Prospective clinical validation of the Eleveld pharmacokinetic and pharmacodynamic model of propofol for procedural sedation in adults.
< Research Register number …..>
(non-WMO study protocol)

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CONTENT

1. STUDY ORGANIZATION

Study title	Prospective clinical validation of the Eleveld pharmacokinetic and pharmacodynamic model of propofol for procedural sedation in adults.
Planned start date	<01-01-2024>
Estimated completion date	<01-01-2025>
Project leader (UMCG or external)	
(Principal) investigator UMCG	
Researcher(s) UMCG	•
Corresponding researcher UMCG	
(Principal) investigator other centers	NA
Sponsor (in Dutch: verrichter/opdrachtgever)	UMCG
Financial support/subsidising party	• NA
Collaboration with non-profit Laboratory / research sites (in- and outside UMCG)	• NA
Collaboration with commercial parties / companies (in- and outside UMCG)	NA or
Name bio- or databank and bankmanager	NA
Name previous study ('FAIR data') and (principal) investigator	NA

2. PROTOCOL SIGNATURE SHEET

The undersigned (Principal) investigator and head of department UMCG confirm that the study and its procedures will comply with the present study protocol and the nWMO Kaderreglement UMCG. Without ethical approval the data/biomaterials will not be used for other (research) purposes (e.g. 'FAIR data').

Name	Signature	Date
(Principal) investigator UMCG:		2-11-2023
Head of the department UMCG:		2-11-2023

3. ABSTRACT

- **Background**
  Propofol is the preferred drug of choice for procedural moderate to deep sedation. This can be titrated by using pharmacokinetic (PK) and pharmacodynamic (PB) models programmed in infusion pumps for target controlled infusion (TCI). In 2021 Vellinga et al published a study on the validation of the Eleveld model in patients undergoing general anesthesia. (Vellinga et al. 386-394) So far, the Eleveld model has not been externally validated for the use of procedural sedation in adult patients.
- **Main research question**
  The primary objective is to identify effect-site target concentrations of propofol for the Eleveld model that is associated with procedural sedation; a modified observer's assessment of alertness and sedation (MOAAS) score 5-1 and the associated depth- of- anesthesia monitor parameter levels in adult patients. The secondary outcome is the time to reach MOASS 5 representing fully awake after having stopped propofol infusion using the Eleveld model.
- **Design (including population, confounders/outcomes)**
  Prospective observational study of adult patients undergoing procedures under sedation by using the Eleveld model for propofol. Descriptive statistics in SPSS.
  Expected results
  To have identified effect site concentrations (CET) of propofol using the Eleveld model for different levels of procedural sedation.

4. BACKGROUND

- **Introduction and rationale**

  - Since the Dutch guideline on procedural sedation outside of the operating room in 2012[1] has been published, procedural sedation practices in Dutch hospitals has taken a huge flight. Propofol is the preferred drug of choice for moderate to deep sedation. This can be titrated by using pharmacokinetic (PK) and pharmacodynamic (PB) models programmed in infusion pumps for target controlled infusion (TCI). Several PKPD models for TCI propofol are available. While most TCI systems incorporate PK or PKPD models for specific patient groups such as adults, children or older patients, the Eleveld model has been developed for TCI of propofol for general anesthesia and sedation in a broad range of patients.[2] In 2021 Vellinga et al published a study on the validation of the Eleveld model in patients undergoing general anesthesia.[3] So far, the Eleveld model has not been externally validated for the use of procedural sedation in adult patients. The aim of this study is to identify effect-site target concentrations of propofol for the Eleveld model that are associated with moderate to deep sedation levels, MOAAS 5-1 and the associated BIS levels in adult patients.[4] The secondary outcomes are: time to introduction of the endoscope and the time to reach MOAAS 5 after having stopped TCI propofol. The use of vasopressors such as ephedrine, phenylephrine or norepinephrine. The need for airway maneuvers such as chin lift, jaw thrust or nasopharyngeal airway.

- **Research question**

  Primary outcome
  To identify CET propofol using the Eleveld model for different levels of procedural sedation as measured by MOAAS and EEG monitoring.

  Secondary outcomes

  - Relevant clinical endpoints i.e. time to introduction of the endoscope, the time to reach MOAAS 5 after having stopped TCI propofol.
  - The use of vasopressors such as ephedrine, phenylephrine or norepinephrine.
  - The need for airway maneuvers such as chin lift, jaw thrust or nasopharyngeal airway.

5. METHOD

5.1 Description study design

This is a prospective observational study. Adult patients undergoing sedation for endoscopic procedures in the UMCG between 01-01-2024 and 01-01-2025 will be included. Written informed consent will be obtained prior to the procedure. Exclusion criteria are: age <18 years, the use of esketamine during the procedure, the use of benzodiazepines prior or during the procedure, hearing disability and a BIS quality index < 50.

Monitoring

All patients will be monitored according to the departmental protocol[5] (https://umcg.zenya.work/portal/#/document/217c7341-ad32-4655-b2e7-6e49665e8869) with a Philips IntelliVue MP30 monitor (Philips Medizin Systeme Boeblingen GmbH, Boeblingen). This consists of continuous 3-lead electrocardiogram (ECG), peripheral hemoglobin oxygen saturation (SpO_2), respiration rate, end-tidal carbon dioxide concentration ($etCO_2$) using a Medtronic Microstream™ Advance Adult Oral-Nasal CO_2 Filter Line, noninvasive blood pressure (NIBP) with a measurement interval of 5 minutes.

Dose-response relationship will be determined with a depth-of-anesthesia-monitor as per the department's standard protocol for sedation. Depth of sedation will be monitored using non-invasive monitoring (BIS® monitor (BIS Vista, Medtronic, Boulder, CO, USA and Masimo Root with Sedline® Masimo Irvine, CA). The Modified Observer's Assessment of Alertness and Sedation score (MOAAS score) will be noted every 10 minutes and is used to record the depth of sedation. All data from the vital signs monitor and infusion pumps will be automatically stored in an electronic medical record system (Epic Systems corporation, 1979 Milky Way, Verona, WI).

Sedation protocol

Sedation will be administered using Target-Controlled Infusions (TCI) of propofol (administered by effect-site TCI using the Eleveld model) and remifentanil (administered by effect site TCI using the Eleveld model). Target controlled infusion of propofol and remifentanil is according the departmental protocol (https://umcg.zenya.work/portal/#/document/217c7341-ad32-4655-b2e7-6e49665e8869). TCI propofol will be administered by stepwise increasing effect-site targets until the desired depth of sedation has been reached as per clinical practice.

5.2 Design

5.2.1 Mono- or multicenter study	Mono-center study yes	Multicenter study
<text>		
5.2.2 Retrospective study (available data/ biomaterials only) or prospective study (data/ biomaterials from [some] participants will be collected in the future).	Retrospective study No **skip** **Sections 5.4.2/5.5.6**	Prospective study Yes **skip** **Sections 5.4.1**
<text>		
5.2.3 Cross-sectional or follow-up study	Cross-sectional study yes	Follow-up study
<text>		
5.2.4 Quantitative or qualitative study (click both if mixed-method)	Quantitative study yes	Qualitative study
<text>		
5.2.4 Pilot study	No	
<text>		

5.3 Population

5.3.1 Inclusion and exclusion criteria	
• Inclusion criteria: Adult patients for procedural sedation in the UMCG between 01-01-2024 and 01-01-2025. • Exclusion criteria: age <18 years; use of esketamine during the procedure, use of benzodiazepines prior or during the procedure, hearing disability, BIS quality index < 50	
5.3.2 Number of participants	
• Target total number of participants: 75 sample size based on previous literature Vellinga et al. • Target number of UMCG participants: three groups of 25 patients; patients age ≥ 18- <65, patients age ≥ 65 and over, patients BMI ≥ 30.	
5.3.3 Study subjects (tick all that apply)	
• Healthy volunteers • Patients	no yes
<text>	
5.3.4 Subject classification (tick all that apply)	
• Participants ≥ 16 years • Children between 12 and 16 years *(if applicable, written informed consent will be obtained from child and both parents - if both have authority, or guardian [or parents/guardian only if incapacitated child])* • Children < 12 years *(if applicable, written informed consent will be obtained from both parents - if both have authority, or guardian)*	yes no no
<text>	
5.3.5 Incapacitated adults	
Participants are incapacitated/ decisionally incompetent adults *(if applicable, written informed consent will be obtained from legal representative)*	no
<text>	

5.4 Recruitment and informed consent/objection

5.4.1	Retrospective study (tick all that apply) ☒ Not applicable (see section 5.2.2) ☐ Data will be copied from (electronic) patient records (e.g. 'EPD UMCG') • Informed consent is not feasible for this number of patient records. ○ Total number of participants who will not be asked informed consent for screening: 50000 ○ Total number of UMCG participants who will not be asked informed consent for screening: 50000 • Informed consent is not feasible for this number of patient records. ○ Total number of participants who will not be asked informed consent: 50000 ○ Total number of UMCG participants who will not be asked informed consent: 50000 ☐ Data/biomaterials will be obtained from an already existing internal or external (UMCG/non-UMCG) bio- or databank (see Section 1. Study organization). <text> ☐ Data/biomaterials will be obtained from a previous study ('FAIR data' - internal/external; see Section 1. Study organization). <text>
5.4.2	Prospective study ☐ Not applicable (see section 5.2.2)

	<text>
5.4.3 Objection (Registry)	
in case one or more participants will not be asked informed consent, the objection registry will be checked for these participants and the data from those who objected will be excluded from the analyses.	yes
<if no, give reasons>	
5.4.4 Informed consent (IC): access to identifiable participant data	
in case one or more study team members will have access to direct/indirect identifiable participant data, informed consent will be/has been obtained for this access.	yes
<if no, explain>	
5.4.5 IC: Collaboration with commercial parties	
In case of collaboration with commercial/profit organizations, informed consent will be/has been obtained for this type of collaboration	NA
<if no, explain>	
5.4.6 IC: Linking with other registries	
In case the data will be linked with other registries, informed consent will be/has been obtained for this linkage(s)	NA
<if no, explain>	
5.4.7 IC: Incidental findings	
In case there is a risk of incidental findings, informed consent will be/has been obtained to return findings to the participant	NA
<text>	
5.4.8 IC: FAIR Data	
In case data collected for the present study will be shared for future studies, informed consent will be obtained for this	yes
<if no, please explain>	
5.4.9 IC: other aspects	
NA or <other relevant aspects of the study for which informed consent will be/has been obtained>	
5.4.10 Withdrawal	
• Can participants withdraw informed consent before publication and will all data/ biomaterials of that participant be destroyed • Does the participant information letter contain information on how to withdraw	yes yes
<if no, please explain>	

5.5 Research Data Management Plan (RDMP)

In this study the data will be collected, processed, and archived in accordance with the General Data Protection Regulation (GDPR) and the FAIR (Findable, Accessible, Interoperable, Reusable) principles under the responsibility of the Principal Investigator. A research data management plan (RDMP) <has been/will be> drawn up to describe the further operational details and procedures. <For details on the RDMP please find the RDMP enclosed in the Appendix>	
The RDMP section below is completed	
5.5.1 Data collection	
• Only essential baseline characteristics and data required to answer the research question(s) will be collected.	yes
Primary outcome:	

• Tooling (eg. software and procedures) used for collecting, processing, analysing, and storing data will be compliant with the UMCG policy and Standard Operating Procedures in the UMCG Research Toolbox.		yes
<if no, explain>		
5.5.2 Anonymization and pseudonymization		
• Data will be anonymised during data collection (i.e. data cannot be linked back to the participant)	Yes **skip section 5.5.2**	
<if no, explain why it is not possible to anonymise the data during collection>		
• Data will be pseudonymized by use of <a code list/an encryption key> during data collection.		yes/no
<if no, explain>		
• Indirect and direct identifiable information collected will be minimized and only collected for the purpose of this study		yes/no
<if no, explain why you collect more information>		
• Direct identifiable information (e.g. contact details, code list/encryption key/subject identification log) will be stored separately from pseudonymized data <in the electronic patient files (EPD), in an electronic file, on paper in the study file, other>		yes/no
<if no, explain>		
5.5.3 Data access (during the study)		
• Direct identifiable information can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.		yes
<if no, explain>		
• Pseudonymized/anonymized data can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.		yes
<if no, explain>		
• Data roles, responsibilities, access and authorization - during the study and after study completion - will be managed and documented (e.g. in the RDMP, on study delegation log).		yes
<if no, explain>		
5.5.4 Data sharing (during and after study completion)		
In case data (and biomaterials) will leave or enter the UMCG, will you contact the loket Contract Research to arrange the proper contracts? (Loket_Contract_Research@umcg.nl)		NA
<if no, explain>		
5.5.5 Data storage (during and after study completion)		
• Digital data will be archived on the UMCG network complying with strict UMCG security and back-up policy.		yes
<if no, explain>		
• Paper source data and study files will be archived within the UMCG facilities.		yes
<if no, explain>		
• Source data, study files and digital data will be stored 15 years after the study is completed.		yes
<If no, explain and give number of years>		
5.5.6 Data re-use and access after completion of the present study ('FAIR data')		

• Data will become available and shared for re-use and participants will be asked informed consent for this ('FAIR data') FAIR data is the UMCG policy. If no is chosen, an explanation is required	no ***specify and explain when no is chosen*** **and then skip section 5.5.6**
<if no, specify and explain>Not applicable	
• Data will be made findable by including the description of the study (and type of data (i.e. metadata) in the UMCG FAIR data catalogue and other discipline specific catalogue(s).	no
<if no, explain> Not applicable	
• Review procedure, conditions and agreements for re-use of data and access to data by other researchers will be drawn up.	yes
<if no, explain>	
• For this study a discipline specific metadata standard will be chosen (i.e. to increase interoperability and re-use).	no
<if no, explain> Not applicable	

5.6 Management of biomaterials

Will biomaterials be collected, processed, analyzed and/or stored for the purpose of this study		No **skip section 5.6**
<text>		
5.6.1 Retrospective study (see sections 1, 5.2.2, and 5.4.1) If biomaterials will be used from a secondary/further use biobank that has not been approved by the Board of Directors of the UMCG, how will be prohibited that biomaterials necessary for future diagnostic/treatment purposes will be used in the present study.		NA ☐
<text>		
5.6.2 Biomaterials collection		
• Only biomaterials required to answer the research question(s) will be collected		yes/no
• What biomaterials will be collected <text>		
• How will the biomaterials be collected and processed <text>		
5.6.3 Pseudonymization and access to biomaterials		
• Does the storage unit of the biomaterials comprise information that the participant (in)directly identifies, other than the participant's number and / or the sample number.		yes/no
<if yes, explain>		
• Biomaterials can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator		yes/no
<if no, explain>		
5.6.4 Sharing of biomaterials (during and after study completion)		
In case biomaterials (and data) will leave the UMCG, will you contact the loket Contract Research to arrange the proper contracts? (Loket_Contract_Research@umcg.nl)		NA/yes/no
<if no, explain>		
5.6.5 Biomaterials storage (during and after study completion)		
• Where and how will the biomaterials be stored <text>		
• Biomaterials will be stored 15 years after the study is completed		yes/no
<If no, explain and give number of years>		
• What will be done with the remaining biomaterials after study completion (eg. destroyed, returned to biobank/previous study, stored) <text>		
5.6.6 Biomaterials re-use and access after completion of the present study		NA ☒ **skip section 5.6.6**
• Biomaterials will become available and shared for re-use and participants will be asked informed consent for this ('FAIR data')		yes/no
<if no, specify and explain>		
• Biomaterials will be made findable by including the description of the study (and type of biomaterials in the UMCG FAIR data catalogue and other discipline specific catalogue(s).		yes/no

<*if no, explain*>	
• Review procedure, conditions and agreements for re-use of biomaterials and access to biomaterials by other researchers will be drawn up.	yes/no
<*if no, explain*>	

5.7 Burden, Risks & Benefits (Prospective studies only)

• If participants are patients: Can be deviated from the standard care / diagnostic procedures (e.g. can medical treatment be postponed or limited)			NA
<text>			
• Burden <text>			
• Will the participants risk any injuries and/or other discomfort when they participate in the proposed study	Yes, minimal risk/burden ☐	Yes, more than minimal risk/burden ☐	No ☒
<text>			
• Participant benefits/reward/incentives: <text>			

5.8 Incidental findings

• Is there a risk of incidental findings?	yes, minimal risk ☐	yes, ≥ substantial risk ☐	No ☒
<text>			
If yes, ○ Procedure to assess if a finding should be returned to the participant, or not <text> ○ Procedure to inform the participant <text>			

5.9 Data analysis

- Justification of sample size (e.g. power analysis)
- Convenience sample size based on pre lit Vell
- Statistical analysis: Describe in detail the statistical analysis used to test the research question.
- **Only descriptive statistics will be used**

5.10 Participant information after the study

Will participants be informed about the study results	no
<text>	

5.11 Research revenue

In case the study will result in revenues (e.g. as a result of the use of data/biomaterials or successful licensing of intellectual property or manufactured products), will you contact the loket Contract Research to arrange the proper contracts?	NA
<if no, explain>	
Describe what will be done with the revenues. <text>	

6. REFERENCES

1. Richtijn Sedatie en/of analgesie (PSA) op locaties buiten de operatiekamer. Deel I: bij volwassen en deel II: op intensive care. Kwaliteitsinstituut voor de Gezondheidzorg CBO 2009.

2. Eleveld D J, Colin P, Absalom A R, Struys M M R F. Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation. Br J Anaesth, 2018;120:942-59

3. Vellinga R, Hannivoort L N, Introna M, Touw, Daan J, Absalom A R; Eleveld D J, Struys M M R F. Prospective clinical validation of the Eleveld propofol pharmacokinetic-pharmacodynamic model in general anaesthesia. British Journal of Anaesthesia, 2021; 126 (2): 386-394

4. Xi C, Sun S, Pan C, Ji F, Cui X, Li. TDifferent effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: Wakefulness, moderate sedation, deep sedation and recovery. . PLoS ONE 13(6): e0199120. https:// doi.org/10.1371/journal.pone.0199120

5. Sedatie door physician assistant of sedatie praktijk specialist (versie 4). https://umcg.zenya.work/portal/#/document/217c7341-ad32-4655-b2e7-6e49665e8869