Visual and Auditory Hallucinations after Cardiac Surgery (VAACS)

Study Protocol (Part 1)

Project Summary

Background: Postoperative hallucinations are a distinct but underrecognized neuropsychiatric complication following cardiac surgery. Patients undergoing major cardiac procedures such as coronary artery bypass grafting (CABG) or heart valve surgery sometimes experience vivid visual or auditory hallucinations after surgery, wherein they see or hear things that are not real. These phenomena can cause significant patient stress, impede recovery, and negatively impact overall well-being. Despite anecdotal links to delirium, emerging evidence suggests hallucinations may occur independently as a specific postoperative complication. Limited data exist on their true incidence and predisposing factors in cardiac surgery populations.

Aim: The VAACS study is a multicenter prospective cohort investigation designed to determine the incidence of visual and auditory hallucinations in the first week after cardiac surgery and to identify patient or perioperative factors that predict their occurrence. By enrolling a large cohort across all cardiac surgical centers in the West Bank, this study seeks to clarify whether certain variables – such as type of surgery (CABG vs. valve), patient demographics, medical history, intraoperative exposures, or postoperative course – are associated with higher risk of hallucinations.

Methods: Approximately 1,600 adult patients undergoing elective CABG or valve surgery at ten hospitals were prospectively followed for 7 days postoperatively. Hallucination presence and severity were assessed daily using the Short Version Questionnaire for Psychotic Experiences (QPE), a validated 30-item instrument for systematic hallucination evaluation. Comprehensive clinical data (including baseline characteristics, surgical details, and postoperative parameters) were collected for each patient to allow multivariable risk factor analysis. The primary outcome is the occurrence of any visual or auditory hallucination within 7 days of surgery, and secondary outcomes include hallucination severity (QPE score) and comparison of patterns between CABG and valve surgery patients.

Significance: The VAACS study will provide robust estimates of how common postoperative hallucinations are after cardiac surgery and pinpoint modifiable risk factors associated with these events. Anticipated findings are that roughly 10–20% of patients will experience hallucinations, and factors indicative of greater physiological stress (e.g. high-dose vasopressors, transfusion needs, or reduced cardiac function) will correlate with increased risk (as suggested by prior observations of hallucination causes). By identifying at-risk patients, the study is expected to inform early monitoring and targeted interventions. Ultimately, improving recognition of

postoperative hallucinations enables appropriate patient education about the typically benign nature of these experiences and prompt reassurance/management by the care team, thereby minimizing distress and preventing further complications. The results will be disseminated through peer-reviewed publication and used to guide postoperative care protocols, contributing to safer and more attentive cardiac surgical recovery.

General Information

- **Study Title:** *VAACS – Predictors and Outcomes of Visual and Auditory Hallucinations following Coronary Artery Bypass Grafting and Valve Replacement Surgery: A Prospective Multicenter Cohort Study*
- **Acronym:** VAACS
- **Protocol Date:** 22 July 2025 (Version 1)
- **Trial Registration:** ISRCTN (Application #47709, submitted 22 July 2025)
- **Sponsor(s):** An-Najah National University (Nablus, Palestine); Palestinian Clinical Research Center (Bethlehem, Palestine)
- **Funding:** No dedicated external funding – the study was supported by Palestinian Clinical Research Center and volunteer efforts
- **Principal Investigators:** Dr. Haitham Abu Khadija; Dr. Mohammad Alnees; Dr. Nizar Abu Hamdeh; Dr. Abdalaziz Darwish; Dr. Duha Najajra
- **Ethics Approval:** Approved 12 Sept 2022 by the Institutional Review Board of An-Najah National University (IRB reference 2022/8), with local ethical clearance obtained at all participating hospitals. Written informed consent was obtained from every patient before enrollment.

Rationale and Background

During the 20th century, a groundbreaking surgical advancement revolutionized the treatment of cardiovascular disease (1). The invention of cardiopulmonary bypass (CPB), which temporarily replaces heart and lung function during surgery, opened doors for open-heart procedures that are transformative in terms of patient morbidity and mortality (2)(3). With over 400,000 procedures done annually in the United States of America (USA), the coronary artery bypass graft (CABG) surgery utilizes a blood vessel graft to bypass a coronary artery occlusion and restore blood supply to the heart, either on pump, with the use of a CPB, or off pump with a beating heart (4)(5). Complications of the surgery include stroke, wound infection, graft failure, postoperative atrial fibrillation, and rarely, mortality, with an overall rate of 1-2%. (5)(6). Heart valve replacement/repair surgery is the second most common heart procedure, with over 1

million procedures performed between 1993 and 2007(7)(8). It replaces damaged heart valves with mechanical or biological prosthetic valves, which differ in their requirement for lifelong anticoagulation and a shorter lifespan, respectively (9). Postoperative complications include arrhythmias, heart failure, and valve dysfunction (10)(11).

Auditory and visual hallucinations, often vivid, colorful, and involving people or objects, are increasingly recognized in critically ill patients after major surgeries (12)(13). While commonly linked to delirium, growing evidence suggests they may occur independently as a distinct neurocognitive complication (12). These hallucinations, particularly after cardiac procedures like CABG or valve surgery, are typically visual, non-distressing, and transient (14)(15)(16)With a prevalence reported to be around 21% in previous studies (17)(18). Proposed causes include disruptions in brain connectivity, cholinergic deficits, inflammation, certain medications, and cerebral changes associated with cardiopulmonary bypass (19) (20) (14). Hallucinations in the perioperative setting are often overlooked, either due to clinician unfamiliarity or misattribution to delirium. To address this, the Questionnaire for Psychotic Experiences (QPE) was developed as a validated tool to systematically assess hallucinations, including auditory, visual, tactile, olfactory, sensed presence, and delusional experiences across clinical populations, including surgical patients (14)(21).

Postoperative hallucinations can impair recovery by causing psychosocial distress, heightening anxiety, prompting self-removal of medical devices, leading to self-harm, and non-compliance with treatment (17)(22). These effects may delay rehabilitation, lead to longer ICU stays, and increase the risk of serious postoperative complications (17)(22). The existing literature classifies general psychiatric or cognitive complications with hallucinations, without clearly defining the associated risk factors, frequency, and characteristics, particularly in patients who underwent CABG versus valve replacement. This has created a gap in the understanding of hallucinations as distinct clinical findings. In this multicenter, prospective cohort study, we will address this gap by comparing the clinical features and incidence of hallucinations between valve surgery and CABG patients.

Justification for Study:

The VAACS study is designed to fill this knowledge gap by providing robust data on the incidence, characteristics, and predictors of postoperative hallucinations in a large, contemporary cardiac surgery cohort. By comparing CABG and valvular surgery patients, the study will determine if the type of surgery or associated care processes influence hallucination occurrence. Identification of independent risk factors (e.g. certain medications, hemodynamic factors, patient comorbidities) will help generate predictive models and guide interventions. Ultimately, the knowledge gained will improve clinical awareness that hallucinations are “measurable, clinically meaningful neuropsychiatric events” in the cardiac ICU/CCU. Recognizing that these events are relatively frequent (yet under-recognized) and associated with specific perioperative factors will challenge the traditional neglect of hallucinations in postoperative care. In turn, this can lead to

integrating hallucination screening into standard practice, allowing early reassurance for patients and potentially reducing any resultant morbidity.

Study Goals and Objectives

Primary Objective: To estimate the incidence of postoperative visual and auditory hallucinations in adult patients during the early postoperative period (within 7 days) following CABG or heart valve surgery.

Secondary Objective: To identify independent predictors of postoperative hallucinations (both visual and auditory) in this population. This includes evaluating a range of patient, surgical, and perioperative factors for association with hallucination occurrence, using multivariable analyses to adjust for confounders.

Secondary Objective: To determine whether patients undergoing CABG versus valvular surgery differ in the frequency of hallucinations and in their risk factor profiles. The study will specifically compare these two surgical subgroups to see if the type of surgery modifies the risk (or nature) of hallucinations.

Secondary Objective: To assess the severity and phenomenology of hallucinations when they occur. Using the QPE's hallucination severity scale, the study will characterize how intense or elaborate the hallucinations are, and document any patterns (e.g. purely visual, purely auditory).

Tertiary/Exploratory Objective: To collect preliminary data on short-term outcomes associated with postoperative hallucinations. Although not a primary focus, the study will observe whether patients who experience hallucinations have any trends toward different clinical outcomes (such as ICU length of stay) compared to those who do not, generating hypotheses for future research.

Study Design and Setting

Design: This study is a prospective, observational cohort study. We are following patients longitudinally in a non-interventional manner – no experimental treatment is given, and all patients receive standard of care. The primary study design is observational (cohort type) in nature, focusing on outcomes (hallucinations) that occur post-surgery and analyzing associations with pre-specified risk factors. The study's overall status is "completed" as of mid-2025 (having finished enrollment and follow-up).

Setting: The research is being conducted at multiple centers. Specifically, it involves *all* major cardiac surgery centers in the West Bank, Palestine. This includes ten hospitals with cardiac surgery and critical care units, ensuring broad geographic and practice representation. These participating centers are: Ibn Sina Specialist Hospital; Specialized Arab Hospital; An-Najah National University Hospital; Al-Razi Hospital; Al-Mezan Hospital; Al-Ahli Hospital; Arab Society for Rehabilitation; Palestine Medical Complex; Nablus Specialty Hospital; and Al-Makassed Hospital. Together, these institutions constitute the full complement of cardiac surgical intensive care units serving the region. By conducting the study across all centers, we maximized

recruitment and enhanced the external validity of findings (capturing variability in patient populations and surgical practices). The study was coordinated through the Palestinian Clinical Research Center (Bethlehem) and An-Najah National University (Nablus), with local principal investigators at each hospital overseeing implementation.

Study Timeline/Duration: Enrollment began in September 2022 (following ethical approval) and continued through June 2025. The overall study duration thus spans approximately 33 months (~3 years) of active recruitment and follow-up, plus additional time for data analysis. Patients were enrolled and followed in sequential cohorts as surgeries occurred; there was no fixed intervention period since observation occurred in the immediate postoperative days. Each individual participant's involvement lasted 7 days post-surgery (for daily assessments) with no long-term follow-up visits beyond the hospitalization in this protocol. The below summarizes key timeline milestones:

- *IRB approval:* September 12, 2022
- *First patient enrollment:* September 20, 2022
- *Last patient enrollment/completion:* June 30, 2025
- *Data analysis and manuscript preparation:* May–September 2025 (planned)
- *Dissemination of results:* Late 2025 (target journal submission)

Participants: The study population consists of adult patients undergoing cardiac surgery (either isolated CABG or valvular heart surgery) under elective or semi-elective (scheduled) conditions. We targeted a total sample size of approximately 1,600 patients, which was deemed sufficient for robust statistical analysis of incidence and risk factors. This large sample was achievable by recruiting across all sites over the study period, and indeed by study end a total of 1,332 patients had been enrolled (reflecting the realities of recruitment rates and eligibility). Enrollment was not randomized; rather, **consecutive eligible patients** at each center were approached and invited to participate, to minimize selection bias. This approach yielded a cohort roughly reflective of the surgical case mix: approximately two-thirds of participants underwent CABG and one-third underwent valve Surgery, paralleling typical surgical volumes.

Inclusion criteria: Patients had to meet *all* of the following criteria to be eligible for the study:

- **Adult patients (≥ 18 years old)** scheduled for cardiac surgery. The study included both men and women and imposed no upper age limit (aside from practical surgical candidacy).
- **Elective or semi-elective isolated CABG or valvular surgery** (including valve replacement or repair). Patients could be scheduled for CABG (on-pump or off-pump) or any type of heart valve surgery (e.g. aortic or mitral valve replacement). Urgent/emergency procedures were not planned to be enrolled (see exclusion criteria).

Exclusion criteria: Patients were excluded if they met *any* of the following conditions, as these could interfere with the ability to report hallucinations or confound the outcomes:

- **Inability to provide informed consent or complete the questionnaire** – for example, due to language barriers or severe baseline cognitive impairment that precluded understanding study procedures.
- **History of major psychiatric or neurological disorders** that could confound hallucination assessment. This includes conditions like schizophrenia, schizoaffective disorder, dementia or other chronic psychoses which themselves can involve hallucinations, making it difficult to attribute new hallucinations to the surgery.
- **Parkinson's disease** – given its association with hallucinations and cognitive changes, Parkinson's could confound the postoperative hallucination assessment.
- **Blindness (pre-existing)** – patients with complete blindness were excluded since visual hallucinations could not be assessed in the standard manner.
- **Active alcohol or substance abuse** – ongoing substance misuse could contribute to hallucinations (e.g. withdrawal hallucinosis) or complicate postoperative neuropsychiatric status.
- **Clinical diagnosis of delirium at screening** – patients who were already delirious (e.g. in the immediate preoperative period) were excluded to avoid confusion between ongoing delirium-related hallucinations and new postoperative events.
- **Pre-existing chronic hallucinations or psychotic disorders** – if a patient had a history of chronic hallucinations or was on antipsychotic therapy for hallucinations, they were not enrolled.
- **Emergency surgery cases** – patients undergoing emergent (unscheduled, life-saving) cardiac surgery were not included, since their acute condition and rushed consent process could preclude proper baseline assessment.

Methodology and Data Collection

Perioperative Care and Assessments:

All participants received standard perioperative care as per their institution's protocols; no experimental interventions were introduced. After obtaining written consent pre/postoperatively, baseline data were recorded including demographic information, medical history, and pre-surgery laboratory values. Each patient's EuroSCORE II (a risk stratification score for cardiac surgery) was calculated as a summary of operative risk. The surgical procedure (CABG or valve, including details like use of cardiopulmonary bypass) was performed according to usual practice. Intraoperative management (anesthesia techniques, perfusion parameters, etc.) was not standardized beyond routine care, but the study prospectively recorded key intraoperative

variables for each case. These included: use of cardiopulmonary bypass (on-pump vs off-pump for CABG), cardiopulmonary bypass duration, aortic cross-clamp time, total operation time, any major adjunct procedures, intraoperative blood transfusions, and peak doses of vasoactive medications administered (e.g. norepinephrine, epinephrine, vasopressin). Postoperatively, all patients were admitted to the cardiac surgical ICU or critical care unit and managed by intensivists per standard protocols (including sedation, analgesia, ventilatory support, etc.). The study captured postoperative variables such as the duration of mechanical ventilation, incidence of major complications (e.g. stroke, acute kidney injury requiring dialysis, reoperation for bleeding), total units of blood products transfused after surgery, length of ICU stay, and total hospital length of stay.

Hallucination Monitoring:

The core of the methodology is the focused monitoring for visual and auditory hallucinations in the first week after surgery. Each enrolled patient was followed daily for 7 days postoperatively for the occurrence of hallucinations. We defined the postoperative Day 0 as the day of surgery (with assessments starting after the patient awoke from anesthesia), and continued through Day 7 or until hospital discharge (whichever came first). Trained research personnel (typically a study nurse or physician at each site) conducted daily assessments for hallucinations, using a structured instrument to ensure consistency across centers.

Specifically, we employed the short Version Questionnaire for Psychotic Experiences (QPE) to identify and characterize any hallucinations. The QPE is a validated, semi-structured interview tool designed to assess the presence, frequency, and phenomenology of psychotic experiences, including hallucinations in various modalities It consists of 30 items covering hallucinations (visual and auditory), with sections to rate the severity associated with these experiences. The QPE has demonstrated strong reliability and validity in diverse populations, making it well-suited for systematically capturing hallucinations in a medical setting (23). For our study, we focused on the portions of QPE relevant to visual and auditory hallucinations. Each day, patients were asked standardized questions from the QPE about whether they had experienced seeing things that were not really there or hearing sounds/voices that were not actually present. If a patient reported a hallucination, follow-up QPE questions documented details such as content, clarity, duration, and how disturbing it was. If the patient was intubated or non-verbal on a given day, the assessment was adapted (e.g. nod/shake or writing) once the patient was able to communicate, to retrospectively capture any hallucination they recall during the period of limited communication. In cases where a patient was unconscious or too sedated on a day, that day's assessment was noted as unable to evaluate, and evaluation resumed when possible.

The primary outcome measure is the occurrence of postoperative hallucinations (visual and/or auditory) within the 7-day postoperative period. For analysis, this is treated as a binary event (did a hallucination occur or not) and also as a time-to-event (the postoperative day on which the first hallucination occurred, if any) for survival analysis. The secondary outcome is the severity of hallucinations, measured using the QPE severity scales and qualitative descriptors. In practice, if a patient experienced hallucinations, we recorded severity metrics such as frequency (e.g. single episode vs. multiple), intensity (e.g. how real or vivid it seemed), and the distress level (e.g. not at all distressing to extremely distressing) per QPE guidelines. These quantitative severity scores

allow us to compare not just whether hallucinations happened, but how impactful they were on the patient. All study data from the case report forms (including baseline data, perioperative variables, and daily QPE assessments) were entered into a secure digital database hosted by the coordinating center. Each participant was assigned a unique study ID; no personal identifiers were included in the analytic dataset to maintain confidentiality. Data entry featured built-in range and consistency checks, and periodic data quality audits were performed by the central research team. Throughout the study, site investigators had access only to their own site's data, while the core data management team aggregated data for analysis. The Palestinian Clinical Research Center oversaw data management procedures and ensured compliance with data protection regulations. All records (electronic and paper consent forms) are stored in locked or password-protected facilities, accessible only to study staff.

Safety Considerations

This is an observational, minimal-risk study. There is no interventional treatment being tested; all patients receive standard medical/surgical care. The primary risk to participants was the potential for psychological discomfort when discussing hallucinations or related symptoms. To mitigate this, all research staff administering the QPE were trained to conduct interviews in a sensitive, empathetic manner. If a patient became upset or fatigued during questioning, the interview was paused or stopped. The QPE itself is a non-invasive questionnaire, and participation did not alter the patient's medical management.

No physical risks beyond routine care were introduced. However, the study had a protocol in place for managing any safety issues related to hallucinations if they arose. In the event that a patient's hallucinations were causing severe distress or prompting unsafe behavior (e.g. attempting to remove IV lines due to a hallucination-related delusion), the research team immediately alerted the clinical care team. These patients would then receive appropriate clinical management per ICU protocols (for example, additional reassurance, presence of a staff member, use of antipsychotic medication or restraints if absolutely necessary for safety). Our study's stance was observational, so we did not direct treatment, but patient safety and well-being took priority – any concerning hallucination was handled as part of standard postoperative care by the clinicians. Fortunately, the literature suggests most postoperative hallucinations after cardiac surgery are benign, and in our cohort the majority were indeed not dangerous; nonetheless, vigilance was maintained.

All adverse events unrelated to hallucinations (e.g. medical complications of surgery) were managed by the clinical teams per standard practice. The study only collected data on such events but did not intervene. There was no Data Safety Monitoring Board given the low-risk nature of the study, but the principal investigators reviewed enrollment and any protocol issues periodically.

Confidentiality: Patient confidentiality was strictly maintained. Each participant was assigned a coded study ID; no names or personal identifiers appear in any reports or databases. Consent forms and linkage logs (connecting patient identity to study ID) are stored securely at each site.

Electronic data were stored on password-protected computers/servers with access limited to the study team. All results are reported in aggregate or with anonymized identifiers.

Follow-Up Plan

The follow-up for each participant was conducted *in-hospital* during the acute postoperative period. There were no long-term follow-up visits as part of this protocol; instead, the emphasis was on intensive monitoring in the week after surgery when hallucinations are hypothesized to occur most frequently. Key points of the follow-up plan:

- **Duration:** 7 days post-surgery (or until hospital discharge if earlier). This window was selected based on prior observations that postoperative hallucinations typically manifest within the first few days' post-op and rarely beyond a week. If a patient remained hospitalized beyond day 7, formal study follow-up ended on day 7 (though any later events could be noted qualitatively). If a patient was discharged before day 7, the follow-up effectively ended at discharge (as daily in-person assessments could not continue after discharge under this protocol). We did not include outpatient follow-up in this study, focusing on the inpatient period.
- **Daily assessments:** A study team member visited the patient at least once per day on postoperative days 1 through 7. Typically, the timing was coordinated with nursing staff to find a suitable time when the patient was awake, comfortable, and not in the middle of care tasks. The QPE interview for hallucinations took approximately 10–15 minutes. If patients were intubated/sedated on day 1, the team attempted assessment once sedation was lightened. Assessments were usually done in the mornings or afternoons. Nights were generally not used for research assessments to avoid disturbing rest, unless a patient's hallucination occurred at night and they reported it the next day (in which case we documented the timing).
- **Clinical data follow-up:** In parallel with the hallucination assessments, the study team reviewed the patient's medical record daily to capture any new clinical events (complications, medication changes, etc.) relevant to our data collection (as described in Methodology). For example, if a patient developed atrial fibrillation or an infection, that was recorded, although our primary outcomes are neuropsychiatric.
- **Follow-up completion:** On postoperative day 7 (or upon earlier discharge), a final evaluation was performed. If the patient had experienced hallucinations during the week, we administered an end-of-study debriefing where we again explained to the patient (if not already) that such experiences can occur after surgery and discussed any persisting concerns. Participants were thanked for their involvement, and it was clarified that their surgeons/physicians would continue to manage any ongoing health issues. We provided a simple feedback form or contact information in case patients or families had questions later, although formal follow-up beyond hospitalization was not in scope.
- **Protocol for lost follow-up:** Loss to follow-up was minimal since patients were captive in the hospital for the duration of interest. In rare cases where a patient left against medical advice or was transferred to another facility within 7 days, that day's assessment ceased and the patient was considered withdrawn for follow-up (data up to the point of withdrawal were kept). Such occurrences were documented; however, none of the

enrolled patients discontinued the study early except by virtue of routine discharge (which was intended end of follow-up).

Data Handling and Statistical Analysis

Data Collection and Entry: As described in the Methodology section, a wide array of data were collected for each patient – from baseline characteristics to perioperative details to outcomes. Data collection was recorded on standardized Case Report Forms (CRFs) at each site. These forms were then entered into a centralized electronic database. Double data entry was performed for critical fields (e.g. outcome occurrence, key risk factors) to ensure accuracy. Any discrepancies or out-of-range values triggered queries which were resolved by referring back to source documents. The database was regularly backed up and stored without patient identifiers. Each site retained a file of original data sheets and consent forms in a secure manner for auditing.

Data Quality Assurance: The coordinating team provided training to site research coordinators on proper data recording. A manual of operations detailed how each variable is defined (for example, how to grade a hallucination's severity, or how to record medication dosages). Throughout the study, periodic teleconference meetings were held with all site investigators to address questions and maintain consistency in data collection practices. An interim data quality review was conducted at the midpoint of the study (after approximately 800 patients) – a sample of records from each site was audited for completeness and accuracy, and feedback was given. This served as an internal monitoring step to catch any systematic issues early. The study main sponsor (PCRC) did assign an independent monitor, and the principal investigators collectively undertook oversight of data integrity.

Statistical Analysis: (This recapitulates the plan with some additional details.)

- *Descriptive statistics:* We will present baseline patient characteristics and perioperative variables using means ± standard deviations (or medians with interquartile ranges for skewed distributions) for continuous variables, and frequencies (percentages) for categorical variables. We will stratify many descriptive results by surgery type (CABG vs valve) to illustrate any notable differences between these groups at baseline.
- *Incidence of hallucinations:* The cumulative incidence by postoperative day will be depicted with Kaplan–Meier curves, and incidence proportions at day 7 will be reported along with 95% confidence intervals. A log-rank test will compare the time-to-event curves between CABG and valve patients as an exploratory analysis (to see if one group tends to experience hallucinations earlier or more frequently over time).
- *Risk factor modeling:* As stated, Cox proportional hazards models will be our main tool for hazard ratio estimation. For each of the two outcomes (visual hallucination, auditory hallucination), we will first perform univariate Cox analyses for each candidate predictor to screen for potential associations ($p<0.10$ threshold likely used to consider for multivariable, although all clinically important variables will be considered regardless of univariate p). Then, multivariable Cox models will be constructed. We intend to build four primary models:
    1. Predictors of visual hallucinations in CABG patients.

2. Predictors of auditory hallucinations in CABG patients.
3. Predictors of visual hallucinations in valve surgery patients.
4. Predictors of auditory hallucinations in valve surgery patients.

This stratified approach aligns with our objective to see group-specific predictors. Each model will include covariates such as age, sex, , CPB time, cross-clamp time, transfusion volume, need for vasopressors, etc., based on both clinical judgment and the literature on postoperative delirium. We will report adjusted hazard ratios (aHR) with 95% confidence intervals and p-values for each covariate. Model fit and assumptions (proportional hazards) will be checked as mentioned. If a proportional hazard assumption is violated for a key predictor (e.g. the effect of a variable changes over the 7-day period), we might incorporate an interaction with time or use a time-dependent covariate model.

- *Additional analyses:* We will also conduct a combined analysis on the overall sample (CABG+valve) for completeness, using a Cox model that includes surgery type as a covariate and possibly interaction terms to see if any risk factor's effect is significantly different between surgery types. This will supplement the separate models approach. We may also use logistic regression to model the odds of "any hallucination vs none" by day7 as a simpler analysis, and linear or ordinal regression to explore predictors of hallucination *severity* among those who hallucinated (though this latter analysis will have a smaller sample of patients and be considered exploratory).
- *Handling of missing data:* We anticipate very little missing data for core variables, given the intensive follow-up. If any key covariates have missing values (e.g. a lab value not measured), we will use appropriate imputation or simply include a missing category for categorical factors. For the outcome, if a patient's hallucination status is uncertain due to early discharge before Day7, we treat them as censored at discharge (i.e. no event observed by that point, and no further follow-up).

The analysis will adhere to STROBE guidelines for observational studies In terms of reporting. All tests will use a two-tailed alpha of 0.05 for significance. Results will be interpreted with caution regarding causality, given the observational design. We will also calculate measures of predictive performance (e.g. C-index for Cox models) to evaluate how well our identified risk factors could discriminate between those who do and do not experience hallucinations.

Quality Assurance and Monitoring

Maintaining high data quality and protocol adherence was a priority in this multicenter study. Several **quality assurance (QA)** measures were implemented:

- **Study Training:** Prior to study initiation, all site investigators and research staff underwent training on the study protocol, including inclusion/exclusion criteria, consent procedures, and uniform administration of the QPE. This training was conducted via a ZOOM meeting and supplemented with written manuals and video demonstrations for

administering the hallucination questionnaire. Ensuring that every assessor approached the patients in a similar way was crucial for data consistency. We emphasized the importance of not prompting or leading patients when asking about hallucinations, and practiced the QPE interview in mock scenarios.

- **Standardization of Procedures:** We provided each site with standardized CRF templates and data dictionaries. For example, there were clear definitions for what constitutes a visual vs. auditory hallucination in our context, how to rate severity, and how to document uncertain cases. Likewise, instructions on how to collect perioperative data (from medical charts) were standardized – such as which lab values to record preoperatively, how to measure durations (rounding conventions), etc. This reduces inter-center variability in data recording.
- **Central Coordination:** The Palestinian Clinical Research Center (PCRC) acted as the coordinating hub. A dedicated study coordinator at PCRC was responsible for daily communications with site teams. This included sending reminders for data submission, clarifying any protocol questions that arose, and ensuring timelines were followed. The coordinator also collected enrollment logs from each site to track recruitment progress.
- **Monitoring and Audits:** Though a formal external monitoring body was not appointed (given resource constraints and observational nature), internal monitoring was performed. Each month, a random sample of 5–10 patient records from each site was checked for completeness and logical consistency by the central data manager. For instance, if a patient was noted to be intubated for 2 days, we checked that hallucination assessments during those days were appropriately handled (likely deferred or noted via alternative communication). Any discrepancies or missing data discovered triggered a query back to the site for resolution. Additionally, the central team conducted two interim audits (at ~500 patients and ~1000 patients enrolled) where de-identified source data (operative notes, etc.) for selected patients were reviewed to verify that the key exposure variables (like CPB time, medication use) had been abstracted correctly. The findings of these audits were favorable, with only minor corrections needed, which were subsequently applied.
- **Site Visits:** Investigators from the coordinating center (sponsor representatives) made brief site visits to the largest recruiting centers (e.g. Makassed General Hospital and Palestine Medical Complex) during the study to observe consent and assessment procedures in practice. These visits helped reinforce protocol compliance and allowed in-person troubleshooting of any local issues. For smaller sites, regular video calls served a similar purpose.
- **Blinded Data Review:** When constructing the analysis dataset, two statisticians independently verified the primary outcome coding (hallucination yes/no and day of occurrence) against the daily assessment logs for all patients. This double-check ensures the outcome data – which drive the primary analysis – are accurate.
- **Documentation of Deviations:** Any protocol deviations (e.g. a missed daily assessment due to patient unavailability) were documented in a deviation log along with reasons. These were reviewed to see if any systematic problems existed. The deviations were infrequent and mostly involved missed assessments on a given day due to early discharge or patient fatigue; these instances were expected and handled per protocol (treating as censored or using partial data).

Quality of Measurements: The use of a validated tool (QPE) lends credibility to the measurement of hallucinations. The QPE's standardized format enhances reliability across different assessors. We also encouraged that wherever possible, the same person assesses a given patient each day for consistency (though this was not always feasible due to staff shifts).

Data Safety: The database had audit trail features (logging any changes made), which helps in quality control and in case any data entry errors had to be tracked and corrected.

Expected Outcomes and Impact

Based on the literature and our study design, we anticipate several key outcomes:

- **Incidence Rate:** We expect to formally quantify the incidence of postoperative hallucinations in cardiac surgery patients. Prior smaller studies indicated that hallucinations could occur in roughly 10–20% of cases. Our large cohort will provide a precise estimate; we hypothesize that around one in ten patients (10%) or slightly more will experience at least one hallucination in the week after surgery. This incidence may differ somewhat by surgery type – one of our analyses will determine if CABG patients have a higher or lower incidence than valve patients. However, we anticipate that both groups will show a non-negligible incidence (on the order of tens of patients per hundred), underscoring that this is not a rare phenomenon.
- **Risk Factor Identification:** We expect to identify specific perioperative factors that are independently associated with the development of hallucinations. Our hypothesis, guided by clinical insight and existing knowledge of delirium, is that factors indicating greater physiological stress or neurological insult will correlate with higher risk of hallucinations. For example, we anticipate that patients requiring high doses of vasopressor medications (like noradrenaline) for hemodynamic support may have an elevated risk of hallucinations; this aligns with the idea that these patients undergo more cardiovascular stress or blood pressure fluctuations which might transiently affect cerebral perfusion or inflammation levels. Similarly, we expect that extensive exposure to cardiopulmonary bypass (i.e. longer pump times) or a greater need for blood transfusions could be risk factors, since both factors can contribute to systemic inflammation or microemboli that affect the brain. A reduced preoperative left ventricular ejection fraction (as a marker of poorer cardiac function) might also emerge as a predictor, as patients with weak hearts often have more complicated postoperative courses and possibly more neuroinflammation (this was suggested in some prior observations). On the other hand, some factors might prove protective – for instance, we have an open hypothesis that longer postoperative ventilation under controlled sedation might paradoxically *reduce* hallucination risk by preventing sleep-wake disruptions (one previous finding noted prolonged ventilation was associated with *fewer* visual hallucinations). Our analysis will clarify these relationships.
- **CABG vs Valve Differences:** We expect to report whether the two surgical subgroups differ in hallucination profile. It could be that CABG (often involving more widespread atherosclerosis and possibly more pump time) shows a slightly higher incidence or a different constellation of risk factors compared to valve surgery. Alternatively, both may be similar. If differences exist, those will be an important finding; for example, we might

find that transfusions significantly predict hallucinations in CABG but not in valve patients, whereas vasopressor use is a stronger predictor in valve patients. These nuanced outcomes will inform tailored strategies depending on surgery type.

- **Severity and Nature of Hallucinations:** We will document the typical characteristics of the hallucinations observed. We expect, consistent with anecdotal reports, that most hallucinations will be visual (e.g. seeing people in the room, seeing insects on the ceiling, etc.) and generally not severely distressing. Auditory hallucinations (such as hearing voices or music) are anticipated to be less common but when present might be more disorienting to patients. We'll quantify severity using the QPE scores. An expected outcome is that the median hallucination severity will be low to moderate (since many patients might experience only one or two brief episodes). We will also note if any hallucinations led to clinical intervention (e.g. needed medication), though we expect few will require such measures given their usually benign course.
- **Predictive Model:** An important deliverable is an evidence-based profile of which patients are at risk. We aim to produce a tentative risk model or risk score for postoperative hallucinations. For instance, if our analysis finds that blood transfusion, low ejection fraction, and long bypass time are major independent predictors, a combination of those could help flag patients who might benefit from closer postoperative monitoring. The expected outcome is not to create a finalized tool (which would require validation), but to lay the groundwork by highlighting key predictors.
- **No Impact on Mortality or Major Morbidity:** We do not expect our study to directly link hallucinations to hard outcomes like mortality or stroke (it's not powered or designed for that). However, we will observe if patients with hallucinations had any trends such as longer ICU stays, as mentioned. We anticipate some correlation: patients with hallucinations might on average stay a bit longer in ICU (perhaps because they often are the sicker patients), but we will be cautious to differentiate correlation vs causation.

Impact on Clinical Practice: The knowledge gained from VAACS will have important implications:

- **Heightened Awareness:** We expect the medical teams in our region (and beyond via publication) to become more aware that hallucinations occur in a notable fraction of cardiac surgery patients and should be actively inquired about. Simply acknowledging this incidence is an outcome that can change practice by prompting routine postoperative cognitive checks.

- **Patient Education:** Armed with incidence data, surgeons and anesthesiologists can better counsel patients preoperatively. For example, if our final incidence is ~10%, we can tell patients "about one in ten patients experiences temporary hallucinations after this surgery; if you see or hear unusual things after the operation, let us know – it can happen and we will help you through it." This addresses the currently unmet need for patient education, reducing fear if it happens, and encouraging patients to speak up about these experiences.

- **Targeted Monitoring:** If specific risk factors are confirmed, clinicians can allocate monitoring resources accordingly. For instance, if a patient needed high-dose vasopressors, the ICU team might pay extra attention to that patient's psychological state, perhaps implementing frequent reorientation or avoiding unnecessary sensory isolation for them. Our expectation is that early recognition and simple interventions (like reassurance or adjusting nighttime lighting) can mitigate the negative impact of hallucinations.
- **Foundation for Interventions:** While our study is not testing an intervention, it sets the stage for future trials. If we find modifiable risk factors (e.g. certain drugs associated with hallucinations), it opens the possibility to alter those practices. Or if we find high-risk patients, one could test prophylactic measures in that subgroup (such as prophylactic melatonin or haloperidol – purely hypothetical at this point). Therefore, the expected outcome includes generating hypotheses for intervention.

Dissemination and Publication Policy

The research team is committed to disseminating the findings of the VAACS study widely, in line with ethical obligations and to maximize the benefit of the research. Key components of our dissemination plan include:

Academic Publication: We will prepare the results of this study for publication in a peer-reviewed medical journal, aiming for an international journal in the fields of cardiac surgery, or critical care, (whichever is deemed most appropriate given the content). The manuscript will follow guidelines for reporting observational studies (STROBE) to ensure transparent reporting of methods and results. All listed investigators will have the opportunity to contribute to and review the manuscript. We intend to publish under open-access terms if feasible, to allow broad accessibility. No publication restrictions exist from any funder, since there was no external funding contract; thus, the team retains full ownership of data and the freedom to publish.

Feedback to Participating Centers: Each participating hospital and investigator will receive a summary of the study results. This will be in the form of a concise report or presentation highlighting the incidence of hallucinations at their center and overall, and recommendations based on the findings. We will offer to hold a grand-round or webinar for the ICU and surgical staff at those hospitals to discuss the outcomes and implications.

Patient and Public Communication: Although the primary audience is scientific and clinical, we recognize the value in informing past and future patients. We will work with hospital communication departments to possibly include an article in hospital newsletters (in lay language) about the study's results and how the hospitals are addressing

postoperative hallucinations. Participants who indicated interest in knowing results (some do during consent) can be provided with a lay summary after publication.

Policy and Practice Impact: We will engage with relevant committees or quality improvement initiatives in our institutions. For example, if the results show a clear benefit to routine screening, we might advocate for adding a "hallucination check" to ICU order sets or postoperative care bundles. The publication and local presentations will serve as evidence to support such changes.

WHO Trial Registry Updates: As this protocol is being revised for WHO registry purposes, we will ensure that the trial registry entry (ISRCTN) is updated with the final status and key results once available, in compliance with registry requirements for reporting outcomes. This guarantees that even those searching the registry can find the outcome of the study.

The authors declare that there are no restrictions or delays to publication imposed by any authority. The data from this study, once anonymized, could be shared with other researchers upon reasonable request, in line with open science principles, provided patient confidentiality is protected. We will follow any applicable data sharing policies of the target journal or institutional guidelines. Authorship for publications will be determined based on contributions, following ICMJE criteria. All principal investigators and key contributors (including those who helped design the study, collect data, and analyze results) will be considered for co-authorship.

Duration of the Project

- Preparation and Ethical Approval: August–September 2022
- Recruitment and Data Collection: September 2022–June 2025
- Data Analysis: July–August 2025
- Manuscript Preparation and Submission: September–October 2025
- Results Dissemination: November 2025–January 2026

Problems Anticipated

Anticipated issues include incomplete data collection, patient withdrawal, variability in hallucination reporting, and resource limitations due to self-funding. Solutions include rigorous staff training, standardized documentation protocols, regular data audits, and proactive communication strategies to reduce participant burden and maintain engagement.

Project Management

Principal Investigators:

1. Dr. Haitham Abu Khadija
2. Dr. Mohammad Alnees
3. Dr. Abdalaziz Darwish
4. Dr. Nizar Abu Hamdeh
5. Dr. Duha Najajra

Central Data Managers:

1. Dr. Hamza A. Abdul-Hafez
2. Dr. Mohammad Masu'd
3. Dr. Omar Qasem Heih

Regular team meetings and structured oversight ensure smooth operation and adherence to the protocol.

Ethics

Ethical approval obtained from An-Najah National University IRB (Ref: 2022/8). Ethical considerations include minimal patient discomfort due to sensitive questioning. Comprehensive informed consent obtained preoperatively, clearly outlining voluntary participation, confidentiality, and withdrawal rights.

Informed Consent Forms

Approved informed consent forms (ICFs) provided in Arabic and English, tailored specifically for patients undergoing cardiac surgery. Forms clearly explain study procedures, potential discomfort, confidentiality measures, and patient rights.

Research Protocol – VAACS – Part 2

Budget

Self-funded; minimal costs for materials and data handling absorbed by investigators' institutions.

Other Support

No external funding or support received.

Collaboration

- **Principal Investigators:** Mohammad Alnees, Haitham Abu Khadija, Abdalaziz Darwish, Nizar Abu Hamdeh, Duha Najajra.

- **Central Data Managers:** Mohammad Masu'd, Hamza A. Abdul-Hafez, Omar Qasem Heih.
- **Participating institutions:** Palestinian Clinical Research Center, An-Najah National University, and multiple hospitals across Palestine.

Links to Other Projects

This core VAACS study serves as the basis for many additional sub-studies focusing on phenomenology, long-term outcomes, and potential biomarkers of postoperative hallucinations.

Curriculum Vitae

Dr. Haitham Abu Khadija

- Cardiology Specialist at Clalit Health Service and Maccabi Health Service, Israel.
- Editor, International Journal of Nutrology.
- Education: MD, An-Najah National University; Cardiology Residency, Kaplan Medical Center (Hebrew University).
- Publications: Over 20 peer-reviewed articles.
- Awards: Multiple research awards including Outstanding Young Investigator Award (Peres Academic Center).

Dr. Mohammad Alnees

- Clinical Research Coordinator and Senior Analyst, Kaplan Medical Center.
- Head of Palestinian Clinical Research Center.
- Education: MD, An-Najah National University; Clinical research training from Harvard Medical School.
- Publications: Over 27 peer-reviewed articles.
- Special Skills: Clinical research methods, advanced statistical analysis (Stata), proposal and manuscript writing.

Dr. Abdalaziz Darwish

- Research & Teaching Assistant, An-Najah National University.
- Completed internship rotations in various specialties.
- International clinical experience: Cleveland Clinic, USA; Florence University, Italy.
- Publications: Multiple peer-reviewed articles in surgery and internal medicine.

Dr. Nizar Abu Hamdeh

- MD Candidate, An-Najah National University.
- Co-Founder and Vice President, Palestinian Clinical Research Centre.
- Publications: Over 10 articles in high-impact journals, presented research at Israel Heart Society Conference.

Dr. Duha Najajra

- MD Candidate, An-Najah National University.

- Experienced researcher with peer-reviewed publications in public health and clinical research.
- Active involvement in multiple multicenter research projects as co-investigator.
- Publications: Over 10 articles in high-impact journals, presented research at Israel Heart Society Conference.

Other Research Activities

Investigators are involved in related clinical research projects focused on cardiovascular outcomes and postoperative complications.

Financing and Insurance

Self-funded by investigators and institutions. Standard institutional insurance applies; ethical approvals obtained from An-Najah National University IRB (Ref: 2022/8).