COVER PAGE

OFFICIAL TITLE

Evaluation of safety and efficacy of non-anesthesia provider-administered different anesthetic regimens during colonoscopy: a single center, prospective double blind, randomized study

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Site: King Saud Hospital, Unaizah, Qaseem, Saudi Arabia

Short title: Sedation during Colonoscopy procedures

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1. Summary and Synopsis:

- **Short title:** Sedation during colonoscopy procedures
- **Methodology:** Single center, prospective randomized, double blinded
- **Research sites:** King Saud Hospital, Qaseem, Kingdom of Saudi Arabia
- **Objectives:** To evaluate safety and efficacy of non-anesthesia provider-administered different anesthesia regimens for sedation during colonoscopy procedures
- **Number of participants: 157**
- **Inclusion and exclusion criteria:**
    1. **Inclusion criteria:**
        - Adults 18 -60 years of age
        - Both Genders
        - Indication of colonoscopy procedure without advance intervention
        - American Society of Anesthesiologist physical status I or II
        - Competent to give informed consent
    2. **Exclusion criteria:**
        - Personal history of allergic reaction or other contra-indications to midazolam, propofol or fentanyl
        - Age below 18 or above 60 years
        - Chronic use of benzodiazepines
        - American Society of Anesthesiologist physcial status III or above
        - Pregnancy
        - History of smoking or alcohol abuse
        - Body mass index > 35 kg/m^2
        - History of airway obstruction or difficult intubation

2. Statistical methodology:

Descriptive statistics will be used to assess the demographic and clinical characteristics of the 3 groups. Continuous variables will be presented by mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. Qualitative variables will be presented by numbers and percents. For univariate analysis, ANOVA test will be applied for continuous variables. Categorical data will be analysed using the chi-square or Fisher's exact tests. For multivariate analysis, Regression analysis will be employed for analyzing the relationship between variables and to adjust for potential confounding factors. In all tests, p value would be considered significant if less than 0.05**.**

- **Sample size is calculated by ANOVA F test.** Fixed effects, omnibus, one-way Analysis: A priori: Compute required sample size Input: Effect size f = 0.25 α err prob = 0.05 Power (1-β err prob) = 0.80 Number of groups = 3 Output: Total sample size = 157
- **Study duration:** December 2024 till completion of the sample size.

2. Introduction:

Colonoscopy is one of the most common procedures in the world and it is commonly performed outpatient method for the diagnosis and treatment of colorectal disorders (1-3). It is an invasive and short-lasting procedure that can cause pain, anxiety, restlessness and rarely vasovagal reactions. Sedation and analgesia can improve experience for both patients and endoscopist and are usually required for successful completion of the procedure (3). Globally, there are certain variations in sedative practices and the regimens used vary by geographic regions and even within same countries (4-6).

The combination of benzodiazepines with short-acting opioids for achievement of proper sedation is in practice since 1980. Short-acting opioids such as fentanyl have been widely used in combination with midazolam for sedation during colonoscopy as both can be administered by endoscopists or nurses without help of anesthesia professional and easily reverted if required (7-10). Over the past fews years, the use of propofol - a

sedative, hypnotic drug- has been increased worldwide due to its rapid onset of action, short recovery time and lesser post operative nausea and vomiting (11, 12). However, the use of propofol alone may require higher doses, which leads to increased incidence and severity of side effects. Propofol has been evaluated in combination with benzodiazepines such as midazolam, and/or short- acting opioids (fentanyl), but there is no clear evidence as to which regimen is better and safer (13). For patients undergoing colonoscopy, the combination regimen of propofol-fentanyl or propofol-midazolam have been used in multiple centers with successful completion of procedure and patient satisfaction (14-16). However, adding sedatives and analgesics to propofol have their own risks and benefits and the selection of drugs is a critical factor in predicting the outcomes (17). Irrespective of the drug administered to achieve sedation, anesthesia during colonoscopy is linked to potential complications like hypoxia, respiratory depression, circulatory depression, postoperative nausea and vomiting and irregular heartbeats (10, 18, 19).

Despite the rise in use of propofol alone or in combination with benzodiazepines or short-acting opioids, few studies have been conducted to compare and evaluate the effectiveness of these regimens. In certain specific conditions like IBD, colonoscopy with deep sedation like propofol gives good outcome in terms of endoscopist as well as patients satisfaction in perspective that IBD patients are mostly young and very sensitive. (20) We plan to conduct a prospective randomized study to compare 3 sedative groups (1) midazolam + fentanyl (2) propofol alone (3) propofol + fentanyl in patients undergoing elective colonoscopy. All the colonoscopies will be performed by experienced endoscopist including consultants and senior specialists. The present study aims to compare the safety and effectiveness of different anesthesia regimens to achieve sedation during colonoscopy.

3. Objectives:

To evaluate safety and efficacy of non-anesthesia provider-administered different anesthesia regimens for sedation during colonoscopy procedures.

4. Methodology:

Selection criteria for study population:

Adults (18 -60 years of age) with indications of colonoscopy who will present at the out-patient department of gastroenterology at King Saud Hospital, Unaizah, Saudi Arabia between December 2024 till completion of the sample size. Following will be the inclusion and exclusion criteria for participation in the study.

1. **Inclusion criteria:**
    - Adults 18-60 years
    - Both Genders
    - Indication of colonoscopy procedure without advance intervention
    - American Society of Anesthesiologist physical status I or II
    - Competent to give informed consent

2. **Exclusion criteria:**
    - Personal history of allergic reaction or other contra-indications to midazolam, propofol or fentanyl
    - Age below 18 or above 60 years
    - Chronic use of benzodiazepines
    - American Society of Anesthesiologist physcial status III or above
    - Pregnancy
    - History of smoking or alcohol abuse
    - Body mass index > 35 kg/m^2
    - History of airway obstruction or difficult intubation

5. Study Design:

A randomized, double-blinded prospective study will be performed at the department of Gastroenterology, Kind Saud Hospital, Unaizah, Qassim, Saudi Arabia, from 1st May 2024 till the completion of the sample size. The study approval will be sought from the Hospital Research Ethics Committee and then ethics committee of the Ministry of Health –Qassim cluster. Patients fulfilling the inclusion criteria who present at the out-patient department of gastroenterology with an indication for elective colonosocpy will be included in this study. Informed consent will be taken from the participants in study after giving them full information about the study project including benefits and possible side effects of the study.

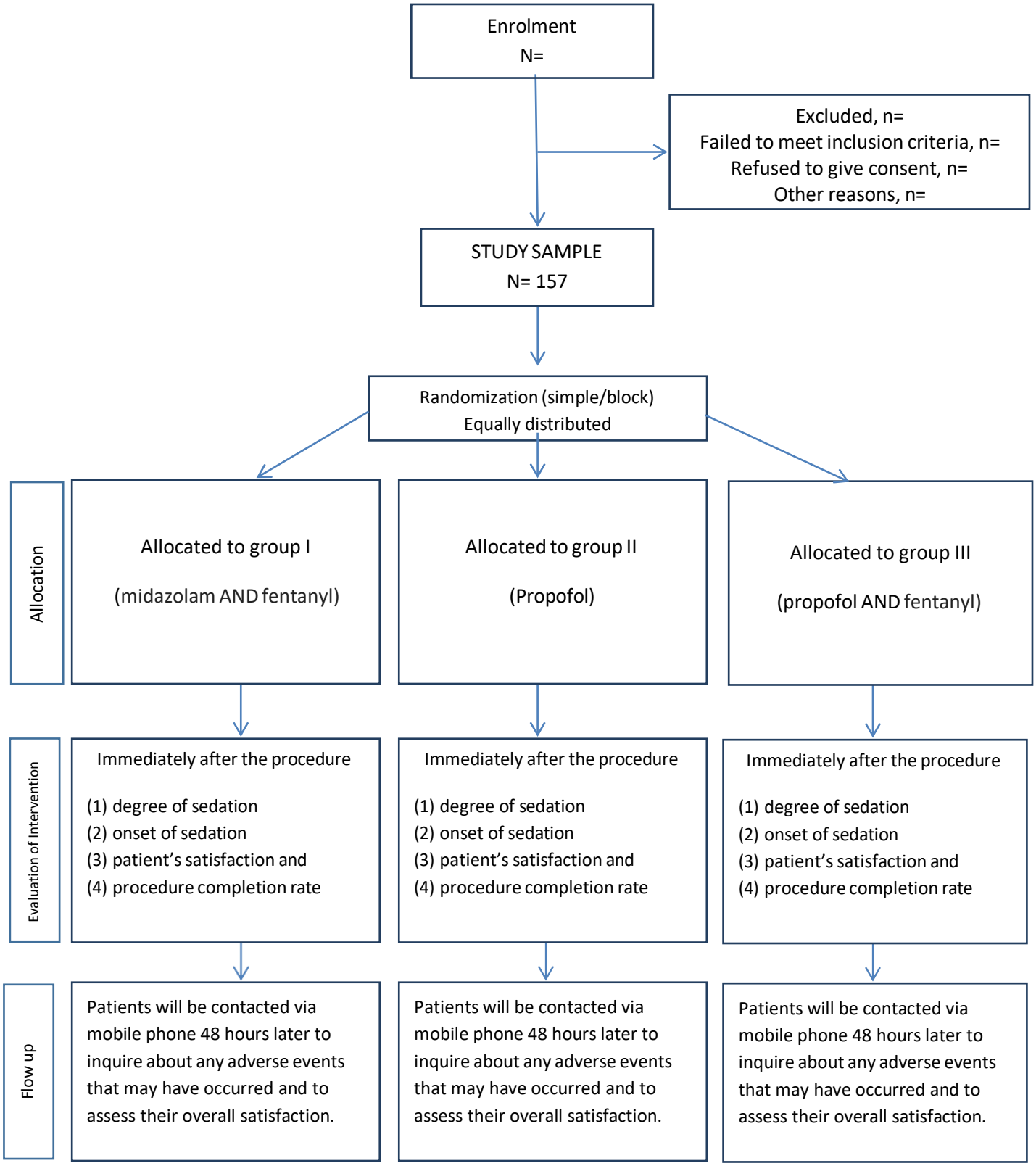
All patients who will undergo colonoscopy with above-mentioned inclusion criteria in the Endoscopy unit from December 2024 till completion of the sample size will be enrolled. Total Sample size calculated by F test ANOVA is 157 as described above. All consecutive patients fulfilling the criteria will be enrolled in the study. After enrolment, patients will be allocated into 3 groups by simple randomization using computer-based Excel spreadsheet. (See flow chart). A separate nurse/doctor will be responsible for the preparation and administration of different sedative regimens. The study participants, endoscopist and principal investigator will be blinded regarding the allocation of patients and medication administration. To ensure patients' safety, colonoscopy procedures involving propofol administration by endoscopists or trained nurses will be conducted under the supervision of an anesthesiologist. The groups will be assigned to three different sedative regimens. Group I will receive intravenous midazolam + fentanyl, Group II participants will receive propofol only, while Group III patients will receive fentanyl + propofol. Dosage of each drug will be titrated according to response and need during the colonoscopy procedure. While there are no standard guidelines on the dose of propofol for sedation in endoscopy (21), a number of studies have used the following doses of the two drugs with very good safety profile. In a study from Venezuela by Ruiz-Curiel RE et al involving a total of 70,696 digestive endoscopy procedures, the incidence of complications was very low. Assisted ventilation with a

mask was required on 78 (0.11%) occasions. In this study propofol was administered by gastroenterologist in an induction bolus of 10 to 50 mg, continuing with intermittent boluses of 10 to 20 mg, according to the patients' response. (22) A study from Japan spanning almost 10 years with nurse-administered propofol sedation (NAPS) demonstrated promising results and a very good safety profile in patients undergoing diagnostic EGD (n = 117,661) or colonoscopy (n = 32,550) from January 2006 through December 2016. The only adverse event was the transient need for supplemental oxygen supply, required by 1950 patients (1.3%): 1689 undergoing EGD (1.4%) and 261 undergoing colonoscopy (0.8%). The median dose of propofol administered for EGD was 77 mg (range, 20–160 mg) and for colonoscopy was 99 mg (range, 40–200 mg). The maximum dose allowed was up to 200 mg (23). Lowest possible doses of these drugs will be administered in the present study to ensure safety. In our study propofol will be administered as intermittent boluses, with an induction dose of 20-50 mg followed by intermittent boluses of 10-20 mg according to the patient's response, with a maximum total dose of 200 mg. (table1). It has been observed that adding opioids like fentanyl to propofol reduces the required dose of propofol to achieve the same level of sedation. Megan E. et al. in one study demonstrated the same (26) (Table1).

Table1. Sedative drugs and dosages (22-27)

DRUG	DOSE	COMMENTS
Midazolam + Fentanyl (Group I)	Initial dose: midazolam 0.5–1 mg + fentanyl 12.5–75 µg Additional dose: midazolam 1 mg (2–3 min), fentanyl 12.5–50 µg (1–3 min)	Midazolam initially 0.015-0.03 mg/kg IV. May repeat with 25% of initial dose after 3-5 min Maximum 6 mg Fentanyl: .5-1 ug/kg IV over 2-3 minutes initially May repeat after 5-10 minutes (maximum 100 ug)
Propofol (Group II)	induction dose of 20-50 mg followed by intermittent boluses of 10-20 mg according to the patient response with maximum total dose of 200 mg	Maximum dose 200 mg
Propofol + Fentanyl (Group III)	Initial bolus of propofol 10–20 mg, followed by boluses of 5–10 mg according to the patient response Fentanyl 12.5–75 µg IV over 2-3 minutes. May repeat 12.5-50 ug	Maximum dose 200 mg Maximum 100 ug

FLOW CHART


Enrolment
N=
Excluded, n=
Failed to meet inclusion criteria, n=
Refused to give consent, n=
Other reasons, n=
STUDY SAMPLE
N= 157
Randomization (simple/block)
Equally distributed
Allocation
Allocated to group I
(midazolam AND fentanyl)
Allocated to group II
(Propofol)
Allocated to group III
(propofol AND fentanyl)
Evaluation of Intervention
Immediately after the procedure
(1) degree of sedation
(2) onset of sedation
(3) patient's satisfaction and
(4) procedure completion rate
Immediately after the procedure
(1) degree of sedation
(2) onset of sedation
(3) patient's satisfaction and
(4) procedure completion rate
Immediately after the procedure
(1) degree of sedation
(2) onset of sedation
(3) patient's satisfaction and
(4) procedure completion rate
Flow up
Patients will be contacted via mobile phone 48 hours later to inquire about any adverse events that may have occurred and to assess their overall satisfaction.
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All participants will be monitored by assigned nurses for vitals, oxygen saturation, ECG and noninvasive blood pressure before, during and post procedure. Colonoscopy will be performed by experienced endoscopists. All patients will be evaluated by assigned physican before going for colonoscopy. It will include hisory, physical examination and noting down for any allergy, comorbidities and ASA class. Following data elements will be collected: age, gender, weight and height of patients, indication of the procedure, total examination time, time to colonoscope into the cecum, dose of sedative drug as metnioned above, changes in blood pressure and oxygen saturation. Any side effects will be noted during or after the procedure. Adverse events were defined as follows: (1) hypotension was defined as a mean arterial pressure < 70 during the procedure and a 25% drop from the presedation baseline. (2) Tachycardia was defined as a heart rate during the procedure >100 and a 25% increase from presedation baseline, (3) bradycardia was defined as a heart rate <60 during the procedure and a 25% drop from the presedation baseline, (4) hypoxia was defined as a desaturation to <90% during the procedure with a concomitant increase in supplemental oxygen. (26)

6. Outcome measures

The primary outcome measures would be (1) degree of sedation (2) onset of sedation (3) patient's satisfaction and (4) procedure completion rate. Degree of sedation will be assessed by observer's assessment of alertness/sedation (OAA/S) scale. Details are given in data collection sheet. The onset of sedation will be documented as "the duration it takes for the patient to exhibit drowsiness and reduced responsiveness following the administration of the sedative medication". Secondary outcome measures will include adverse events, recovery time, and endoscopist's satisfaction. Regarding adverse events, risk matrix sheet is attached with for each drug separately. The time to recover from sedation will be assessed every 10 minutes after the procedure using the Aldrete score. Aldrete score of 10 will be considered as full recovery and time will be noted from completion of the procedure till full recovery (27). Patient can be discharged 10 minutes after achieving Aldrete score of 10. The satisfaction of both, the endoscopist

and the patient, will be evaluated at the end of the procedure with 0 being dissatisfied and 10 being extremely satisfied.

7. Statistical considerations:

Descriptive statistics will be used to assess the demographic and clinical characteristics of the 3 groups. Continuous variables will be presented by mean with standard deviation (SD) or median with interquartile range (IQR) when appropriate. Qualitative variables will be presented by number and percent. For univariate analysis, ANOVA test will be applied for continuous variables. categorical data will be analysed using the chi-square or Fisher's exact tests. For multivariate analysis, Regression analysis will be employed for analyzing the relationship between variables and to adjust for potential confounding factors. In all tests, P-value of less than 0.05 will be considered statistically significant. SPSS version 23 will be used for the analysis of data.

Interim Analysis

Interim analysis will be done by safety and monitoring board intermittently at completion of 25%, 50% and 75% of the study. Study will be stopped if significant difference is observed in different groups.

8. Ethical considerations:

The study will be conducted in accordance with the Declaration of Helsinki and the guidelines of the International Conference on Harmonisation. After approval from Hospital ethical committee, the study protocol will be submitted for approval to the ministry of Health-Qassim local ethics committee. All the data will be de-identified and only after de-identification, data will be analysed to ensure data safety and confidentiality. The data will only be accessible to approved personnel involved in the study.This data will be kept secure and protected by password. Nor the identity neither the personal information will be revealed in the research publication.

9. Data handling and record keeping:

Data Collection will be done by manual recording and subsequently transcribed to an electronic excel sheet. A separate doctor will be assigned to fill the data sheet of the participants with all details mentioned in the data collection sheet. All the manual recorded sheets will be kept in a locked and secure place. And its electronic form will be recorded and protected with secure password protected files.

10. Confidentiality:

The Principal Investigator and designees, employees and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy and security of a participants' health information.

11. Record Retention and Archiving:

Original source documents, study records, and reports will be maintained by the investigator for a period of ten years after the investigation is terminated or completed. This record will not be shared and will be kept safe and protected.

12. Safety reporting

Any adverse events that occur during the study that the investigator believes are serious and qualify as either an unanticipated adverse device effect OR are related to study-specific procedures as defined must be immediately (but at least within 24 hours) reported to local hospital administration and healthcare body. The local Institutional Review Board will also be informed in a timely manner. The investigator will then submit a detailed written report to the Institutional Review Board no later than 5 days after the investigator discovers the event. PI will be responsible for reporting any reportable serious, unexpected, study-related adverse events from this study to the applicable regulatory agencies.

- Adverse Events (AEs): An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention.

An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

- Adverse Reaction (ARs): An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions.
- Notification and reporting of Adverse Events and Reactions: If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants' source documents, the Case Report Form (CRF), and, where appropriate, medical records.
- Serious Adverse Events (SAEs) or reactions: A serious adverse event (SAE) is defined as an untoward occurrence that:
    - Results in death,
    - Is life-threatening,
    - Requires hospitalisation or prolongation of existing hospitalisation,
    - Results in persistent or significant disability or incapacity,
    - Consists of a congenital anomaly or birth defect, or
    - Is otherwise considered medically significant by the investigator.

- SARs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and: ***Related*** (it may have resulted from administration of any of the research interventions), and ***Unexpected*** (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

- Notification and reporting of Serious Adverse Events Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor or PI within 24 hours of learning of the event, and to the REC within 15

days in line with the required timeframe. The treatment code for the participant will be broken when reporting an 'unexpected and related' SAE. The un-blinding of individual participants by the PI in the course of a clinical study will only be performed if necessary for the safety of the study participant.

- Urgent Safety Measures: The PI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the PI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately. The PI will inform the REC in writing within 3 days, in the form of a substantial amendment.

Overview of the Safety Reporting responsibilities: The PI is the medical assessor on behalf of the sponsor and will review all events reported. The PI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

13. Finance and Funding:

- None declared.

14. Conflict of interests:

- None declared.

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