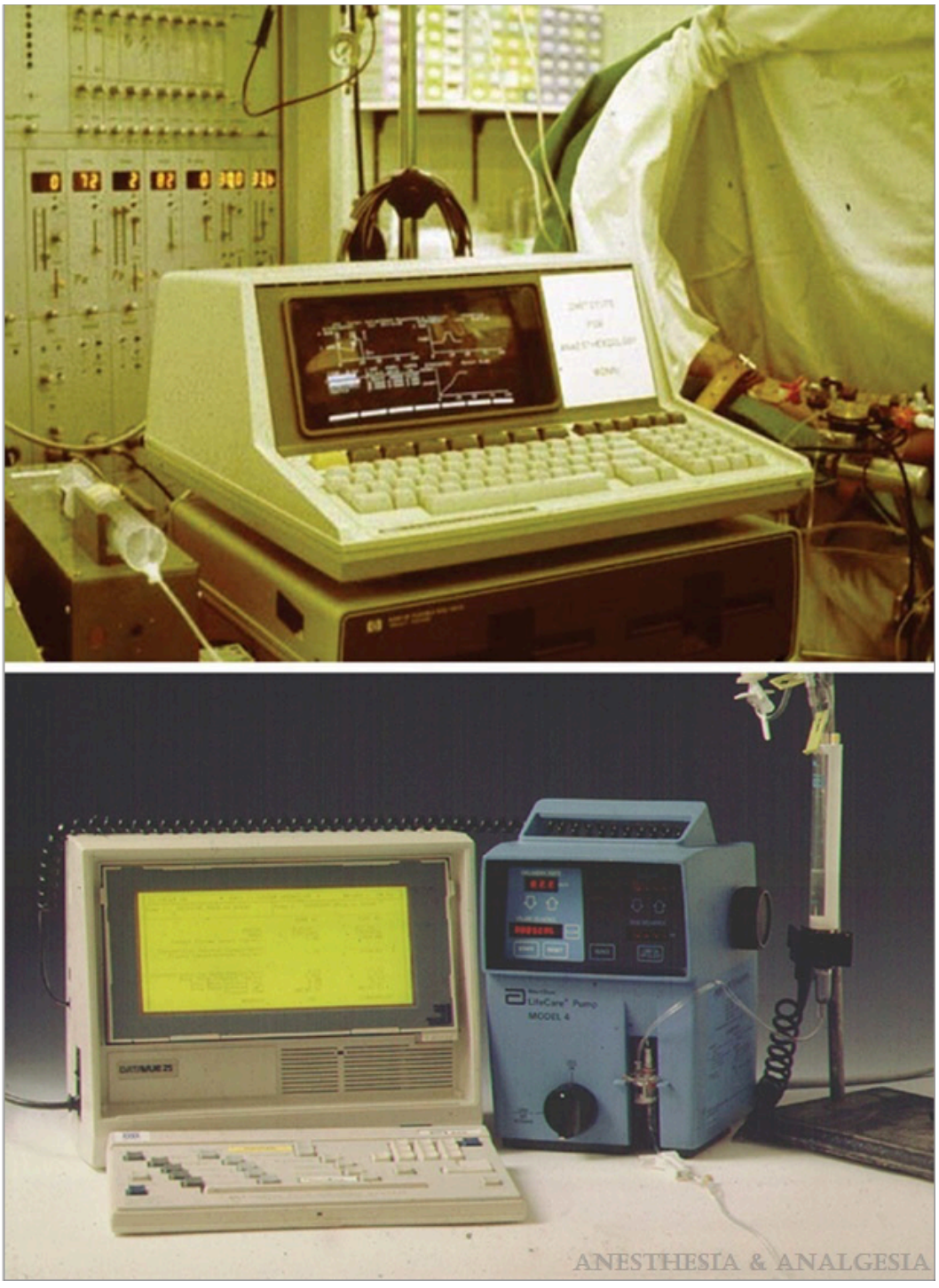


Figure 2-3 Computer TIVA systems.
Top image, Computer-assisted total IV anesthesia system; Bottom image, Computer-assisted continuous infusion II system. Reproduced with permission (Struys et al., 2016).

2.2.2 Diprifusor

White and Kenny (Glen, 1998, Gray and Kenny, 1998) from the University of Glasgow developed the Diprifusor module. The Diprifusor module utilises two microprocessors to solve the PK equations based on the three compartment Marsh model (Marsh et al., 1991) aiming for a target plasma concentration defined by the clinician. There was an error in the Marsh manuscript published that was subsequently used to develop the Diprifusor software (Glen and Servin, 2009). The publication was meant to detail a k_{12} of 0.112min^{-1} but it accidentally retained a k_{12} of 0.114 min^{-1} from the Gepts model which Marsh was based on (Gepts et al, 1987).

The second microprocessor was employed as a safety feature to check the calculations of the first microprocessor. This module was placed into a conventional syringe infusion pump allowing it to now function as a Diprifusor TCI system (Figure).

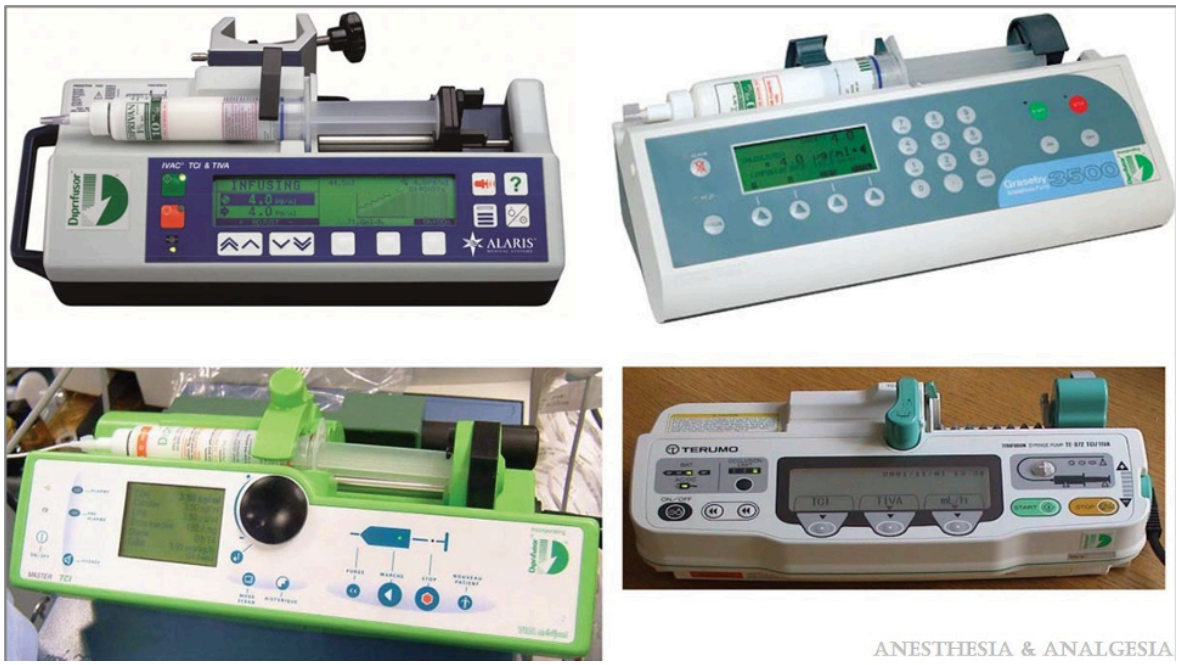


Figure 2-4 TCI pumps incorporating Diprifusor module.
Top Left - Alaris IVAC P6000 TCI pump, Top Right - Graseby 3500 syringe pump, Bottom Left - Fresenius Master TCI pump, Bottom Right - Terumo TE-372 syringe. Reproduced with permission (Struys et al., 2016)

The Diprifusor system could only be used with pre-loaded Diprivan™ syringes that had unique identifier labels (Struys et al., 2016). As generic Propofol was manufactured and replaced Diprivan™, the commercial market opened for development of new open TCI systems capable of delivering other medications, using other PK models, and targeting the effect site. Whilst this has led to a decrease in the number of Diprifusor pumps, they paved the way for TCI moving it from the research tool to clinical use.

2.3 TCI model Development

2.3.1 PK/PD Modelling

A PK/PD model can outline the relationship between dose, concentration, desired effects, and side effects. It is an alternative to conventional "dose-effect" analysis of drug effects.

2.3.2 TCI Models

There are three commonly used and one more novel model for Propofol TCI. Models commonly used are the Marsh, Modified Marsh and Schnider. The Eleveld model is the most recent. All are based on three compartment models.

2.3.2.1 Marsh Model

The Marsh (Marsh et al., 1991, Gepts et al., 1987) model has a central compartment volume, V1 of 0.228 ml/kg^{-1}. The only PK variable used in this model is the volume of V1. The Marsh model increases the volume of V1 as the body weight increases. Rate constants in the Marsh model are fixed with a k_{e0} of 0.26 min^{-1}. There are no adjustments made based on age and inputting the age when setting up the pump is a safety feature to ensure it cannot be used in the paediatric population.

2.3.2.2 Modified Marsh Model

A 'modified' Marsh (Struys et al., 2000) module was developed to allow effect site targeting. On the original Diprifusor TCI pump screens, the C_{et} was for information only. To allow effect-site targeting using the Marsh model a new k_{e0} of 1.2 min^{-1} was suggested and is currently used in TCI systems for effect site targeting using the 'modified' Marsh method.

2.3.2.3 Schnider Model

The third commonly used model in commercially available TCI systems is the Schnider (Schnider et al., 1998, Schnider et al., 1999) model. This contrasts with the Marsh model by looking at multi-covariates; age, height, total body weight and lean body mass (LBM) as opposed to just weight. Compartment volumes of V1 (4.7 L) and V3 are fixed with the volume of V2 decreasing with age. This impacts upon the rate of the infusion after the initial bolus as the decrease in compartment size and associated clearances signifies a slower decrease in the plasma concentrations. This is used to estimate the $k_{10,}$ the elimination rate constant and allows the system to adjust the infusion rate to compensate for the anticipated losses. PK/PD modelling was used to derive a k_{e0} of 0.456 min^{-1} for this model.

2.3.2.4 Eleveld model

Researchers have developed the Eleveld Propofol PK-PD model as one that they feel is more applicable to the general population (Eleveld et al., 2018). The development of this model incorporated PK data derived from 30 published studies. A total of 1033 patients were included spanning age range from 27 weeks to 88 years old. This model uses age, post-menstrual age (PMA), weight, height, sex, and administration of concomitant anaesthetic agents as variables when determining drug dosages. The Eleveld model was developed using a large group of patients in comparison to both Marsh and Schnider and has incorporated a greater number of covariates in the model to potentially deliver safer, more accurate Propofol TCI.

A recent study (Vellinga et al., 2021) seeking clinical validation of the Eleveld Propofol model in general anaesthesia recruited four groups of 25 patients undergoing elective surgical procedures. Results showed a low population bias and that the model performed at least as well as the other TCI models designed for specific populations.

2.4 TCI Site Targeting

TCI systems can be programmed to target either plasma (C_{pt}) or effect (C_{et}) site concentrations.

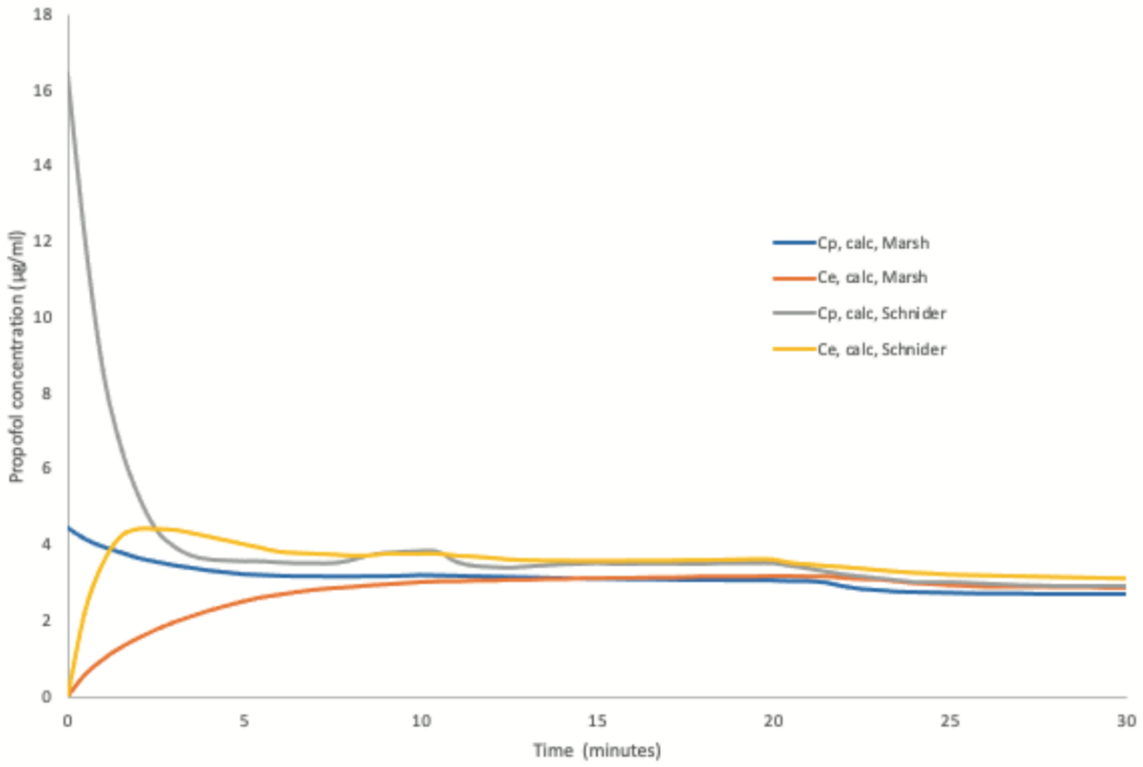


Figure 2-5 Estimated Propofol concentration at C_{et} & C_{pt} using Schnider vs Marsh model during a TCI infusion set with for a target concentration of 3 µg ml^{-1}

2.4.1 Plasma Site Targeting (C_{pt})

When a clinician enters the desired plasma target concentration, there is a delay to the onset of the intended clinical effect when the target plasma concentration has been reached. This is due to the three compartment PK model that describes eventual equilibration with the effect site. This lag between plasma concentration and clinical effect is known as hysteresis.

The size of the initial bolus in plasma targeting is directly proportional to the value of V1. Bolus dose (mg)= ($C_{p,\ target,\ new}$-$C_{p,target,\ old}$) x V_1 ÷ drug concentration in syringe.

In the Marsh model, V1 varies with the weight of the patient (22.8 ml/kg) but is fixed at 4.27L regardless of the patient's weight in the Schnider model. This means that all patients regardless of age, weight and height receive the same initial dose using Schnider. This isn't adequate and the Marsh model is the preference for plasma site targeting as it delivers a larger initial bolus dose as the weight increases.

2.4.2 Effect Site Targeting (C_{et})

Effect site targeting is an alternative when we want to decrease the time taken to achieve the intended clinical effect. Equilibrium between the plasma and effect site is dependent on many factors only one of which we can influence and that is the concentration gradient.

The k_{e0} describes the rate at which the drug moves between the central compartment and the effect site. The movement of Propofol between compartments is dependent on the concentration gradients between compartments, this follows first-order kinetics, and the rate constant is the k_{e0}.

The slower the $k_{e0,}$ the longer it takes to achieve plasma and effect site equilibration. This is important to appreciate when considering the various TCI models commercially available and choosing which is most appropriate for the patient.

Effect site targeting requires plasma overshoot with the initial bolus dose based on the PK model used and the associated k_{e0} (Figure 2-5). The Schnider model is

favoured for effect site targeting. This PK model incorporates age, weight, and height. Despite the k_{e0} of 0.456 min^{-1} being larger (faster) than the 0.26 min^{-1} of the Marsh model, the initial dose administered via the Marsh model is significantly higher for the same given body weight because of the relationship between V1 and weight in the Marsh model. This difference may have undesired PD effects on the patient. The modified Marsh model uses a higher k_{e0} of 1.2 min^{-1} which partially compensates for the larger V1 volumes with a smaller increment in the initial dose.

2.5 Special Circumstances

2.5.1 Frail & Elderly

In the UK, the population is growing (Dunnell, 2008). Adults aged 85 years and older account for the fastest growing age group. Those over state pension age exceeded the size of the group aged under 16 in 2007. The population is predicted to continue to grow and become increasingly older. As patients age, their physiology (Aalami et al., 2003) changes and this must be considered when choosing the most appropriate TCI model.

Unlike the Marsh model, development of the Schnider model (Schnider et al., 1999, Schnider et al., 1998) used age as a co-variate. As a patient's age increases, doses and infusion rates are adjusted accordingly. As a result, this may be the chosen model for some clinicians for their older, frailer patients. Other models can still be used in this group with the choice dependent on the individual clinician and their preference.

2.5.2 Obesity

A Body Mass Index (BMI) ≥ 30kg/m^2 defines obesity as outlined in a WHO consultation report (Prevention, 1997), with a BMI ≥ 50 kg/m^2 classed as super morbid obese. These patient groups were not included in any of the studies from which the Marsh and Schnider models were derived. Super morbid obese patients would generally be out with the patient population that would be sedated in the Emergency Department but those that sit between BMI 30-40 are not uncommon as we have an increasingly overweight population (Wang et al., 2011). Obesity impacts the PK properties of Propofol as the increased fat compartments create a larger reservoir for lipophilic drugs by increasing the volume of distribution. It also impacts upon the peak plasma concentration, elimination half-life and clearance of drugs. This impact on plasma concentrations has a subsequent effect on the PD of Propofol.

As an individual's total body weight (TBW) increases, so too does the amount of fat and lean body weight. The relationship is not proportionate when the BMI >35kg/m2 in females and >42kg/m2 in males and fat accounts for an increasing proportion of the TBW (Coetzee, 2014). Most of the blood flow is to the lean tissue groups and the fat compartments have a relatively poor blood supply. The risk of this is when the TBW is used, as in the Marsh model, there is an assumption that the lean body weight has increased proportionately, and the bolus dose calculated results in an overdose. The use of Servin's formula (Servin et al., 1993) in this group to calculate a corrected body weight to enter in place of the TBW has been advocated (Al-Rifai and Mulvey, 2016):

- [Ideal Body Weight (IBW) + 0.4 x (TBW-IBW)] When - IBW = Ideal BM (male 26, female 22) × height^2(m)

Lean body mass (LBM) is the difference between TBW and fat mass. The Schnider model uses LBM as a covariate derived from the James' formula (Waterlow, 1976, Absalom et al, 2009):

- LBM (male) = 1.1 x weight – 128 x (weight/height)^2
- LBM (female) = 1.07 x weight – 148 x (weight/height)^2

The Schnider model uses weight and LBM to calculate k_{10} min $^{-1}$:

- 0.443 + 0.0107 × (weight−77) − 0.0159 × (LBM−59) + 0.0

Using the James' formula to calculate the LBM functions well in the non-obese patients but as the BMI >35kg/m^2 in females and >42kg/m^2 in males the LBM begins to decrease towards zero. Instead of the weight and LBM increasing simultaneously as expected, the LBM begins to decrease and the calculated k_{10} increases resulting in increased infusion rates.

Emerging models developed using data from obese patients may be possible solutions in the future (Cortinez et al, 2010, Eleveld et al, 2018).

2.6 Which model should be used?

I have discussed various TCI models and when one may be more appropriate than another dependent on the clinical scenario.

Development of the Eleveld PK/PD (2018) model could possibly have simplified this choice. It suggests it is appropriate for all co-variants with a reassurance that the population being sedated were considered when it was developed. Having one accepted model could potentially increase clinician 'buy-in' to the use of TCI

technology. Clinicians may be more trusting of a one size fits all model, potentially combatting decision fatigue (Zheng et al., 2020) but could this possibly result in the clinician understanding less about how it works, and the calculations made?

Whilst each model has its merits, one of the key factors is to achieve consistency and familiarity with the model being used (Absalom, Mani and Struys, 2009). Consistency should ideally be achieved within departments using TCI to avoid potential patient safety disasters. Users must be familiar with the model they are using to allow them to programme them safely for each patient and trouble shoot if the sedation is not occurring as expected. Patient safety and aviation history have taught us the importance of this (Mongan & Kohli, 2020, Van Beuzekom et al., 2010).

2.7 Summary

TCI has been called ‘a mature technology’ by Absalom et al (2016) but this is within the realms of anaesthesia and not in other clinical settings delivered by non-anaesthetists. In the Emergency Department TCI is perceived as something novel and complex.

The feasibility of a future RCT using Propofol TCI in the Emergency Department for procedural sedation had to be considered. Was TCI technology already being considered in other Emergency Departments? Is this something that had already been researched? If not, what barriers might be present to the introduction of this technology?

Chapter 3 Research standards for studies involving procedural sedation

3.1 Introduction

Inconsistencies in research standards exist for research on procedural sedation. In 2017, the Sedation Consortium on Endpoints and Procedures for Treatment, Education, and Research (SCEPTER) published a two-part paper (Ward et al., 2018, Williams et al., 2017) evaluating patient-centred outcomes in clinical trials of procedural sedation. Their aim was to define domains that should be consistently considered when planning a research study. They identified four key domains that are as applicable in routine procedural sedation as well as the research environment. Procedural sedation should be safe, effective, patient centred and efficient.

3.2 Safe

Safety of any new development in procedural sedation is key. We want to avoid patient harm and the incidence of adverse events. My aim is to show that TCI is superior or at the very least, non-inferior to bolus administration of Propofol. Extensive use of TCI technology in other clinical settings satisfied us and the ethics committee that it was safe to explore further in Emergency Medicine procedural sedation.

3.2.1 Adverse Events

Inconsistency with definitions and recording across research studies makes it difficult to ascertain what the actual incidence of adverse events are and what the term itself means.

Prior to publication of a consensus document by the Society of Intravenous Anaesthesia (SIVA) in 2012 describing an adverse event reporting tool, there was no agreed definition of sedation related adverse events due to the wide disparity in what people consider to be an adverse event. Generally, the vast majority of adverse events in procedural sedation impact on the respiratory and cardiovascular systems. However, there is not only variation in the definition of cardiovascular and respiratory adverse events but in the severity of the events classified as significant adverse events.

Recording of adverse events for research in procedural sedation is also important (Ward et al., 2018, Williams et al., 2017). Both researchers and clinicians are aiming to have an instance where the incidence of adverse events with a new sedation technique or novel drug is almost negligible, or at the very least less than or equal to the existing procedural sedation practice.

3.2.1.1 Definition of Adverse Events

Sentinel events were defined by the Joint Commission (Chen et al., 2015) as:

> *'an unexpected occurrence involving death, serious physical or psychological injury.'*

Sentinel events are rare in procedural sedation (Roback et al., 2018) and as a result, occur so infrequently that they can't be used alone to comment on the safety of the procedural sedation being undertaken (Ward et al., 2018). This is when adverse events prove useful to identify the potential to deteriorate into a sentinel event. Thresholds for these are very different with some choosing limits related to duration whilst others have no associated duration. Others are only identified as 'adverse' if an intervention was undertaken. In one study hypoxia was defined as oxygen

saturations (SpO_2) below <85% (Messenger et al., 2008) whilst in another study it was defined as SpO_2 <93% (Deitch et al., 2010). Consistency is required to allow meaningful statistical comparisons of procedural sedation studies and the pooling of results in a meta-analysis.

3.2.1.2 World Society of Intravenous Anaesthesia (SIVA) Adverse Event Reporting Tool

Many attempts were made by various organisations to define an adverse event; the Institute of Medicine (Kohn et al., 2000), European Medicines Agency (1994), World Health Organisation (World Health Organization, 2002) and the United States Food and Drug Administration (Sonawane et al., 2018) all published definitions, but experts felt they weren't specific enough for sedation related adverse events. An international group of experts were gathered to form the World Society of Intravenous Anaesthesia (SIVA) International Sedation Task Force (ISTF) to define sedation related adverse events and develop a reporting tool to help with research in the area and drive excellence in clinical care. In 2012 they published a paper that defined sedation related adverse events as:

> *'unexpected and undesirable response(s) to medication(s) and medical intervention used to facilitate procedural sedation and analgesia that threaten or cause patient injury or discomfort.'*

As part of this exercise, they developed an adverse event reporting tool to standardise reporting and thresholds for recognition of an adverse event (Mason et al., 2012). The intention was to help reporting in research by being able to combine and contrast results and in the clinical environment so that subjectivity could be removed to allow accurate recording of adverse events.

The SIVA adverse event reporting tool has five steps. Firstly, it asks the reporter to identify the adverse event in a predetermined list divided into minimal, minor and sentinel categories. Secondly, they then identify any interventions undertaken to treat the adverse event in a predetermined list divided into minimal risk, minor risk, moderate risk and sentinel intervention. The reporter then notes the outcome of the adverse event; no adverse outcome to sentinel outcome and assigns a severity rating to the adverse event. Severity ratings range from a Sentinel adverse event to a minimal risk adverse event.

In the RCEM 2017/18 national audit of ED procedural sedation (2018) they reported on adverse events. Of the 8815 patient encounters included in the sample, 3% had an adverse event documented. These were reported as 0.6% oxygen desaturation (severe <75% at any time or prolonged <90% for >60 seconds), 0.8% apnoea (prolonged >60 seconds), 0.3% cardiovascular collapse/shock (no definition), 0.2% cardiac arrest/absent pulse and 1.7% other (no definition). In the outcome analysis it shared that of the 8815 patient encounters, 0.1% died (nine patients), 0.06% had a permanent neurological deficit and 0.01% developed pulmonary aspiration syndrome. The RCEM contacted the centres that reported these outcomes. They found that of the deaths, seven were not directly attributable to the sedation, they were unable to get details of one and the remaining case was felt to be directly attributable to the sedation and was under investigation. At that point in time the SIVA adverse event reporting tool was the tool recommended by international experts. It was reported as being used in 0.2% of the adverse events.

In 2019, results from the SIVA adverse event reporting tool database were published (Mason et al., 2019). The data was collected between 14/12/2010 to 12/11/2018 and contained information on 7952 sedations entered during that time. Of these entries, 622 were reported as adverse events. The mean age of the population was 33 years (0.02-98.7) with the distribution of adult versus paediatric sedations at 50.9% and

49.1% respectively. Countries, settings, and procedures were reflective of the international, multispecialty use of the tool. Most patients, 94.5%, were ASA 1 or 2 and were having procedural sedation for non-emergent procedures. Only 2% of the population, approximately 159 patients, were undergoing emergent procedures.

In the group who experienced adverse events, the mean age was 32.1 (0.1-98.7) years. Twelve (2.9%) had sentinel outcome risks with no deaths being reported. There were 94 sentinel events (15.1%); 65 patients had an Oxygen desaturation (75% at any time), 25 had prolonged apnoea (>60 seconds), three experienced cardiovascular collapse/shock and three had a cardiac arrest/absent pulse.

The majority of the adverse events were classified as moderate. There were 389 (62.5%) moderate adverse events; 128 oxygen desaturation (75-90% for <60 seconds) and 89 incidents of airway obstruction. Most interventions for adverse events were categorised as minor on 457 (59.5%) sedations. There were 167 (21.7%) minimal interventions and 20 (2.6%) sentinel interventions.

With the minority of procedures being non emergent, the best representation of EM procedural sedation was identified in the results by looking at the time the procedure was undertaken. Two time periods; 6:00pm-12:00am and 12:00-06:00am were defined as being out of normal working hours and as such, it was more likely to be emergent procedures being undertaken. Both time periods were identified as being predictors of adverse events; 6:00pm-12:00am (OR 8.74, 95%CI 5.43-14.06, p=0.0027) and 12:00-06:00am (OR 5.86, 95% CI 2.24-15.34, p=0.0003). Interpretation of any results from a voluntary database such as SIVA must bear in mind the potential of reporting bias. They could opt to report nothing or only report minor adverse events. Likewise, some clinicians may have only reported more serious adverse events as they felt that the minor adverse events were relatively unimportant.

Results from other trials with procedural sedation being administered by non-anaesthetists show interesting variation. A group of GPs in Australia sedated patients for endoscopy with an incidence of adverse events of 4.1 (95% CI 3.3 to 4.9)/1000 patients (Clarke et al., 2002). In the Glasgow Royal Infirmary two non-medical personnel provided sedation for oocyte retrieval; one was a theatre senior nurse and the other was an operating department practitioner. Their adverse incident rate was only 0.3 (95% CI -0.3 to 0.9)/1000 patients (Edwards et al., 2010).

3.2.1.3 Tracking and Reporting Outcomes of Procedural Sedation (TROOPS)

Despite the ISTF being disbanded, there remained a group of its members and other experts who felt there was a need for a team to guide development in procedural sedation internationally. In 2014, the International Committee for the Advancement of Procedural Sedation (ICAPS, proceduralsedation.org) was formed by co-chairs Professor Green and Professor Mason both from the USA. Professor Steven M. Green is a Professor of Emergency Medicine and Professor Keira P. Mason is an Associate Professor of Anesthesiology. Both have published extensively in procedural sedation. ICAPS is an independent organisation, and their mission is

> *'to provide an independent, international, multidisciplinary forum to facilitate open dialogue and consensus generation between experts in the area of sedation, and to promote optimal, evidence-based, safe and effective practices for worldwide procedural sedation and analgesia in patients of all ages.'*

ICAPS retained the definition of sedation related adverse events generated by ISTF but sought to simplify the SIVA adverse event reporting tool. They recognised the importance of having such a tool to promote improvement in the clinical environment and standardisation for research reporting but felt that two separate reporting tools were better. One tool is to promote quality improvement in the clinical environment and the other tool is to provide consistency in reporting for research studies.

Using a Delphi approach, ICAPS recognised that certain elements of the SIVA adverse event reporting tool were potential barriers to its wider acceptance. It was felt better to remove the threshold and time parameters outlined in the SIVA adverse event reporting tool and instead use the format of the Quebec Guidelines. The Quebec Guidelines (Bhatt et al., 2009) were developed for use in paediatric ED procedural sedation and noted the interventions taken in response to adverse events. This was also part of the SIVA adverse event reporting tool. ICAPS also noted the absence of patient-centred outcomes in previous tools.

In 2018, ICAPS presented their new reporting tool (Mason et al., 2019); Tracking and Reporting Outcomes of Procedural Sedation (TROOPS). TROOPS focused on interventions undertaken in response to the adverse event and outlines it as an 'unplanned' intervention as some felt interventions were planned/anticipated to an extent during certain procedural sedations. It is a pragmatic tool laid out to mirror the clinical systems that may require the interventions. These are then divided into categories to denote the implied severity of the intervention undertaken, each colour coded to green, yellow and red. Inclusion of a minor category with some additional intermediate interventions is the only addition to the research version.

The TROOPS reporting tool is relatively new and there are no studies within the Emergency Department using it. It has been endorsed in the most current RCEM Best Practice Guideline on Procedural Sedation in the Emergency Department (2022). A large-scale observational study using the TROOPS tool in Emergency Departments would be helpful to set our baseline incidence of adverse events.

Regardless of which reporting tool is used, responsible clinicians should employ clinical governance to minimise adverse events occurring during procedural sedation. One of the ways in which they do this is to choose the most appropriate medication for sedation.

A systematic review (Williams et al., 2016) of prospective randomised double blind involving procedural sedation estimated the incidence of adverse events at 5%. The studies included Emergency Department settings as well as others. This compares to the reported 3% in the national RCEM audit (2018) and as high as 11% in an observational study (Smits et al., 2017) conducted in a Dutch ED using the SIVA adverse event reporting tool.

3.2.2 Supplemental Oxygen

Use of supplemental Oxygen is recommended for procedural sedation in the Emergency Department guidelines (2022). Evidence recommending a certain method of supplemental Oxygen over another is currently lacking (American Society of Anesthesiologists, 2018). High Flow Nasal Oxygen (HFNO) is becoming increasingly available. It might be a safer, more comfortable way of delivering supplemental oxygen which is humidified and heated.

HFNO was developed in the paediatric setting (Shoemaker et al., 2007) and over the past decade has become an increasingly popular way to deliver supplemental Oxygen. HFNO delivers heated and humidified oxygen up to a rate of 15-60L/min and an FiO2 of 21% to 100%. Flow and FiO2 can be altered independently.

A systematic review and metanalysis was undertaken by Liu et al (2021) to evaluate the efficacy of HFNO when compared to standard oxygen therapy during procedural sedation. Their primary outcome was desaturation events (SpO_2 <90%). Six studies were included, five of which delivered oxygen via nasal cannula. HFNO was associated with a significantly lower risk of intraprocedural desaturation (RR 0.18, 95% CI 0.04-0.87) compare with standard oxygen therapy. None of the studies included in this metanalysis were undertaken in the Emergency Department setting.

The results of Liu et al (2021) are interesting but not directly transferable to the ED setting. However, it does pose the question of whether a study should be undertaken in the ED setting to compare oxygen delivered HFNO versus nasal cannula for procedural sedation? We have evidence that it is tolerated by patients, and would this be a justification for using it routinely? Whilst this may be the case in 'normal' times, recent events with the COVID pandemic have highlighted that interventions once perceived as minimal risk can suddenly be reclassified as high risk and stopped with immediate effect for all except those requiring it as a lifesaving intervention.

3.2.3 Fasting

Fasting before procedural sedation was advised, if possible, to minimise the risk of pulmonary aspiration of gastric contents. Best practice advice was taken from a guideline developed for healthy, elective patients (American Society of Anesthesiologists, 2011) for anything but minimal sedation. This guideline advised two hours for clear fluids and six hours for solids.

A systematic review conducted in 2017 (Green et al.) aimed to identify published reports of pulmonary aspiration in procedural sedation. They identified 292 incidences of pulmonary aspiration with eight subsequent deaths. All incidences of pulmonary aspiration occurred during endoscopy.

There is an argument that trauma and the associated pain and opiate administration can delay gastric emptying and that perhaps this group of patients are at higher risk of pulmonary aspiration. In some regions it is normal practice to undertake a point of care ultrasound assessment of gastric contents before elective procedures. A systematic review (Van de Putte and Perlas, 2014) was conducted to summarise the use of this imaging modality. The review contained information on how it was performed. Emergency Physicians are skilled in the use of bedside ultrasounds and

developing this skill would be achievable without relative difficulty. However, the main concern is that suitable views would require moving the patient into multiple positions and given the nature of the presenting complaint requiring procedural sedation this is probably not feasible. This has not been assessed in the Emergency Department population yet and may be of interest for future research.

We adopted the guidance from a multidisciplinary consensus practice guideline for unscheduled procedural sedation (Green et al., 2019) which has also been endorsed by the RCEM (2022). This guideline advocates an individualised approach to aspiration risk management which considers the urgency of the procedural sedation, the level of sedation we want to achieve, and the drugs being used. This is combined with information on the patient's past medical history, when and what they last had to eat and drink along with their current physiology.

3.3 Effective

When we are evaluating the efficiency of a procedural sedation regime, we need to consider the physician's satisfaction as well as the ability to sedate the patient.

3.3.1 Sedation Scales

There are several tools designed to assess the level of sedation. The Modified Observer of Alertness and Sedation Scale MOAA/S is derived from the Observer's Assessment of Alertness and Sedation scale (OAA/S). It is a simple tool used to assess the depth of sedation by attempted interactions with the patient. The MOAA/S has six-points ranging from 'responds readily to name spoken in normal tone' to 'no response after painful trapezius squeeze'.

Table 3-1 The Modified Observer of Alertness and Sedation Scale (MOAA/S) outlining the score and description associated with each score.

Score	Score Description
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Another sedation scale to be considered was the Ramsay Sedation Scale (RSS). The RSS was first described in 1974 during a study assessing the sedating properties of alphaxalone-alphadone (Althesin) on thirty patients in an 'intensive therapy unit' (Ramsay et al., 1974). Like the MOAA/S (Table 3-1) there are six levels in the RSS ranging from 'anxious and agitated' to no response (Table 3-2).

Table 3-2 The Ramsay Sedation Scale outlining the score and clinical descriptor for each score.

Score	Score Description
1	Patient anxious and agitated or restless or both
2	Patient co-operative, orientated, and tranquil
3	Patient responds to commands only
4	Patient exhibits a brisk response to a light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to a light glabellar tap or loud auditory stimulus
6	Patient exhibits no response to a light glabellar tap or loud auditory stimulus

In 2016, Williams et al, conducted a systematic review that looked at the efficacy outcome measures for adult procedural sedation.

The authors of the systematic review reviewed the various scales and measurements used in procedural sedation studies. Their aim was to create evidence-based recommendations to improve and standardise the reporting of efficacy in procedural sedation studies. They included 245 studies in their analysis and found that 47% of the studies used the OAA/S or one of its modifications.

Whilst they noted that the RSS had been validated extensively in the ICU setting, no studies existed that validated its use in procedural sedation. One paper was identified that compared it with OAA/S and electroencephalographic (EEG) based monitors for patients undergoing elective surgery requiring mild to moderate sedation

(Chisholm et al, 2006). This study showed that the two scales correlated well but again did not validate the RSS in isolation.

Chernik et al (1990) published a paper describing the validity and reliability of this scale in a population of 18 healthy volunteers. The volunteers received a placebo dose and two doses of midazolam in a randomised fashion to enable this. The OAA/S contains four assessment categories; responsiveness, speech, facial expression, and eyes (Table 3-3). An individual's level of sedation is assessed by working through each category starting first with responsiveness. A composite score is given which reflects the lowest level in one of the categories. A patient may receive a score of 4 in the face category but 2 in the speech category, their resultant composite score would be 2.

Table 3-3 the Observer's Assessment of Alertness and Sedation Scale (OAA/S) showing the constituent parts of the assessment and composite score level

Assessment Categories				Composite Score level
Responsiveness	Speech	Facial Expression	Eyes	
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (Alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	-	-	2
Does not respond to mild prodding or shaking	-	-	-	1 (Deep Sleep)

Chernik et al reported that the OAA/S scale was both reliable and valid, taking less than one minute to perform. Each category influenced the composite score at one point in time, with responsiveness being the most influential on the resultant composite score. In the systematic review the authors comment that the MOAA/S

mirrors the responsiveness category but there is variability amongst the various scales calling themselves the 'modified' OAA/S scale. Versions ranging from 5 points to 7 points have been used in the reviewed papers.

Whilst Chernik et al commented that responsiveness appeared to be the most influential on the composite score, it was not validated by itself and there is a gap in the literature with no validation of a standardised 'modified' OAA/S. The authors of the systematic review concluded that there was no robust evidence of the responsiveness, reliability and validity of the current sedation scales being used in procedural sedation. This means that no recommendations can be made to inform the future study.

The use of electroencephalographic (EEG) signals to indicate the depth of patient sedation is emerging and may be of use in ED procedural sedation.

3.3.2 Electroencephalographic (EEG) signals

Depth of anaesthesia (DOA) monitors exist that process EEG signals to provide an index number indicating 'depth' of anaesthesia alongside the EEG waveforms. This is called processed EEG monitoring (pEEG) and has been studied extensively.

Many systems exist but one of the most used in the UK is the bispectral index (BIS) monitor which was introduced in 1994 (Sigl and Chamoun). BIS monitoring is achieved by attaching four adhesive electrodes to the patient's forehead. These electrodes can monitor the frontal EEG and by applying an algorithm, process this to generate the waveform and index number on a monitor for the clinician to see.

The index number displayed on the monitor is between 0 to 100 and there is up to a 30 second delay as the EEG is processed. Ranges have been suggested to indicate varying depths of anaesthesia with depth increasing as the number decreases (Table 3-4).

Table 3-4 BIS Index Ranges related to level of sedation (Doshi et al., 2011). Reproduced with permission of Pediatric on call.

BIS Index Range	Level of Sedation
100 – 80	Responds to normal voice
80 – 60	Light/moderate sedation - Responds to loud commands or mild prodding/shaking
60 – 40	General Anaesthesia - Low probability of explicit recall - Unresponsive to verbal stimulus
40 – 20	Deep Hypnotic State
20 – 0	Burst Suppression
0	Flat Line EEG

The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia (AAGA) reported that DOA monitors were used in just 2.8% of all general anaesthetics (Pandit et al.). Certain or probable AAGA was reported in 141 patients, six of whom (4.3%) had DOA monitoring attached. This result shows that despite optimal monitoring, depth can be incorrectly assessed. Suggestions have been made in the literature that perhaps clinicians are focusing too much on the index number and not considering the basic waveforms themselves (Mulvey and Klepsch, 2020) thus limiting their ability to interpret the information provided by the DOA monitor. This is echoed in the recent Association of Anaesthetists guideline on 'Recommendations for standards of monitoring during anaesthesia and recovery' (2021) which states:

> *'Anaesthetists should not rely solely on index values displayed by pEEG monitors. Rather, they should develop a basic understanding of EEG waveforms and the interpretation of information from power spectral analysis, density spectral array ('spectrograms') and relative band powers.'*

Propofol has been described as having a distinctive EEG signature as the patient traverses the stages of the sedation continuum (Purdon et al., 2013). The ability to identify this Propofol EEG signature and where the patient is on the continuum would enhance the use of the DOA monitor to ensure an appropriate depth is maintained (Figure 3-1).

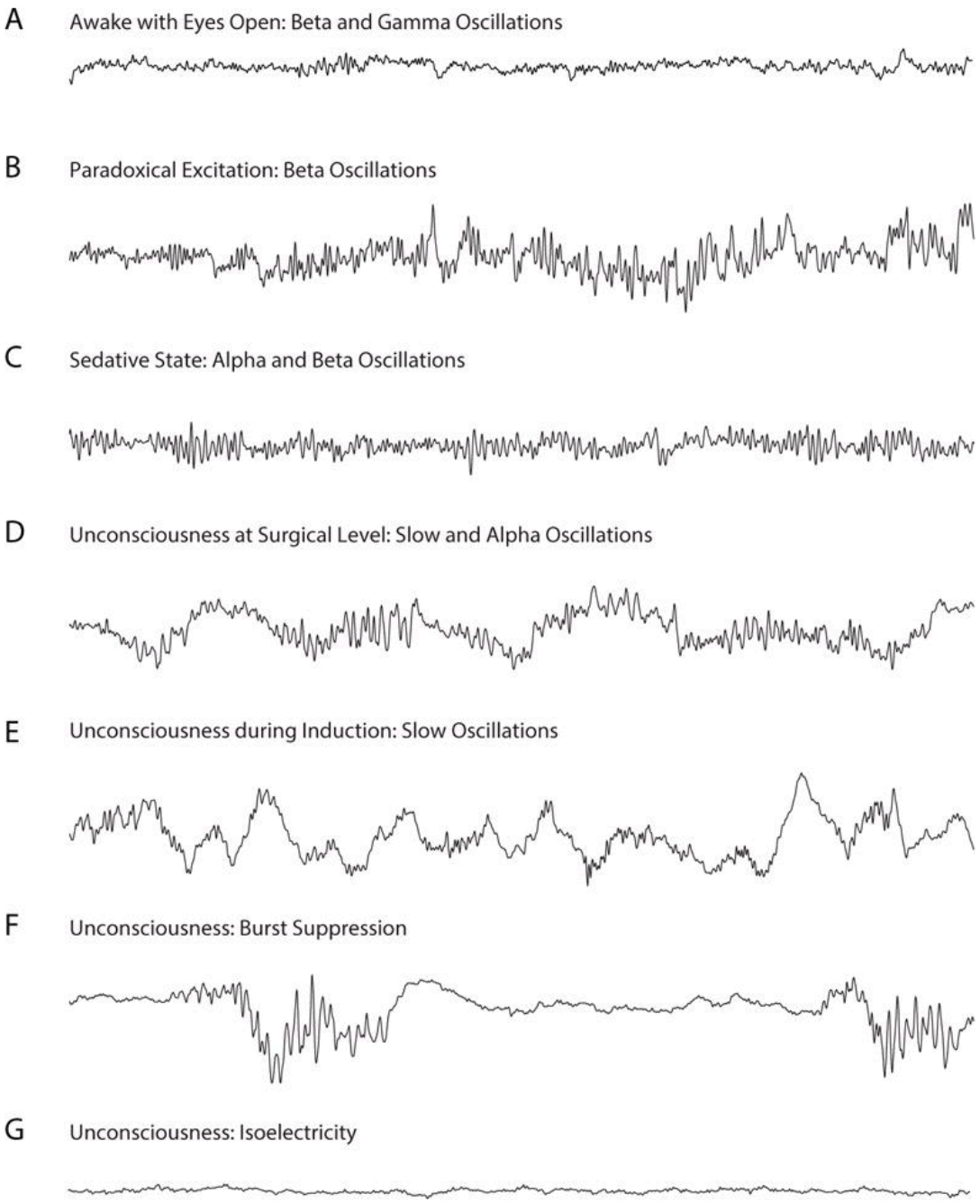


Figure 3-1 Unprocessed electroencephalogram signature of Propofol-induced sedation and unconsciousness.
A) Awake eyes open electroencephalogram pattern. (B) Paradoxical excitation. (C) Alpha and beta oscillations commonly observed during Propofol-induced sedation. (D) Slow-delta and alpha oscillations commonly seen during unconsciousness. (E) Slow oscillations commonly observed during unconsciousness at induction with Propofol. (F) Burst suppression, a state of profound anesthetic-induced brain inactivation. (G) Isoelectric electroencephalogram pattern commonly observed in anesthetic-induced coma. Reproduced, with permission, from Purdon et al (2015).

Whilst Propofol produces this distinctive signature, other drugs used for ED procedural sedation may confuse the picture. Ketamine and nitrous oxide can produce a higher index number because of faster EEG oscillations that would normally be associated with a more wakeful state (Yamamura et al., 1981, Hayashi et al., 2007). An adequate dose of these agents can be administered, the patient appears to be clinically sedated, but the BIS index number would suggest otherwise. Care would also have to be taken when opioids are being used as they potentiate the effects of other sedatives with minimal effects on BIS score. Noticeable EEG changes would only be induced by opiates at approximately five times that of the analgesic doses (Dahaba, 2005, Shafer and Varvel, 1991). If a clinician were using only the DOA monitor to guide depth, they could potentially be misled by a static index number and waveform as their patient becomes over sedated.

Studies were conducted using BIS in Emergency Departments for a variety of reasons including procedural sedation (Gill et al., 2003, Miner et al., 2003, Miner et al., 2005, Fatovich et al., 2004, Miner et al., 2007). In the early 2000's, most of the studies were observational and no randomised interventional validation studies were published. The authors did however conclude that BIS had the potential to improve safety.

Gill et al. (2003) conducted an observational study on a convenience sample of 270 patients undergoing procedural sedation in the ED. All patients had BIS attached and the clinicians were blinded to it. They noted the BIS index number and sedation score using the RSS every five minutes. Their results showed that BIS reliably predicted patients 'sedated' to the point of general anaesthesia from less deeply sedated patients. It did not however discern between mild to moderate sedation, or moderate to deep sedation as measured by the sedation scale.

Fatovich et al. (2004) ran an observational pilot study comparing the BIS index number with the OAA/S Scale on a convenience sample undergoing procedural sedation in the ED. Twelve patients were enrolled with results from eleven patients.

They showed that there was poor correlation between both and recommended a larger study.

Miner et al. (2003) enrolled 108 patients into their observational study of patients undergoing procedural sedation in the ED. All patients had BIS applied and the treating clinical teams were blinded. Their results describe a BIS index range of 70-85 as the point at which patients were optimally sedated. They described equivalent VAS outcomes for pain, recall and satisfaction as those more deeply sedated and the same rates of respiratory depression; (SpO_2 <90%, a change from baseline $EtCO_2$ >10 mm Hg or an absent $EtCO_2$ waveform at any point during the procedure) as those less deeply sedated.

Further research from Miner et al. (2005) was conducted in the ED with the aim of using BIS to recognise adequately sedated patients and reduce the incidence of respiratory depression. A total of 100 patients were randomised to either a group where physicians were blinded to the BIS information or to a group where clinicians could view the BIS information. Their results showed that there was a lower rate of respiratory depression in the group with clinicians unblinded to the BIS information and who had received more than one dose of Propofol for the procedural sedation. There was no difference in incidence of respiratory depression when only a single dose of Propofol was required. This result is interesting as it highlights my initial concern that repeated boluses of Propofol make it difficult to predict the effect site concentration and increase the risk of adverse events.

Challenges to using BIS in my RCT would include cost and unfamiliarity with this technology amongst Emergency Department teams. Given that the research into this is inconclusive and new recommendations urge clinicians to interrogate all information provided by the DOA monitors, not just the index number, it is unlikely that we will use this in the future RCT. However, this is a promising technology which has the potential to enhance the safety of procedural sedation and a study validating its utilization in ED for procedural sedation should be considered at a later point.

3.3.3 Clinician Satisfaction

Currently there are no validated tools to measure clinician satisfaction for procedural sedation undertaken in the Emergency Department. A tool has been developed for use in endoscopy, the Clinician Sedation Satisfaction Index (Vargo et al., 2009). It is a 21-item questionnaire that asks the clinician to rate each from very satisfied to very dissatisfied. It has not been validated for procedural sedation in the ED.

3.4 Patient Centred

Studies regarding procedural sedation must include patient related outcomes with regards to satisfaction. It is also key that they are included as much as possible with the development of the design and outcome measures chosen to ensure they are felt to be representative of what the patient wants.

3.4.1 Patient Satisfaction

Patient satisfaction is a nebulous term with no real agreed definition of what it is or how best to measure. Measurement depends on what aspect of this multifactorial variable we want to assess, and the term patient satisfaction minimises the true complexity of this patient-centred outcome. Trying to assess patient satisfaction with the sedation in isolation is difficult and is recognised as such in the literature.

The Sedation Consortium on Endpoints and Procedures for Treatment, Escalation, and Research (SCEPTER) met in 2014 (Williams et al., 2017) to discuss, agree by consensus and design recommendations for adult procedural sedation trials. These recommendations set out the core sedation outcome domains and suitable measures to evaluate those domains.

3.4.1.1 Iowa Satisfaction with Anesthesia Scale

One of the domains was to ensure that the sedation was patient and family centred. They noted that the end points had to be procedure and context dependent as not all are equivalent. One of the proposed measures was the Iowa Satisfaction with Anesthesia Scale (ISAS) (Dexter et al., 1997, Dexter and Candiotti, 2011). Professor Dexter is a researcher based in the department of Anaesthesia at the University of Iowa. He was pivotal in the design and validation the ISAS tool. ISAS had been assessed as a reliable and valid tool in single and multicentre clinical trials but interestingly not for comparing satisfaction scores between centres.

This tool had been designed to measure satisfaction with the anaesthetic and not the overall experience. We noted that it had been used in other studies relating to sedation and not general anaesthesia too (Fung et al., 2005, Rüschen et al., 2005, Ryu et al., 2009, Kwak et al., 2006).

It consists of 11 questions (Table 3-5) presented on a sheet of paper handed to the patient post procedure, prior to discharge. They are left to complete the form by themselves. The statements are a mix of positive and negative. Patients are asked to choose one of six responses (Table 3-6) for each of the statements.

Each response is marked from -3 for disagree very much to +3 for agree very much. If the statement is a negative one, the response score is reversed. This means that a patient who is completely satisfied would score +3 after reversal for the response. Each patient's ISAS score is the mean response of the patient's responses to the 11 statements.

Table 3-5 Questions from the Iowa Satisfaction with Anesthesia.
Printed with permission, copyright in the Iowa Satisfaction with Anesthesia Scale (ISAS) is the property of Franklin Dexter and the University of Iowa Research Foundation.

Order	Statement
1	I threw up or felt like throwing up
2	I would want to have the same anesthetic again
3	I itched
4	I felt relaxed
5	I felt pain
6	I felt safe
7	I was too cold or hot
8	I was satisfied with my anesthetic care
9	I felt pain during surgery
10	I felt good
11	I hurt

In 2017, Johnson et al conducted a study in Australia with the aim to determine patient satisfaction with procedural sedation in the Emergency Department. Patient satisfaction was measured with the ISAS after full recovery. In this study full recovery was detailed as GCS 15 and talking normally. Their study was observational over a twenty-month period. A convenience sample was recruited from patients requiring procedural sedation for a painful procedure and depth of sedation measured using OAA/S. A total of 163 patients were recruited. Their conclusion was patient satisfaction with procedural sedation was good with greater satisfaction associated with deeper sedation.

In reply to this study, Professor Dexter (2017) wrote a letter to the journal and authors.

Table 3-6 Participants responses for Iowa Satisfaction with Anesthesia Scale.
Printed with permission, copyright in the Iowa Satisfaction with Anesthesia Scale (ISAS) is the property of Franklin Dexter and the University of Iowa Research Foundation.

Disagree very much
Disagree moderately
Disagree slightly
Agree slightly
Agree moderately
Agree very much

In his letter, Professor Dexter asked if the authors had established the validity and reliability of the ISAS tool in this population, asking specifically about the three questions that explored different aspects of pain. He also noted that satisfaction was lower in those undergoing Orthopaedic procedures and wondered if patients in this group related to the question, 'I felt pain during my surgery' whereas those undergoing procedural sedation for other procedures might not have considered themselves to have had surgery and scored higher at this point as a result. These points raised awareness of the difficulties in creating a tool (Boateng et al., 2018) and that it was more complex than first appreciated. A tool tested in one population cannot be directly imported for use in another without testing for reliability and validity. Such a tool for measuring patient satisfaction in procedural sedation in the Emergency Department did not exist. I contacted Professor Dextor to discuss this further.

I met with Professor Dexter virtually to explore what could be developed for use in studies focusing on procedural sedation in the Emergency Department. We discussed satisfaction and what aspect of it we were looking to assess. We agreed that whatever we chose to measure, it must reflect what is important to the patient. The simplest way to achieve this is by asking our patients undergoing procedures what it is that they are looking for, what matters to them. We can look at their responses for

emerging themes and ask specifically about them as opposed to a tool to measure 'satisfaction' en masse. He also raised the added complication of when to ask our patients questions relating to satisfaction. To be able to measure patient satisfaction the patient must be able to recall the events.

Chadha et al. (2020) evaluated the validity of obtaining patient satisfaction in a group of patients being discharged forty-five minutes after sedation with midazolam. Twenty patients undergoing cataract surgery were recruited. They were sedated with midazolam and fentanyl. Patient satisfaction was assessed using the ISAS at approximately 30 minutes after the sedation. Patients were then called 24 hours later and asked to share as many of the 11 questions they were asked whilst recovering with the researcher.

Their results showed that 15 out of 20 patients recalled 0 or 1 of the themes. They concluded that assessing patient satisfaction in such a short space of time is invalid. Whilst patients may report being comfortable at this time and appear to be alert and orientated, the lack of recall indicates that satisfaction can't be assessed. Interestingly they also point out that provision of discharge information solely to the patient in this period is not advisable. Safe but prompt discharges are required in the ED and therefore patient satisfaction should be collected after discharge from the ED.

3.4.1.2 What matters to You?

Since 2017 Scotland has had a national "What matters to you?" day. This simple question has been used across lots of settings and populations allowing us insight into what's important in people's lives. This patient-centred approach reflects Realistic Medicine Scotland which was first introduced in the Chief Medical Officer's annual report 2014-15 (Scotland, 2014). Realistic Medicine puts the patient at the centre of

the decisions made about their care and actively seeks to find out what matters most to them (Christie, 2016).

I looked for examples of co-produced patient outcome measures that may be suitable for my future study. Professor Paul Bowie was identified as a researcher with an interest in this area. Professor Paul Bowie is the programme director for the Safety, Skills, and Improvement Research Collaborative (SKIRC) at NHS Education for Scotland. He agreed to meet with us to discuss patient centred outcome measures.

Professor Bowie has conducted research (Bowie et al., 2015, Houston and Bowie, 2015) in always events and how these can be used to improve patient experience in healthcare. Always events were first described by the Picker Institute in the US. They were defined as "*those aspects of the care experience that should always occur when patients, their family members or other care partners, and service users interact with healthcare professionals and the healthcare delivery system*". In 2012 the Picker Institute transferred the strategic oversight of always events to the Institute for Healthcare Improvement (IHI) (Institute for Healthcare Improvement, 2014). The basic principles and four criteria (Table 3-7) have remained the same.

Table 3-7 Four criteria an Always Event must meet (Institute for Healthcare Improvement, 2014)

	Criteria	Description
1	Important	Patients, their family members or other care partners, and service users have identified the event as fundamental to improving their experience of care, and they predict that the event will have a meaningful impact when successfully implemented.
2	Evidence-based	The event is known to contribute to the optimal care of and respect for patients, care partners, and service users (either through research or quality improvement measurement over time)
3	Measurable	The event is specific enough that it is possible to determine whether the process or behaviours occur reliably. This requirement is necessary to ensure that Always Events are not merely aspirational, but also quantifiable.
4	Affordable and Sustainable	The event should be achievable and sustainable without substantial renovations, capital expenditures, or the purchase of new equipment or technology. This specification encourages organisations to focus on leveraging opportunities to improve the care experience through improvements in relationship-based care and in care processes.

Ascertaining Always Events for our local population undergoing procedural sedation would be relatively easy and outlined in Figure 3-2, generating always events (The Health Foundation, 2017). Whilst this would be applicable locally there would be a

need for a larger piece of work if we wanted to develop Always Events at a national level.

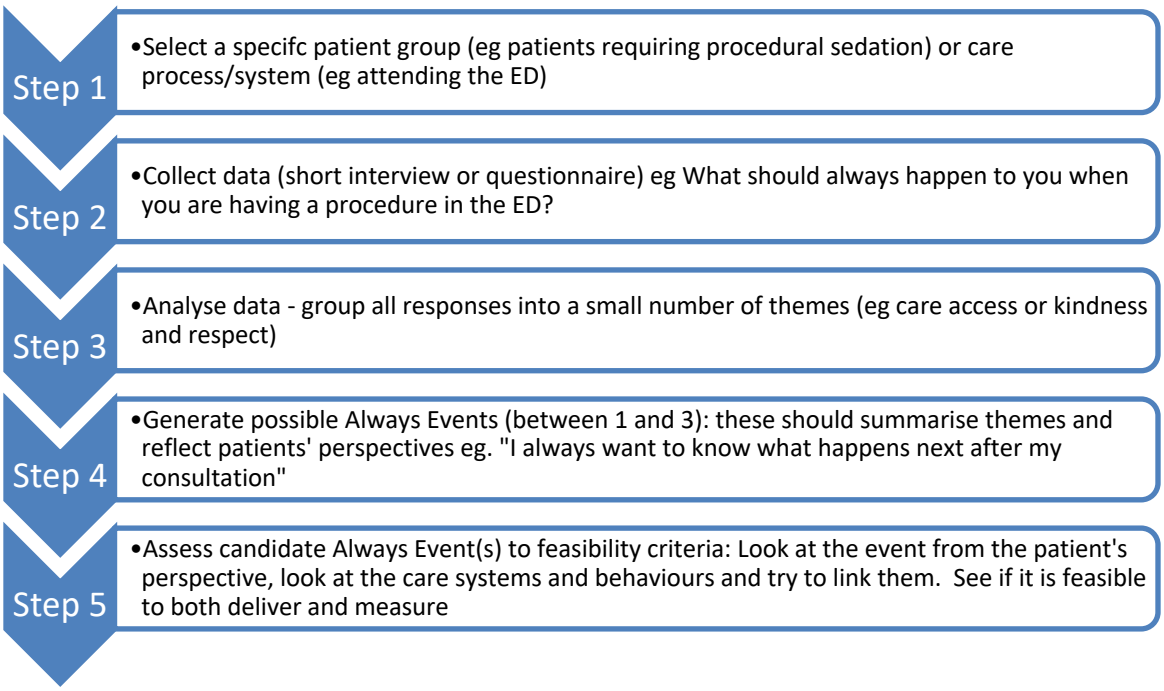


Figure 3-2 Generating Always Events
Five step approach adapted from illustration 1 in the Health Foundation (2017) report

3.4.2 Patient & Public Involvement

Patient and public involvement (PPI) has been shown to mainly have a positive impact on identification of relevant research topics, study design, identifying important patient outcomes, ability to obtain consent, analysis, dissemination and implementation of results (Brett et al., 2014). PPI has also been reported to have some negative impacts with public feeling disempowered, frustrations about ability to influence and the emotional toll (Popay and Collins, 2014, Barber et al., 2012).

3.4.2.1 Background of PPI

The National Institute for Health and Care Research (NIHR) defines public involvement in research as research being carried out ‘with’ or ‘by’ members of the public rather

than ‘to’, ‘about’ or ‘for’ them (Hayes et al., 2012). Members of the public include; patients and potential patients, people who use health and social care services, carers and people from organisations that represent people who use services.

The UK Standards for Public Involvement in research are a set of six standards that describe what good public involvement looks like (Crowe et al., 2020). They were developed across the four nations and each standard provides the opportunity for the researcher to reflect on their activities. The six standards are inclusive opportunities, working together, support and learning, governance, communication, and impact.

In 2014 The British Medical Journal (BMJ) set out a strategy co-produced with their International Patient and Public Advisory Panel that promotes co-creation of content in their journals. Requesting a statement on PPI in the methods section was one of the changes they adopted to encourage researchers to consider how this would benefit their research. They anticipate that over time this nudge/prompt will shift consideration of PPI to the initial stages of research when the research question is being formed and will become part of normal business.

To help researchers report PPI in their research, Staniszewska et al. (2017) developed a checklist in both a long and short format to guide them. The checklists were produced as it was recognised that improvements were needed to provide quality, transparency, and consistency in reporting. The first version of the Guidance for Reporting Involvement of Patients and the Public (GRIPP) was developed by using published review evidence. The developing team acknowledged that input from the wider international PPI community was required. The GRIPP2 was published using a delphi approach. It exists in two formats; long and short with the former of use in studies where PPI is the primary objective and the latter for studies where PPI is of secondary focus. Table 3-8 outlines the GRIPP2 short checklist. Reporting of any subsequent research would include this to outline the PPI.

Table 3-8 GRIPP2 short form – reporting checklist designed to improve reporting of patient and public involvement in research (Staniszewska et al., 2017). Reproduced with permission from the authors.

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	
2: Methods	Provide a clear description of the methods used for PPI in the study	
3: Study results	Outcomes – Report the results of PPI in the study, including both positive and negative outcomes	
4: Discussion and conclusions	Outcomes – Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	
5: Reflections/critical perspective	Comment critical on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	

Chapter 4 Feasibility of TCI for procedural sedation in the Emergency Department

4.1 Introduction

The UK Medical Research Council (MRC) recommends a phase of assessing feasibility; can something be done, should we proceed and if so, how, before undertaking a large-scale study (Eldridge et al., 2016) (Figure 4-1). In line with this recommendation, outlined below are the steps I have taken to assess the feasibility of performing a RCT of TCI propofol for procedural sedation in the Emergency Department as detailed in the subsequent four chapters. Discussion within my clinical teams allowed me to identify emerging themes and uncertainties amongst my colleagues. I used these to guide and target the exploratory, feasibility work.

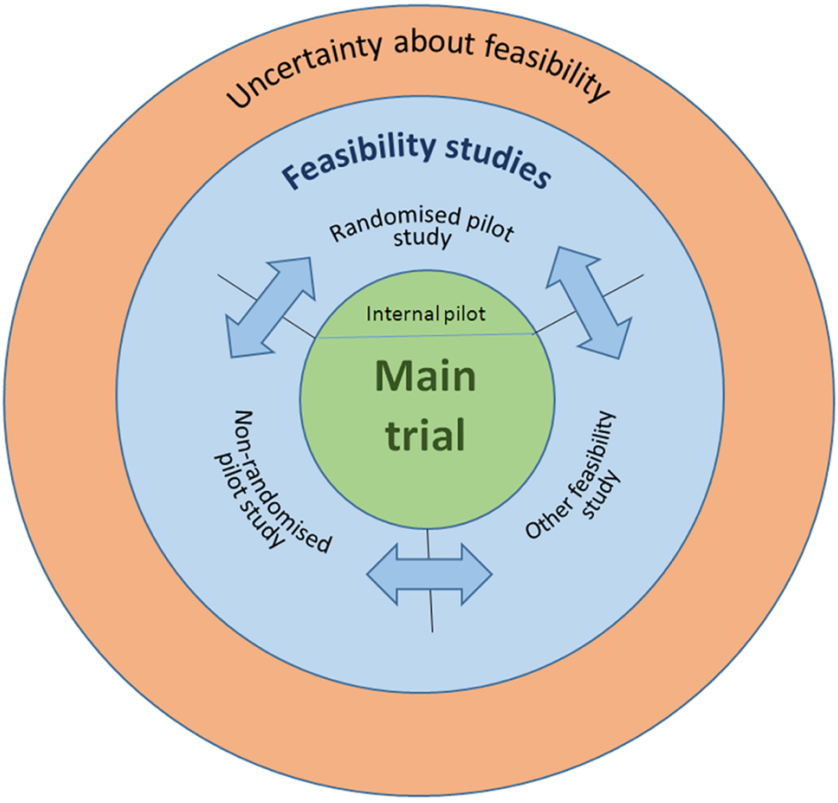


Figure 4-1 Feasibility & Pilot Studies, a Conceptual Framework.
Stages of feasibility assessment in preparation for Randomised Controlled Trials, reproduced with permission © 2016 Eldridge et al, https://doi.org/10.1371/journal.pone.0150205

4.2 Local Practice

Whilst the Royal College of Emergency Medicine national audit of Procedural Sedation in Adults (2018) showed that the use of Propofol was increasing I was unsure if that was reflected locally. I therefore conducted a survey of ED procedural sedation in the West of Scotland. I was concerned that my TCI intervention might be considered too complex by Emergency Medicine physicians.

4.3 Barriers to TCI

Target-controlled infusion is a relatively new technology in Emergency Medicine practice and something that is perceived to be in the domain of anaesthetic clinical practice. Colleagues were aware that it involved a syringe driver and were concerned that it would be overly complicated to set up and increase the procedural time. I was concerned that this would negatively impact upon recruitment to the feasibility study (Burton et al., 2019a) and therefore conducted an experiment to quantify the additional time taken to set up TCI in the ED.

4.4 Systematic Review

Prior to undertaking research in this area, I wanted to ascertain if this was something that had already been investigated. I wanted to identify if the question had already been answered or if there was a need to research the use of Propofol TCI for procedural sedation in the ED. I was unable to find a systematic reviews on this topic so I conducted a systematic review (Burton et al., 2020).

4.5 Feasibility Study

A feasibility study (Burton et al., 2019b, Burton et al., 2021) looking primarily at patient satisfaction, recruitment rates and the incidence and severity of adverse events was conducted to address the remaining uncertainties.

Chapter 5 Does the local picture reflect the national picture?

5.1 Background

I sought to establish if Propofol was used as a sedating agent in the population and centres that I planned to recruit from. The Scottish deanery is divided into the North, East, Southeast and West regions. We are situated in the West region.

The West region comprises NHS Greater Glasgow and Clyde, Ayrshire and Arran, Lanarkshire, Forth Valley and Dumfries and Galloway. It serves a population of approximately 2.5 million people across ten Emergency Departments, a mix of district general and city centre hospitals. Adults present to these departments and there is an additional paediatric Emergency Department in the West region.

The RCEM procedural sedation audit 2017/18 (2018) suggested that Propofol was used in just over half (52%) of 8815 recorded procedural sedations. Reading the audit report, I noted that three of the ten ED's in the West of Scotland had taken part in the national RCEM procedural sedation audit 2017/18. There was no representation from Greater Glasgow and Clyde, Ayrshire and Arran, or Dumfries and Galloway. I felt it was not reasonable to extrapolate for the seven Emergency Departments that hadn't taken part.

To answer my question, I developed a survey to gather information from the adult Emergency Departments in the West of Scotland. The aim of my survey was to describe current procedural sedation practice of consultant and associate specialists in Emergency Medicine.

5.2 Population

My population was clinically active consultant and associate specialists in the West of Scotland Emergency Departments. Dumfries and Galloway Royal Infirmary was excluded as they were not a potential site for recruitment owing to anticipated difficulties in supporting the site during the planned research study.

5.3 Methodology

I designed a survey covering fasting, drugs, complications and continuing professional development (CPD) in procedural sedation. I chose a selection of sedating agents based on the results of the RCEM national audit and asked the provider if they used the agent by ticking yes or no. If they did, I asked them to identify their comfort level on a visual analogue scale (VAS) ranging from 'not at all comfortable' at 0mm to 'completely comfortable' at 100mm on a 100m horizontal line. Sedating agents are often co-administered with analgesia. I asked respondents to select which analgesic agents they would normally use.

I asked participants to share their fasting requirements before undertaking procedural sedation for food, clear fluid, and other fluids. Complications encountered were laid out in a vertical tick list asking participants to tick yes or no for those they had encountered. The list incorporated events as well as interventions.

The survey domains and questions were written by senior clinicians in Emergency Medicine, anaesthesia and intensive care trained in delivering procedural sedation. Initial piloting with Higher Specialist Trainees in Emergency medicine was conducted (Appendix 1) and led to amendments before medical illustration formatted and produced the final version that was to be distributed in paper format (Appendix 2).

Face and content validity were assessed by both medical education and anaesthetic colleagues.

All surveys were anonymous with no identifiable data collected. An introduction to the survey was placed at the top of the sheet as was the aim with the plan to distribute the results afterwards. Procedural sedation was framed as in a requirement to achieve the anatomical reduction of a dislocated joint. This study fulfilled the criteria for service evaluation under local research ethics committee guidelines and therefore did not require ethical approval.

Clinical leads were approached on each site to ask for approval. When obtained they identified an Emergency Medicine trainee to act as a liaison and provided information on which staff in their departments represented my target population. Further to trainee consent to be involved, the departmental trainee acted as a liaison distributing and collecting the surveys before returning them to myself. A reminder email was sent to each clinical lead midway during the two-month period the survey was open for to share with their colleagues. The results of this work have been presented in a descriptive fashion using the functions of the Excel spreadsheet.

5.4 Results

The survey was opened for a two-month period from February 2017 to March 2017. Nine Emergency Departments were involved: University Hospital Hairmyres, University Hospital Wishaw, University Hospital Monklands, University Hospital Crosshouse, University Hospital Ayr, Forth Valley Hospital, Glasgow Royal Infirmary, Royal Alexandra Hospital, and the Queen Elizabeth University Hospital. A total of 126 doctors were eligible all of whom received a copy of the survey. Of these 112 were returned. There was an 89% response rate.

Clinicians most commonly co-administered Morphine (79%) or Fentanyl (57%) for analgesia with fewer using alfentanil (21%) or remifentanil (2%). Entonox was comfortably used by 99% of clinicians. Midazolam was used comfortably by 96%, followed by 79% of clinicians using Propofol with a VAS Comfort median (IQR) of 88 (72-100). The full results of sedating agents and comfort levels are described in Table 5-1.

Table 5-1 Drugs used for procedural sedation, whether the clinician uses it or not & comfort levels of the clinician using.

(N=112)	Yes	VAS Comfort Median (IQR)	No	VAS Comfort Median (IQR)	No Answer
Entonox	111	100 (93-100)	1	-	0
Midazolam	108	100 (86-100)	4	-	0
Propofol	88	88 (72-100)	19	11 (4-30)	5
Ketamine	73	78 (65-99)	36	4 (0-16)	3
Etomidate	16	89 (60-100)	92	0 (0-10)	4

The most common complication experienced by clinicians was respiratory compromise requiring a simple airway manoeuvre (81%) followed by oversedation (80%). They had to use an airway adjunct, an oropharyngeal (Guedel) airway to manage respiratory compromise. Table 5-2 outlines the complications and the number of clinicians that experienced them.

Table 5-2 Complications experienced by participating clinicians during procedural sedation

(N=112)	Yes	No	No answer
Simple Airway manoeuvre	91	21	0
Over-sedation	90	22	0
Guedel insertion	44	67	1
Bag Valve Mask ventilation	43	69	0
Regurgitation	8	104	0
Laryngospasm	6	106	0
Profound Hypotension (SBP ≤70mmHg)	5	107	0
Laryngeal Mask Airway (supraglottic airway)	3	109	0
Cardiac Arrest	2	110	0
Intubation required	1	111	0

5.5 Discussion

My results demonstrated that EM doctors trained in procedural sedation both used and were comfortable using Propofol in the departments surveyed. At first it would appear that the percentage use of Propofol is higher in this survey, but we must bear in mind that a different question was being asked compared to the RCEM national audit. In my survey, I asked individual clinicians about their routine practice as opposed to reporting procedural sedation episodes.

Most clinicians surveyed have experienced a complication in relation to their procedural sedation over the duration they had been undertaking procedural sedation. Minimal numbers have experienced what would be classed as a sentinel adverse event per SIVA adverse event reporting tool (Mason et al., 2012) but a high percentage, 80%, have experienced over sedation. The survey was not able to

provide details of these events, but it has highlighted that one of my main motivators, the avoidance of oversedation using Propofol TCI is relevant in this population (Fanti et al., 2015, Kenny, 1996).

Remifentanil (Michelsen and Hug Jr, 1996) was used by 2% of the participants as an analgesic. Remifentanil TCI (Eleveld et al., 2020) is becoming increasingly popular in other non-ED settings and may be a potential method of procedural sedation in the ED in the future.

5.6 Limitations

Given the anonymous nature of the survey we cannot analyse the information from a demographic point of view. Focusing on centres I would potentially be recruiting from was a pragmatic decision to provide information to inform this research project. However, the survey results are therefore not representative of the West of Scotland regional practice and the EM trainees trained in procedural sedation.

It is possible that short periods of respiratory compromise needing a simple airway manoeuvre may have been anticipated (Roback et al., 2018) and the clinician did not perceive it to be unexpected, an adverse event or something that should be improved upon. If clinicians do not perceive them to be an adverse event, then there is no incentive to improve nor change clinical practice.

All surveys are open to self-reporting bias. Individuals may be inclined to be very honest owing to the anonymous nature but equally there is the possibility that they overestimate their confidence with various sedating agents and under report their experience of complications. Recall bias will inevitably be present when asking, as I

did, for participants to recall events from the past, from their memory. There is a chance that they may not be able to recall an event or recall it completely.

The layout of the survey appears in hindsight to be cluttered making it difficult for participants to follow the questions being asked. I would move the introductory section to a separate sheet to create more room for the participant to see the questions. It could also be commented that the survey was looking at what was 'nice' to know as opposed to what I needed to know. The aim of this survey was to ascertain if the local picture reflected the national picture and questions relating to fasting and CPD were perhaps unnecessary.

The two areas of interest were the sedating agent being used and the complications encountered. If I had focused on these two areas, there would have been room to expand and ask about frequency of the complications as opposed to asking if they've ever experienced it or not. On reflection I noticed that I used the word 'complications' as opposed to adverse event. I believe this was a subconscious decision and can only postulate that I felt it was less emotive than adverse events and perhaps would lead to participant's answering more honestly. There was no space on the survey for an open question. If this had been included, participants may have shared some useful thoughts on procedural sedation practice in the ED that would have informed subsequent feasibility work. I included Etomidate as a sedating agent choice. Most clinicians use Etomidate for the induction of general anaesthesia. The inclusion of Etomidate may have created confusion with respondents potentially recalling events from general anaesthesia delivered in the department and not procedural sedation.

Not including trainees was deliberate and unhelpful. An opportunity to engage with the groups that are actively training was missed. This survey could have generated many conversations and been a chance to influence their practices. Trainee EM

physicians were most likely to have had experience in this field given the proximity of their training time in anaesthesia compared to that of most consultants.

5.7 Conclusion

Propofol is a commonly used sedating agent in the consultant and associate specialist West of Scotland ED population surveyed. Propofol is used by 79% of clinicians and they are comfortable with its use, VAS Comfort median (IQR) of 88 (72-100). Most clinicians have experienced complications with 80% having experienced oversedation. These results would indicate that further investigation of Propofol TCI to reduce adverse events in ED procedural sedation is relevant to the study population.

Chapter 6 Does setting up TCI in the ED take too long?

6.1 Background

Target controlled infusion (TCI) is not currently being used in any ED in the West of Scotland. The details about how TCI works, why it works and how it is set up are poorly understood and I was concerned they may prove to be insurmountable barriers to the introduction of a potentially safer delivery system.

When discussing the use of TCI in the ED, one of the main concerns raised was that setting up for Propofol TCI would take considerably longer compared to the setup for bolus administration. These concerns were reinforced by the unfamiliarity with TCI Propofol for procedural sedation.

6.2 Aims

6.2.1 Primary Endpoints

- Median difference in set up time for Propofol TCI vs for bolus administration

6.2.2 Secondary Endpoints

- Anticipated set up time for bolus administration
- Anticipated set up time for TCI administration
- Anticipated ease of set up for TCI
- Acceptable difference in set up time

6.3 Methodology

I invited all Emergency Medicine consultants in five EDs in the West of Scotland to take part. Departments were identified as those that may potentially be recruitment sites for the later RCT. Eligible consultants were members of the departments currently using bolus Propofol for procedural sedation.

This study fulfilled the criteria for service evaluation under local research ethics committee guidelines and therefore did not require ethical approval.

Eligible consultants were invited to attend an educational session in their department. Each participant was asked to complete an anonymous questionnaire before the session began. My questionnaire scoped their previous experience and current use of TCI. Participants were then asked to estimate set up times for both bolus and TCI and what they perceived to be an acceptable difference. They were asked to rate their anticipated ease of setup for TCI on a visual analogue scale. At the end there was a free text box asking if they had, 'Any thoughts you'd like to share?' (Appendix 3).

Following completion of the questionnaire they received an educational session from a subject matter expert. My subject matter expert was a Consultant Anaesthetist familiar with TCI and who was using it regularly in clinical practice. The session consisted of a tutorial on TCI and a practical demonstration on how to set up the TCI pump. Time was given for questions and answers throughout the session.

Following the session each participant was then randomised using an online list randomizer (www.random.org) to be timed preparing for set up of standard bolus administration followed by timing of set up of the TCI system, or vice versa.

A prompt sheet outlining the steps for both methods was provided. Preparing for bolus administration comprised taking a 21G needle and 20ml syringe out of their wrapping, drawing up 20mls of 1% Propofol and disposing of the sharp. Preparing for TCI administration comprised removing the wrapping from a 21G needle and 50ml syringe, drawing up 40mls of 1% Propofol, flushing through a giving line, inserting the syringe in a pump, and programming the pump for an initial plasma concentration of one microgram/ml. Each participant was allowed two practice attempts before the timed TCI set.

6.4 Results

Thirty consultants across the five hospitals participated. None of the participants were currently using TCI in their routine practice for procedural sedation in the ED. Many of the participants (28/30) were familiar with the term TCI with just under half of them (14/30) having had previous experience during anaesthetic training.

I utilised a visual analogue score (VAS) with 'not very difficult' at point 0 and 'very difficult' at point 100, participants reported a median (IQR) score of 34 (18) when asked to score how difficult they anticipated TCI set up would be.

Table 6-1 summarises participants estimated set up times for both techniques versus the actual times taken. The median (IQR) difference in set up time that was deemed to be acceptable by participants was 300 (30) seconds. The actual difference in median set up time was 143 seconds ($U=0$, $p<0.00001$), approximately half of what participants felt was acceptable.

Table 6-1 Estimated median (IQR) time in seconds to set up Propofol TCI vs actual median (IQR) time taken to set up Propofol TCI

	Bolus	TCI
Estimated time median (IQR) seconds	120 (180)	300 (360)
Actual time median (IQR) seconds	56 (10)	199(57)

6.5 Discussion

My results showed that the actual difference in set up time for TCI was less than participants expected. The results also demonstrated that the time difference was well within the mean acceptable time difference suggested by participants. Whilst it is not currently routinely used in the ED most of the participants have heard of the technology with half having had clinical experience of TCI Propofol.

In terms of feasibility this was reassuring as I have shown that it is not a completely new technology for most. I can also reassure my colleagues that it will take approximately 2.4 additional minutes to set up compared with that required for bolus administration.

Those that contributed free text comments were generally positive with one participant sharing, *"increased time for preparation is not important to me. Patient safety and efficacy is much more important to me. If this works, then it is a winner in my opinion.*". However, one participant reflected upon the reality of the simulation and shared that in real life it wouldn't be them drawing up the drug but most likely one of the trained nursing staff. Whilst this is true for that individual, it highlights that wastage of any team members time is not in the best interests of the patient nor the department.

6.6 Limitations

I know that most participants had heard of the technology, however I didn't assess the extent of their knowledge. This is something that would have been good to explore further as I cannot assume knowing about something is the same as understanding or the ability to utilise it.

Questionnaires were completed at the beginning of the session and then gathered by the research team before commencing with the set-up timing. They contained a free text box and collecting them at this point prevented participants from documenting their thoughts after they had the opportunity to set up the systems. As a result, I have likely missed out on important feedback as it's likely that given the opportunity to experience set up, this would have prompted participants to reflect on the set-up process.

There were obvious limitations to how effectively I could replicate the clinical environment. Attempts were made to recreate a bay in the resuscitation area, but this will never be completely authentic as there as so many other factors that would be involved in the real time situation. This will have impacted upon timings for both preparations. I don't know if it would have had a significant impact but timing from the point the equipment was available attempted to standardise for the simulated nature.

6.7 Conclusion

My results suggest that the time to set up TCI would not act as a feasibility barrier to using TCI Propofol in the Emergency Department. Combined with my greater understanding of current procedural sedation practice in local sites which showed that Propofol was a familiar sedative drug for procedural sedation, the possibility of

using Propofol TCI in the ED was a realistic proposition. I proceeded to conduct a systematic review (Burton et al., 2020) to critically appraise the available evidence for the use of TCI Propofol for procedural sedation in Emergency Medicine.

Chapter 7 A systematic review : Effect of target-controlled Propofol infusion to reduce the incidence of adverse events for procedural sedation in the emergency department

7.1 Introduction

A systematic review was completed in the early stages of the research project (Burton et al., 2020) to critically appraise the available evidence base to determine if target controlled Propofol infusion reduced the incidence of adverse events for procedural sedation in the Emergency Department.

The systematic review protocol was registered prospectively on PROSPERO, the international prospective register of systematic reviews (Burton, 2015).

7.2 Methodology

7.2.1 Review question

My objective was to determine whether the use of Propofol target-controlled infusion reduced the incidence of adverse events as described in the World SIVA adverse sedation event reporting tool (Mason et al., 2012) when compared to other methods of administration of Propofol for procedural sedation. Search methods for identification of studies

7.2.1.1 Electronic searches

A computer-assisted search was performed without language restrictions for RCTs comparing Propofol (Diprivan; Fesofol; Pofol; Propofol; Recofol) with an alternative

sedating regimen for adult procedural sedation in any hospital setting. I searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (2019, Issue 1), MEDLINE (1946 to January 28, 2019), EMBASE (1974 to 2019 January 29) and CINAHL (Appendix 4, 5, 6 & 7). I used the Cochrane sensitivity maximising randomised control trials (RCT) RCT filter (Higgins et al, 2017). I also searched the International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform, January 2019).

7.2.1.2 Searching other resources

Additionally, I searched the reference list of review articles, relevant trials, and abstracts of scientific meetings to identify further RCTs. The titles and abstracts were reviewed to identify all potential RCTs. I obtained the full -text versions of these articles. Additional efforts were made to identify potential RCTs relevant to the topic from the following data sources:

- grey literature
- references cited in primary sources

I did not impose a language restriction and no articles required translation.

7.2.2 Types of studies

I included Randomised Controlled Trials (RCTs). I defined an RCT as a study in which participants were randomly allocated to a treatment group.

7.2.3 Types of participants

Included studies involved adult service users that required procedural sedation in any hospital setting.

7.2.4 Types of interventions

The target intervention was administration of intravenous Propofol by target-controlled infusion compared with alternate methods of intravenous Propofol administration.

7.2.5 Comparator

Included studies compared the Propofol target-controlled infusion with another sedating strategy that was delivered by someone other than the patient.

7.2.6 Main Outcome

My main outcome was the incidence of adverse events. The definition of adverse events was set by the study authors and varied between studies.

7.2.7 Inclusion criteria

All studies which compared Propofol TCI to another Propofol administration regime in adult hospital for procedural sedation were included.

7.2.8 Exclusion criteria

I excluded paediatric patients. I also excluded studies using patient controlled Propofol administration regimes as a comparator and those receiving general anaesthesia.

7.2.9 Types of outcome measures

7.2.9.1 Primary outcomes

- Incidence of adverse events (as defined by the study authors)

7.2.9.2 Secondary outcomes

- Severity of the adverse event in relation to the World Society for Intravenous Anaesthesia adverse sedation event reporting tool (Mason et al., 2012).

- Dosing range for Propofol TCI

7.2.10 Data collection and analysis

Data collection and analysis was conducted following the guidelines available in the *Cochrane Handbook of Systematic Reviews of Interventions (Higgins et al., 2017).*

7.2.10.1 Selection of studies

All titles and abstracts for potentially relevant studies were screened independently by two authors. Full-text copies of all papers considered potentially eligible by the

two authors were retrieved. Both authors proceeded to screen these papers against the prospectively agreed inclusion criteria. A third author was consulted to resolve differences by consensus and inclusion when authors 1 and 2 disagreed.

7.2.10.2 Data extraction and management

A piloted, standardised data collection form was designed and agreed prospectively by the research team. Using this form two authors extracted data from the included studies and populated the form independently. The data collection form included the year of publication, name of the first author, methodology, study population, study design, participant characteristics, study exclusion and inclusion criteria, details of interventions and study outcomes.

An internet-based data storage system was used to store the extracted data. Covidence.org was the platform used. When clarification was needed on details from individual studies the study authors of the relevant papers were contacted via email. A third author was consulted to resolve any disagreements.

7.2.10.3 Assessment of risk of bias in included studies

Using The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2017), two authors independently assessed and rated the methodological quality of each included trial. Six domains were evaluated when each author judged the quality of the included studies:

- Utilisation of allocation randomisation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data

- Other bias

In addition, bias was assessed as:

- Low risk of bias
- High risk of bias
- Unclear risk (lack of information or uncertainty over the potential for bias).

Authors of included studies were contacted via email for further information if clarity was required regarding an included study. A third author resolved any disagreement to reach a consensus within the research team.

7.2.10.4 Assessment of heterogeneity

Clinical and methodological heterogeneity was assessed by the authors. In addition, statistical heterogeneity assessment was planned by creating a forest plot of adverse event and the P value for the x^2 test of heterogeneity (Higgins et al., 2017).

7.3 Results

7.3.1 Study selection and search results

Four hundred and sixty-two records were identified after duplicates were removed by searching sources using the methodology described previously. Of the 462 records identified, abstracts were obtained from 32 to allow further screening against the inclusion and exclusion criteria. All abstracts qualified for full-text analysis. Seven of the 32 full-text studies met the a priori criteria for inclusion in the final analysis. Figure 7-1 details the flow of information through the various phases of the

systematic review as outlined in the 'preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement' (Moher et al., 2009).

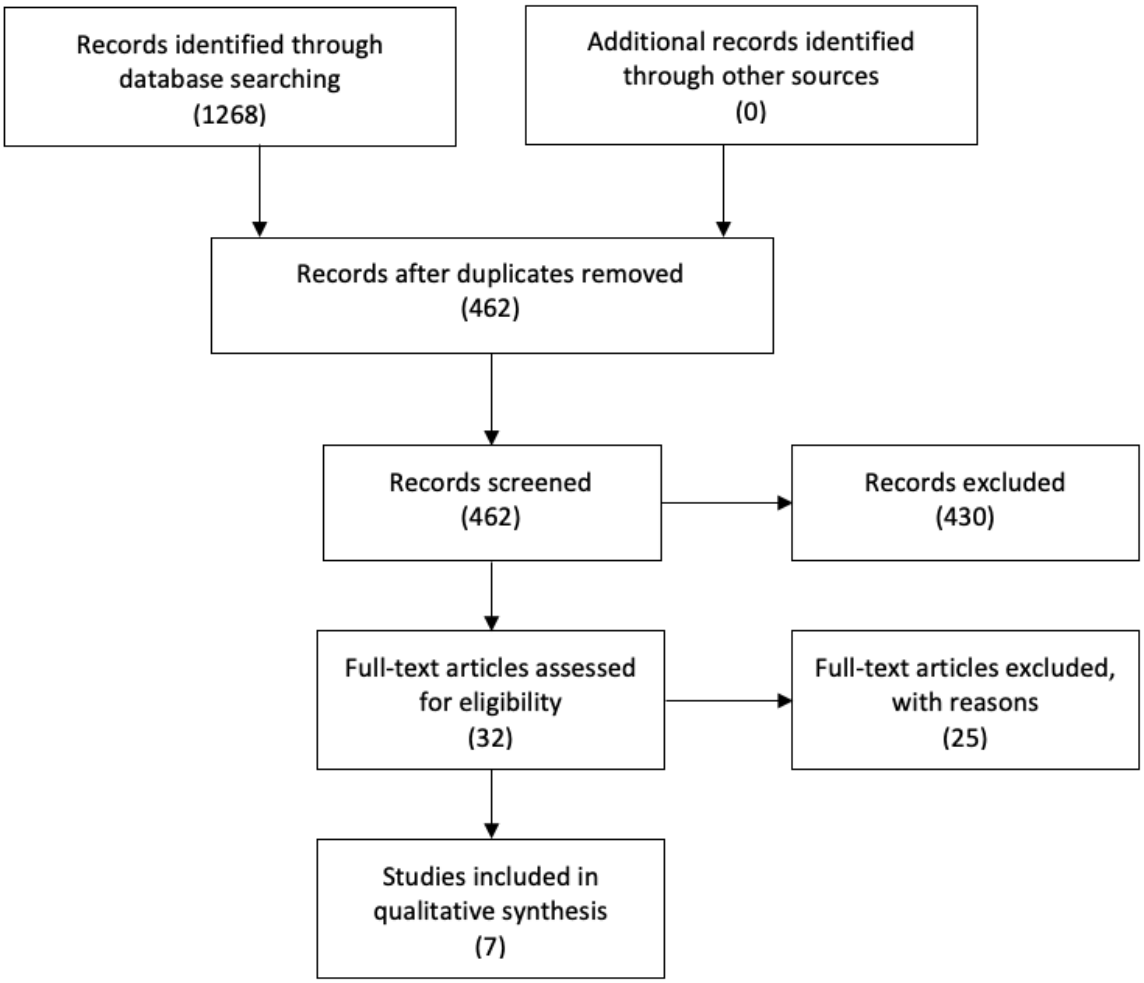


Figure 7-1 PRISMA flow diagram of studies identified for the systematic review (Moher et al., 2009, Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

7.3.2 Risk of Bias assessment

A summary of the Risk of Bias assessment using the Cochrane Collaboration's tool for all studies combined is shown in Figure 7-2.

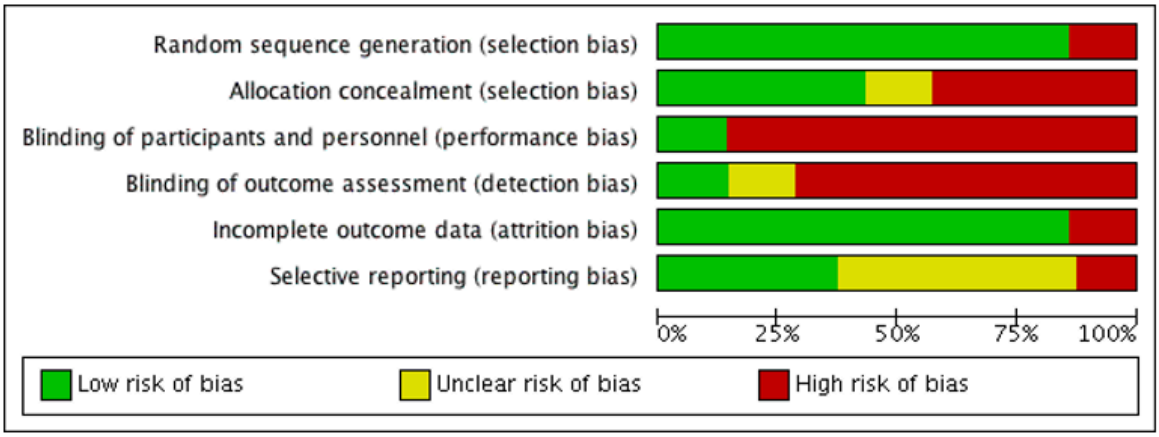


Figure 7-2 Risk of Bias Graph.Review authors' judgements about each risk of bias item presented as percentages across all included studies. Developed using Cochrane Collaboration. 2014. Review Manager (RevMan) [Computer program]. Version 5.3. 5.(Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

7.3.3 Heterogeneity

Authors found that significant methodological and clinical heterogeneity (Gagnier et al., 2012) existed between the seven studies. Pooling of the results in a meta-analysis was not appropriate. A narrative synthesis was undertaken (Popay et al., 2006).

7.3.4 Description of the studies

Seven studies in total were included in the systematic review (Burton et al., 2020). A summary of the study characteristics is outlined in Table 7-1. Five of the studies were parallel group Randomised Control Trials (Newson et al., 1995, Sakaguchi et al., 2011, Vučićević et al., 2016, De Vito et al., 2011, Chiang et al., 2013), one was a randomised non-inferiority trial (Franzen et al., 2016) and one was a prospective randomised crossover trial (Wang et al., 2016).

Gender of the patients was reported in all but one of the studies (Newson et al., 1995) and all reported a mean age for participants. Study duration was reported in

six of the included trials (Franzen et al., 2016, Sakaguchi et al., 2011, Vučićević et al., 2016, Wang et al., 2016, De Vito et al., 2011, Chiang et al., 2013) and ranged from 6 to 23 months.

There was variation between the settings and procedures undertaken in the included studies. Three of the studies included patients undergoing visualisation and/or biopsy of the gastrointestinal tract (Vučićević et al., 2016, Wang et al., 2016, Chiang et al., 2013). Upper airway visualisation and/or instrumentation was undertaken in one study (De Vito et al., 2011). One study involved dental procedures (Sakaguchi et al., 2011), one study involved bronchoscopy (Franzen et al., 2016) and one study involved patients undergoing a breast biopsy (Newson et al., 1995). All the trials recruited elective patients. None of the seven studies were conducted in the Emergency Department.

Additional analgesia was routinely administered alongside the sedating regimes under investigation in six of the trials (Sakaguchi et al., 2011, Newson et al., 1995, Franzen et al., 2016, Vučićević et al., 2016, Wang et al., 2016, Chiang et al., 2013). De Vito et al. (2011) was the only study not to use additional analgesia

In Chiang et al. (2013), patients received premedication of 10 μg/kg alfentanil before commencement on their allocated Propofol sedation. Wang et al. (2016) administered fentanyl 2μg/kg to both groups of patients undergoing colonoscopy.

In Franzen et al. (2016), both groups received 5mg hydrocodone intravenously immediately prior to flexible bronchoscopy. In addition to this, 2% lignocaine gel was used to achieve nasal anaesthesia with further aliquots of 1% lignocaine being used on both main bronchi, trachea, and vocal cords. No other additional analgesia was

permitted. Lignocaine 1% was also used to infiltrate the incision area in Newson et al. (1995) with additional lignocaine being permitted up to 300mg.

Midazolam was given at a dose of 0.04mg/kg intravenously as a premedication in Sakaguchi et al. (2011) for both groups of patients undergoing dental procedures. Vućićević (2016), administered midazolam to both groups in a 2mg bolus for patients weighing up to 70kg and 3mg bolus for patients >70kg. They also administered fentanyl 50mcg for patients weighing 50-60 kg, 75mcg for patients weighing 60-80kg and 100mcg for those weighing >80kg.

Routine Oxygen supplementation was used in six of the trials (Franzen et al., 2016, Newson et al., 1995, Sakaguchi et al., 2011, Vučićević et al., 2016, Wang et al., 2016, Chiang et al., 2013).

Table 7-1 Summary of Study Characteristics (Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

First Author	Year	Country	Study Design	Sample Size	Female (%)	Duration (months)	Mean Age (yrs)	Procedure	Additional Analgesia	Routine Oxygen	Alternative Sedation
Chiang	2013	Taiwan	RCT	220	45.9	23	51	Bidirectional endoscopy	Yes	3L/min NC	Propofol manual controlled infusion (MCI)
Franzen	2016	Switzerland	Randomized non-inferiority	77	61	9	65	Flexible Bronchoscopy	Yes	4L/min NC	Propofol boluses
Newson	1995	USA	RCT	63	-	-	35	Excisional breast biopsy	Yes	5L/min NC	Propofol boluses or MCI
Sakaguchi	2011	Japan	RCT	40	33	6	31	Dental treatment	Yes	2L/min NC	Propofol MCI
De Vito	2011	Italy	RCT	40	18	6	48	Drug induced sleep endoscopy (DISE)	Nil	Nil	Propofol boluses
Vucicevic	2016	Serbia	RCT	90	62	6	50	Diagnostic Colonoscopy	Yes	6L/min mask	Propofol MCI
Wang	2016	China	Randomized Crossover	72	39	12	41	Colonoscopy	Yes	2L/min NC	Propofol MCI

Propofol TCI was compared with alternative Propofol administration regimes in all the seven studies. In four of the studies TCI was compared to manually controlled infusions (MCI) (Sakaguchi et al., 2011, Vučićević et al., 2016, Chiang et al., 2013, Wang et al., 2016). In two of the studies TCI was compared to bolus administration (Franzen et al., 2016, De Vito et al., 2011). Newson et al. (1995) had three intervention arms consisting of; bolus, manually controlled infusion and TCI.

7.3.5 TCI models

Two Propofol TCI models were used; Schnider and Marsh. Table 7-3 outlines which were used in each study.

7.3.6 Outcome Measures and adverse events

Adverse events featured as part of the primary outcome measures in one of the studies included (Franzen et al., 2016) with the others including these as secondary outcomes. The 'adverse events' per the author's description for each study have been displayed in Table 7-2.

Franzen et al. (2016) sought to evaluate the safety of TCI Propofol compared to bolus administration for flexible bronchoscopy. The study used two coprimary outcome measures, safety, and the mean lowest arterial oxygen saturation. This non-inferiority trial comparing Propofol TCI with intermittent boluses for 77 patients undergoing flexible bronchoscopy requiring sedation. This was the only trial with safety as a primary outcome measure. This was defined as the mean lowest arterial oxygen saturation during the flexible bronchoscopy. Their secondary outcomes included the number of occasions of SpO_2 <90% and/or oxygen desaturation of >4% from baseline, number of occasions with systolic blood pressure <90mmHg and the mean SpO_2. They defined a serious adverse event as one requiring laryngeal mask or

endotracheal tube insertion. There were no serious adverse events and no life-threatening oxygen desaturations. The author did not define life-threatening oxygen desaturation. They reported that TCI was non-inferior to fractionated Propofol administration in terms of mean (SD) lowest SpO_2 during the procedure (88.3% (5.4%) vs 86.9% (7.3%)). The other secondary outcomes were comparable between bolus and TCI Propofol. Interventions required in the bolus vs the TCI groups to maintain SpO_2 were similar; increase in oxygen delivery (53% vs 56%, p=0.8), chin lift and jaw thrust manoeuvre (49% vs 53%, p=0.7) and insertion of nasopharyngeal airway (18% vs 18%, p=0.9).

Vućićević et al (2016) recruited 90 patients undergoing colonoscopy to compare TCI vs MCI. They defined adverse events as; mean arterial pressure (MAP) <60mmHg, MAP>105mmHg, bradycardia heart rate (HR) <45bpm, tachycardia HR>115bpm, hypoxaemia SpO_2<90% for longer than 30 seconds, bradypnoea <6 breaths/min and apnoea. There were no reported physiological adverse events. The authors noted that despite that pre-procedure MAP values being similar in both groups, ten minutes into the colonoscopy they were significantly lower in the MCI compared to the TCI group (86.50 $\pm$ 9.04 vs 92.39 $\pm$ 6.37 mmHg, p= 0.017) and likewise at the end of the colonoscopy (86.55 $\pm$ 9.28 vs 91.50 $\pm$ 7.05 mmHg, p= 0.006). Whilst the oxygen saturations in both groups were in the range of 97% to 100%, it was noted that they were significantly lower in the MCI group compared to the TCI group in both the fifth (98.84 $\pm$ 1.67 vs 99.48 $\pm$ 0.82%, p=0.033) and 15^{th} minute (97.38 $\pm$ 2.26 vs 99.60 $\pm$ 0.51%, p=0.008).

Vućićević (2016), stated that the aim of their clinical study was to compare patients' safety and endoscopists' comfort during colonoscopy when using Propofol TCI compared to a manually controlled infusion of Propofol. This initially gave the impression that adverse events would be part of the primary outcome measures but further reading described that the effect size was calculated from the differences in

time taken to eye opening following cessation of sedation in another study (Passot et al., 2002) and not derived from safety data.

Sakaguchi et al. (2011) recruited 40 patients with intellectual disabilities requiring dental sedation to undergo a dental procedure. They compared a manual control infusion (MCI) with a target-controlled infusion (TCI). Within the study procedures section of their paper, the authors state that if there was a severe haemodynamic change or severe airway obstruction that they stopped both the treatment and sedation. They planned to exclude the patients with these haemodynamic or respiratory complications from the study analysis. No patients were excluded, and no significant complications were reported. They did not provide a definition of haemodynamic change beyond hypotension or bradycardia nor what constituted a severe airway obstruction. Cardiovascular and respiratory variables did not differ between groups and were within clinically normal limits during the sedation.

Newson et al. (1995) recruited 63 patients scheduled to receive Propofol sedation for an excisional breast biopsy. Patients were allocated to one of three intervention arms: intermittent bolus, variable rate infusion or TCI. Adverse events were not formally recorded by the authors, but they did report that none of the patients in any of the three groups had a SpO_2<90% during the Propofol administration period. Physiological parameters are not recorded, but the authors did report that the cardiovascular and respiratory variables were similar in all groups. The authors also reported the number of interventions made by the anaesthetists delivering the sedation. Significantly fewer interventions were made in both the TCI and variable rate infusion groups when compared to the intermittent bolus group (median (range) 4 (1-11) vs 4 (1-11) vs 19 (5-52); $p<0.01$). No description of the interventions or trigger for intervention was provided.

De Vito et al. (2011) recruited 40 patients undergoing drug induced sleep endoscopy and randomised them to one of two Propofol sedation groups: TCI or bolus. The authors included the safety of the sedation plan as a secondary endpoint. It is unclear which parameters were defined as the safety of the sedation plan. They report that two patients in their non-TCI group needed oxygen because of a severe desaturation (65% and 61%) following the first Propofol bolus of $1mgkg^{-1}$. Their table outlining safety of the groups reported safety in 18/20 in the bolus arm vs 20/20 in the TCI arm. There is no other mention of safety nor of adverse events.

Table 7-2 Key Results from papers reviewed in the systematic review (Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

First Author	Key Results
Chiang	Incidence of mild desaturation (SpO_2<90%) 34 (30.9%) vs 49 (44.5%) p0.037 (RR 0.694; 95%CI 0.490-0.983). Incidence of moderate desaturation (SpO_2<85%) – 17 (15.5%) vs 34 (30.9%) p0.007 (RR 0.5; 95%CI 0.298-0.840).
Franzen	No significant difference between the incidence of SpO_2<90%, SBP<90mmHg.
Newson	Boluses vs MCI vs TCI; median number of interventions 19 (5-52) vs 4 (1-11) vs 4 (1-11) p<0.01. No SpO_2<90%.
Sakaguchi	MCI vs TCI; cardiovascular & respiratory variables within clinically normal limits during sedation.
De Vito	In bolus group 10% required Oxygen because of a severe desaturation (SpO_2 61% & 66%) because of first bolus 1mg/kg.
Vucicevic	None of the patients required increase in oxygen flow, placement of an oropharyngeal airway, the assisted ventilation with bag-mask, or endotracheal intubation. Chin lift in one patient from the MCI group.
Wang	TCI vs MCI; Lowest SpO_2(%) 97.4±2.0 vs 95.6±3.0, p 0.008. No severe adverse events occurred.

Wang et al. (2016) recruited 78 patients into their crossover trial comparing Propofol sedation administered via TCI vs MCI for colonoscopy. They defined severe adverse events as a SpO_2<90%, heart rate lower than 50bpm or a MAP lower than 55mmHg. They reported no severe adverse events. When comparing TCI vs MCI, they reported that the lowest MAP was higher in the TCI group (72.9 ± 6.6 vs 67.7 ±7.8; p=0.001), the highest MAP was lower in the TCI group (95.4 ± 6.5 vs 100.3 ± 8.5; p=0.009) and the lowest SpO_2 was higher in the TCI group (97.4 ± 2.0 vs 95.6 ± 3.0; p=0.008). They also noted that there were no significant differences in heart rate between the two groups and the recovery time (min) was shorter in the TCI group (9.1 ± 2.4 vs 11.3 ± 2.6; p=<0.001).

Chiang et al. (2013) recruited 220 patients requiring sedation for bidirectional endoscopy and randomised them into a Propofol TCI group or Propofol MCI group. Haemodynamic performance and respiratory manifestations were stated as secondary endpoints. The authors described haemodynamic performance as the duration of decreased mean arterial pressure (MAP) >20%/30% and respiratory manifestations as periods of bradypnoea, desaturation as well as the incidence of desaturation. Bradypnoea was defined as a respiratory rate of less than 8 breaths per minute. Desaturation events were classified as mild (SpO_2<90%) and moderate (SpO_2<85%).

The results show that no endotracheal intubation or emergent resuscitation occurred in any patients. The authors reported the periods of decreased MAP as percentages of the total procedure time and the MCI group experienced more hypotension than those in the TCI group. The duration of 20% decreased MAP was shorter in the TCI group than in the MCI group (16.24 ± 16.61% vs 24.43 ± 26.69%; p = 0.007). The duration of 30% decreased MAP was also shorter in the TCI group (1.82 ± 5.15% vs 7.37 ± 15.46%; p<0.001).

The duration of mild desaturation during the procedure was shorter in the TCI group (1.11 $\pm$ 2.48 vs 3.81 $\pm$ 6.74%; p<0.001) as was the incidence (30.9% vs 44.5%; p=0.037), a 30.6% risk reduction (relative risk [RR] 0.694; 95% confidence interval [CI] 0.490 - 0.983). A 50% reduced risk (RR 0.50; 95% CI 0.298- 0.840) of moderate desaturation was observed in the TCI group (TCI vs MCI: 15.5% vs 30.9%; p=0.007).

There is significant statistical and clinical heterogeneity amongst the studies and a meta-analysis will not be conducted. However, the forest plot generated is still of interest. Whilst there is no consistency in the definition of adverse events, the forest plot is a useful visualisation to compare the studies and the total number of adverse events as defined by the respective authors across each study. Sample sizes in the studies are relatively small except for Chiang et al. (2013) which recruited 110 patients in each arm. The summary forest plot does not cross the line of no effect (odds ratio =1) but Chiang et al is one of only two trials reporting adverse events and it is the largest population making it the most influential study within the forest plot. The forest plot shows reduced adverse events for TCI Propofol but due to the small number of adverse events and the disproportionate influence of Chiang et al, this report cannot be relied upon.

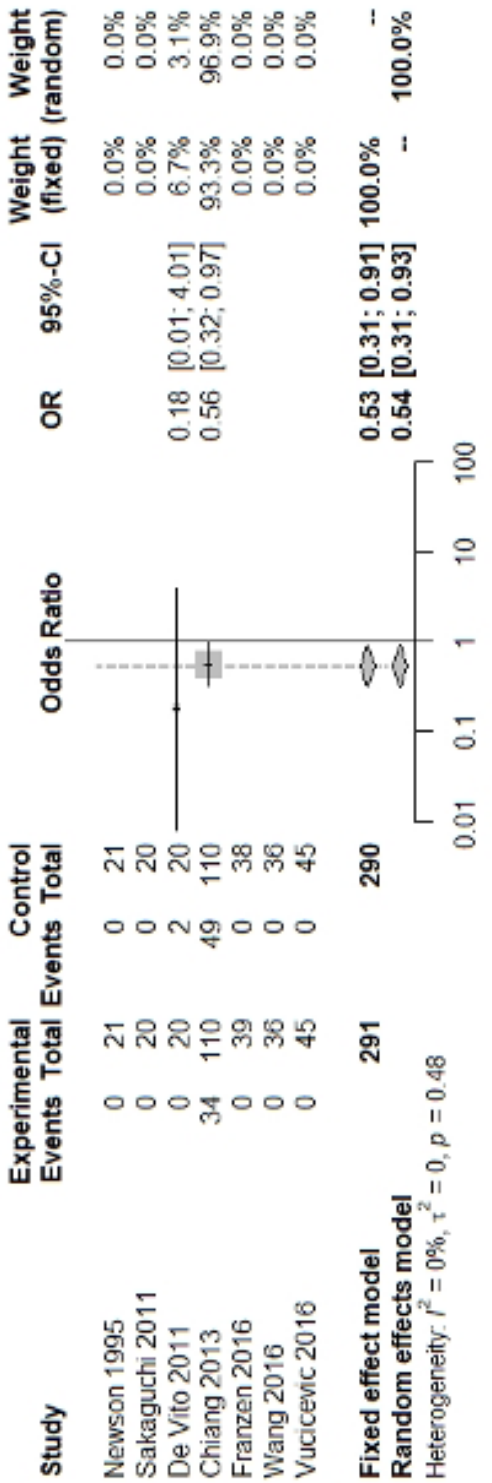


Figure 7-3 Forest plot of all adverse events as defined by the study authors (Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

7.4 Discussion

7.4.1 Population and Procedures

None of the seven studies were conducted in the Emergency Department. The populations in all the studies were fasted elective patients. There are physiological and psychological differences between the acutely unwell, distressed patients in the ED (Gray and Morris, 2013) requiring urgent reduction of a dislocated joint compared to the populations involved in the studies who were undergoing instrumentation of their alimentary tract (Vučićević et al., 2016, Chiang et al., 2013, De Vito et al., 2011, Wang et al., 2016) or airway (Franzen et al., 2016). Aspiration is a possible complication during procedural sedation and delayed gastric emptying secondary to pain and opioid use will increase the incidence of pulmonary aspiration (Gray and Morris, 2013, Søreide et al., 2005). Pain and anxiety in emergent situations may require higher doses of adjuvant analgesia which could theoretically result in an increased incidence of hypotension, respiratory depression and airway loss (Tobias and Leder, 2011).

7.4.2 TCI models

The Marsh model calculates the compartment volumes by the patient's actual weight whilst the Schnider model takes account of other variables to calculate the volumes per the patient's lean body mass (Al-Rifai and Mulvey, 2015). As described in this thesis (Chapter 2), both models will traditionally aim for different targets with the Schnider model using the effect site (C_{et}, brain) as opposed to the traditional plasma (C_{pt}) target concentration when using the Marsh model. The use of the C_{et}, the bolus administered in the Schnider model will initially overshoot to achieve the target more rapidly. These significant variations between the models will lead to different Propofol pharmacokinetics and pharmacodynamics which makes comparison of study outcomes statistically invalid.

Table 7-3 TCI targets and models used in research studies included in the systematic review (Burton et al., 2020). Reproduced with permission from Wolters Kluwer.

First Author	Initial TCI target	Dosing adjustments	Comment	TCI Model
Chiang	C_{et} 4μg/ml	C_{et} ↑ 1μg/ml if unsettled. After caecal intubation ↓ C_{et} by 1μg/ml. ↓ C_{et} by 1μg/ml if 20% MAP fluctuation reached or mild desaturation not better after chin lift.	-	Schnider
Franzen	C_{et} 2.5μg/ml	↑ 0.2μg/ml to maintain level of sedation.	-	Schnider
Newson	C_{pt} 2μg/ml	-	Range C_{pt} 1-4 μg/ml	Marsh
Sakaguchi	C_{pt} 1.5μg/ml	BIS>70 ↑ 0.3μg/ml. BIS<50 ↓ 0.3μg/ml.	-	Marsh
De Vito	Concentration set 1.5μg/m	↑ 0.2μg/ml every 2mins to desired BIS.	Mean C_{et} was 2.71 ± 0.75μg/ml	Schnider
Vucicevic	C_{et} 2.5μg/ml	↑ or ↓ by 0.5-1μg/ml to desired level of sedation.	Range C_{et} 1-4.5 μg/ml	Schnider
Wang	C_{pt} 3μg/ml	↑ 0.2μg/ml to desired level of sedation.	-	Marsh

7.4.3 Additional Analgesia

Propofol is a sedative with no analgesic properties. As such it makes sense that it is administered with additional analgesic drugs when procedural sedation is being undertaken for a painful procedure. Consistency in the additional analgesia used for each group was achieved in every individual study. This consistency was helpful when interpreting the individual study results. However, variability in the additional analgesia used between each of the studies made it more difficult to identify emerging trends in the incidence of adverse between the studies, it was a confounding factor. Meta-analysis of the study results was inappropriate due to intra-study protocol heterogeneity.

7.4.4 Adverse Events

There was no consistency between studies of what constituted an adverse event. The 'adverse events' per the author's description for each study have been displayed in Table 7-3.

Definitions and reporting of adverse events and other events were not consistent across the studies. Severe desaturation was described in one paper (Wang et al., 2016) as SpO_2 <90%, whilst in another (Chiang et al., 2013) this was classified as mild.

In 2012, the World SIVA International Sedation Task Force launched an adverse event reporting tool to allow standardisation of reporting and tracking of adverse events during procedural sedation (Mason et al., 2012). Three of the studies (Franzen et al., 2016, Vučićević et al., 2016, Wang et al., 2016) were published after the launch of the adverse event reporting tool in 2012, none of the studies used this standard. As a result, all adverse events as defined by the authors have been included in the forest plot (Figure 7-2).

7.5 Conclusion

This systemic review identified a paucity of studies involving procedural sedation in the Emergency Department using Propofol TCI. Results from each of the studies included from other clinical areas suggests a trend towards fewer respiratory adverse outcomes and hypotension with Propofol TCI versus other methods of administering Propofol.

It was not possible to conclude that Propofol TCI reduces the incidence of adverse events when compared with other sedating regimens using Propofol using a systematic review and meta-analysis of the relevant literature. This has highlighted the importance of standardising the reporting of adverse events (Roback et al., 2018).

I identified a gap in the published literature and designed a feasibility study protocol using the information I had gained (Burton et al., 2019b) with the aim to facilitate a multicentre RCT.

Chapter 8 Propofol Target-Controlled Infusion in Emergency Department Sedation (ProTEDS) a multicentre, single-arm feasibility study

8.1 Background

Widespread adoption of TCI in the Emergency Department (ED) requires evidence that it is safe and acceptable to both patients undergoing procedural sedation and those providing sedation. As the multicentre RCT is considered the gold standard of study design due to the rigor with which it is designed and conducted (Hariton and Locascio, 2018), I felt it was the obvious next step following the feasibility study with the incidence of adverse events as the primary outcome measure.

Other study designs exist that would possibly aid adoption of TCI in the ED including the more pragmatic approaches of cluster randomized trials (Hemmings et al., 2015) designed to recruit in a traditional parallel fashion or in the more novel stepped wedge design (Figure 8-1). For a mature technology like TCI there have been suggestions that perhaps an observational study would be more pragmatic. TCI Propofol was introduced into the world of Anaesthesia without a large-scale RCT (Absalom et al., 2016, The Academy of Medical Sciences & Royal Academy of Engineering., 2013).

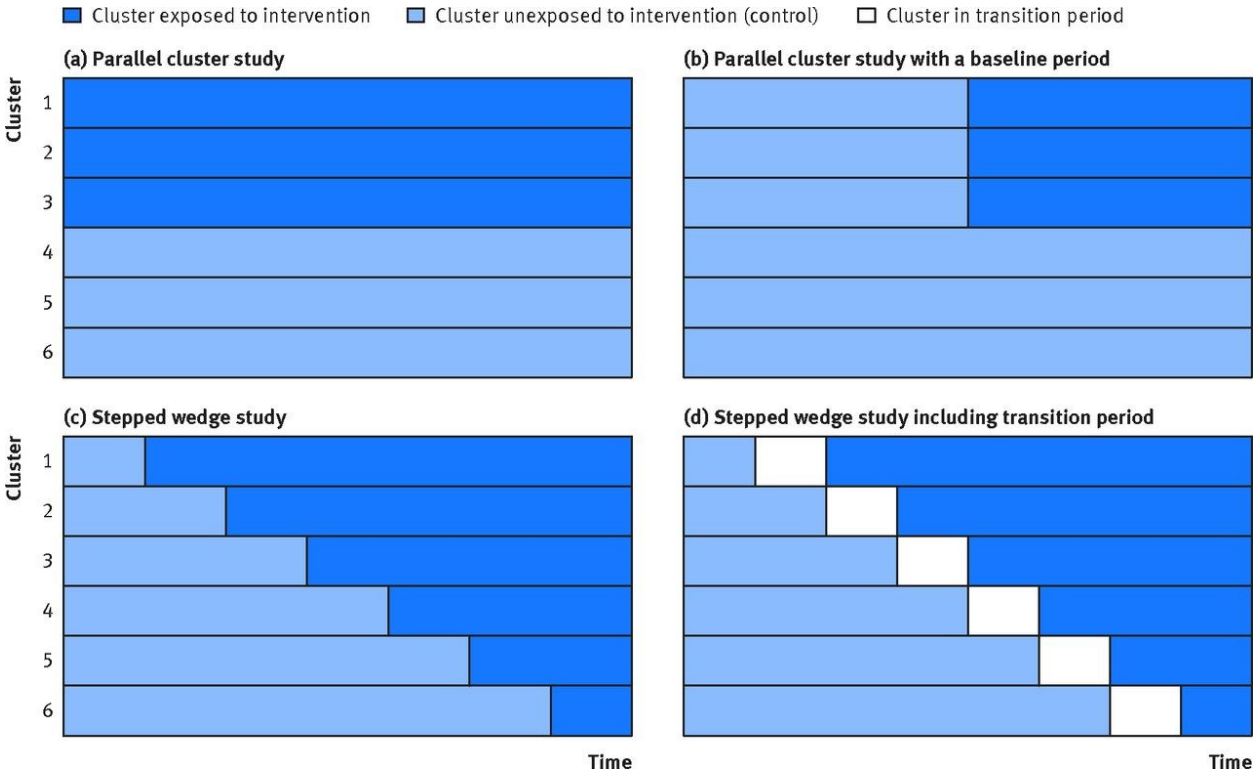


Figure 8-1 Conventional parallel cluster study & stepped wedge study
Schematic illustration (Hemming et al., 2015). Reproduced with permission from the BMJ.

To aid future study design, there were unanswered questions regarding the feasibility which the research team sought to answer by conducting a multicentre, single-arm feasibility study. At this point I wanted to know if TCI Propofol was acceptable to my patients and if I would be able to recruit to the study. Recruitment to research trials in the ED is often reported as being challenging (Cofield et al., 2010, Johnson et al., 2016, Kendrick et al., 2007, Price et al., 2020).

8.2 Methods

8.2.1 Setting & Population

Patients were recruited from the Emergency Department in four hospitals in the West of Scotland. Three were in busy urban hospitals and one in a district general hospital. My population included all adults (≥18 years) with an acute traumatic anterior

shoulder dislocation requiring procedural sedation to reduce the dislocation. The procedure and sedation were to be administered in the Emergency Department of the hospital they presented to.

8.2.2 Ethics & Trial Registration

Permission for the study was obtained from the West of Scotland Research Ethics service and individual consent from the patients obtained (Appendix 8). Ethical and amendment approval was given by the West of Scotland Research Ethics Committee 5, reference number 17/WS/0020 on 24th January 2017 (Appendix 23).

The trial was registered at ClinicalTrials.gov (NCT03442803). The study protocol, (Burton et al., 2019b) was published in Pilot and Feasibility studies following The Standard Protocol Items Recommendations for Trials (SPIRIT) checklist (Appendix 9). The reporting followed CONSORT guidelines (Appendix 10).

8.2.3 Inclusion Criteria

- 18-65 years old
- Body weight ≥50kg
- Clinical and/or radiological evidence of acute anterior shoulder dislocation
- American Society of Anesthesiologists (ASA) Physical Status Classification I or II
- Fasted ≥ 90mins, (The Royal College of Anaesthetists and The College of Emergency Medicine Working Party on Sedation, 2012, Thorpe and Benger, 2010)

8.2.4 Exclusion Criteria

- Inability to provide or refusal of informed consent
- Previous attempt at reduction during the same presentation
- Previously enrolled in the study
- Clinical and/or radiological evidence of acute posterior shoulder dislocation
- Clinical and/or radiological evidence of concomitant ipsilateral upper limb fracture
- Concomitant multi-system injury
- History of difficult intubation/airway surgery
- ASA grade III, IV or V
- Haemodynamic instability
- Pregnancy
- Contraindication to sedation
- Allergy to study drugs or eggs
- Clinician decision
- Morphine administration within the preceding 20 minutes prior to starting TCI

There was no objection to subsequent co-enrolment of patients to clinical trials amongst those already enrolled to ProTEDS.

8.2.5 Aim

The primary aims of the feasibility study were to:

- Measure patient satisfaction using a visual analogue scale (VAS),(McCormack et al., 1988) (Appendix 11)
- Calculate recruitment rates by reviewing the number recruited vs the number of patients screened

Secondary objectives were:

- Safety:
    - Incidence & severity adverse events as per World Society for Intravenous Anaesthesia adverse event sedation reporting tool,(Mason et al., 2012)
- Potential Effectiveness:
    - Successful completion of the procedure
    - Number of reduction attempts
- Patient Centered:
    - Patient reported pain score VAS (McCormack et al., 1988, Breivik et al., 2000) (Appendix 12)
    - Nursing opinion of the patient's experience VAS (Appendix 13)
    - Patient recall of the procedure (Pandit et al., 2014)
    - Free text comments from all staff at the end of the procedure
- Timely:
    - Time from commencement of induction to Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) 3 (Chernik et al., 1990a)
    - Time from commencement of sedation to fit for discharge (The Royal College of Anaesthetists and The College of Emergency Medicine Working Party on Sedation, 2012)
        - Patient returned to their baseline level of consciousness
        - Vital signs are within normal limits for that patient
        - Respiratory status is not compromised
        - Pain and discomfort have been addressed

A member of the emergency medicine nursing team separated from the clinical or research teams asked each patient the satisfaction question. I did not use a tool to measure clinician satisfaction instead opting for free text comments on the data collection sheet.

8.2.6 Study Procedures

Emergency Medicine consultants who routinely used bolus Propofol for procedural sedation practice were the recruiting clinicians for this feasibility study. They all had valid Good Clinical Practice Certificates and had received additional training in TCI prior to the start of study. Training sessions were developed and delivered by an experienced anaesthetist familiar with TCI Propofol. A two-hour interactive session was delivered with the objective of outlining the concept of TCI and how this would be delivered in the ED setting. Training sessions were offered to all members of staff in the departments recruiting to the study, not just the recruiting consultants.

Three consultants were trained on each site, approximately 16% of the regional consultant workforce. Regular contact was made between the research team and recruiting sites throughout with offers of refresher training sessions.

Consultants recruiting to the study did so when working clinically in the EDs. Potential participants presenting to the Emergency Department with a suspected shoulder dislocation received a patient information sheet (Appendix 14). On confirmation of a shoulder dislocation patients were screened against the study inclusion/exclusion criteria by the recruiting consultant using the physician information sheet (Appendix 15).

If the patient was deemed eligible, recruitment to the trial was discussed further and consent obtained if the patient was agreeable. A screening log was provided on each site to record the interaction and outcome along with reasons for refusal.

When consent was obtained, monitoring in line with current best practice, (The Royal College of Anaesthetists and The College of Emergency Medicine Working Party on

Sedation, 2012) was established. All patients received supplemental oxygen (via nasal cannula at 4 L min^{-1}) for the duration of the sedation episode. The patient could have received morphine analgesia if it was administered at least 20 minutes before commencement of sedation. A prompt sheet was included in all recruitment packs to assist consultant's delivery of procedural sedation (Appendix 16).

The TCI Propofol sedation flow sheet was followed (Appendix 17 & 18) to guide procedural sedation. This was a coloured step by step illustration to guide the starting plasma (C_{pt}) target concentration of Propofol, increments and upper limit C_{pt}. When the patient reached the point of MOAA/S 3 a weight-based bolus of the analgesic alfentanil was given immediately prior to commencement of the procedure.

Start time for the procedure was defined as the time the TCI was commenced. When the patient's modified observer's assessment of alertness/sedation Scale (MOAA/S) (Chernik et al., 1990a) reached the target of three it was recorded every three minutes until the procedure was completed. The MOAA/S was chosen due to the recruiting sites general familiarity with its utilization and the lack of recommendations from the systematic review on the topic (Williams et al., 2016).

Completion of the procedure was defined as the point that the TCI infusion was discontinued. A patient reported pain and satisfaction score for the procedure were recorded after full recovery by nursing staff not directly involved in the procedure. Patients were also asked for their last memory after the onset of procedural sedation. Procedural sedation using Propofol TCI was not routine practice in the ED and because of this I decided to proceed with caution and use the Marsh model. Both versions of my TCI dosing protocol were written with the assistance of Dr Keith Anderson, an expert with peer reviewed publications in this field. My study of reference from which the protocol was devised involved a similarly painful procedure, oocyte retrieval, requiring procedural sedation,(Edwards et al. 2010). Computer simulation

programmes were not used. After the trial closed, I contacted all recruiting clinicians via email asking for feedback.

Infusion pumps were provided by BD CareFusion to each participating department for the duration of the study. If a department were to buy the pump the average cost would be £3000 (www.bd.com). One pump would be sufficient for the vast majority of EDs as it would be highly unusual to reduce more than one shoulder simultaneously. Bolus administration would normally require 20mls of Propofol to be drawn. The total consumables cost was estimated at £3 per patient if an additional 20ml of 1% (10mg/ml) Propofol was prepared as standard for the TCI group.

8.2.7 Sample Size

A formal sample size was not calculated for this feasibility study (Dixon, 1965). I aimed to recruit at least 20 patients within a fixed time period to allow calculation of the recruitment rate. The time period was agreed by auditing the average number of anterior shoulder dislocations presenting weekly at each site along with the number of recruiting consultants.

8.2.8 Data Collection and Planned Analysis

A standardised data collection sheet was used to record information for each patient enrolled (Appendix 19). This document acted as my source document with all data being hand-written. Information was transcribed from a screen.

Descriptive statistics were used to analyse the data.

8.2.9 Patient and public involvement

This research study was designed without patient or public involvement.

8.2.10 Raising Awareness

The study was named with the intent to create a memorable acronym, Propofol Target-Controlled Infusion in Emergency Department Sedation – ProTEDS (Pottegård et al., 2014). Posters were designed (Appendix 20) and displayed in both patient and staff areas.

A graphic designed was consulted to create a logo for the trial. The end product was a logo that encompassed the Emergency Department environment by using the RCEM colours, involved TCI by incorporating the display unit of a TCI pump and clearly displayed the study name (Figure 7-2). This logo was used on all presentation materials and study documentation to build memory of the study and encourage recruitment.

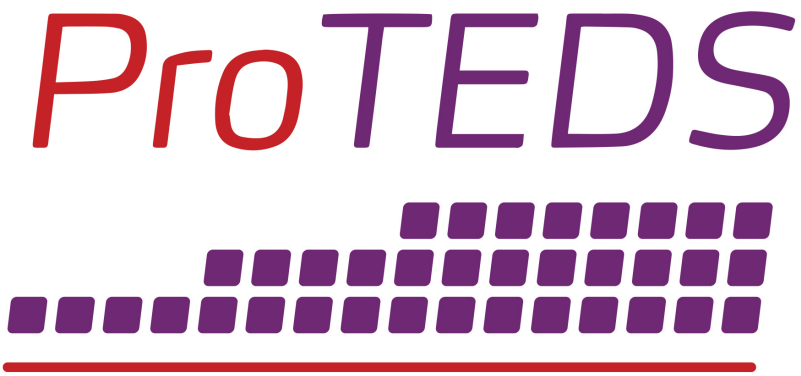


Figure 8-2 ProTEDS feasibility study logo

8.3 Results

The three urban teaching hospitals recruited ten, six and three patients respectively whilst six patients were recruited in the district general hospital, but screening logs were not maintained. Twenty-five patients were recruited across all four sites between April 3rd, 2017, and 31st December 2018 as outlined in the CONSORT diagram (Figure 8-3). Recruitment was temporarily halted between the 25th April 2017 to 9th October 2017, whilst a substantial protocol amendment was approved. The approved amendment allowed an increase in the initial and maximal set plasma concentrations of Propofol (Appendix 17 & 18).

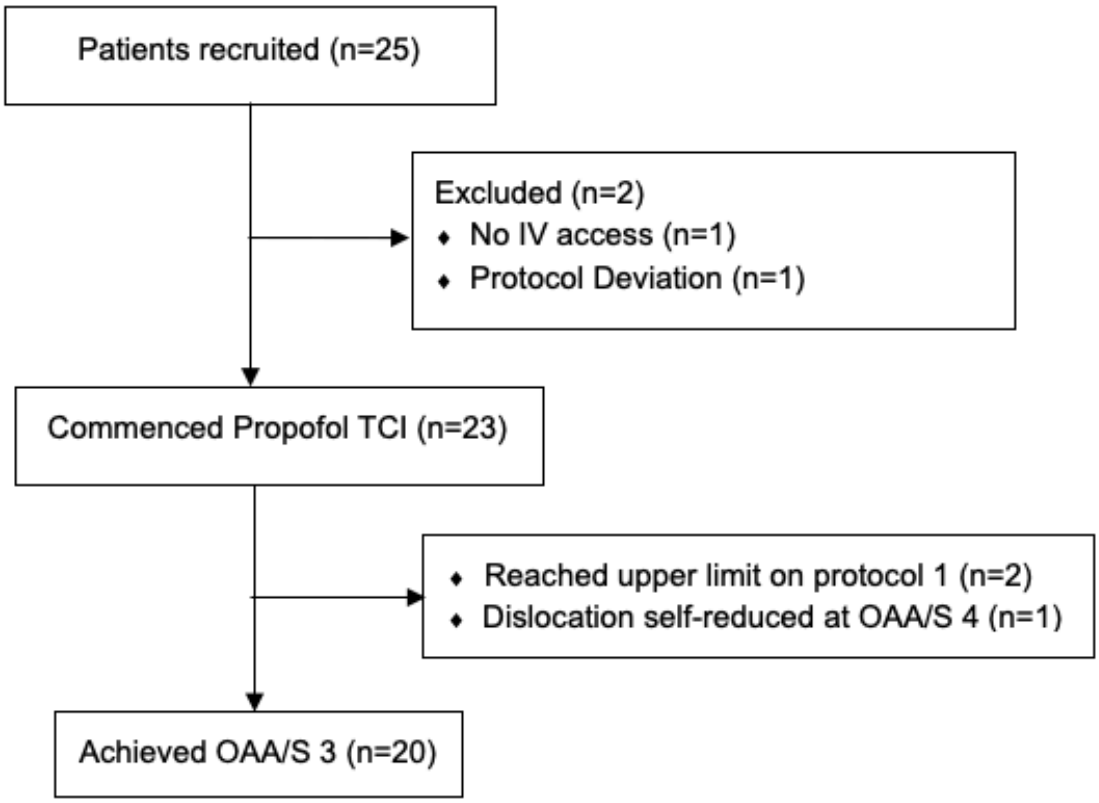


Figure 8-3 Number of Patients undergoing procedural sedation achieving OAA/S 3 (Burton et al., 2021). Reproduced with permission from BMJ.

Two patients were excluded; one had no IV access, and the infusion was never commenced, the other was a protocol deviation where the patient received 2% (20mg/ml) Propofol. No harm came to the patient and the incident was reported to the pharmacovigilance unit and medical ethics. The mean ± SD dose of morphine administered as part of standard care at least 20 mins before commencing the protocol was 8.9±3.3 mg.

Summary demographics and results for the 23 patients commenced on TCI Propofol are displayed in Table 8-1 and Table 8-2 respectively.

Table 8-1 Summary of patient characteristics for patients commenced on TCI (Burton et al., 2021). Reproduced with permission from BMJ.

	No (%) or median (IQR)
Female	6 (26%)
Male	17 (74%)
Age (years)	37 (18)
Weight (kg)	81 (21)

Twenty patients achieved an OAA/S of 3. Of the three who did not, two were prior to the protocol amendment and the third post amendment. The patient post protocol amendment self-reduced their dislocation when OAA/S 4. The median (IQR) time to OAA/S 3 was 26 (12) minutes. All twenty patients achieved successful shoulder joint reduction. The median (IQR) time to reduction for the 19 recorded was 29 (14) minutes. There were no adverse events reported.

Five patients were recruited, and procedural sedation attempted with the initial drug protocol (Appendix 17). Two of the five patients did not reach OAA/S 3 despite receiving the maximum dose of Propofol TCI (C_{pt}2 μg ml^{-1}, Appendix 18).

Table 8-2 Summary of Results for participants sedated using Version 1 protocol, Version 2 protocol and combined results for all patients commenced on Propofol TCI, N=23 (Burton et al., 2021). Reproduced with permission from BMJ.

	Version 1 Protocol (n=5)	Version 2 Protocol (n=18)	Total (N=23)
	No. (%) or Median (IQR)	No. (%) or Median (IQR)	No. (%) or Median (IQR)
Reduction Successful[a]	3 (60%)	18 (100%)	21 (91%)
Adverse Events	0 (0%)	0 (0%)	0 (0%)
Max C_{pt} (μg ml-1)[b]	2 (0)	2.5 (0.8)	2.2 (0.8)
Time to OAA/S 3 (mins)[c,d]	14 (10)	27 (16)	26 (12)
Time to Reduction (mins)[e]	17 (10)	30 (12)	29 (14)

1 patient self-reduced at OAA/S 4[a], 1 patient did not have Max C_{pt} documented[b], 4 patients did not have Time to OAA/S 3 documented[c], 2 patients did not achieve OAA/S 3, 3 patients did not have Time to Reduction documented[e]

Patient and nursing reported outcomes are shown in Figure 8-4. Overall nursing and patient satisfaction with TCI Propofol and the procedure was high.

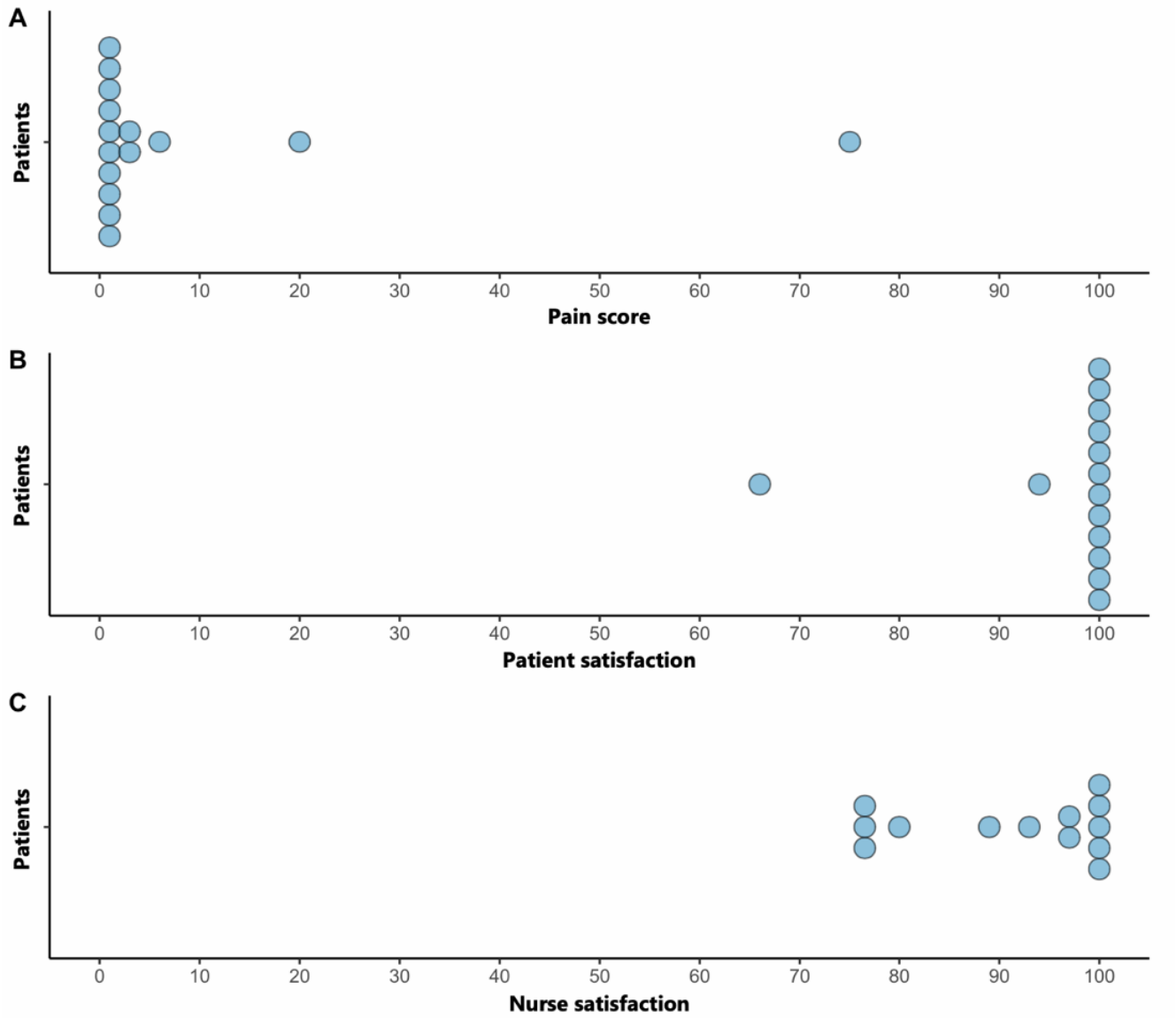


Figure 8-4 Patient and nursing reported outcomes as plotted on the VAS scale.

A – Pain score, B – Patient Satisfaction, C – Nurse Satisfaction (Burton et al., 2021). Reproduced with permission from BMJ.

Patient reported pain scores were low, non-parametric with a positive skew. Results are displayed in Table 8-3.

Table 8-3 Median Patient and nursing reported outcomes in numerical format (Burton et al., 2021). Reproduced with permission from BMJ.

	Median (IQR)
Procedural Pain (n = 15)	0 (3)
Patient Satisfaction (n = 14)	100 (0)
Nurse Satisfaction (n= 13)	96 (20)

Two nurses commented that the initial stages in achieving OAA/S 3 felt slow but overall, it was a better experience for the patient. Seventeen patients had amnesia of the procedure with two patients able to recall the procedure. Recall was not recorded for one patient.

E mail feedback from recruiting clinicians indicated that ongoing education and support would have been useful.

8.4 Discussion

My feasibility study demonstrated acceptability of the technique to the patient and staff. Successful joint reduction was achieved in 100% of the 20 patients achieving OAA/S 3 with no recorded adverse events, (Mason et al., 2012). These positive findings are encouraging. Used in conjunction with the information I have gathered on barriers to recruitment and TCI Propofol administration, they will enable us to design a future study.

8.4.1 Adverse Events – Is there a problem?

Safety of any new development in procedural sedation is key. We want to avoid patient harm and the incidence of adverse events. My aim is to show that TCI is superior or at the very least, non-inferior to bolus administration of Propofol.

Extensive use of TCI technology in other clinical settings satisfied us and the ethics committee that it was safe to explore further in Emergency Medicine procedural sedation. My feasibility study was the first ever research conducted in the ED using Propofol TCI.

Adverse events have been reported inconsistently in past studies of Propofol sedation making meaningful comparisons difficult, (Newstead et al., 2013). Even locally, procedural sedation audits vary in their criteria between hospitals and boards. To overcome this the World Society of Intravenous Anaesthesia (World SIVA) developed an adverse event reporting tool, (Mason et al., 2012).

One of the recruiting sites used this tool routinely and reports a minor adverse event rate of 3%, a moderate adverse event rate of 0.5% and a sentinel adverse event rate of 1%. In this study, I prospectively used the SIVA adverse event reporting tool to allow standardised reporting of adverse events. The SIVA adverse event reporting tool has now been superseded by the 'Tracking and reporting of procedural sedation outcomes tool (TROOPS) (Roback et al., 2018).

A systematic review (Williams et al., 2016) of prospective randomised double blind involving procedural sedation approximated the incidence of adverse events at 5%. If I used the approximation of 5% from the systematic review to calculate my sample size for a future RCT, it would result in a sample size of >10,000 patients if I was looking to reduce the risk to 4% (Ward et al., 2018). This would prohibit us from using the incidence of adverse events as a primary outcome measure and most likely is the reason why so few studies have it as a primary outcome measure.

Franzen (2016) overcame this by adopting a non-inferiority design when looking at Propofol TCI vs bolus Propofol for flexible bronchoscopy. A non-inferiority study is

designed to show that the intervention is no worse than the standard treatment or control group. This would have a smaller, more achievable sample size whilst retaining safety as the primary outcome measure and making a valuable contribution to the existing research.

8.4.2 Recruitment

The total recruitment was less than I expected at only 25 patients, and I was unable to maintain an accurate screening log on any of the sites. It became clear from the feasibility study that support from a research team would have been useful and any future proposals would include funding for this support (Cofield et al., 2010). There was no onsite research support in any of the sites recruiting. Whilst the Emergency teams want to support research, they do not have the capacity to do all the steps required.

Consultant presence in the clinical area did not equate to availability to screen patients for recruitment as their primary role was to deliver clinical patient care. Consultant availability was limited by other operational demands, and they would have to weigh up departmental safety vs recruiting patients. Their primary role when on clinical duty is to maintain patient safety by supervising staff, maintaining flow, and reviewing patients.

In future research I would more accurately map the departmental activity requiring procedural sedation to allow the research team staffing to be aligned with the times of maximal potential recruitment. This would maximise the use of funding awarded.

8.4.2.1 Environment

Emergency Departments are unique in that they receive acutely unwell, undifferentiated patients 24 hours a day. Priorities are continuously shifting to ensure that emergency care is delivered to patients arriving unpredictably. The priority and focus for the clinical team was to provide lifesaving emergency care to patients. Providing emergency care in this current climate is proving very challenging with four-hour performance in Scotland at an all-time low since it was introduced in 2013. The intention of this target was to ensure 95% of patients were to wait no longer than four hours from arrival to admission or discharge. Since the introduction of the 4-hour target, there has been a rise in the number of patients in departments for greater than 12 hours (Griffin, 2022, O'Dowd, 2022). Compounded with staffing shortages, overcrowding and lack of flow, asking clinical teams to take part in research in any capacity is challenging (Worster et al., 2005) and must be borne in mind for subsequent planning as the situation will not improve soon.

8.4.2.2 Screening

Screening for patients in the Emergency Department is not straight forward (Cofield et al., 2010). Within departments there is an awareness of the various research studies ongoing but the ability to be able in that moment to recall each and whether your patient is suitable is difficult. One of the strategies employed to overcome this has been to ask the triage nurse is asked to identify patients (Fry and Stainton, 2005). However, many individuals have had this thought when it comes to interventions and the triage nurse is often overloaded and unable to triage patients.

I was unable to maintain screening logs on any of my sites. I anticipated it would be relatively easy, but the reality proved otherwise (Borys, 2009, Hollnagel, 2017). Details including who should be included, where it would be stored etc had been decided in advance in the absence of other clinical commitments. In hindsight asking

clinical teams to maintain this was unreasonable. One of the purposes of my screening log was to review those that hadn't been recruited to identify barriers to recruitment (Elm et al., 2014). The absence of screening logs identified the lack of clinical resources to undertake Emergency Medicine research and the requirement for research specific staffing support.

I had hoped that the screening log would also give us a more accurate idea of the numbers of patients presenting to the participating departments with shoulder dislocations. I had to look at other ways to gather the numbers of potentially eligible patients. Details on this patient group can be sourced in a variety of ways both electronic and paper. Electronic systems are maintained in all health boards to a greater or lesser extent. Unfortunately, there is no consistency across the nation regarding the capabilities of each system. All systems are capable of registering patients with some associated details. All systems will have a presenting complaint registered. This is formed from the words the patient uses when registering at the front desk. It is encouraged that a final discharge diagnosis is entered for all patients but is not mandatory in each board. Discharge diagnoses are identified from an ICD-10 drop-down list, there are more than 55,000 codes to choose from. If a clinician doesn't find the appropriate diagnosis it is possible, they will opt for the best fit. This makes data extraction complicated with duplication and the possibility of missing patients.

8.4.2.3 Data Collection

Having the capability to provide a dedicated member of staff purely for research data collection is unrealistic in busy, short-staffed Emergency Departments. This was evidenced in my study by incomplete data collection and feedback from site teams after the study had closed. Having a research team member dedicated to this is the obvious solution but perhaps an even better one is the ability to use wearable technology (Bonato, 2010, Dunn et al., 2018, Huhn et al., 2022, Niknejad et al., 2020)

to monitor and record data that is automatically stored electronically. This may be a more cost-efficient solution cutting down on paper transcription error and increasing the quality of the data (Reich et al., 2000, Taenzer et al., 2014).

8.4.3 Patient Satisfaction

Patient satisfaction was measured by asking the patients to use a VAS (Voutilainen et al., 2016, Brokelman et al., 2012) ranging from not satisfied to very satisfied to record their satisfaction levels. This question was asked when the patient was deemed fit for discharge. This was a method that I read about in other articles regarding sedation and felt it was a good fit for what I was trying to achieve.

I recognised that procedural sedation is not solely about achieving the procedure (Holzman, 2021) but achieving it in a manner that is felt to be acceptable to the patient with high patient satisfaction levels. My chosen measurement tool was suboptimal as it did not take account of the complex, multi-dimensional nature of patient satisfaction. Ideally, I would co-create a suite of 'always events' locally with my patients that have undergone procedural sedation in the ED.

8.4.4 Time to OAA/S 3

Whilst departments involved in the research were happy that the procedure was smooth and recovery quick when OAA/S 3 had been achieved, they were unhappy with the time it took to get to that point. My mean (±SD) time to OAA/S 3 was 25 (±9) min. To some this may not seem like an unreasonable length of time but when you compare it to one participating centre's normal practice taking 10 (±6) min it is an understandable perception. This data was obtained from their regular audit data gathered for adult procedural sedation in their department. The time taken to

achieve MOAA/S 3 in this study was considered an unacceptable barrier to clinicians adopting TCI Propofol for procedural sedation.

I approached the feasibility study with caution and my data shows that in hindsight I designed the TCI Propofol dosing regime too cautiously and inadvertently increased the time to reach OAA/S 3. The TCI Propofol regime can be amended to reduce the time it takes to achieve OAA/S 3. Changing the starting level of my dosing or increasing the dosing increments are possibilities.

8.4.4.1 Effect Site Targeting

By using effect site targeting I would anticipate the time taken to reach OAA/S 3 would be decreased as the system is designed to achieve the brain effect site concentration as quickly as possible. It does this by delivering a greater initial bolus of Propofol to create a gradient between the plasma and effect site. This gradient allows faster movement of Propofol to the effect site in comparison to plasma targeting. A larger initial bolus may create concern about possible adverse events, however, the commercially available pumps capable of effect site targeting with Propofol use the Schnider model.

The Schnider model was developed considering more variables than the Marsh model which may indicate it is safer in some groups. The Marsh model was developed using weight as the only variable whereas the Schnider model uses age, height, weight, age, and gender. Some anaesthetists would recommend using the Schnider model in frail, older, more unwell patients (Al-Rifai and Mulvey, 2016).

8.4.4.2 Drug protocol

I acknowledge that my drug protocol was cautious, and it took time to achieve the desired sedation level. My data obtained during the feasibility study shows that I could review my titration strategy with a view to increasing the titration amounts and decrease the timings between titrations. Maintaining safety whilst increasing speed is what I want to achieve.

My first draft of a revised protocol was reviewed by a world TIVA expert, Dr Keith Anderson. One of his main questions was how long we would hold the TCI infusion at a set level to assess whether the patient is adequately sedated, over sedated or under sedated. To answer this question, I realised that I would need to understand the time taken to reach equilibration between the C_{pt} and C_{et} as at this point the clinical sedation should be steady whereas if the $C_{pt}>C_{et}$ then clinically I would expect my patients to become increasingly sedated as equilibration is achieved without altering the infusion target.

Computer programmes exist which allow us to simulate the pharmacokinetics of TCI infusions. I can use the results of my feasibility study with this technology to inform a new drug protocol whilst maintaining safety. Tivatrainer (Engbers) is one of these programmes. It can simulate the various TCI models and correlating PD. This programme can simulate the various TCI models and displaying the accompanying PD effects including heart rate and OAA/S.

8.4.4.3 Remifentanil TCI

The short context-sensitive half-life of remifentanil would make it an attractive option for TCI instead of Propofol for procedural sedation in the Emergency Department. Normally we seek to provide analgesia for patients with more prolonged analgesic requirements. However, when we consider the short duration of painful

procedures in the Emergency Department requiring procedural sedation and analgesia perhaps it merits further consideration.

Whilst it is not commonly used in the Emergency Department, various studies have sought to evaluate the usefulness of remifentanil in the ED for painful procedures. A systematic review from 2017 (Kisilewicz et al.) concluded that the only evidenced benefit from the trials was the shorter times to recovery and discharge (Dunn et al., 2006, Dunn et al., 2011). The authors also commented on the incidence of anxiety in two studies (Sacchetti et al., 2012, Litman, 1999) that required additional benzodiazepines to provide the anxiolysis required for completion of the procedure. Interestingly this compares to a transient rise in systolic blood pressure and heart rate observed by Glass et al. (1993) which they thought was most likely due to a degree of anxiety caused by the rapid onset of the drug effect. If I pursue remifentanil as an alternative to Propofol I would need to reconsider my approach to anxiolysis.

In their systematic review, Kisilewicz et al. (2017) were unable to identify any studies that evaluated the resource utilisation of using remifentanil for procedural sedation and analgesia in the ED. They felt that future research including a cost-benefit analysis would be incredibly useful. Theoretically the use of TCI may allow shorter procedural duration and recovery times with the obvious impact on staff, space, and flow.

Remifentanil patient-controlled analgesia (PCA) is often used for labour analgesia. It has been implemented successfully in many institutions owing to the lack of side effects and high patient satisfaction (Melber, 2022, Weibel et al., 2017, Wilson et al., 2018). This could also be considered for ED procedural analgesia.

8.4.5 Inclusion Criteria

My feasibility study recruited adult patients with an anterior shoulder dislocation requiring procedural sedation for reduction of the shoulder. This is only one of many procedures that require sedation in the Emergency Department. In the last RCEM audit of adult procedural sedation (2018) just over 80% of the patients requiring sedation were for joint reduction. This was mirrored in an observational study where 78% of the procedures were Orthopaedic in nature (Smits et al., 2017). This could include elbow dislocations, ankle dislocations, hip dislocations and manipulation of limb fractures. Each of these procedures will have similar requirements to reduction of a shoulder dislocation with none of them being lengthy or complex. If I expanded the inclusion criteria, I would by default increase the number of patients I could recruit and increase my recruitment rates.

8.4.6 Study Awareness

Measuring the impact of my marketing strategy on recruitment was not one of my aims. However, I will continue to use a brand to increase visibility and subsequent awareness of further studies. Feedback from all recruiting sites suggested a newsletter or webinar would be useful. If framed from a positive angle they could act as positive reinforcements reminding departments of the trial and encouraging recruitment.

A recent example of this has been the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial. It has maintained an updated webpage (www.recoverytrial.net) open to both professionals and public. They have encouraged engagement and held regular webinars for professionals. The webinars have provided opportunities to be updated on trial progress and ask questions. There have also been public webinars and the option for participants to register for a participant newsletter.

I will be considering how I can embed increased contact with sites in my future trials to raise awareness and encourage recruitment.

8.4.7 Patient & Public Involvement

There was no PPI in this study. PPI is important for all stages in the research process. I searched for help locally and discovered the College of Medical, Veterinary & Life Sciences (MVLS) public and patient involvement and engagement (PPIE) support at the University of Glasgow.

As well as an online bank of resources, the MVLS PPIE steering group hosted meetings that allowed researchers to present their proposals with an ask from the group. I was kindly allowed to attend and present at one of the meetings. In preparation for the meeting an overview of the research proposal had to be submitted (Appendix 21) to allow the group time to read the proposal and formulate both questions and suggestions.

8.4.7.1 Research Question

It was a very constructive, positive experience with lots of great questions being asked. After presenting the proposal to the group time was given for discussion. Firstly, some of the group had experienced dislocations themselves requiring treatment in the Emergency Department and they thanked me for the research question. This gesture validated that the research question was relevant to both clinicians and patients. However, the group acknowledge that they were not solely the population of interest in the research study and made helpful suggestions to reach out to local sports clubs.

8.4.7.2 Consent

It was acknowledged that whilst circumstances within the ED are not always pleasant, research is vital to improve care and experience for patients. Informed consent is mandatory before recruiting patients into research, but I was asked by patient groups if it could be made more comfortable? It was suggested that I could interview patient's that had been consented for research in the ED and ask them about their experience. Ask them how did they feel when they were being consented, was there anything I could do to make it better?

8.4.7.3 Patient Centred Outcomes

The most talked about aspect of the study design were the patient centred outcomes. One of my proposed measures was the nursing satisfaction of the procedure using a VAS scale as I did in the feasibility study. I was using this as a surrogate measure for patient satisfaction during the procedure as given the drugs being used, the patient wouldn't be able to comment on their own satisfaction. It was commented that often the health care provider is seen as being the proxy for the patient and was this right as they often don't equate (Rickert, 2014, Harrison et al., 2020). It was suggested that, if possible, the study design would allow us to correlate the satisfaction scores from both groups and include qualitative feedback for more detail.

8.4.7.4 Adverse events

It was noted that the definition of the adverse event was tailored to the clinician. Which of these adverse events would a patient like to know about? Apnoea, not prolonged, was classified as a minor adverse event even if it required airway repositioning if no adverse outcome occurred. To a clinician this indeed would seem to be minor but to a patient, the fact that they stopped breathing because of the medication administered by the clinician would be considered significant and

potentially life threatening (Schwaneberg et al., 2019). The question is, should we be designing studies to minimise adverse events as perceived by patients as opposed to clinicians?

8.5 Conclusion

In hindsight I realised that the protocol was not as simple as I first anticipated. Even if I put the protocol to the side there's still the matter of a novel technology not currently used in the ED. Many clinicians had heard of it but very few had any clinical experience with TCI Propofol. Introducing a new technology and complex protocol makes it unlikely that the intervention will be adopted (Cofield et al., 2010) and patients recruited.

Chapter 9 Conclusions & next steps

My TCI feasibility study is the first in any Emergency Department in the world and adds to the wider body of evidence that TCI is usable, safe, and efficacious. Originally, I had planned for the next study to be an RCT and my research has centred on assessing the feasibility of running a large-scale study in Emergency Medicine looking at the use of Propofol TCI as a potentially safer option to our current bolus administration. All of my results have been encouraging and whilst I believe that this study is feasible, it is not necessary.

9.1 Alternative Trial Design

A stepped wedged cluster trial (Figure 8-1) would create the opportunity to focus on one site at a time. A traditional parallel cluster trial involves randomising clusters (departments) to either the intervention or the control so that they are running simultaneously, in parallel. Whilst this would make the process of patient randomisation easier given the cluster randomisation, it would mean that many centres are using the intervention at the same time which would dilute available support.

Adapting the parallel cluster to a stepped wedge design means that all departments would start in the control arm and move into the intervention arm in a sequential, randomised fashion. The timings of this would be pre-determined prior to the study opening, this would allow support to be focused on the perceived time of greatest need which would be as the intervention was opening on each site. It would also mean that each site would have the opportunity to experience the intervention.

Disadvantages of this approach would include having to obtain agreement from numerous departments as the sample size would be in excess of the predicted >10,000

patients for a traditional RCT with the primary outcome of incidence of adverse events and an incidence reduction from 5% to 4% (Ward et al., 2018). The unfamiliarity of the ED community with TCI technology would make such an agreement challenging and time consuming. Whilst both a traditional RCT and stepped wedge design are possible, they would be extremely challenging to conduct and would require significant funding from investors who could legitimately argue that TCI is already an accepted technology for procedural sedation outside of Emergency Medicine. The significant funding required for a large-scale trial would be very difficult to achieve.

9.2 What further research is necessary?

If we consider that TCI was introduced into Anaesthetic practice without a large scale RCT then it is possible that similar could be achieved in the ED. My research has provided an evidence base that TCI is usable, safe, and efficacious in Emergency Medicine. It may be a more realistic option to concentrate on one centre with interested, skilled and knowledgeable physicians who would like to adopt it as a way in which to provide procedural sedation.

Support can be concentrated in this centre, ideally where services are co-located with experts. TCI could be commenced as part of service design and monitored through a surveillance programme. Using this model, we also create an environment that can support research studies aimed at answering some of the remaining questions. These would include the TCI model preferred by ED clinicians and optimisation of the protocol to deliver safe and timely procedural sedation.

As experience and confidence builds, it may influence others to consider adoption of the technique and importantly, trainees rotating through the department will be introduced to its use. Combined, all of this may help to make it the new norm with widespread adoption in the UK starting with the creation of a centre of excellence willing to share its learning.

9.3 Conclusions

My research has demonstrated that introducing TCI of Propofol for procedural sedation in the Emergency Department is feasible. My initial intention had been to proceed to a RCT to support a change in practice but instead I plan to adopt a quality improvement model. I will work collaboratively with my clinical team to introduce Propofol TCI as the main method of delivering procedural sedation within my department. I do not believe that further research is required and will not proceed to conduct an RCT.

My recommendations are to devise a training package that familiarises all team members with the TCI technique, both practical and theoretical. Alongside this, the introduction and maintenance of a procedural sedation audit is essential in line with current RCEM guidelines (2022). When Propofol TCI is established, there will also be a responsibility for the team to share their materials and audit results to allow others to consider adoption for their own Emergency Departments.

Appendices

Appendix 1 - Pilot version of sedation survey

Dear Dr,

Thank you for taking the time to complete our questionnaire, it's really appreciated. We're trying to establish what the current procedural sedation practice is in our Emergency Departments. For the purposes of this questionnaire we are referring to procedures like reductions of dislocated joints, not emergency cardioversion.

The results will be completely anonymous and we really appreciate your honesty as it will allow us to form the most accurate picture possible and will help guide future research in this area.

When we have compiled the replies we will share with all of the departments involved. We may proceed to publish the results too.

Thank you once again for your time.

Fasting

What are your fasting requirements before undertaking procedural sedation?:
Last Meal _____
Last Fluid _____

Drugs

Which of the following do you
a. Use
b. How comfortable are you with using them? Please mark with a vertical line

1.	Midazolam	Yes ☐ No☐
1.	Propofol	Yes ☐ No☐
2.	Thiopentone	Yes ☐ No☐
3.	Etomidate	Yes ☐ No☐

Complications

Have you ever had the following complications:

- Cardiac Arrest — Yes ☐ No☐
- Regurgitation — Yes ☐ No☐
- Oversedation — Yes ☐ No☐
- Respiratory Compromise requiring:
  - Intubation — Yes ☐ No☐
  - BVM Ventilation — Yes ☐ No☐
  - LMA Insertion — Yes ☐ No☐
  - Guedel Insertion — Yes ☐ No☐
  - Simple airway Maneouvres — Yes ☐ No☐

CPD

1. How many months experience do you have in anaesthetics? _____
2. How many intubations have you undertaken in the last year? _____
3. Within your CPD how do you keep your airway skills up to date?
   - Theatre sessions ☐
   - Simulation ☐
   - Other (please specify) ☐

_____

THANK YOU!

PSA Survey V0.1 Sep 2016

Appendix 2 - Final version of sedation survey

Dear Dr,

Thank you for taking the time to complete our questionnaire, it's really appreciated. Following the recent RCEM audit we want to establish what the current procedural sedation practice is in our Emergency Departments. For the purposes of this questionnaire we are referring to procedures like reductions of dislocated joints, not emergency cardioversion. We are also looking at the adult population not paediatrics.

The results will be completely anonymous and we really appreciate your honesty as it will allow us to form the most accurate picture possible and will help guide future research in this area.

When we have compiled the replies we will share with all of the departments involved. We may proceed to publish the results too.

Thank you once again for your time.

Fasting

What are your fasting requirements before undertaking procedural sedation?:

Food ..... hours

Clear Fluid, eg. Water ..... hours

Other Fluid, eg. Coffee with milk, fizzy drinks ..... hours

Drugs

Which of the following do you
a. Use (Yes/No)

b. How comfortable are you with using them? Please mark with a vertical line

1. Entonox ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable
2. Midazolam ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable
3. Propofol ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable
4. Ketamine ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable
5. Thiopentone ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable
6. Etomidate ☐ Yes ☐ No
   Not at all comfortable _____ Completely Comfortable

Do you use a concurrent opiate? (please tick those applicable)

- ☐ Morphine
- ☐ Fentanyl
- ☐ Alfentanil
- ☐ Remifentanil

Complications

Have you ever had the following complications following procedural sedation:

Cardiac Arrest	☐ Yes	☐ No
Regurgitation	☐ Yes	☐ No
Oversedation	☐ Yes	☐ No
Respiratory Compromise requiring:		
Simple airway Manoeuvres	☐ Yes	☐ No
Guedel Insertion	☐ Yes	☐ No
BVM Ventilation	☐ Yes	☐ No
LMA Insertion	☐ Yes	☐ No
Intubation	☐ Yes	☐ No
Laryngospasm	☐ Yes	☐ No
Profound Hypotension (SBP≤70mmHg)	☐ Yes	☐ No

CPD

1. How many months experience do you have in:
   a. Anaesthetics? .....
   b. ITU? .....
2. How many intubations have you undertaken in the last year?
3. Within your CPD how do you keep your airway skills up to date?
   - ☐ Theatre sessions
   - ☐ Simulation
   - ☐ Other (please specify)

PSA Survey V0.3 Sep 2016

NHS Lanarkshire

FRM.QUESTN.16_17807.L

Appendix 3 - Time to Set Up Questionnaire

NHS Lanarkshire NHS Greater Glasgow and Clyde

Time taken to prepare Propofol Target-Controlled Infusion (TCI) vs Bolus for Reduction of Anterior Shoulder Dislocation

Dear Dr,

Thank you for taking part today. As you know, when using Propofol for sedation we administer it in a bolus fashion.

TCI is another way in which we can administer Propofol by means of a steadier, continuous infusion. In the future we plan to compare these methods to see if there is any advantage in using one over the other with regards to adverse events and patient satisfaction.

TCI is not a method that we are currently familiar with and as such some clinicians are concerned that it may take a longer period to set up for than our current practice. We feel it would be useful to examine this further.

Firstly, I would ask that you take a few minutes to complete a questionnaire regarding TCI. Following that Malcolm Sim, Consultant Anaesthetist QEUH, will give a short presentation on TCI and how to prepare it for your patients.

Our aim today is to record the time it takes to set up for both and compare these. Each person will be given a couple of attempts at practicing the TCI set up before the timed version. You will then be randomly assigned to start with either the TCI or bolus set up followed by the other.

We plan to present our findings when complete and we will ensure you are included in the distribution.

If you have any questions, then please do not hesitate to ask.

On behalf of the team thank you and we hope that you too get something from today.

Steps to be Completed

Bolus

- Open 20ml syringe
- Attach needle to syringe
- Open one 20ml vial of Propofol
- Draw up 20mls Propofol
- Remove needle
- Flush Propofol to tip ready to bolus

Target-Controlled Infusion

- Weigh patient
- Open 50ml syringe
- Attach needle to syringe
- Open two 20ml vials of Propofol
- Draw up 40mls of Propofol
- Attach extension cable
- Flush Propofol to end of cable
- Insert syringe into the TCI pump
- Programme pump – Age - 30

V0.7 – preparation of TCI

TCI Survey **Hospital**_____ **Participant No** _____

- Have you heard of Target-Controlled Infusion? Yes / No
- How difficult do you anticipate setting up for TCI will be?

  Please mark using a vertical line on the scale below

Not very difficult *Very Difficult*

- How long do you think it will take you to set up for bolus administration?

  - Open 20ml syringe
  - Attach needle to syringe
  - Open one 20ml vial of Propofol
  - Draw up 20mls Propofol
  - Remove needle
  - Flush Propofol to tip ready to bolus.

  → Time -

- How long do you think it will take you to set up for TCI administration?

  - Weigh patient
  - Open 50ml syringe
  - Attach needle to syringe
  - Open two 20ml vials of Propofol
  - Draw up 40mls of Propofol
  - Attach extension cable
  - Flush Propofol to end of cable
  - Insert syringe into the TCI pump
  - Programme pump.

  Time -

- What time difference do you think is acceptable? → Time -
- Do you have any experience of using Target-Controlled Infusion?
- Any thoughts you'd like to share?

V0.7 – preparation of TCI

1. Time Bolus _____

2. Time TCI_____

Appendix 4 - Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

CENTRAL search strategy

2017, Issue 11

#1 MeSH descriptor: [Propofol] explode all trees #2 diprivan
#3 fresofol
#4 pofol

#5 propofol
#6 recofol
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 target-controlled infusion
#9 target controlled infusion
#10 TCI
#11 #8 or #9 or #10
#12 MeSH descriptor: [Conscious Sedation] explode all trees #13 sedat*
#14 procedural sedation
#15 #12 or #13 or #14
#16 #7 and #11 and #15

Appendix 5 - Cumulative Index of Nursing and Allied Health Literature (CINAHL) search strategy

CINAHL search strategy

1. S1 MJ propofol
2. S2 TX diprivan OR TX fresofol OR TX pofol OR TX propofol OR TX recofol
3. S3 TX Target-controlled infusion OR TX target controlled infusion OR TX TCI
4. S4 TX sedat* OR TX procedural sedation OR TX conscious sedation
5. S5 S1ORS2
6. S6 S3ANDS4andS5
7. S7 ((MH "Random Assignment") or (MH "Random Sample+") or (MH "Crossover Design") or (MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Control (Research)+") or (MH "Control Group") or (MH "Factorial Design") or (MH "Quasi-Experimental Studies+") or (MH "Placebos") or (MH "Meta Analysis") or (MH "Sample Size") or (MH "Research, Nursing") or (MH "Research Question") or (MH "Research Methodology+") or (MH "Evaluation Research+") or (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") or (MH "Nursing Practice, Research-Based") or (MH "Solomon Four-Group Design") or (MH "One-Shot Case Study") or (MH "Pretest-Posttest Design+") or (MH "Static Group Comparison") or (MH "Study Design") or (MH "Clinical Research+")) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)
8. S8 S6&S7

Appendix 6 - Excerpta Medica Database (EMBASE) search strategy

EMBASE search strategy

1974 to 2017 November 21

1 Diprivan.mp.

2 Fresofol.mp.

3 Pofol.mp.

4 Propofol.mp.

5 Recofol.mp.

6 exp propofol/

7 target-controlled.mp.

8 target controlled infusion.mp.

9 target-controlled infusion.mp.

10 TCI.mp.

11 1or2or3or4or5or6

12 7or8or9or10

13 sedat*.mp.

14 conscious sedation.mp.

15 procedural sedation.mp.

16 13or14or15

17 11and12and16

18 random:.tw

19 clinical trial:.mp

20 exp health care quality/

21 18or19or20

22 17 and 21

Appendix 7 - Medical Literature Analysis and Retrieval System Online (MEDLINE) search strategy

MEDLINE search strategy

1946 to November 21, 2017

1 Diprivan.mp.
2 Fresofol.mp.
3 Pofol.mp.
4 Propofol.mp.
5 Recofol.mp.
6 exp propofol/
7 target-controlled.mp.
8 target controlled infusion.mp.
9 target-controlled infusion.mp.
10 TCI.mp.
11 1or2or3or4or5or6
12 7or8or9or10
13 sedat*.mp.
14 conscious sedation.mp.
15 procedural sedation.mp.
16 13or14or15
17 11and12and16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 randomized.ab.
21 placebo.ab.
22 drug therapy.fs.
23 randomly.ab.
24 trial.ab.
25 groups.ab.
26 18or19or20or21or22or23or24or25
27 exp animals/ not humans.sh.
28 26 not 27
29 17 and 28

Appendix 8 - PROTEDS patient consent form

NHS Greater Glasgow and Clyde NHS Lanarkshire

PROTEDS-**Pro**pofol **T**arget-Controlled Infusion in **E**mergency **D**epartment **S**edation

Patient's Identification Number for this study: ☐

Site Name:

Name of Researcher:

		Please initial box
1.	I confirm that I have read and understand the Participant Information Sheet dated..... (Version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities, NHS Lanarkshire and NHS GG&C where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I agree to my GP being informed of my participation in the study.	☐
5.	I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 copy for patient, 1 copy for researcher site file, 1 copy (original) to be kept in medical notes

Appendix 9 - Standard Protocol Items: Recommendations for interventional Trials (SPIRIT) checklist for PROTEDS protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	2, 3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3,4,7
	6b	Explanation for choice of comparators	6,7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11,12,13,14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11,12,13,14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10,11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9,10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12,13,14,15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15,16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

158

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Appendix 10 - Consolidated Standards of Reporting Trials (CONSORT) checklist of information to include when reporting a pilot or feasibility trial – PROTEDS

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	5,6
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	4,5
	2b	Specific objectives or research questions for pilot trial	5,6
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
	4c	How participants were identified and consented	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5,6
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	5,6
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	5
Sample size	7a	Rationale for numbers in the pilot trial	6,7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	5,6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the pilot trial ended or was stopped	6,7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8,9
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	7,8,9,10
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	Figure 1
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	10,11,12
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	12,13
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	10,11,12,13
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	12,13
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	14
Protocol	24	Where the pilot trial protocol can be accessed, if available	14
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14
	26	Ethical approval or approval by research review committee, confirmed with reference number	14

Appendix 11 - Patient Satisfaction

How satisfied were you with the procedure? Please mark on the line below with a vertical mark.

Not satisfied Very satisfied

Appendix 12 - Patient Reported Pain Score

How painful did you find the procedure? Please mark on the line below with a vertical mark.

No pain

Worst possible pain

Appendix 13 - Nursing Opinion of Patient Experience

How would you rate the patient's experience of the procedure whilst sedated? Please mark on the line below with a vertical mark.

Poor Experience — Excellent Experience

Appendix 14 - Patient Information Sheet PROTEDS

NHS Lanarkshire NHS Greater Glasgow and Clyde

Patient Information Sheet – PROTEDS

Trial Title - Propofol target-controlled infusion for the sedation of adult patients with acute shoulder dislocation in the Emergency Department (PROTEDS) – A multicentre feasibility study.

We would like let you know about a study that may be relevant to you and your injury. At this point in time we are investigating you for a possible shoulder dislocation. If this is confirmed we may invite you to take part in this study. If we do it is important that you understand why the research is being done and what it would involve for you before agreeing to take part. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

When a person dislocates their shoulder they need to have it put back into place. To allow this doctors need the surrounding shoulder muscles to be very relaxed. To relax these muscles patients need to be sedated. These medicines can have side effects. We believe that giving the medication to patients in a different way might produce less of these side effects.

In this study we are looking at a medicine called Propofol and the way in which we administer it. Normally Propofol is given in a bolus. A bolus is when we give a few mls of the medicine at a time through the drip in your arm. We continue to do this until you are sleepy enough to reduce your shoulder.

In this study we will be giving Propofol via a continuous infusion to achieve a more precise dose. Continuous infusion of Propofol to sedate patients is widely recognised for other procedures in other departments. We anticipate that the more precise dose will produce less side effects.

Who is organising and funding this study?

This study is being sponsored by NHS Greater Glasgow & Clyde and is being undertaken here and in NHS Lanarkshire. Dr Fiona Burton is the Chief Investigator. Funding has been provided by Carefusion UK, the manufacturers of the device used to administer the medicine.

What am I giving my consent for?

We are asking you to consent to being a participant in research and allow us to give you the Propofol sedating medicine in a different way to our current norm and look at the information we routinely

gather for all of our patients during sedation episodes. We will analyse this in a confidential anonymous way.

Why have I been invited?

You have been invited to take part as you have dislocated your shoulder and will be undergoing sedation to have it relocated. Your treating doctor has assessed you and feels that Propofol is the correct medicine to use.

What will happen to me if I take part?

All of the usual emergency treatment for dislocated shoulders will be given. You will be given painkillers and have an x-ray to confirm dislocation. You will receive Propofol medicine via a continuous infusion through a drip in your arm to sedate you and allow your shoulder to be put back into place. You will be monitored closely throughout per the national safety guidelines.
The whole procedure will take about 20 mins. We will be talking to you and asking how you feel throughout. You will have no recollection of the procedure. We will x-ray your shoulder after the procedure to ensure it is in the right place.

Normally you will be able to go home when your doctor is happy with your condition. You will be in the department for approximately 2-4 hours. You will be seen again in a clinic by one of the bone doctors and an appointment for this will be given before you leave.

You will not need to undergo any extra tests or spend any significant extra time in hospital as a result of taking part in this study. You will be asked to rate your pain and satisfaction at the end of the procedure. This is not routinely collected on all sites currently. By using a continuous infusion of propofol, there is a very slight increased chance that you may need to go on to have a full general anaesthetic, if the amount of sedation given was not sufficient for your needs.

What are the possible disadvantages and risks of taking part?

It is not known if this method is as effective as the standard method although there is evidence, from other patient groups that it will be as effective as the standard method.

What are the side effects of any treatment received when taking part?

Propofol affects your breathing, and can sometimes put you into a deeper sleep than is desirable, causing your breathing to slow down. This is the reason why you will be closely monitored. You will be treated by the doctor and all of the effects of the drug wear off in minutes. There is also a possibility that it will lower your blood pressure. In this instance you will be given fluid through the small tube in your vein. Sometimes you may feel some pain as the propofol is injected. It is always possible that despite the doctor trying they will not be able to put the shoulder back into place. In this case you will be referred to the bone doctors for further management.

What are the possible benefits of taking part?

We hope that the continuous infusion will decrease the number of side effects experienced by patients. The knowledge gained from this study will potentially help improve the treatment of people undergoing sedation in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the research doctor/nurse who will do their best to answer your questions.

If taking part in this research study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay your legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

If you have private medical insurance, you may wish to check with your company before agreeing to take part in the study to ensure that participation in the study will not affect your insurance cover.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. Information collected may still be used. If you withdraw your consent, the study team may still use data that was shared with it before you withdrew your consent unless you specifically request to your study doctor that you do not want this information to be used.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised.

Involvement of the General Practitioner (GP)

We will inform your GP, with your permission of your participation in this study.

What will happen to the results of the research study?

We will publish the study results in a professional medical journal as soon as possible after the study finishes. You would not be identified individually in any published report. We do not intend to inform participants of the study results but if you wish to be informed then we will contact you with them.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Research Ethics Committee.

Further information and contact details

If you have any questions or concerns about any aspect of this study you should ask to speak with the study doctors who will do their best to answer your questions. Dr Fiona Burton is in charge of this study at this hospital. You can contact the doctor at:

Address: Emergency Department,
Hairmyres Hospital,
G75 8RG

Telephone:

If you have any questions about your rights as a research subject, questions about taking part in the study, or complaints about the study, you may contact someone independent from the study at:

Prof Alasdair Gray, Edinburgh Royal Infirmary (questions about research in general)

Patient Complaints - NHS Greater Glasgow and Clyde Complaints Service

Phone: (24 hrs answering machine service)

Email:

Appendix 15 - Physician Information Sheet PROTEDS

Place patient ID sticker here

PROTEDS Feasibility Study - Physician Information

Dear Doctor,

You have chosen Propofol to sedate your patient with. They are potentially eligible for inclusion in the Feasibility study of Propofol via TCI infusion.

Please assess them against the formal inclusion and exclusion criteria outlined below. If they meet with the inclusion criteria and do not meet any of the exclusion criteria then please proceed with the TCI protocol as outlined and fill in the attached data collection sheet.

Patients are to be monitored and verbally consented in the usual manner with formal written consent for use of their data being sought when they are comfortable and have the capacity.

Thank you.

Inclusion Criteria – please tick all that apply

Aged 18-65 years	
Acute anterior shoulder dislocation	
ASA I or II	
Fasted ≥ 90 mins	
Weight ≥ 50kg	

Exclusion Criteria – please tick all that apply

Inability to provide or refusal of informed consent	
Prisoner	
Previously enrolled in the study	
Clinical and/or radiological evidence of acute posterior shoulder dislocation	
Clinical and/or radiological evidence of concomitant ipsilateral upper limb fracture (with the exception of an isolated avulsion fracture of the greater tuberosity or a fracture of the glenoid labrum)	
Concomitant multi-system injury	
ASA III, IV or V	
Haemodynamic Instability	
Pregnancy	
Contraindications to sedation	
Allergy to study drug or eggs	
Clinical Decision (please outline)	

Is the patient eligible? Yes / No Sign:…… Date:……

Has the Patient been recruited? Yes / No Allocate Study Number:……

Appendix 16 - PROTEDS trial prompt sheet

ProTEDS for dummies

Some hints to keep us all on track:

- Morphine must be given at least 20 mins before commencing TCI.
- All patients should be receiving $4LO_2$ via NC for duration of the sedation episode.
- Written consent is required. Three copies should be made. The original and one other put in pack and one copy given to the patient (not the original).
- BP cuff should be applied to leg. It should NOT be applied to the TCI arm!
- Flush the Propofol to the end of the line to fill the dead space before attaching to the patient.
- It's ok to attach fluids to the Octopus connector and deliver along with the TCI.
- OAA/S every 2 minutes when dose adjusted until you reach 3 upon which time every 3 minutes until procedure complete.
- NIBP should be set to 3 min cycle. When patient is 15 minutes post reduction, obs can be reduced to 15 minute intervals.
- Please enter the following codes in the comments section of data collection sheet

✓	Cpt=Cet = 1.4µg ml^{-1}
✚	C_{pT} is 2.6µg ml^{-1} –= not sedated as checked by x 2 Healthcare professionals
Δ	Alfentanil Given
□	Reduction Commenced
O	Reduction Achieved
×	TCI stopped

- If you reach the limits on TCI setting and the patient is not adequately sedated, it should be deemed as a failed attempt and limits must NOT be exceeded, procedure must stop and refer to Ortho.
- VAS and recall should be assessed at time of discharge.
- Remember to sign the bottom of each data collection page.
- Fit for discharge means:
    1. Patient returned to baseline level of consciousness
    2. Vital signs are within normal limits for that patient
    3. Respiratory status is not compromised
    4. Pain and discomfort have been addressed
- Remember to send the GP letter.

ENJOY!

V0.3 June 2017

Appendix 17 - TCI Drug Protocol Version 1

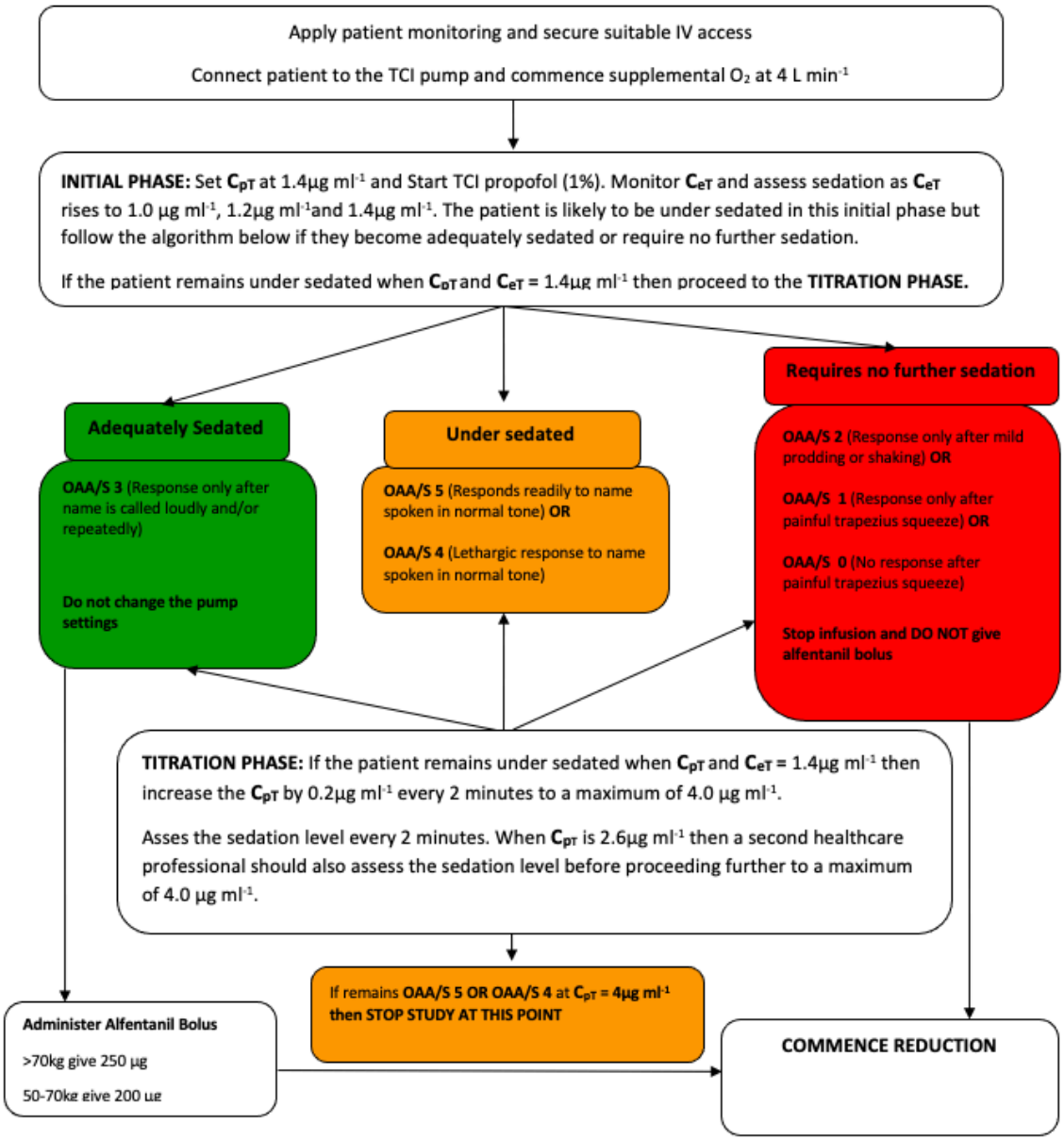
On completion of the reduction the infusion should be stopped and the patient observed until complete recovery

If an adverse event occurs, the TCI should be stopped immediately

Appendix 18 - TCI Drug Protocol Version 2

ProTEDS

TCI Sedation Flowsheet



On completion of the reduction the infusion should be stopped and the patient observed until complete recovery

If an adverse event occurs, the TCI should be stopped immediately

Appendix 19 - PROTEDS Data Collection Sheets

Study Number:…… Patient initials:…… Date:……

PROTEDS Study

Pre and Post Intervention Data Collection Sheet

Date of Visit:……

Medical Staff Present:

1)…….. Grade:……..

2)…….. Grade:……..

Medical Assessment	Sign	Date
Mechanism of Injury:		
Weight (kg) =		

Initial Events	Time	Initials
Time of Presentation at department		
Time of First Assessment		
Time of Initial X-ray		
Time of Injury confirmed on X-ray		
Intervention	**Time**	**Initials**
TCI Stopped		
Time OAA/S 3		
Full Recovery		
Drug Doses	**Amount**	**Initials**
Total Morphine Given		
Total Alfentanil Given		
Post Intervention	**Time**	**Initials**
Repeat X-ray		
X-ray reviewed		
Fit for discharge		
Discharged		

Outcomes			Initials
Number of Attempts			
Successful Reduction	Y / N		
Adverse Events	Y / N	(if yes, complete form)	
Recall?	Y / N		

PTO……..

Study Number:…… Patient initials:…… Date:……

Staff Reported Outcomes

Nurse - How satisfied were you with the procedure? Please mark on the line below.

Not satisfied Very satisfied

Doctor - How satisfied were you with the procedure? Please mark on the line below

Not satisfied Very satisfied

Study Number:……. Patient initials:……. Date:…….

Patient Reported Outcomes

How painful did you find the procedure? Please mark on the line below.

No pain Worst possible pain

How satisfied were you with the procedure? Please mark on the line below.

Not satisfied Very satisfied

Study Number:_____ Patient Initials:_____ Date:_____

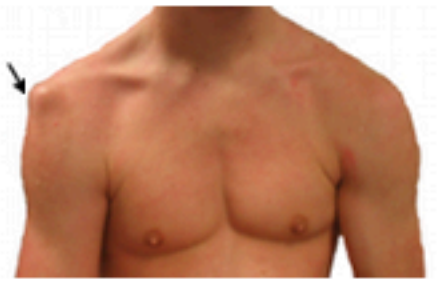
Intra-Procedural Data

	Time	HR	BP	$EtCO_2$	RR	SpO2	Target Plasma Conc (Cpt)	OAA/S	Comments
Baseline measurements									
1 mins post start of TCI									
2 mins post start of TCI									
3 mins post start of TCI									
4 mins post start of TCI									
5 mins post start of TCI									
6 mins post start of TCI									
7 mins post start of TCI									
8 mins post start of TCI									
9 mins post start of TCI									
10 mins post start of TCI									
11 mins post start of TCI									

Name of person collecting data:…… Signature:…….. Date:……

Appendix 20 - Departmental Poster advertising PROTEDS

DISLOCATED SHOULDER?



THINK

ProTEDS

PROPOFOL TARGET-CONTROLLED INFUSION
IN EMERGENCY DEPARTMENT SEDATION

		CALL	
Fiona **4103**	Mo	Gareth	Andrew

Appendix 21 - Public and Patient Involvement and Engagement Steering Group Proposal

MVLS Public and Patient Involvement and Engagement Group

Plain English Summary Form

Applicant Details	
Name of Chief Investigator (CI): Fiona Burton	
Contact for any queries in relation to the project (if not the CI):	
Project Details	
Title: Propofol target-controlled infusion for the sedation of adult patients with acute shoulder dislocation in the Emergency Department (PROTEDS)	
Plain English Title:	
Project Funding	
Funding Received: NO/YES Delete as appropriate	Not applied yet
If funded: Funder: Project start date:	**If pre-funding:** Potential funder: National Institute for Health Research or CSO Application submission date: Expected decision notification date:
Plain English Summary	
What is the background to the research? When a person dislocates their shoulder they need to have it put back into place. To allow this doctors need the surrounding shoulder muscles to be very relaxed. To relax these muscles patients need to be sedated. Unfortunately sedation medications have some side effects. Doctors believe that giving the medication to a patient in a different way might produce less of these side effects. Propofol is a commonly used drug for sedation in the Emergency Department. It is commonly administered in repeat boluses of a few mls at a time until the desired sedation effect is achieved.	

When administered as a bolus, the operator may under-dose, delivering an insufficient effect site concentration, or over-dose, exceeding the desired effect site concentration. Propofol affects your breathing causing it to slow down and sometimes stop. There is also a possibility that it will lower blood pressure.

Target-controlled infusion (TCI) has been suggested as a potential solution to the adverse events experienced with the bolus administration of propofol. In contrast to bolus administration of propofol, TCI allows the operator to accurately target a specific clinical effect. TCI is widely used in anaesthetic practice and has been studied in a number of settings including gastrointestinal endoscopy, dental surgery, oocyte retrieval and bronchoscopy.

How will the research have an impact on patients?

We are hoping that it will decrease the incidence of adverse events as described above. We also hope that it will improve patient satisfaction

What are the research questions?

Does the use of propofol target controlled infusion decrease the incidence of adverse events when compared to bolus administration?

Does the use of propofol target controlled infusion increase patient satisfaction of the procedure when compared to bolus administration?

Does the use of propofol target controlled infusion increase the nursing satisfaction of the procedure when compared to bolus administration?

What methods will you use to answer the research questions?
Who can participate in the research and how will they be recruited?
What does the research involve for taking part?
Wil people have to travel to take part and will you pay their expenses?

Patients will be those who have sustained an acute (new) shoulder dislocation and have presented to the Emergency Department. Participants will be from the population who would routinely have their shoulder reduced in the ED and that the clinician has identified as someone they wish to use propofol for the sedation. They only thing that will be different is the way in which the drug is administered.

Patients will be asked to complete a patient satisfaction sheet when they have recovered from the sedation and are ready to be discharged home. This is a validated tool called the Iowa Satisfaction

with Anesthesia scale. This consists of 11 statements with the patient responding from disagree very much to agree very much:

1. I threw up or felt like throwing up
2. I would want to have the same sedation again
3. I itched
4. I felt relaxed
5. I felt pain
6. I felt safe
7. I was too cold or hot
8. I was satisfied with my sedation care
9. I felt pain during surgery
10. I felt good
11. I hurt

Patient and public involvement

How do you propose to involve patients and the public involvement in the research?

Consulting with public at the protocol writing stage.

Would you like your public involvement costings to be reviewed? If so, please attach

No

Do you have any specific questions/ discussion points for the Group relating to the public involvement aspect of the work? If so please specify

Good to know if the group feel that this is a worthwhile area of research and if there are any oversights or things they feel we need to consider that we haven't already.

Discussion with the MVLS PPIe Group
What would you like to get from the PPI meeting discussion/ specific questions you would like the Group to consider? I will benefit from discussing this with the group and hearing the thoughts of the group. It will certainly help me shift my mindset from researcher/medic centred to a more patient centred one. I fully expect to be met with questions that I haven't considered and in doing so this will help me to refine the protocol.
Glossary
Please define any medical terms or abbreviations you have used **Bolus -** give the medicine from a syringe into the small tube in your vein. It will be given a few ml's at a time until the patient is sleepy enough and the muscles have relaxed. **Target Controlled Infusion –** we will attach a piece of tubing to the small tube in your vein. This is then attached to a syringe that is placed in a machine called a syringe driver. This will continucusly be giving smaller amounts of the medicine until the patient is sleepy enough and the muscles have relaxed. The syringe driver contains a microprocessor is aiming for a theoretical target that reflects the concentration of the medicine around the brain. The microprocessor uses variables like age, sex and weight.

Thank you for taking the time to complete this form

Please return to Tracy Ibbotson:

Appendix 22- PROTEDS feasibility study protocol

Burton *et al. Pilot and Feasibility Studies* (2019) 5:27
https://doi.org/10.1186/s40814-019-0412-y

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

A study protocol for a feasibility study: Propofol Target-Controlled Infusion in Emergency Department Sedation (ProTEDS)—a multi-centre feasibility study protocol

Fiona M. Burton[1,2*], David J. Lowe[3], Jonathan Millar[4], Alasdair R. Corfield[5] and Malcolm A. B. Sim[2,4]

Abstract

Background: Procedural sedation is a core skill of the emergency physician. Bolus administration of propofol is widely utilised in UK emergency departments to provide procedural sedation. Bolus administration of propofol, titrated to an endpoint of sedation, has a rapid effect but can easily result in apnoea and loss of airway patency. The use of a target-controlled infusion of propofol allows for controlled titration to an effect site concentration and may reduce the rate of adverse incidents. Target-controlled infusion of propofol is not currently used in emergency departments.
The primary aim of this feasibility study is to ensure that propofol target-controlled infusion (TCI) is acceptable to the patient and that recruitment rates are adequate to power a randomised controlled trial comparing propofol target-controlled infusion versus bolus administration.

Methods: This study will recruit in four emergency departments in Scotland, UK. Patients aged 18–65 years with anterior shoulder dislocation, weighing ≥ 50 kg and fasted ≥ 90 min, will be screened. Recruited patients will undergo emergency reduction of a dislocated shoulder facilitated by procedural sedation utilising TCI of propofol.
The widespread adoption of TCI propofol by emergency departments will require evidence that it is safe, potentially effective, patient centred and a timely method of providing procedural sedation. The primary endpoint will be acceptability measured by patient satisfaction. The secondary endpoints will include incidence and severity of adverse events, number of shoulder reduction attempts, nursing opinion of patient experience, patient's reported pain score and time from commencement of TCI propofol sedation to desired sedation level.
The study will be open for recruitment from April 2017 to December 2018.

Discussion: If the study demonstrates patient acceptability with adequate recruitment, we will be in a position to determine the feasibility of progression to a randomised controlled clinical trial of TCI compared to bolus administration of propofol.

Trial registration: ClinicalTrials.gov Identifier: NCT03442803. Registered retrospectively on 22 February 2018.

Keywords: Target-controlled infusion, Propofol, Procedural sedation, Adverse events

* Correspondence: fionaburton@nhs.net
[1]Department of Emergency Medicine, University Hospital Hairmyres, Eaglesham Road, Glasgow G75 8RG, UK
[2]Glasgow University Section of Anaesthesia, Pain and Critical Care, Glasgow, Scotland
Full list of author information is available at the end of the article

Background

Sedation in the emergency department

Procedural sedation and analgesia (PSA) has long been a core skill of the emergency physician, although over the last decade, developments in patient monitoring and the use of newer sedative and analgesic agents have served to improve both safety and efficacy [1]. Despite these advances and their consolidation into well-designed guidelines [2, 3], concern regarding the safety of emergency department (ED) PSA persists [4, 5].

More specifically, concerns have been raised regarding the use of propofol, an ultra-short acting anaesthetic agent [6]. The practice of using sub-anaesthetic doses of propofol to achieve sedation in ED PSA originated around the turn of the millennium [7] and has since become the most common choice of sedative in the ED [4, 8]. Propofol offers a number of advantages as a sedative agent, including a short onset and recovery time, amnesiac properties and good efficacy [9–11]. The cost of these properties is, in part, a narrow therapeutic range. Propofol in the ED is currently given as a repeated bolus (normally a few millilitres at a time until the desired effect is achieved).

When given as a bolus, propofol will induce a spectrum of states up to and including general anaesthesia, dependent on the dosage. The correlation between dose and effect varies based on several patient factors. Whilst targeting a state of sedation, it is possible for the operator to 'overshoot' moving rapidly from conscious sedation to deep sedation to general anaesthesia. The inadvertent induction of general anaesthesia may result in unanticipated complication. The principle complications associated with accidental over-sedation or general anaesthesia relate to the patency of the patient's airway. The reported frequency of airway complications during ED PSA with propofol range from 5.0 to 9.4% [7]; this includes a rate of supplemental ventilation of between 3.0 and 9.4%, with oxygen desaturation occurring in between 5 and 7% of cases [12]. In addition, the bolus administration of propofol may result in transient hypotension [12]. Despite being a relatively short-lived effect, this may be pronounced in those with intravascular volume depletion [13] or in the elderly [14], and in some may be profound, with one series demonstrating that 3.5% of those undergoing PSA with propofol experience ≥ 20% falls in blood pressure [15]. At first inspection, the reported rate of complication may appear low and has by some been interpreted as evidence of the relative safety of ED PSA; however, alternative views have been expressed in the context of much lower rates of adverse events seen in elective painful procedures requiring conscious sedation [6, 16]. This is compounded by the non-standard way in which adverse events have been reported across studies [17].

A potential solution to the adverse events experienced with the bolus administration of propofol is the use of a target-controlled infusion (TCI). This method is widely used in anaesthetic practice, and whilst the PK remains the same irrespective of if you give a bolus or infusion of propofol, TCI allows the titration in perhaps a more controlled manner.

Target-controlled infusion

The aim when administering propofol, as with any drug, is to induce a desired clinical effect, in this context a level of sedation. As previously alluded to, when administering propofol in a bolus fashion or as a fixed rate infusion, without regard to those factors which cause biologic variability (e.g. age, gender, weight), it is difficult to accurately and consistently predict clinical effect. The development, in the early 1990s, of computer-assisted infusion devices, for the first time, allowed the clinician to target a plasma concentration, with the pump automatically altering the rate of infusion based on a pre-programmed pharmacokinetic model [18]. These target-controlled infusion (TCI) devices have undergone significant development and are now in widespread clinical use. Their operation uses a mathematical mode that reflects a theoretical 'three-compartment' model that may comprise the central compartment (plasma), and two peripheral compartments (highly perfused tissue, e.g. brain, and poorly perfused tissue, e.g. adipose). In a state of equilibrium, propofol will diffuse between compartments at a constant rate. These rate constants have been used in pharmacokinetic models to mathematically predict the plasma concentration and latterly the effect site concentration, in this case that in the brain [19].

In practical terms, TCI allows the operator to more accurately target a specific clinical effect. When propofol is administered as a bolus, the operator is likely to either underdose, delivering an insufficient effect site concentration, or overdose, exceeding the desired effect site concentration. TCI allows the operator to titrate to effect and then to maintain a steady state, potentially eliminating the risk of 'over shooting' and reducing the rate of adverse events. TCI is not without limitation. PK models are an estimate as they have been derived from a healthy population, but any inherent inaccuracy is consistent in different populations and accounted for by careful titration.

The use of propofol TCI has been studied in a number of settings, including gastrointestinal endoscopy [20–22], dental surgery [23, 24], oocyte retrieval [6] and bronchoscopy [25, 26]. To our knowledge, propofol TCI in sedation has not been studied in an ED setting. Trials have demonstrated a good safety profile for propofol TCI, with at least one large randomised controlled trial [20] in an endoscopy setting, showing a reduction in

both respiratory and cardiovascular adverse events in comparison to the bolus administration of propofol. Unfortunately, trials to date have suffered from a high degree of heterogeneity, leading the Cochrane review, on the subject of propofol TCI versus manually controlled infusion in both general anaesthesia and sedation, to conclude that there was insufficient evidence to make firm recommendations regarding its use in clinical practice [27].

Study rationale

There exists continued controversy over the use of propofol in ED PSA; this is despite its widespread existence in clinical practice for at least a decade. These concerns are not limited to the ED setting and are primarily related to the pharmacological properties of the drug itself and its potential for harm. The bolus administration of propofol, aimed at a target of sedation, offers several advantages over more traditional agents, yet these advantages are also its limitations. The use of a target-controlled infusion makes titration of propofol easier with fewer adjustments, thus potentially reducing the incidence of adverse incidents.

The incidence of adverse events using bolus propofol versus TCI propofol in the emergency department will be recorded in the future randomised controlled trial (RCT). This current feasibility study is needed first before a main trial in order to provide evidence that TCI is safe, potentially effective, patient centred and a timely method of providing procedural sedation. It will also provide information about recruitment to ensure that the randomised controlled trial can be adequately powered.

Aim

The primary aim of this feasibility study is to ensure that propofol TCI is acceptable to the patient and that recruitment rates are adequate to power a future RCT.

Secondary objectives are:

- Safety:
  - Incidence of adverse events
- Potential effectiveness:
  - Successful completion of the procedure
  - Number of reduction attempts
- Patient centred:
  - Patient-reported pain scores
  - Nursing opinion of the patient's experience
  - Patient recall of the procedure
  - Free text comments from all staff at the end of the procedure
- Timely:
  - Time taken to reach the appropriate sedation level
  - Time from commencement of sedation to 'fit for discharge'

Progression

Progression to a multi-centre randomised control trial will require evidence of the ability to adequately recruit and that it is safe, potentially effective, patient centred and a timely method of providing procedural sedation.

Methods

Study design

Multi-centre feasibility study

Participating centres

- University Hospital Hairmyres ED, UK
- Royal Alexandra Hospital ED, UK
- Glasgow Royal Infirmary ED, UK
- Queen Elizabeth University Hospital ED, UK

Study population

Adult patients (≥ 18 years), requiring sedation to facilitate the reduction of an acute traumatic anterior shoulder dislocation in the emergency department

Inclusion criteria

- Aged 18–65 years
- Clinical and/or radiological evidence of acute anterior shoulder dislocation
- American Society of Anesthesiologists (ASA) Physical Status Classification I or II
- Fasted ≥ 90 min [2, 3, 28, 29]
- Weight ≥ 50 kg

Exclusion criteria

- Inability to provide or refusal of informed consent
- Previous attempt at reduction during the same presentation
- Previously enrolled in the study
- Clinical and/or radiological evidence of acute posterior shoulder dislocation
- Clinical and/or radiological evidence of concomitant ipsilateral upper limb fracture (with the exception of an isolated avulsion fracture of the greater tuberosity or a fracture of the glenoid labrum)
- Concomitant multi-system injury
- History of difficult intubation/airway surgery
- ASA grades III, IV or V
- Haemodynamic instability
- Pregnancy
- Contraindication to sedation
- Allergy to study drugs or eggs

- Clinician decision
- Morphine administration within the preceding 20 min prior to starting TCI (can be included if > 20 min)

There is no objection to subsequent co-enrolment of patients to clinical trials amongst those already enrolled to ProTEDS.

Sample size rationale

A formal sample size should not be calculated for this feasibility study [30]. We aim to recruit at least 20 patients within a fixed time period to allow calculation of recruitment rate. This time period was agreed by reviewing the average number of anterior shoulder dislocations attending at each site per week.

University Hospital Hairmyres	1
Royal Alexandra Hospital	3
Glasgow Royal Infirmary	4
Queen Elizabeth University Hospital	5

Recruitment commenced on April 2017 and will continue until 31 December 2018. If 13 patients per week present for 86 weeks of the planned duration of the study, then a total of 1118 potential patients could potentially be recruited. After we account for those patients who are willing and able to give consent (approximately 1 in 5) to research in an emergency care setting (1118/5), we estimate that 224 potential patients could be recruited. A total of one in five of the consultant staff at the recruiting sites was trained to undertake this procedure using TCI propofol (224/5) leaving 45 patients presenting at any time during a 24-h period. The consultant presence in the emergency department is approximately 12 h per 24 h (45/2), leaving approximately 22 patients from the total of 1116 anterior shoulder dislocations.

This information will allow assessment of the feasibility of recruiting to an adequately powered randomised controlled trial with the incidence of adverse events as the primary endpoint.

Emergency departments have a unique set of challenges that make recruiting to research studies difficult [31]. Patients may present at any point, 24 h per day, 7 days a week to an unpredictable, high-risk setting. All research activity is undertaken by emergency medicine consultants.

Primary endpoints

- Patient satisfaction—visual analogue scale (VAS) (Additional file 1) [32]
- Percentage of patients recruited vs percentage of patients approached

Secondary endpoints

- Incidence and severity of adverse events per World Society for Intravenous Anaesthesia (SIVA) adverse event sedation reporting tool [33]
- The successful reduction of the anterior shoulder dislocation
- Number of reduction attempts
- Patient-reported pain score VAS (Additional file 2) [32, 34]
- Nurse opinion of patient experience VAS (Additional file 3) [32]
- Patient recall of the procedure [35]
- Free text comments from all staff at the end of the procedure
- Time from commencement of induction to Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) 3 [36]
- Time from commencement of sedation to fit for discharge [2]
  - Patient returned to their baseline level of consciousness
  - Vital signs are within normal limits for that patient
  - Respiratory status is not compromised
  - Pain and discomfort have been addressed

Figure 1 displays the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of enrolment, interventions and assessments.

Study procedures

Recruiting clinicians will be consultants in emergency medicine who currently use bolus propofol as sedation. They have a valid Good Clinical Practice Certificate. They are responsible for obtaining consent from patients and delivering the TCI propofol as per the flowsheet (Additional file 4). The clinicians have received aditional training in TCI propofol by an experienced anaesthetist (author MS). The recruiting clinician will be solely responsible for the administration of TCI propofol but not in the reduction of the anterior shoulder dislocation.

Potential participants presenting to the emergency department with a suspected shoulder dislocation will receive a patient information sheet in addition to their standard clinical care. On confirmation of a shoulder dislocation, they will be screened against the inclusion

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Trial End
TIMEPOINT (hours)	$-t_1$	0	t_1	t_2	t_3	*Discharge from Emergency Department* t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X	X				
[Baseline Data Collection]		X				
Allocation		X				
INTERVENTIONS:						
[Propofol TCI]			⟷			
ASSESSMENTS:						
[Patient Satisfaction]						X
[Nurse Opinion of Patient Experience]						X
[Time from commencement of sedation to fit for discharge]			X	X	X	X
[% of patients recruited vs % of patients approached]	X					
[Incidence and severity of adverse events]			X	X	X	X
[Successful Reduction?]				X		
[Number of reduction attempts]				X		
[Patient reported pain score]						X
[Time from commencement of induction to OAA/S 3]			X	X	X	
[Total dose of propofol]						X
[Total dose of opiates]						X
[Cpt propofol TCI]			X	X	X	

Fig. 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of enrolment, interventions and assessments

criteria by clinical staff within participating emergency departments.

Where a patient satisfies these criteria, the trained clinician, if on duty, will liaise with the clinical team to establish whether or not the patient is eligible for enrolment based on the formal inclusion and exclusion criteria detailed in the protocol.

In line with the current best practice [2], a minimum array of patient monitoring will be prescribed: 3-lead electrocardiogram, non-invasive blood pressure, peripheral oxygen saturation and end-tidal carbon dioxide monitoring. There will be one clinician responsible for sedating the patient and another clinician undertaking the reduction. The sedating clinician will be assisted by

a skilled assistant, normally an emergency department nurse. This is already undertaken as routine in all patients undergoing procedural sedation [2]. In addition, all patients will receive supplemental oxygen (via nasal cannulae at 4 L min^{-1}) for the duration of the sedation episode.

Following patient enrolment, the TCI sedation flow sheet (Additional file 4) will be followed. The patient can receive morphine analgesia as long as it is administered at least 20 min before commencement of sedation. The dose and time of administration of morphine will be recorded.

The patient's physiological parameters including heart rate, blood pressure and end-tidal carbon dioxide levels will be recorded prior to the administration of sedation and every 3 min until 15 min post reduction; thereafter, these will be recorded on a 15-min basis until full recovery. Likewise, the peripheral oxygen saturation will be recorded except with increased frequency, at 1-min intervals until 15 min post reduction upon which time they will be recorded on a 15-min basis. The non-invasive blood pressure will be obtained by measuring the posterior tibial pressure as we will be unable to use either arm owing to the dislocation and the TCI. When the patient's modified observer's assessment of alertness/sedation score (Additional file 5) reaches the target of 3, it will be recorded every 3 min until the procedure is complete. A patient-reported pain score for the procedure will be obtained after full recovery (Additional file 3).

Patients will be consented for the procedure and inclusion in the study by the responsible clinician. Written consent for use of the patient's information and administering the propofol via TCI route as opposed to the standard bolus administration will be obtained pre-procedure.

Written consent will be sought from the patient to allow usage of their data collected during their stay in the ED and for administering the propofol via the TCI route. The procedure to relocate the shoulder and sedative agent being used would be the same regardless of their inclusion or exclusion in the study; it is only the method of administering the propofol that differs. The patient will be asked to sign the patient consent form that will then be counter signed by the responsible clinician. The patient will retain one copy of the signed consent form, and a further copy will be placed in the patient's medical records whilst the original will be retained by the principal investigator.

The right of the participant to refuse to participate without giving reasons must and will be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. Any data collected that is additional to the routine will be destroyed.

For each patient, a number of demographic, clinical and physiological parameters will be collected via clinical information systems and previous healthcare records.

Data collection and management

A standardised data collection sheet will be utilised to record information for each patient enrolled in the study. The data collection sheet will be our source document. All data entered on the data collection sheet is hand written, and the information transcribed from a screen. On completion of the data collection sheet, they will be signed and dated. These will be maintained in an investigator file to be secured in a locked office within the study site. Information recorded on the data collection sheet will be recorded in a database located on a secure server.

Required data, other than that recorded at the time of sedation, will be retrieved from existing clinical IT systems and by review of the patient's hospital notes. It is the principal investigators responsibility to ensure that all data is handled in a confidential fashion and in compliance with the protocol, local policy and statutory requirements.

The following is a non-exhaustive list of variables that will be recorded for each enrolled patient:

- Age
- Gender
- ED length of stay
- ED discharge destination
- Mechanism of shoulder dislocation
- Number of previous presentations following anterior shoulder dislocation
- Pre-sedation physiology
- Time of verbal and written consent

Planned analysis

The plan of analysis for study data will be designed with the assistance of a biomedical statistician from the University of Strathclyde. Descriptive statistics will be presented.

Following the completion of this feasibility study, we plan to proceed to an RCT. The primary endpoint for our multi-centre RCT will be the incidence and severity of adverse events.

Ethical approval and amendments

Ethical and amendment approval were obtained from the West of Scotland Research Ethics Committee 5, reference number 17/WS/0020 on 24 January 2017.

Patient confidentiality

The principal investigator will preserve the confidentiality of participants taking part in the study in line with

the Data Protection Act. Data held centrally by the principal investigator will be anonymised were practical and identified by a unique code. Documents that are not anonymised, such as signed informed consent forms, will be kept in a strictly confidential file by the principal investigator.

Adverse event reporting

A serious adverse event occurring to a research participant will be reported to the main REC within 15 days of the chief investigator, or designee becoming aware where in the opinion of the chief investigator the event was related and unexpected. They will be reported as outlined in the 'Safety and Progress Reports Table (non--CTIMPs) for UK health departments' RES version 2.1 05.06.2015'.

Protocol deviation reporting

A protocol deviation is any departure from the approved protocol. All deviations will be recorded and reported to the sponsor. Prospective protocol deviations will not be authorised by the sponsor unless the deviation is necessary to eliminate an immediate hazard.

Publication policy

All publications and presentations relating to the study will be authorised by the chief investigator. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Our sponsor will review all documents prior to publication.

Discussion

Research in emergency medicine is challenging owing to the unpredictable nature of the specialty and paucity of research support [31]. In the context of this challenging environment, a decision will be taken as to whether recruitment is adequate to allow progression to a randomised controlled trial. All observational studies have potential bias, and the results should generally not be used to change practice. The results of observational studies can be used to inform the development protocols for randomised clinical trials. The purpose of this study is to determine whether TCI propofol has the potential in terms of patient satisfaction to offer an alternative method for procedural sedation in the emergency department. The chosen primary endpoint of patient satisfaction scores will be inherently less prone to bias as patients are unlikely to have a bias for procedural sedation. In order to progress to a randomised control trial of TCI propofol against bolus propofol, TCI propofol would have to be no worse than standard bolus propofol in terms of patient satisfaction and also offer the potential of improved patient safety to be an acceptable clinical alternative for procedural sedation.

The purpose of the future multi-centre randomised trial is to compare the safety of propofol sedation, delivered via a target-controlled infusion, in comparison to that of usual bolus administration for the relocation of acute traumatic shoulder dislocation in adult patients in the emergency department. Our primary endpoint for that RCT will be the incidence of adverse events as recorded on the World SIVA adverse event sedation reporting tool [33]. We believe that the results will be generalisable to other painful procedures in the emergency department.

Trial status

The trial is currently open for recruitment. The Standard Protocol Items Recommendations for Trials (SPIRIT) checklist has been added as Additional file 6.

Additional files

Additional file 1: Patient satisfaction—visual analogue scale (VAS) (PDF 30 kb)
Additional file 2: Nurse opinion of patient experience VAS (PDF 24 kb)
Additional file 3: Patient-reported pain score VAS (PDF 27 kb)
Additional file 4: The TCI sedation flow sheet (PDF 71 kb)
Additional file 5: A patient's modified observer's assessment of alertness/sedation score (PDF 37 kb)
Additional file 6: The Standard Protocol Items Recommendations for Trials (SPIRIT) checklist (PDF 78 kb)

Abbreviations

ASA: American Society of Anesthesiologists; ED: Emergency department; OAA/S: Observer's Assessment of Alertness/Sedation Scale; PSA: Procedural sedation and analgesia; SIVA: Society for Intravenous Anaesthesia; TCI: Target-controlled infusion; VAS: Visual analogue scale

Acknowledgements

The authors would like to thank all of the centres and colleagues recruiting. They would also like to extend their thanks to all who have participated in this trial.

Funding

Funding has been awarded by CareFusion BD. Funders have had no input to the study design; collection, management, analysis, and interpretation of data and will have no input to the writing of the report; and the decision to submit the report for publication. They will not have ultimate authority over any of these activities.

Availability of data and materials

The data sets generated or analysed during the current study are not publicly available because the trial is ongoing but are available from the corresponding author in due time on reasonable request.

Authors' contributions

JM and DJL conceptualised the study and drafted the initial study protocol. FMB, ARC and MABS participated in the study design along with reviewing and revising the protocol. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

Ethical and amendment approval was given by the West of Scotland Research Ethics Committee 5, reference number 17/WS/0020 on 24th January 2017.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Department of Emergency Medicine, University Hospital Hairmyres, Eaglesham Road, Glasgow G75 8RG, UK. [2]Glasgow University Section of Anaesthesia, Pain and Critical Care, Glasgow, Scotland. [3]Department of Emergency Medicine, Queen Elizabeth University Hospital, Glasgow, Scotland. [4]Department of Anaesthesia and Critical Care, Queen Elizabeth University Hospital, Glasgow, Scotland. [5]Department of Emergency Medicine, Royal Alexandra Hospital, Paisley, Scotland.

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References

1. Green SM. Research advances in procedural sedation and analgesia. Ann Emerg Med. 2007;49(1):31–6.
2. The Royal College of Anaesthetists and The College of Emergency Medicine Working Party on Sedation. Safe sedation of adults in the emergency department. 2012.
3. Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, Silvers SM, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2014;63(2):247–58. e18.
4. Jacques KG, Dewar A, Gray A, Kerslake D, Leal A, Lees F. Procedural sedation and analgesia in a large UK emergency department: factors associated with complications. Emerg Med J. 2011;28(12):1036–40.
5. Mathieu N, Jones L, Harris A, Hudson A, McLauchlan C, Riou P, et al. Is propofol a safe and effective sedative for relocating hip prostheses? Emerg Med J. 2009;26(1):37–8.
6. Edwards J, Kinsella J, Shaw A, Evans S, Anderson KJ. Sedation for oocyte retrieval using target controlled infusion of propofol and incremental alfentanil delivered by non-anaesthetists. Anaesthesia. 2010;65(5):453–61.
7. Miner JR, Krauss B. Procedural sedation and analgesia research: state of the art. Acad Emerg Med. 2007;14(2):170–8.
8. Bell A, Taylor DM, Holdgate A, MacBean C, Huynh T, Thom O, et al. Procedural sedation practices in Australian emergency departments. Emerg Med Australas. 2011;23(4):458–65.
9. Hohl CM, Sadatsafavi M, Nosyk B, Anis AH. Safety and clinical effectiveness of midazolam versus propofol for procedural sedation in the emergency department: a systematic review. Acad Emerg Med. 2008;15(1):1–8.
10. Zed PJ, Abu-Laban RB, Chan WWY, Harrison DW. Efficacy, safety and patient satisfaction of propofol for procedural sedation and analgesia in the emergency department: a prospective study. Can J Emerg Med. 2007;9(6):421–7.
11. Miner JR, Danahy M, Moch A, Biros M. Randomized clinical trial of etomidate versus propofol for procedural sedation in the emergency department. Ann Emerg Med. 2007;49(1):15–22.
12. Miner JR, Burton JH. Clinical practice advisory: emergency department procedural sedation with propofol. Ann Emerg Med. 2007;50(2):182–7.
13. Illievich UM, Petricek W, Schramm W, Weindlmayr-Goettel M, Czech T, Spiss CK. Electroencephalographic burst suppression by propofol infusion in humans: hemodynamic consequences. Anesth Analg. 1993;77(1):155–60.
14. Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, et al. Comparison of the effect-site keOs of propofol for blood pressure and EEG bispectral index in elderly and younger patients. J Am Soc Anesthesiol. 1999;90(6):1517–27.
15. Burton JH, Miner JR, Shipley ER, Strout TD, Becker C, Thode HC. Propofol for emergency department procedural sedation and analgesia: a tale of three centers. Acad Emerg Med. 2006;13(1):24–30.
16. Davison M, Stewart R. Is propofol a safe and effective sedative for relocating hip prostheses? Emerg Med J. 2009;26(11):841.
17. Newstead B, Bradburn S, Appelboam A, Reuben A, Harris A, Hudson A, et al. Propofol for adult procedural sedation in a UK emergency department: safety profile in 1008 cases. Br J Anaesth. 2013;111(4):651–5.
18. Goudra BG, Mandel JE. Target-controlled infusions/patient-controlled sedation. Tech Gastrointest Endosc. 2009;11(4):181–7.
19. Frölich M, Dennis D, Shuster J, Melker R. Precision and bias of target controlled propofol infusion for sedation. Br J Anaesth. 2005;94(4):434–7.
20. Chan W-H, Chang S-L, Lin C-S, Chen M-J, Fan S-Z. Target-controlled infusion of propofol versus intermittent bolus of a sedative cocktail regimen in deep sedation for gastrointestinal endoscopy: comparison of cardiovascular and respiratory parameters. J Dig Dis. 2014;15(1):18–26.
21. Gillham MJ, Hutchinson RC, Carter R, Kenny GNC. Patient-maintained sedation for ERCP with a target-controlled infusion of propofol: a pilot study. Gastrointest Endosc. 2001;54(1):14–7.
22. Eberl S, Preckel B, Bergman J, Hollmann M. Safety and effectiveness using dexmedetomidine versus propofol TCI sedation during oesophagus interventions: a randomized trial. BMC Gastroenterol. 2013;13(1):176.
23. Sakaguchi M, Higuchi H, Maeda S, Miyawaki T. Dental sedation for patients with intellectual disability: a prospective study of manual control versus Bispectral Index-guided target-controlled infusion of propofol. J Clin Anesth. 2011;23(8):636–42.
24. Oei-Lim V, Kalkman C, Makkes P, Ooms W. Patient-controlled versus anesthesiologist-controlled conscious sedation with propofol for dental treatment in anxious patients. Anesth Analg. 1998;86(5):967–72.
25. Lin T, Lo Y, Hsieh C, Ni Y, Wang T, Lin H, et al. The potential regimen of target-controlled infusion of propofol in flexible bronchoscopy sedation: a randomized controlled trial. PLoS One. 2013;8(4):e62744.
26. Franzen D, Bratton DJ, Clarenbach CF, Freitag L, Kohler M. Target-controlled versus fractionated propofol sedation in flexible bronchoscopy: a randomized noninferiority trial. Respirology. 2016;21(8):1445–51.
27. Leslie K, Clavisi O, Hargrove J. Target-controlled infusion versus manually-controlled infusion of propofol for general anaesthesia or sedation in adults. Cochrane Database Syst Rev. 2016;7:CD006059.
28. Thorpe RJ, Benger J. Pre-procedural fasting in emergency sedation. Emerg Med J. 2010;27(4):254–61.
29. Kanji A, Atkinson P, Fraser J, Lewis D, Benjamin S. Delays to initial reduction attempt are associated with higher failure rates in anterior shoulder dislocation: a retrospective analysis of factors affecting reduction failure. Emerg Med J. 2016;33:130–3.
30. Dixon WJ. The up-and-down method for small samples. J Am Stat Assoc. 1965;60(312):967–78.
31. Cofield SS, Conwit R, Barsan W, Quinn J. Recruitment and retention of patients into emergency medicine clinical trials. Acad Emerg Med. 2010; 17(10):1104–12.
32. McCormack HM, David JL, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18(4):1007–19.
33. Mason KP, Green SM, Piacevoli Q. Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. Br J Anaesth. 2012;108(1):13–20.
34. Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain. 2000;16(1):22–8.
35. Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth. 2014;113(4):549–59.
36. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/ Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990;10:244.

Appendix 23 - Ethics approval for PROTEDS

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SW

Dr Fiona Burton
Hairmyres Hospital
G75 8RG

Date 26 January 2017

Direct line
E-mail

Dear Dr Burton

Study title: **Propofol Target-Controlled Infusion in Emergency Department Procedural Sedation (PROTEDS)Propofol target-controlled infusion versus usual bolus administration for the sedation of adult patients with acute shoulder dislocation in the Emergency Department**
REC reference: **17/WS/0020**
Protocol number: **GN16AE183**
IRAS project ID: **180111**

Thank you for your response that was received today. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 24 January 2017.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant information sheet (PIS) [Patient Information]	1.9	24 January 2017

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP letter]	1.1	01 October 2015
GP/consultant information sheets or letters [Physician Information]	1.7	05 August 2016
Instructions for use of medical device [TCI Flow Sheet]		
Other [MHRA Email]		09 April 2015

Participant consent form [Consent Form]	1.3	01 April 2016
Participant information sheet (PIS) [Patient Information]	1.9	24 January 2017
REC Application Form [REC_Form_06012017]		06 January 2017
Research protocol or project proposal [Feasibility Protocol]	v1.12	19 December 2016
Summary CV for Chief Investigator (CI) [CI CV]		dated 2016
Summary CV for supervisor (student research) [Supervisor CV]		17 September 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

17/WS/0020 **Please quote this number on all correspondence**

Yours sincerely

Sharon Macgregor
REC Manager

Copy to: Ms Joanne McGarry, NHS Greater Glasgow and Clyde

List of References

Aalami, O.O., Fang, T.D., Song, H.M. and Nacamuli, R.P. 2003. Physiological features of aging persons. *Archives of Surgery*. **138**, pp.1068-1076.

Absalom, A.R., Mani, V., De Smet, T. and Struys, M.M.R.F. 2009. Pharmacokinetic models for Propofol—defining and illuminating the devil in the detail. *British journal of anaesthesia*. **103**(1), pp.26-37.

Absalom, A.R., Glen, J.B., Zwart, G.J.C., Schnider, T.W. and Struys, M.M.R.F. 2016. Target-Controlled Infusion: A Mature Technology. *Anesthesia & Analgesia*. **122**(1), pp.70-78.

Al-Rifai, Z. and Mulvey, D. 2016. Principles of total intravenous anaesthesia: basic pharmacokinetics and model descriptions. *BJA Education*. **16**(3)**,** pp.92-97.

American Society of Anesthesiologists Committee. 2011. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. **114**(3)**, pp.**495-511.

American Society of Anesthesiologists. 2018. Practice guidelines for moderate procedural sedation and analgesia 2018: a report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology*. **128**(3)**,** pp.437-479.

American Society of Anesthesiologists. 2019. Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia. *Approved by ASA House of Delegates on October 13, 1999, and last amended on October 23, 2019.*

Anderson, K.J., Sim, M, Puxty, A. and Kinsella, J. 2010. Propofol is not safe for sedation for hip relocation. *Emergency Medicine Journal*. **27**(11)**,** pp.885-885.

Arslan, G. and Sezen, Ö. 2020. Comparison of target controlled infusion and manual infusion of Propofol for sedation in spinal anesthesia. *Ain-Shams Journal of Anesthesiology*. **12**(1), pp.1-7.

Aubrun, F., Mazoit, J.X. and Riou, B. 2012. Postoperative intravenous morphine titration. *British journal of anaesthesia*. **108**(2), pp.193-201.

Bailey, J.M. 2002. Context-sensitive half-times. *Clinical pharmacokinetics*. **41, pp.**793-799.

Bainbridge, J.M. 1972. Accident and emergency services. *Postgraduate Medical Journal*. **48**(559), p.254.

Baker, M.T., Naguib, M. and Warltier, D.C. 2005. Propofol: The Challenges of Formulation. *Anesthesiology*. **103**(4), pp.860-876.

Barber, R., Boote, J.D., Parry, G.D., Cooper, C.L., Yeeles, P. and Cook, S. 2012. Can the impact of public involvement on research be evaluated? A mixed methods study. *Health Expectations*. **15**(3), pp.229-241.

Bhatt, M., Kennedy, R.M., Osmond, M.H., Krauss, B., McAllister, J.D., Ansermino, J.M., Evered, L.M. and Roback, M.G. 2009. Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. *Annals of emergency medicine*. **53**(4), pp.426-435.

Boateng, G.O., Neilands, T.B., Frongillo, E.A., Melgar-Quiñonez, H.R. and Young, S.L. 2018. Best practices for developing and validating scales for health, social, and behavioral research: a primer. *Frontiers in public health*. **6,** p.149.

Bonato, P. 2010. Wearable sensors and systems. *IEEE Engineering in Medicine and Biology Magazine*. **29**(3), pp.25-36.

Borgeat, A., Wilder-Smith, O.H.G, Saiah, M. and Rifat, K. 1992. Subhypnotic Doses of Propofol Possess Direct Antiemetic Properties. *Anesthesia & Analgesia*. 74(4), pp.539-541.

Borys, D. 2009. Exploring risk-awareness as a cultural approach to safety: Exposing the gap between work as imagined and work as actually performed. *Safety Science Monitor*. **13**(2), pp.1-11.

Bowie, P., McNab, D. Ferguson, J., De Wet, C., Smith, G., MacLeod, M., McKay, J. and White, C. 2015. Quality improvement and person-centredness: a participatory mixed methods study to develop the 'always event'concept for primary care. *BMJ open*. **5**(4), p.e006667.

Boyle, A., Townend, W., Beet, E. and Bloom, B. 2021. The Royal College of Emergency Medicine's curriculum in the UK. *European Journal of Emergency Medicine*. **28**(4), pp.249-251.

Breivik, E.K., Bj*örnsson*, G.A. and Skovlund, E. 2000. A comparison of pain rating scales by sampling from clinical trial data. *The Clinical journal of pain*. **16**(1), pp.22-28.

Brett, J.O., Staniszewska, S., Mockford, C., Herron-Marx, S., Hughes, J., Tysall, C. and Suleman, R. 2014. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health expectations*. **17**(5), pp.637-650.

Briggs, L.P., Clarke, R.S.J. and Watkins, J. 1982. An adverse reaction to the administration of disoprofol (Diprivan). *Anaesthesia*. **37**(11), pp.1099-1101.

Brokelman, R.B.G., Haverkamp, D., Van Loon, C., Hol, A., Van Kampen, A. and Veth, R. 2012. The validation of the visual analogue scale for patient satisfaction after total hip arthroplasty. *European orthopaedics and traumatology*. **3**, pp.101-105.

Bruce, J. 1971. Report of a joint Working Party. *Joint Consultants Committee*.

Burton, F. 2012. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 2: should capnography be routinely used during procedural sedation in the emergency department? *Emergency Medicine Journal: EMJ*. **29**(2), pp.164-166.

Burton, F.M. 2015. *Propofol target-controlled infusion versus bolus administration for sedation, does it reduce the incidence and severity of adverse events?* [Online]. Available: https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015026067&ID=CRD42015026067 [Accessed 15th December 2022].

Burton, F.M., Coady, G. and Sim, M.A.B. 2019a. Is there time for target-controlled infusion in the Emergency Department? *European Journal of Emergency Medicine*. **26**(4), pp.309-310.

Burton, F.M., Lowe, D.J., Millar, J., Corfield, A.R. and Sim, M.A.B. 2019b. A study protocol for a feasibility study: Propofol Target-Controlled Infusion in Emergency Department Sedation (ProTEDS)—a multi-centre feasibility study protocol. *Pilot and feasibility studies*. **5**(1), pp.1-8.

Burton, F.M., Lowe, D.J., Millar, J., Corfield, A.R., Watson, M.J. and Sim, M.A.B. 2021. Propofol target-controlled infusion in emergency department sedation (ProTEDS): a multicentre, single-arm feasibility study. *Emergency Medicine Journal*. **38**(3), pp.205-210.

Burton, F.M., Lowe, D.J., Millar, J.E., Corfield, A.R., Watson, M.J., Shaw, M. and Sim, M.A.B. 2020. Effect of target-controlled Propofol infusion to reduce the incidence of adverse events for procedural sedation in the emergency department: a systematic review. *European Journal of Emergency Medicine*. **27**(4), pp.253-259.

Caron, M., Parrot, A., Blayau, C., Hafiani, E.M., Fulgencio, J.P., Labbé, V., Djibré, M., Decavèle, M., Quesnel, C., Fartoukh, M. and Pham, T. 2015. Remifentanil target-controlled infusion for fiberoptic bronchoscopy in the ICU: feasability, safety and tolerance evaluation. *Intensive Care Medicine Experimental*. **3**(1), pp.1-2.

Chadha, R.M., Dexter, F. and Brull, S.J. 2020. Lack of recall after sedation for cataract surgery and its effect on the validity of measuring patient satisfaction. *Korean journal of anesthesiology*. **73**(4), pp.319-325.

Chan, W.H., Chang, S.L., Lin, C.S., Chen, M.J. and FAN, S.Z. 2014. Target-controlled infusion of Propofol versus intermittent bolus of a sedative cocktail regimen in deep sedation for gastrointestinal endoscopy: comparison of cardiovascular and respiratory parameters. *Journal of digestive diseases*. **15**(1), pp.18-26.

Chen, T.C., Schein, O.D. and Miller, J.W. 2015. Sentinel events, serious reportable events, and root cause analysis. *JAMA ophthalmology*. **133**(6), pp.631-632.

Chernik, D.A., Gillings, D., Laine, H., Hendler, J., Silver, J.M., Davidson, A.B., Schwam, E.M. and Siegel, J.L. 1990. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *Journal of clinical psychopharmacology*. **10**(4), pp.244-251

Chiang, M.H., Wu, S.C., You, C.H, Wu, K.L., Chiu, Y.C., Ma, C.W., Kao, C.W., Lin, K.C., Chen, K.H., Wang, P.C. and Chou, A.K. 2013. Target-controlled infusion vs. manually controlled infusion of Propofol with alfentanil for bidirectional endoscopy: a randomized controlled trial. *Endoscopy*. **45**(11), pp.907-914.

Chisholm, C.J., Zurica, J., Mironov, D., Sciacca, R.R., Ornstein, E. and Heyer, E.J. 2006, January. Comparison of electrophysiologic monitors with clinical assessment of level of sedation. In *Mayo Clinic Proceedings*. **81**(1), pp.46-52. Elsevier.

Christie, B.. 2016. Doctors need to adopt “realistic” medicine, says Scotland’s chief medical officer. *BMJ*. **352**, p.i392.

Clarke, A.C., Chiragakis, L., Hillman, L.C. and Kaye, G.L. 2002. Sedation for endoscopy: the safe use of Propofol by general practitioner sedationists. *Medical journal of Australia*. **176**(4)**,** pp.159-161.

Cochrane Collaboration. 2014. Review Manager (RevMan) [Computer program]. Version 5.3. 5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.

Coetzee, J.F. 2014. Dose scaling for the morbidly obese. *Southern African Journal of Anaesthesia and Analgesia*. **20**(1)**,** pp.69-72.

Cofield, S.S., Conwit, R., Barsan, W. and Quinn, J. 2010. Recruitment and retention of patients into emergency medicine clinical trials. *Academic Emergency Medicine*. **17**(10)**,** pp.1104-1112.

Collins, J. 1972. Staffing of casualty departments. *British Medical Journal*. **4**(5840)**,** p.607.

Corssen, G. and Domino, E.F. 1966. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative Cl-581. *Anesthesia & Analgesia*. **45**(1)**,** pp.29-40.

Cortinez, L.I., Anderson, B.J., Penna, A., Olivares, L., Munoz, H.R., Holford, N.H.G., Struys, M.M.R.F. and Sepulveda, P. 2010. Influence of obesity on Propofol pharmacokinetics: derivation of a pharmacokinetic model. *British journal of anaesthesia*. **105**(4), pp.448-456.

Crowe, S., Adebajo, A., Esmael, H., Denegri, S., Martin, A., McAlister, B., Moore, B., Quinn, M., Rennard, U. and Simpson, J. 2020. 'All hands-on deck', working together to develop UK standards for public involvement in research. *Research involvement and engagement*. **6,** pp.1-9.

Cummings, G.C., Dison, J., Kay, N.H., Windsor, J.P.W., Major, E., Morgan, M., Sear, J.W., Spence, A.A. and Stephenson, D.K. 1984. Dose requirements of ICI 35,868 (Propofol,'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia*. **39**(12)**,** pp.1168-1171.

Dahaba, A.A. 2005. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesthesia & Analgesia*. **101**(3)**,** pp.765-773.

Davison, M. and Stewart, R. 2009. Is Propofol a safe and effective sedative for relocating hip prostheses? *Emergency Medicine Journal*. **26**(11)**,** pp.841-841.

Dawidowicz, A.L., Fornal, E., Mardarowicz, M. and Fijalkowska, A. 2000. The role of human lungs in the biotransformation of Propofol. *The Journal of the American Society of Anesthesiologists*. **93**(4), pp.992-997.

Deitch, K., Miner, J., Chudnofsky, C.R., Dominici, P. and Latta, D. 2010. Does end tidal CO2 monitoring during emergency department procedural sedation and analgesia with Propofol decrease the incidence of hypoxic events? A randomized, controlled trial. *Annals of emergency medicine*. **55**(3)**,** pp.258-264.

De Castro, V., Godet, G., Mencia, G., Raux, M. and Coriat, P. 2003. Target-controlled infusion for remifentanil in vascular patients improves hemodynamics and decreases remifentanil requirement. *Anesthesia & Analgesia*. **96**(1), pp.33-38.

DeVito, A., Agnoletti, V., Berrettini, S., Piraccini, E., Criscuolo, A., Corso, R., Campanini, A., Gambale, G. and Vicini, C. 2011. Drug-induced sleep endoscopy: conventional versus target controlled infusion techniques--a

randomized controlled study. *European archives of oto-rhino-laryngology*. **268,** pp.457-62.

Dexter, F. 2017. Iowa Satisfaction with Anesthesia Scale for emergency medicine procedures. *Emergency medicine Australasia: EMA*. **29**(4)**,** pp.477-477.

Dexter, F. and Candiotti, K.A. 2011. Multicenter Assessment of the Iowa Satisfaction with Anesthesia Scale, an Instrument that Measures Patient Satisfaction with Monitored Anesthesia Care. *Anesthesia & Analgesia*. **113**(2), pp.364-368.

Dexter, F., Aker, J. and Wright, W.A. 1997. Development of a measure of patient satisfaction with monitored anesthesia care: the Iowa Satisfaction with Anesthesia Scale. *The Journal of the American Society of Anesthesiologists*. **87**(4)**,** pp.865-873.

Dixon, W.J. 1965. The Up-and-Down Method for Small Samples. *Journal of the American Statistical Association*. **60**(312)**,** pp.967-978.

Domino, E.F. and Warner, D.S. 2010. Taming the ketamine tiger. *The Journal of the American Society of Anesthesiologists*. **113**(3)**,** pp.678-684.

Doshi, H.N., Sheth, K. and Joshi, N.C. 2011. Comparing Bispectral Index Score to COMFORT Score in assessing sedation in pediatric patients. *Pediatric On Call Journal*. **8**(2)**,** pp.31-33.

Driscoll, P., Cope, A. and Miles, S.A. 1988. Adequacy of senior registrar training in accident and emergency medicine over the last 5 years. *Emergency Medicine Journal*. **5**(3)**,** pp.162-168.

Dundee, J. 1980. THE IDEAL INTRAVENOUS ANAESTHETIC. *ɔ CLINICAL EVALUATION OF PROPOFOL*. p.3.

Dunn, J., Runge, R. and Snyder, M. 2018. Wearables and the medical revolution. *Personalized medicine*. **15**(5)**,** pp.429-448.

Dunn, M.J.G., Mitchell, R., DeSouza, C.I., Drummond, G.B. and Waite, A. 2011. Recovery from sedation with remifentanil and Propofol, compared with morphine and midazolam, for reduction in anterior shoulder dislocation. *Emergency Medicine Journal*. **28**(1)**,** pp.6-10.

Dunn, M.J.G., Mitchell, R., Souza, C.D. & Drummond, G. 2006. Evaluation of Propofol and remifentanil for intravenous sedation for reducing shoulder dislocations in the emergency department. *Emergency Medicine Journal*. **23**(1), pp.57-58.

Dunnell, K. 2008. Ageing and mortality in the UK. *Popul Trends*. **134**, pp.6-23.

Edwards, J.A., Kinsella, J., Shaw, A., Evans, S. and Anderson, K. J. 2010. Sedation for oocyte retrieval using target controlled infusion of Propofol and incremental alfentanil delivered by non-anaesthetists. *Anaesthesia*. 65(5), **pp.**453-461.

Egan, T.D., Westphal, M., Minto, C.F. and Sschnider, T.W. 2020. Moving from dose to concentration: as easy as TCI! *British Journal of Anaesthesia*. **125**(6), pp.847-849.

Eldridge, S.M., Lancaster, G.A., Campbell, M.J., Thabane, L., Hopewell, S., Coleman, C.L. and Bond, C.M. 2016. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PloS one*. **11**(3), p.e0150205.

Eleveld, D.J., Colin, P., Absalom, A.R. and Struys, M.M.R.F. 2018. Pharmacokinetic–pharmacodynamic model for Propofol for broad application in anaesthesia and sedation. *British journal of anaesthesia*. **120(**5), pp.942-959.

Eleveld, D.J., Colin, P., Absalom, A.R. and STRUYS, M.M.R.F. 2020. Target-controlled-infusion models for remifentanil dosing consistent with approved recommendations. *British Journal of Anaesthesia*. **125**(4), pp.483-491.

Ellis, M. 1972. Staffing of casualty departments. *British Medical Journal*. 4(5840), p.608.

Elm, J.J., Palesch, Y., Easton, J.D., Lindblad, A., Barsan, W., Silbergleit, R., Conwit, R., Dillon, C., Farrant, M., Battenhouse, H., Perlmutter, A. and Johnston, S.C. 2014. Screen failure data in clinical trials: Are screening logs worth it? *Clinical Trials*. **11**(4), pp.467-472.

Engbers, F. H. *TivatrainerX* [Online]. Available: https://www.tivatrainerx.com [Accessed 15th December 2022].

Fanti, L., Gemma, M., Agostoni, M., Rossi, G., Ruggeri, L., Azzolini, M.L., Dabizzi, E., Beretta, L. and Testoni, P.A. 2015. Target controlled infusion for non-anaesthesiologist Propofol sedation during gastrointestinal endoscopy: the first

double blind randomized controlled trial. *Digestive and Liver Disease*, **47**(7), pp.566-571.

Fatovich, D.M., Gope, M. and Paech, M.J. 2004. A pilot trial of BIS monitoring for procedural sedation in the emergency department. *Emergency Medicine*. **16**(2), pp.103-107.

Forkin, K.T. and Nemergut, E. C. 2016. Miller's anesthesia. *Anesthesiology,* **124**(4), pp.977-978.

Franzen, D., Bratton, D.J., Clarenbach, C.F., Freitag, L. and Kohler, M. 2016. Target-controlled versus fractionated Propofol sedation in flexible bronchoscopy: A randomized noninferiority trial. *Respirology*. **21**(8), pp.1445-1451.

Fry, M. and Stainton, C. 2005. An educational framework for triage nursing based on gatekeeping, timekeeping and decision-making processes. *Accident and emergency nursing*. **13**(4), pp.214-219.

Fung, D., Cohen, M., Stewart, S. and Davies, A. 2005a. Can the Iowa Satisfaction with Anesthesia Scale be used to measure patient satisfaction with cataract care under topical local anesthesia and monitored sedation at a community hospital? *Anesthesia & Analgesia*. **100**(6), pp.1637-1643.

Fung, D., Cohen, M.M., Stewart, S. and Davies, A. 2005b. What determines patient satisfaction with cataract care under topical local anesthesia and monitored sedation in a community hospital setting? *Anesthesia & Analgesia*. **100**(6) pp.1644-1650.

Gagnier, J.J., Moher, D., Boon, H., Beyene, J. and Bombardier, C. 2012. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. *BMC medical research methodology*. **12**(1), pp.1-15.

García Guzzo, M.E., Fernandez, M.S., Sanchez Novas, D., Salgado, S.S., Terrasa, S.A., Domenech, G. and Teijido, C.A. 2020. Deep sedation using Propofol target-controlled infusion for gastrointestinal endoscopic procedures: a retrospective cohort study. *BMC anesthesiology*. **20**, pp.1-8.

Garden, R.S. 1965. The casualty consultant. *The Lancet*. **285**(7399), p.1333.

Gepts, E., Camu, F., Cockshott, I.D. and Douglas, E.J. 1987. Disposition of Propofol administered as constant rate intravenous infusions in humans. *Anesthesia & Analgesia*. **66**(12), pp.1256-1263.

Gill, M., Green, S.M. and Krauss, B. 2003. Can the bispectral index monitor quantify altered level of consciousness in emergency department patients?. *Academic emergency medicine*. **10**(2), pp.175-179.

Glass, P.S., Gan, T.J. and Howell, S. 1999. A review of the pharmacokinetics and pharmacodynamics of remifentanil. *Anesthesia & Analgesia*. **89**(4S), p.7.

Glass, P.S., Glen, J.B., Kenny, G.N., Schuttler, J. and Shafer, S.L. 1997. Nomenclature for computer-assisted infusion devices. *The Journal of the American Society of Anesthesiologists*. **86**(6), pp.1430-1431.

Glass, P.S., Hardman, D., Kamiyama, Y., Quill, T.J., Marton, G., Donn, K.H., Grosse, C.M. and Hermann, D. 1993. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesthesia & Analgesia*. **77**(5), pp.1031-1040.

Glen, J.B. 1998. The development of 'Diprifusor': a TCI system for Propofol. *Anaesthesia*. **53**, pp.13-21.

Glen, J.B. and Hunter, S.C. 1984. Pharmacology of an emulsion formulation of ICI 35 868. *British journal of anaesthesia*. **56**(6), pp.617-626.

Glen, J.B. 1980. Animal studies of the anaesthetic activity of ICI 35 868. *British Journal of Anaesthesia*. **52**(8), pp.731-742.

Glen, J.B. 2019. Try, try, and try again: personal reflections on the development of Propofol. *British Journal of Anaesthesia*. **123**(1), pp.3-9.

Glen, J.B. and Servin, F. 2009. Evaluation of the predictive performance of four pharmacokinetic models for Propofol. *British journal of anaesthesia*. **102**(5), pp.626-632.

Gray, J.M. and Kenny, G.N.C. 1998. Development of the technology for 'Diprifusor'TCI systems. *Anaesthesia*. **53**, pp.22-27.

Gray, L.D. and Morris, C. 2013. The principles and conduct of anaesthesia for emergency surgery. *Anaesthesia*. **68**, pp.14-29.

Green, S.M. and Krauss, B.S. 2016. Target-controlled infusions could improve the safety and efficacy of emergency department Propofol sedation. *Anesthesia & Analgesia*. **122**(1), pp.283-284.

Green, S.M., Irwin, M.G., Mason, K.P., International Committee for the Advancement of Procedural Sedation, Absalom, A., Alcaino, E., Andolfatto, G., Babl, F., Barbi, E., Carlson, D. and Rezende Costa, L. 2021. Procedural sedation: providing the missing definition. *Anaesthesia*. **76**(5), pp.598-601.

Green, S.M., Mason, K.P. and Krauss, B.S. 2016. Ketamine and Propofol sedation by emergency medicine specialists: mainstream or menace?. *BJA: British Journal of Anaesthesia*. **116**(4), pp.449-451.

Green, S.M., Mason, K.P. and Krauss, B.S. 2017. Pulmonary aspiration during procedural sedation: a comprehensive systematic review. *BJA: British Journal of Anaesthesia*. **118(**3), pp.344-354.

Green, S.M., Roback, M.G., Krauss, B.S., Miner, J.R., Schneider, S., Kivela, P.D., Nelson, L.S., Chumpitazi, C.E., Fisher, J.D., Gesek, D. and Jackson, B. 2019. Unscheduled procedural sedation: a multidisciplinary consensus practice guideline. *Annals of emergency medicine*. **73**(5), pp.e51-e65.

Griffin, S. 2022. Emergency care is in "dire" situation after loss of NHS beds, says royal college. *BMJ*.**377.**

Guideline, I.H.T. 1994, October. Clinical safety data management: definitions and standards for expedited reporting E2A. In *International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use*.

Guly, H. 2005. *A history of accident and emergency medicine, 1948-2004*. Springer.

Haberman, E. and Oliver, A. 2013. The practical aspects of Propofol target controlled infusion for magnetic resonance imaging in children: An audit from the Royal Marsden Hospital. *Indian Journal of Anaesthesia*. **57**(1), pp.80-82.

Hariton, E. and Locascio, J.J. 2018. Randomised controlled trials—the gold standard for effectiveness research. *BJOG: an international journal of obstetrics and gynaecology*. **125**(13), p.1716.

Harrison, R., Kuteesa, W., Kapila, A., Little, M., Gandhi, W., Ravindran, D., Van Reekum, C.M. and Salomons, T.V. 2020. Pain-free day surgery? Evaluating pain and pain assessment during hysteroscopy. *British Journal of Anaesthesia*. **125**(6), pp.e468-e470.

Hayashi, K., Tsuda, N., Sawa, T. and Hagihira, S. 2007. Ketamine increases the frequency of electroencephalographic bicoherence peak on the α spindle area induced with Propofol. *British journal of anaesthesia*. **99**(3), pp.389-395.

Hayes, H., Buckland, S. and Tarpey, M. 2012. INVOLVE briefing notes for researchers: involving the public in NHS. *Public Health and Social Care Research. Eastleigh: INVOLVE*.

Hemmings, K., Haines, T.P., Chilton, P.J., Girling, A.J. and Lilford, R.J. 2015. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*. **350**.

Higgins, J.P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J. and Welch, V.A. eds. 2017. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons.

Hoke, J.F., Cunningham, F., James, M.K., Muir, K.T. and Hoffman, W.E. 1997. Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs. *Journal of Pharmacology and Experimental Therapeutics*. ***281***(1), pp.226-232.

Hollnagel, E. 2017. Why is work-as-imagined different from work-as-done? In *Resilient health care, Volume 2* (pp. 279-294). CRC Press.

Holzman, R.S., 2021. The history of sedation. *Pediatric Sedation Outside of the Operating Room: A Multispecialty International Collaboration*, pp.3-19.

Houston, N. and Bowie, P. 2015. The Scottish patient safety programme in primary care: context, interventions and early outcomes. *Scottish medical journal*. **60**(4), pp.192-195.

Hu, C., Horstman, D.J. and Shafer, S.L. 2005. Variability of target-controlled infusion is less than the variability after bolus injection. *The Journal of the American Society of Anesthesiologists*. **102**(3), pp.639-645.

Huhn, S., Axt, M., Gunga, H.C., Maggioni, M.A., Munga, S., Obor, D., Sié, A., Boudo, V., Bunker, A., Sauerborn, R. and Bärnighausen, T. 2022. The impact of wearable technologies in health research: scoping review. *JMIR mHealth and uHealth*. **10**(1), p.e34384.

Institute for Healthcare Improvement. 2014. Always Events® Getting Started Kit. Available at: https://www.ihi.org/education/IHIOpenSchool/Courses/Documents/CourseraDocuments/06_IHIAlwaysEventsGettingStartedKit.pdf (Accessed: 26th August 2023).

James, R. and Glen, J.B. 1980. Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. *Journal of Medicinal Chemistry*. **23**(12), pp.1350-1357.

Johnson, G., Brown, R. and Howell, M. 1997. Higher specialist training in accident and emergency medicine--past, present and future. *Emergency Medicine Journal*. **14**(2), pp.104-106.

Johnson, O.G., Taylor, D.M., Lee, M., Ding, J.L., Ashok, A., Johnson, D., Peck, D., Knott, J. and Weinberg, L. 2017. Patient satisfaction with procedural sedation in the emergency department. *Emergency Medicine Australasia*, **29**(3), pp.303-309.

Johnson, R., Kuczawski, M. and Mason, S. 2016. Why is it so difficult to recruit patients to research in emergency care? Lessons from the AHEAD study. *Emergency Medicine Journal*. **33**(1), pp.52-56.

Kendrick, D., Lyons, R., Christie, N., Towner, E., Benger, J., Groom, L., Coffey, F., Miller, P. and Murphy, R. 2007. Recruiting participants for injury studies in emergency departments. *Injury Prevention*, **13**(2), pp.75-77.

Kenny, G.N. 1996. Patient sedation: technical problems and developments. *European Journal of Anaesthesiology| EJA*. **13**, pp.18-21.

Khan, K.S., Hayes, I. and Buggy, D.J. 2014. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *Continuing Education in Anaesthesia Critical Care & Pain*. **14**(3), pp.100-105.

KisilewiczI, M., Rosenberg, H. and Vaillancourt, C. 2017. Remifentanil for procedural sedation: a systematic review of the literature. *Emergency Medicine Journal*. **34**(5), pp.294-301.

Klein, A.A., Meek, T., Allcock, E., Cook, T.M., Mincher, N., Morris, C., Nimmo, A.F., Pandit, J.J., Pawa, A. and Rodney, G. 2021. Recommendations for standards of monitoring during anaesthesia and recovery 2021: Guideline from the Association of Anaesthetists. *Anaesthesia*. **76**(9), pp.1212-1223.

Kohn, L.T., Corrigan, J.M., Donaldson, M.S., McKay, T. and Pike, K.C. 2000. To err is human. *building a safer health system*.

Kurt, A., Kincaid, H.M., Curtis, C., Semler, L., Meyers, M., Johnson, M., Careyva, B.A., Stello, B., Friel, T.J. and Knouse, M.C. 2017. Factors influencing participation in clinical trials: emergency medicine vs. other specialties. *Western Journal of Emergency Medicine*. **18**(5), p.846.

Kwak, H.J., Kim, J.Y., Kwak, Y.L., Park, W.S. and Lee, K.C. 2006. Comparison of a bolus of fentanyl with an infusion of alfentanil during target-controlled Propofol infusion in third molar extraction under conscious sedation. *Journal of oral and maxillofacial surgery*. **64(**11), pp.1577-1582.

Lamb, A.R. and Harper, M. 2014. Procedural sedation: it is not what you do, it is how you do it. *British Journal of Anaesthesia*. **112**(5), pp.939-940.

Ledingham, I.M. and Watt, I. 1983. Influence of sedation on mortality in critically ill multiple trauma patients. *The Lancet*. **321**(8336), p.1270.

Lee, Y.S. 2004. Effects of Propofol target-controlled infusion on haemodynamic and respiratory changes with regard to safety. *Journal of international medical research*. **32**(1), pp.19-24.

Lewin, W. 1978. Medical staffing and accident and emergency services. *London, Joint Consultants Committee*.

Litman, R.S. 1999. Conscious Sedation With Remifentanil and Midazolam During Brief Painful Procedures in Children. *Archives of Pediatrics & Adolescent Medicine*, **153**(10), pp.1085-1088.

Liu, H.Y., Tam, K.W., Loh, E.W., Liu, W.C., Kuo, H.C., LI, C.C., Cherng, Y.G., Chen, J.T. and Tai, Y.H. 2021. High-flow nasal oxygenation reduces the risk of

desaturation in adults receiving procedural sedation: a meta-analysis of randomized controlled trials. *Perioperative Medicine*. **10**(1)**,** pp.1-9.

Marsh, B.M.W.M.N., White, M., Morton, N. and Kenny, G. 1991. Pharmacokinetic model driven infusion of Propofol in children. *BJA: British Journal of Anaesthesia*. **67**(1), pp.41-48.

Mason, K.P., Green, S.M. and Piacevoli, Q. 2012. Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. *British journal of anaesthesia*. **108**(1), pp.13-20.

Mason, K.P., Roback, M.G., Chrisp, D., Sturzenbaum, N., Freeman, L., Gozal, D., Vellani, F., Cavanaugh, D. and Green, S.M. 2019. Results from the adverse event sedation reporting tool: a global anthology of 7952 records derived from> 160,000 procedural sedation encounters. *Journal of Clinical Medicine*. **8**(12), p.2087.

Mathieu, N., Jones, L., Harris, A., Hudson, A., McLauchlan, C., Riou, P. and Lloyd, G. 2009. Is Propofol a safe and effective sedative for relocating hip prostheses?. *Emergency Medicine Journal*. **26**(1), pp.37-38.

McCormack, H.M., David, J.D.L. and Sheather, S. 1988. Clinical applications of visual analogue scales: a critical review. *Psychological medicine*. **18**(4), pp.1007-1019.

Melber, A. 2022. SP43 Has remifentanil PCA a place in labour analgesia? *Regional Anesthesia & Pain Medicine*. **47,** A51-A52.

Messenger, D.W., Murray, H.E., Dungey, P.E., Van Vlymen, J. and Sivilotti, M.L. 2008. Subdissociative-dose ketamine versus fentanyl for analgesia during Propofol procedural sedation: a randomized clinical trial. *Academic emergency medicine*. **15**(10), pp.877-886.

Michelsen, L.G. and Hug Jr, C.C. 1996. The pharmacokinetics of remifentanil. *Journal of clinical anesthesia*. **8**(8), pp.679-682.

Miner, J.R., Biros, M.H., Heegaard, W. and Plummer, D. 2003. Bispectral electroencephalographic analysis of patients undergoing procedural sedation in the emergency department. *Academic Emergency Medicine*. **10**(6), pp.638-643.

Miner, J.R., Biros, M.H., Seigel, T. and Ross, K. 2005. The utility of the bispectral index in procedural sedation with Propofol in the emergency department. *Academic emergency medicine*. **12**(3), pp.190-196.

Miner, J.R., Huber, D., Nichols, S. and Biros, M. 2007. The effect of the assignment of a pre-sedation target level on procedural sedation using Propofol. *The Journal of emergency medicine*. **32**(3), pp.249-255.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P. and Stewart, L.A. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. **4**(1), pp.1-9.

Mongan, J. and Kohli, M. 2020. Artificial intelligence and human life: five lessons for radiology from the 737 MAX disasters. *Radiology: Artificial Intelligence*. **2**(2), p.e190111.

Morton, N.S. 2004. Ketamine is not a safe, effective, and appropriate technique for emergency department paediatric procedural sedation. *Emergency medicine journal*. **21**(3), pp.272-273.

Mulvey, D.A. and Klepsch, P. 2020. Use of processed electroencephalography in the clinical setting. *Current anesthesiology reports*. **10,** pp.480-487.

Muret, J., Fernandes, T.D., Gerlach, H., Imberger, G., Jörnvall, H., Lawson, C., McGain, F., Mortimer, F., Pauchard, J.C., Pierce, T. and Shinde, S. 2019. Environmental impacts of nitrous oxide: no laughing matter! Comment on Br J Anaesth 2019; 122: 587–604. *British Journal of Anaesthesia*. **123**(4), pp.e481-e482.

Nazir, M.S., Sharp, C., Fryer, J. and Edwards, M. 2011. Acute care common stem pathway. *BMJ*. **343**.

Newson, C., Joshi, G., Victory, R. and Wwhite, P. 1995. Comparison of Propofol administration techniques for sedation during monitored anesthesia care. *Anesthesia and analgesia*. **81**(3), pp.486-491

Newstead, B., Bradburn, S., Appelboam, A., Reuben, A., Harris, A., Hudson, A., Jones, L., McLauchlan, C., Riou, P. and Jadav, M. 2013. Propofol for adult

procedural sedation in a UK emergency department: safety profile in 1008 cases. *British journal of anaesthesia*. **111**(4), pp.651-655.

NHS England. 2022. Delivering a "net zero" National Health Service.

NHS Scotland. 2014. Realistic Medicine: The Chief Medical Officer's Annual Report 2014–15. *Edinburgh: The Scottish Government*.

Niknejad, N., Ismail, W.B., Mardani, A., Liao, H. and Ghani, I. 2020. A comprehensive overview of smart wearables: The state of the art literature, recent advances, and future challenges. *Engineering Applications of Artificial Intelligence*. **90,** p.103529.

O'Dowd, A. 2022. NHS in England: Four hour emergency department target hits record low.

Oei-Lim, V.L., Kalkman, C.J., Makkes, P.C. and Ooms, W.G. 1998. Patient-controlled versus anesthesiologist-controlled conscious sedation with Propofol for dental treatment in anxious patients. *Anesthesia & Analgesia*. **86**(5), pp.967-972.

Øie, S. 1986. Drug Distribution and Binding. *The Journal of Clinical Pharmacology*. **26,** pp.583-586.

Pai, A. and Heining, M. 2007. Ketamine. *Continuing Education in Anaesthesia, Critical Care & Pain*. **7**(2), pp.59-63.

Pandit, J.J., Andrade, J., Bogod, D.G., Hitchman, J.M., Jonker, W.R., Lucas, N., Mackay, J.H., Nimmo, A.F., O'Connor, K., O'Sullivan, E.P. and Paul, R.G. 2014. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. *British journal of anaesthesia*. **113**(4), pp.549-559.

Passot, S., Servin, F., Allary, R., Pascal, J., Prades, J.M., Auboyer, C. and Molliex, S. 2002. Target-controlled versus manually-controlled infusion of Propofol for direct laryngoscopy and bronchoscopy. *Anesthesia & Analgesia*. **94**(5), pp.1212-1216.

Popay, J., Collins, M. and with the PiiAF Study Group, 2014. The public involvement impact assessment framework guidance. *Universities of Lancaster, Liverpool and Exeter*.

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., Roen, K. and Duffy, S. 2006. Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme Version*. **1**(1), p.b92.

Pottegård, A., Haastrup, M.B., Stage, T.B., Hansen, M.R., Larsen, K.S., Meegaard, P.M., Meegaard, L.H.V., Horneberg, H., Gils, C., Dideriksen, D. and Aagaard, L. 2014. SearCh for humourIstic and Extravagant acroNyms and Thoroughly Inappropriate names For Important Clinical trials (SCIENTIFIC): qualitative and quantitative systematic study. *Bmj*. **349.**

Prevention, W.H.O. 1997. management of the global epidemic of obesity. Report of the WHO Consultation on Obesity (Geneva, 3-5 June, 1997). *Geneva: WHO*, *11*.

Price, D., Edwards, M., Carson-Stevens, A., Cooper, A., Davies, F., Evans, B., Hibbert, P., Hughes, T., Rainer, T., Siriwardena, N. and Edwards, A. 2020. Challenges of recruiting emergency department patients to a qualitative study: a thematic analysis of researchers' experiences. *BMC Medical Research Methodology*. **20**(1), pp.1-10.

Purdon, P.L., Pierce, E.T., Mukamel, E.A., Prerau, M.J., Walsh, J.L., Wong, K.F.K., Salazar-Gomez, A.F., Harrell, P.G., Sampson, A.L., Cimenser, A. and Ching, S. 2013. Electroencephalogram signatures of loss and recovery of consciousness from Propofol. *Proceedings of the National Academy of Sciences*. **110**(12), pp.E1142-E1151.

Purdon, P.L., Sampson, A., Pavone, K.J. and Brown, E.N. 2015. Clinical electroencephalography for anesthesiologists: part I: background and basic signatures. *Anesthesiology*. **123**(4), pp.937-960.

Ramsay, M.A.E., Savege, T.M., Simpson, B.R.J. and Goodwin, R. 1974. Controlled sedation with alphaxalone-alphadolone. *Br med J.* **2**(5920), pp.656-659.

Raoof, A.A., Augustijns, P.R. and Verbeeck, R.K. 1996. In Vivo Assessment of Intestinal, Hepatic, and Pulmonary First Pass Metabolism of Propofol in the Rat. *Pharmaceutical Research*. **13,** pp.891-895.

Reich, D.L., Wood Jr, R.K., Mattar, R., Krol, M., Adams, D.C., Hossain, S. and Bodian, C.A. 2000. Arterial Blood Pressure and Heart Rate Discrepancies Between

Handwritten and Computerized Anesthesia Records. *Anesthesia & Analgesia*. **91**(3) pp.612-616.

Rickert, J. 2014. Measuring patient satisfaction: A bridge between patient and physician perceptions of care. *Health Aff Blog. May*, 9.

Roback, M.G., Green, S.M., Andolfatto, G., Leroy, P.L. and Mason, K.P. 2018. Tracking and reporting outcomes of procedural sedation (TROOPS): standardized quality improvement and research tools from the international committee for the advancement of procedural sedation. *British Journal of Anaesthesia*. **120**(1), pp.164-172.

Rosow, C.E. 1999. An Overview of Remifentanil. *Anesthesia & Analgesia*. **89**(4S), p.1.

Royal College of Anaesthetists and The College of Emergency Medicine Working Party on Sedation. 2012. Safe Sedation of Adults in the Emergency Department.

Royal College of Anaesthetists. 2001. Safety notice on prevention of hypoxic gas mixtures. *Royal College of Anaesthetists Bulletin*. **8,** p354.

Royal College of Emergency Medicine. 2021. Curriculum 2021. Available at: https://rcem.ac.uk/wp-content/uploads/2023/03/RCEM_Curriculum_2021_Master-Version-1.5-2023.pdf (Accessed 26th August 2023).

Royal College of Emergency Medicine. 2016. Procedural Sedation in Adults 2015/16.

Royal College of Emergency Medicine. 2018. Procedural Sedation in Adults 2017/18.

Royal College of Emergency Medicine. 2022. Procedural Sedation in the Emergency Department - Best Practice Guideline.

Royal College of Emergency Medicine. 2023. UK Training Programmes. Available at: https://rcem.ac.uk/emergency-medicine-training-programmes/ (Accessed:26th August 2023).

R*ü*schen, H., Celaschi, D., Bunce, C. and Carr, C. 2005. Randomised controlled trial of sub-Tenon's block versus topical anaesthesia for cataract surgery: a comparison of patient satisfaction. *British journal of ophthalmology*. **89**(3), pp.291-293.

Ryu, J.H., Kim, M., Bahk, J.H., Do, S.H., Cheong, I.Y. and Kim, Y.C. 2009. A comparison of retrobulbar block, sub-Tenon block, and topical anesthesia

during cataract surgery. *European Journal of Ophthalmology*. **19**(2), pp.240-246.

Sacchetti, A., Jachowski, J., Heisler, J. and Cortese, T. 2012. Remifentanil use in emergency department patients: initial experience. *Emergency Medicine Journal*. **29**(11), pp.928-929.

Sahinovic, MM., Struys, MMRF., Absalom, AR. 2018. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clinical Pharmacokinetics*. **57**(12), pp.1539-1558.

Sakaguchi, M., Higuchi, H., Maeda, S. and Miyawaki, T. 2011. Dental sedation for patients with intellectual disability: a prospective study of manual control versus Bispectral Index-guided target-controlled infusion of Propofol. *Journal of clinical anesthesia*. **23**(8), pp.636-642.

Saunders, D.I. and Meek, T. 2001. Almost 30% of anaesthetic machines in UK do not have anti-hypoxia device. *BMJ*. **323**(7313), p.629.

Schnider, T.W., Minto, C.F., Gambus, P.L., Andresen, C., Goodale, D.B., Shafer, S.L. and Youngs, E.J. 1998. The influence of method of administration and covariates on the pharmacokinetics of Propofol in adult volunteers. *The Journal of the American Society of Anesthesiologists*. **88**(5), pp.1170-1182.

Schnider, T.W., Minto, C.F., Shafer, S.L., Gambus, P.L., Andresen, C., Goodale, D.B. and Youngs, E.J. 1999. The Influence of Age on Propofol Pharmacodynamics. *Anesthesiology*. **90**(6), pp.1502-1516.

Schwaneberg, T., Witt, C.M., Roll, S. and Pach, D. 2019. Comparing physicians' and patients' reporting on adverse reactions in randomized trials on acupuncture—a secondary data analysis. *BMC complementary and alternative medicine*. **19**(1), pp.1-12.

Servin, F., Farinotti, R., Haberer, J.P. and Desmonts, J.M. 1993. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. *Anesthesiology*. **78**(4), pp.657-665.

Shafer, S.L. and Varvel, J.R. 1991. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. **74**(1), pp.53-63.

Shoemaker, M.T., Pierce, M.R., Yoder, B.A. and DiGeronimo, R.J. 2007. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *Journal of Perinatology*. **27**(2), pp.85-91.

Sigl, J.C. and Chamoun, N.G. 1994. An introduction to bispectral analysis for the electroencephalogram. *Journal of clinical monitoring*. **10,** pp.392-404.

Smith, D.A., Beaumont, K., Maurer, T.S. and Di, L. 2015. Volume of distribution in drug design: Miniperspective. *Journal of medicinal chemistry*. **58**(15), pp.5691-5698.

Smith, E. and RCEM Service Design and Configuration Committee. 2018. Consultant staffing in emergency departments in the UK.

Smits, G.J., Kuypers, M.I., Mignot, L.A., Reijners, E.P., Oskam, E., Van Doorn, K., Thijssen, W.A. and Korsten, E.H. 2017. Procedural sedation in the emergency department by Dutch emergency physicians: a prospective multicentre observational study of 1711 adults. *Emergency Medicine Journal*. **34**(4), pp.237-242.

Sonawane, K.B., Cheng, N. and Hansen, R.A. 2018. Serious adverse drug events reported to the FDA: analysis of the FDA adverse event reporting system 2006-2014 database. *Journal of managed care & specialty pharmacy*. **24**(7), pp.682-690.

Søreide, E., Eriksson, L.I., Hirlekar, G., Eriksson, H., Henneberg, S.W., Sandin, R., Raeder, J. and (Task Force on Scandinavian Pre-operative Fasting Guidelines, Clinical Practice Committee Scandinavian Society of Anaesthesiology and Intensive Care Medicine). 2005. Pre-operative fasting guidelines: an update. *Acta Anaesthesiologica Scandinavica*. **49**(8), pp.1041-1047.

Standing Medical Advisory Committee. 1962. Accident and emergency services. *London: HM Stationery Office*.

Staniszewska, S., Brett, J., Simera, I., Seers, K., Mockford, C., Goodlad, S., Altman, D.G., Moher, D., Barber, R., Denegri, S. and Entwistle, A. 2017. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ*. **358**.

Struys, M.M.R.F., De Smet, T., Depoorter, B., Versichelen, L.F., Mortier, E.P., Dumortier, F.J., Shafer, S.L. and Rolly, G. 2000. Comparison of plasma compartment versus two methods for effect compartment–controlled target-controlled infusion for Propofol. *The Journal of the American Society of Anesthesiologists*. **92**(2), pp.399-399.

Struys, M.M.R.F., De Smet, T., Glen, J.I.B., Vereecke, H.E., Absalom, A.R. and Schnider, T.W. 2016. The history of target-controlled infusion. *Anesthesia & Analgesia*. **122**(1), pp.56-69.

Sun, G.C., Hsu, M.C., Chia, Y.Y., Chen, P.Y. and Shaw, F.Z. 2008. Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study. *British journal of anaesthesia*. **101**(5), pp.632-639.

Sustainable Development Unit. 2013. Carbon footprint from anaesthetic gas use.

Taenzer, A.H., Pyke, J., Herrick, M.D., Dodds, T.M. and McGrath, S.P. 2014. A Comparison of Oxygen Saturation Data in Inpatients with Low Oxygen Saturation Using Automated Continuous Monitoring and Intermittent Manual Data Charting. *Anesthesia & Analgesia*. **118**(2), pp326-331.

The Academy of Medical Sciences & Royal Academy of Engineering. 2013. Establishing high-level evidence for the safety and efficacy of medical devices and systems. Available at https://acmedsci.ac.uk/publications (Accessed 26th August 2023).

The Health Foundation. 2017. Desgining and testing 'always events' as a person-centred quality improvement approach in multiple care settings.

Thompson Bastin, M.L., Baker, S.N. amd Weant, K.A. 2014. Effects of Etomidate on Adrenal Suppression: A Review of Intubated Septic Patients. *Hospital Pharmacy*. **49**(2), pp.177-183.

Thorpe, R.J. and Benger, J. 2010. Pre-procedural fasting in emergency sedation. *Emergency Medicine Journal*. **27**(4), pp.254-261.

Tobias, J.D. and Leder, M. 2011. Procedural sedation: A review of sedative agents, monitoring, and management of complications. *Saudi journal of anaesthesia*. **5**(4), p.395.

Van Beuzekom, M., Boer, F., Akerboom, S. and Hudson, P. 2010. Patient safety: latent risk factors. *British journal of anaesthesia*, **105**(1), pp.52-59.

Van de Putte, P. and PERLAS, A. 2014. Ultrasound assessment of gastric content and volume. *British Journal of Anaesthesia*. **113**(1), pp.12-22.

Vargo, J., Howard, K., Petrillo, J., Scott, J. and Revicki D.A. 2009. Development and validation of the patient and clinician sedation satisfaction index for colonoscopy and upper endoscopy. *Clinical Gastroenterology and Hepatology*. **7**(2), pp.156-162.

Vellinga, R., Hannivoort, L.N., Introna, M., Touw, D.J., Absalom A.R., Eleveld, D.J. and STRUYS, M.M.R.F. 2021. Prospective clinical validation of the Eleveld Propofol pharmacokinetic-pharmacodynamic model in general anaesthesia. *British Journal of Anaesthesia*. **126**(2), pp.386-394.

Vinson, D.R. and Bradbury, D.R. 2002. Etomidate for procedural sedation in emergency medicine. *Annals of emergency medicine*. **39**(6), pp.592-598.

Voutilainen, A., Pitkäaho, T., Kvist, T. and Vehviläinen-Julkunen, K. 2016. How to ask about patient satisfaction? The visual analogue scale is less vulnerable to confounding factors and ceiling effect than a symmetric Likert scale. *Journal of advanced nursing*. **72**(4), pp.946-957.

Vućićević, V., Milaković, B., Tesićš, M., Djordjević, J. and Djuranović, S. 2016. Manual versus target-controlled infusion of balanced Propofol during diagnostic colonoscopy–A prospective randomized controlled trial. *Srpski arhiv za celokupno lekarstvo*. **144**(9-10), pp.514-520.

Vuyk, J., Engbers, F.H., Lemmens, H.J., Burm, A.G., Vletter, A.A., Gladines, M.P. and BOVILL, J. G. 1992. Pharmacodynamics of Propofol in female patients. *Anesthesiology*. **77**(1), pp.3-9.

Wade, C.N. 2014. Journal club response. *British Journal of Anaesthesia*. **112**(5), p.939.

Wang, J.F., Li, B., Yang, Y.G., Fan, X.H., Li, J.B. and Deng, X.M. 2016. Target-controlled infusion of Propofol in training anesthesiology residents in colonoscopy sedation: a prospective randomized crossover trial. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*. **22**, p.206.

Wang, Y.C., McPherson, K., Marsh, T., Gortmaker, S.L. and Brown, M. 2011. Health and economic burden of the projected obesity trends in the USA and the UK. *The Lancet*. **378**(9793), pp.815-825.

Ward, D.S., Williams, M.R., Berkenbosch, J.W., Bhatt, M., Carlson, D., Chappell, P., Clark, R.M., Constant, I., Conway, A., Cravero, J. and Dahan, A. 2018. Evaluating patient-centered outcomes in clinical trials of procedural sedation, part 2 safety: sedation consortium on endpoints and procedures for treatment, education, and research recommendations. *Anesthesia & Analgesia*. **127**(5), pp.1146-1154.

Waterlow, J.C. 1976. *Research on Obesity: a Report of the DHSS/MRC Group*. HM Stationery Office.

Weibel, S., Jelting, Y., Afshari, A., Pace, N.L., Eberhart, L.H., Jokinen, J., Artmann, T. and Kranke, P. 2017. Patient-controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour. *Cochrane Database of Systematic Reviews*, (4).

Whitaker, D.K. and Benson, J.P. 2016. Capnography standards for outside the operating room. *Current Opinion in Anesthesiology*. **29**(4), pp.485-492.

Williams, M.R., McKeown, A., Dexter, F., Miner, J.R., Sessler, D.I., Vargo, J., Turk, D.C. and Dworkin, R.H. 2016. Efficacy outcome measures for procedural sedation clinical trials in adults: an ACTTION systematic review. *Anesthesia & Analgesia*. **122**(1), pp.152-170.

Williams, M.R., Ward, D.S., Carlson, D., Cravero, J., Dexter, F., Lightdale, J.R., Mason, K.P., Miner, J., Vargo, J.J., Berkenbosch, J.W. and Clark, R.M. 2017. Evaluating patient-centered outcomes in clinical trials of procedural sedation, part 1 efficacy: sedation consortium on endpoints and procedures for treatment, education, and research recommendations. *Anesthesia & Analgesia*. **124**(3), pp.821-830.

Wilson, M.J.A., MacArthur, C., Hewitt, C.A., Handley, K., Gao, F., Beeson, L. and Daniels, J. 2018. Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial. *The Lancet*. **392**(10148), pp.662-672.

World Health Organization. 2002. *Safety of medicines: a guide to detecting and reporting adverse drug reactions: why health professionals need to take action*. World Health Organization.

Worster, A., Rowe, B.H,, Stiell, I.G., Borgundvaag, B., Silvotti, M.L., Campbell, S.G., Fernandes, C.M., Mackey, D.S., Woolfrey, K., Abu-Laban, R.B. and Lee, J.S. 2005. Clinical research in the emergency department conducted by non emergecny physicians: potential problems and proposed recommendations. *Canadian Journal of Emergency Medicine*. **7**(4), pp.241-248.

Yamamura, T., Fukuda, M., Takeya, H., Goto, Y. and Furukawa, K. 1981. Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man. *Anesthesia & Analgesia*. 60(5)**,** pp.283-288.

Zheng, B., Kwok, E., Taljaard, M., Nemnom, M.J. and Stiell, I. 2020. Decision fatigue in the Emergency Department: How does emergency physician decision making change over an eight-hour shift? *The American Journal of Emergency Medicine*. **38**(12)**,** pp.2506-2510.