Direct REporting of Awareness in MaternitY patients (DREAMY): A prospective evaluation of accidental awareness under general anaesthesia in obstetric surgery patients

Sponsor's JREO Registration Number: 16.0063
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Signature Page and Statement

The Chief Investigator (CI) and the Sponsor Representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the study in compliance with the approved protocol, GCP, the Data Protection Act 1998, the St George's NHS Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd edition) and the Sponsor's SOPs, as appropriate.

This protocol has been written in accordance with the Sponsor's procedure identified as JREOSOP0039 'Protocol Design' and is intended for UK sites only

Chief Investigator	Signature	Date
Peter Odor Anaesthetic Registrar St George's University Hospitals Healthcare NHS Trust		09/12/16

Acknowledgements and Protocol contributories

Peter Odor (St. George's University Hospitals NHS Foundation Trust) and Sohail Bampoe conceived the study; Peter Odor initiated the study design. Jaideep Pandit, Nuala Lucas, Jackie Andrade, Ramani Moonesinghe and Sohail Bampoe assisted with study design and helped with implementation. All of the above are grant holders, PO and JP provided statistical expertise in clinical trial design and PO is conducting primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Contents

1 List of abbreviations

AAGA	Accidental awareness under general anaesthesia
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Assistant
EUA	Exploration Under Anaesthesia
GCP	Good Clinical Practice
GA	General Anaesthetic
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
LSCS	Lower Segment Caesarean Section
MROP	Manual Removal of Placenta
NAP5	National Audit Project 5
NIHR	National Institute for Health Research
NHS R&D	National Health Service Research & Development
OAA	Obstetric Anaesthetists Association
PI	Principal Investigator
PIS	Participant Information Sheet
PLAN	Pan-London Perioperative Audit and Research Network
PTSD	Post-Traumatic Stress Disorder
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMF	Trial Management File

2 Study Personnel

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DREAMY Research Team: Designated collaborators, Clinical Trials Assistants and/or Research Nurses for the DREAMY study. Led by Peter Odor.

3 Protocol synopsis

Official title:	Direct reporting of awareness in maternity patients: a prospective evaluation of accidental awareness under general anaesthesia in obstetric surgery patients
Brief title /Acronym:	DREAMY
Sponsor reference number:	16.0063
Public database trial ID:	TBC
Research Question	What is the incidence of AAGA (accidental awareness under general anaesthesia) using a Brice questionnaire in obstetric anaesthesia in the UK?
Study design	Observational non-interventional
Eligibility criteria:	*Inclusion criteria:* 1. Female adults (≥18 years) of ≥ 24/40 gestation 2. Receiving general anaesthesia (de novo or regional anaesthesia converted to GA) for surgery with an obstetric indication
	Exclusion criteria: 1. Patients too unwell or confused to be able to complete the questionnaire 2. Patient refusal 3. General anaesthesia for non-obstetric indication (e.g. colorectal or orthopaedic surgery in a pregnant patient) 4. Surgery ≥48 hours post-partum 5. Unable to communicate verbally/in writing in English language
Anticipated start date	February 2017
Anticipated end date	February 2019
Target number of participants	2250
Primary aim	Establish the incidence of AAGA using a Brice questionnaire in obstetric anaesthesia in the UK
Secondary aim(s)	Investigate the experience and psychological implications of Brice positive AAGA episodes in obstetric patients. This will include 12 month outcome reporting, using structured follow up and the Post-Traumatic Stress Disorder Checklist (PCL-5), alongside case review of the surgical, anaesthetic and patient factors that make obstetric patients more likely to report AAGA than the non-obstetric population.
Sources of funding	*OAA/NIAA Large Project Grant 2016 for £29,757*
Sponsor	*St George's NHS Hospitals Foundation Trust*
Contact name	*Sponsor representative: Debbie Rolfe* *Email: drolfe@sgul.ac.uk* *Tel: 020 8725 5013* *Fax: 020 8725 0794* *Chief Investigator: Peter Odor* *Email: peter.odor@nhs.net* *Tel: 07746 399221*

4 Background

Accidental awareness during general anaesthesia (AAGA) can be defined as the unintended experience and explicit recall of sensory perceptions during surgery [Joint commission 2014]. As one of the few direct "complications" of anaesthesia, AAGA has received increasing attention, most notably by the recent 5th National Audit Project (NAP5) [NAP5]. AAGA is considered important to patients and anesthetists, ranked as the second most important complication of anaesthesia by both groups [Macario 1999, Macario 1999]. Patient experiences of AAGA vary considerably; ranging from neutral with no adverse consequence [Sebel 2004], to intense distress with subsequently post-traumatic stress disorder [Aceto 2013]. NAP5 identified 41% of AAGA cases as being associated with moderate to severe longer-term harm, which was more common in patients experiencing pain and/or paralysis, with 51% reporting moderate to severe harm versus 25% of those reporting only auditory or tactile sensations.

One of the headline results from NAP5 was the disproportionately high incidence of AAGA for obstetric patients undergoing LSCS (~1:670 versus ~1:19,000 overall). General anaesthetics for obstetric patients recurrently typify many of the risk factors for AAGA identified by NAP5 and previous studies: rapid sequence induction, neuromuscular blockade, difficult airway management, obesity and frequent performance out-of-hours by non-consultant grade anaesthetists. This combination of factors is particular, if not unique, to obstetric anaesthetic practice and mandates classification of the subspecialty as high risk for AAGA. Furthermore, in n = 3/14 (21%) of cases of obstetric AAGA identified by NAP5, new significant psychological morbidity was reported. In one case the patient indicated a decision to litigate, which may also indicate further psychological harm.

The James Lind Alliance Anaesthesia and Perioperative Care Priority Setting Partnership identified the following question as being one of the top ten most important research topics in anaesthesia: "What long-term harm may result from anaesthesia, particularly following repeated anaesthetics?" [JLA PSP]. As the highest risk subgroup for one of the most important causes of harm following anaesthesia, obstetric anaesthetic practice warrants further research into AAGA. More explicitly, NAP5 set specific research implications for obstetrics, suggesting that further research was needed to "…define the incidence of AAGA as identified by the Brice questionnaire" [Research Implication 16.6, NAP5] and "to explore whether factors make obstetric patients more likely to report episodes of AAGA than the non-obstetric population" [Research Implication 16.7, NAP5].

The Brice questionnaire [Brice 1970] has been used as a common standard in awareness research. Although minor variations have been applied [Avidan 2009], all retain the same five questions on recall of any events between induction of anaesthesia and emergence. Importantly, direct and systematic questioning is applied when using Brice questionnaires, which contrast with spontaneously patient reporting of AAGA in NAP5. This difference in methodology may partly account for the apparent divergence between the proportion of AAGA consistently reported in the overall surgical population with Brice questioning (~1:660) versus that by NAP5 (~1:19,000 overall). Although few studies have compared methods of AAGA testing, the Brice questionnaire is known to detect more cases of AAGA than unstructured direct questioning [Mashour 2013, Mashour 2009], and timing/repetition of Brice questioning may also influence the output [Mashour 2013, Sandin 2007, Davidson 2005, Leslie 2007]. These limitations, coupled with the debated gulf between incidence of AAGA established by Brice responses alone versus spontaneously reported incidence, mean that Brice has been regarded by some as not the "gold standard" methodology it is frequently implied to be [Cook 2015]. However, where Brice is uniquely important is as a common tool for comparison and as a screening method to identify a subpopulation that may be at need of further investigation.

Brice questionnaires have been applied only once before in obstetric patients [Paech 2009]. This observation study was primarily designed to investigate difficult airways in obstetric patients receiving a GA, but Brice questionnaires were also offered up to day two following surgery. A total 763 of 1095 obstetric patients were provided Brice questionnaires, of whom five cases were "Brice positive", yielding an estimate of AAGA incidence of ~1:152. Of these, two were classed as "definite" and three as possible awareness. This preliminary study indicates that Brice positivity may indeed be much higher than it is in the general population. However, the lack of follow up beyond 48 hours, the wide confidence intervals and the fact that AAGA was not the study's primary outcome make these results somewhat difficult to interpret.

The most complete approach to investigating AAGA would be to screen all eligible individuals with a standardised tool, then rigorously assess each potential report with further investigation, before reaching a consensus classification of the event against pre-established definitions of AAGA. This is exactly the methodology to be adopted by our DREAMY study, using Brice questionnaire as the screening tool, but adding structured follow up, where appropriate, to elucidate the nature of the possible AAGA experience and its consequences. By taking this approach the research team aim to produce the most comprehensive analysis of AAGA in obstetric patients to date.

5 Research Question

The DREAMY study aims to fulfil research implications 16.6 and 16.7 from the National Audit Project 5 (NAP5) Report, in relation to AAGA in the obstetric population. These implications are to "…define the incidence of AAGA as identified by the Brice questionnaire" [Research Implication 16.6, NAP5] and "to explore whether factors make obstetric patients more likely to report episodes of AAGA than the non-obstetric population" [Research Implication 16.7, NAP5].

There are three competing research hypotheses: that the incidence of Brice positivity in obstetrics is similar to that of the general population (~1:660), similar to Paech's [Paech 2009] already reported incidence (~1:152) or that the ratio between "Brice positive" and spontaneous reporting is maintained with the general population (~1:19).

5.1 Primary Aim

The primary aim is to determine, using direct questioning with a Brice questionnaire, the proportion of women who report AAGA following general anaesthesia for obstetric indication surgery in the UK.

5.2 Secondary Aim(s)

A secondary aim is to investigate the experience and psychological implications of AAGA in obstetric patients. This will include 12 month outcome reporting, using structured follow up and the Post-Traumatic Stress Disorder Checklist (PCL-5); alongside case review of the surgical, anaesthetic and patient factors that make obstetric patients more likely to report AAGA than the non-obstetric population.

6 Study design

DREAMY is a prospective, observational, multi-centre cohort study, with recruitment planned for 12 months. Written consent will be obtained from all participants. Any NHS hospital with maternity services and obstetric anaesthesia personnel will be eligible to participate. The study has been designed to maximise feasibility by complementing nationally recommended anaesthetic follow up practice [OAA/AAGBI 2013] for obstetric patients following surgery.

6.1 Methods

Patients receiving GA for obstetric indication surgery will be eligible to participate in the DREAMY study. Participants will be screened for AAGA using three repetitions of the Brice questionnaire, before assessment with structured investigation of their AAGA experience and its psychological consequences. No clinical interventions will form part of the study protocol, but local clinical teams will be encouraged to offer AAGA patient care in accordance with the NAP5 AAGA Support Pathway [NAP5 Anaesthesia Awareness Support Pathway]. Analysis and classification of events will follow pre-established AAGA definitions.

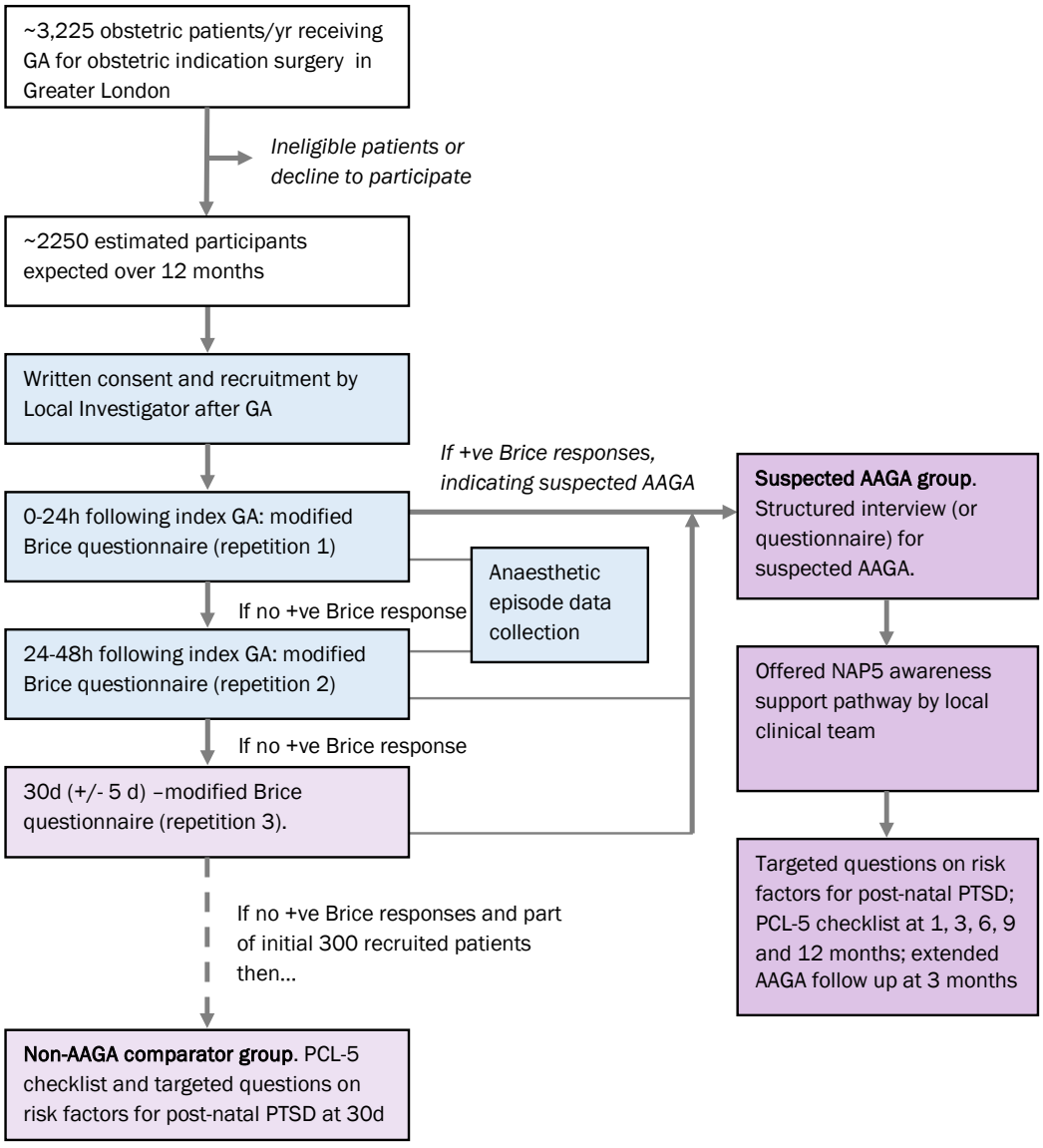

Figure 1. Schematic diagram of study design

6.2 Data collection procedures

There are three stages to participant data collection:

1. In hospital: Screening for AAGA with modified Brice questionnaires and collection of baseline anaesthetic episode data
2. After hospital: telephone follow up with repetition of the Brice questions at 30 days after the index GA
3. Conditional follow up, dependent upon Brice response: structured interview schedules for participants reporting Suspected AAGA, extended follow up of AAGA patients after 3 months, identification of PTSD risk factors and PTSD symptom screening for 12 months.

Initial AAGA screening will occur at three time intervals following a participant's index GA: 0-24 hours, 24-48 hours and 30 days. 0-24h and 24-48h follow up will consist of a modified Brice questionnaire [Brice 1970, Avidan 2009], including categorical and free text responses (see Appendix 2 for the modified Brice questions). Day 30 (+/- 5 days) follow up will be conducted via telephone (or via email, at participant request) using the same Brice question format and response options. Data collection following discharge of the patient from the local hospital site will be coordinated and conducted by the DREAMY Research Team, rather than local site investigators. Modification to the above timeline for Brice questionnaire administration will only be made in exceptions when patients are unable to provide responses at the pre-specified time points and in agreement with the local PI/CI.

Any patient with Brice questionnaire responses indicating possible recall of events during the anaesthetic episode (hereafter termed "Brice positive") will be provided with a specific structured interview schedule or questionnaire to further delineate the characteristics and psychological response to their experience (adapted from the BAG-RECALL trial [Avidan 2011]). Further repetitions of the Brice questionnaire will not be required after a participant has been declared "Brice positive". See section 9.2 for further detail on Brice questionnaire response classification.

Suspected AAGA face-to-face or telephone structured interview schedules will be organised and led by the DREAMY Research Team and provided at the earliest available opportunity. See Appendix 4 for the structured follow up questions for patients with Suspected AAGA.

The default follow up methodology for encounters led by the DREAMY Research Team will be telephone structured interview schedules. At the start of the study equivalent written/email questionnaire forms of the interview questions will be provided to maximise follow up data collection. Alignment of responses between different data collection formats will be maximised by using interview schedules structured identically to paper questionnaires and presenting both with simple, equivalent contextual information. During interim analysis if a response format (i.e. telephone, face-to-face or written) is found to be infrequently selected by participants, then this choice may later be removed to further maximise data concordance.

"Brice positive" respondents will receive targeted questions on risk factors for post-natal PTSD (Appendix 6) during 30 day follow up and be offered the PCL-5 PTSD checklist (Appendix 5) at 30 days, 3, 6, 9 and 12 months following the index anaesthetic episode. The questions and checklist will be administered by telephone (or via email, at participant request) by the DREAMY Research Team.

An extended questionnaire for "Brice positive" participants will also be undertaken during the 3 month PTSD follow up episode (Appendix 7). This questionnaire is designed to explore the nature of local clinical follow received by patients and how the AAGA episode has impacted on attitudes towards future anaesthetics and post-natal experience.

Anaesthetic episode data collection will be conducted retrospectively by the anaesthetic Local Investigators from patient notes and anaesthetic records after each participant has provided written consent for study involvement. Data collected on the anaesthetic episode is detailed in Appendix 3 and includes: age of patient, parity, procedure, urgency of surgery/LSCS, ASA status, booking BMI, anaesthesia start/finish time, induction agents (and doses), de novo or conversion to GA, indication for GA, rapid sequence induction, maintenance agent, nitrous oxide use, MAC, (lowest, highest, estimated median), primary airway device, difficult intubation, grade of laryngoscopy, local/regional anaesthesia, neuromuscular blockade, nerve stimulator use, reversal use, depth of anaesthesia monitor use, most senior anaesthetist present, location of extubation, post op destination, estimated blood loss.

1. 0h = Time of GA for obstetric indication surgery.
2. 0-24h following index GA = Written consent obtained. Modified Brice questionnaire (repetition 1). Data collected for the anaesthetic episode.
3. 24-48h following index GA = Modified Brice questionnaire (repetition 2).
4. Day 30 (+/- 5 days) from index GA = Modified Brice questionnaire (repetition 3).

If a participant reports possible recall of events during the anaesthetic episode ("Brice positive"):

1. Participants will be offered a further Suspected AAGA structured interview schedule or questionnaire (adapted from the BAG-RECALL trial [Avidan 2011]). Questionnaires are available in paper form for distribution to inpatients by Local Investigators. Interviews can be conducted via telephone or face-to-face. Suspected AAGA follow up will be made at the earliest available opportunity and in a format of the participant's preference.
2. "Brice positive" notification will be shared between the local clinical teams and the DREAMY Research Team.
3. Local clinical care teams will be encouraged to offer care in accordance with the NAP5 awareness support pathway [NAP5 Anaesthesia Awareness Support Pathway].
4. Post-Traumatic Stress Disorder (PTSD) Checklist (PCL-5) at day 30, 3, 6, 9 and 12 months.
5. Post-natal PTSD risk factor questions at day 30.
6. AAGA Extended follow up at 3 months, exploring patient attitudes and post-AAGA clinical support.

An initial minimum sample of the first 300 Brice -ve patients completing day 30 follow up will also receive:

1. PCL-5 checklist and targeted questions on risk factors for post-natal PTSD at day 30. This provides a comparator group for PTSD incidence and baseline characteristics in the post-natal period for AAGA vs. non-AAGA patients.

Figure 2. Summary of in-hospital, telephone and conditional DREAMY data collection procedures

6.3 Analysis of AAGA event proportion

Brice questionnaire and Suspected AAGA follow up responses will be analysed to determine the incidence of suspected AAGA in patients undergoing GA for obstetric indication surgery. An expert panel consisting of a minimum of four assessors – including consultant anaesthetists, DREAMY

study representatives and project board members for NAP5 – will independently evaluate all the responses from patients with possible intraoperative awareness. AAGA events will be graded by consensus opinion in accordance with the Michigan Awareness Classification Instrument [Mashour 2010]. Catagorisation for impact on the patient will be in accordance with the NAP5 methodology [NAP5], using the same modified NPSA tool to determine severity of psychological impact. Denominator data, based upon the total number of eligible participants enrolled in the study, will be used to calculate a AAGA event proportion for all recruited patients. Site recruitment logs, detailing numbers of excluded patients or patients that declined to participate, will also be used to provide estimates of how representative this is for all obstetric patients undergoing general anaesthesia. Subgroup analysis for emergency LSCS and other surgical procedures will be performed to determine respective event proportions. Agreement between "Brice positive" classification (based upon Brice questionnaire responses alone) and AAGA classification following full review of the Suspected AAGA follow up responses will be declared.

6.4 Clinical support for AAGA patients

Local care teams at the recruitment centres (or wherever is clinically most appropriate) will maintain responsibility for follow up and management of clinical problems, including AAGA, that are identified through structured follow up as part of the DREAMY research study. Relevant support materials and existing NAP5 guidelines for the care of AAGA patients will be provided to all local investigator centres. Further details on investigation of suspected AAGA patients is provided in Section 9.3 and the NAP5 Anaesthesia Awareness Support Pack can be found here: http://www.nationalauditprojects.org.uk/NAP5-Anaesthetia-Awareness-Pathway [NAP5 Anaesthesia Awareness Support Pathway].

6.5 Comparator sample for PTSD follow up at 30 days

To provide a baseline incidence of PTSD symptoms in patients undergoing obstetric surgery under GA but who do not experience AAGA, an initial sample of participants will also be asked to complete the PCL-5 checklist and post-natal risk factors for PTSD questionnaire at 30 days. Data collection for this comparator sample will end once at least 300 participants have provided responses.

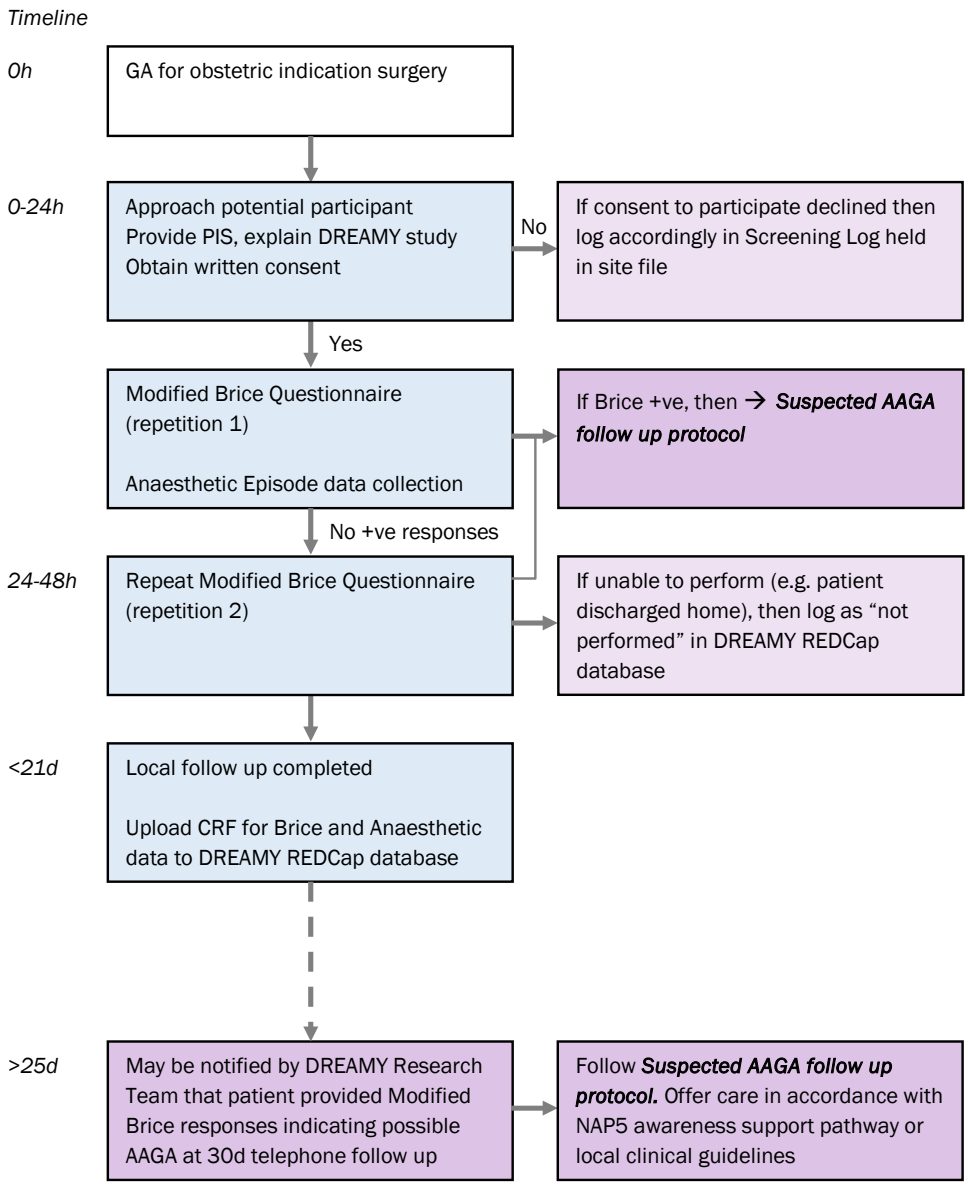

Figure 3. Flowchart of methodology for local investigators

7 Participant Selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the study results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital that exceptions are not made to the following detailed selection criteria.

All participants that are screened for inclusion into the study must be entered onto the Sponsor screening log JREOLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this study if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the Sponsor's Subject ID log JREOLOG0002 and assigned a trial specific Identification number in a pre-agreed format in accordance with site identifier and next sequential numerical value e.g. SG001.

7.1 Inclusion criteria

The aim of the study is to provide an inclusive investigation of AAGA in patients with physiological adaptations of pregnancy.

- Female adults (≥18 years) of ≥ 24/40 gestation
- Receiving GA (de novo or regional anaesthesia converted to GA) for surgery with an obstetric indication
- Informed consent obtained

Eligible obstetric indication surgical procedures (examples, but not limited to): caesarean section (LSCS), manual removal of placenta (MROP), exploration under anaesthesia (EUA).

7.2 Exclusion criteria

- Patients too unwell or confused to be able to complete the questionnaire
- Patient refusal
- General anaesthesia for non-obstetric indication (e.g. colorectal or orthopaedic surgery in a pregnant patient)
- Surgery ≥48 hours post-partum
- Unable to communicate verbally/in writing in English language

7.3 Discontinuation/withdrawal of participants

Subjects will be able to withdraw at any time up until they have completed the questionnaires and handed them back to the local study investigators. If after this time they change their mind about their participation, they will need to contact the local investigators who would then either return or confidentially destroy their questionnaire responses and demographic information. Participants may also withdraw from the 30 day follow up process by contacting the DREAMY Research Team.

8 Participant Recruitment process

Participant recruitment at a site will only commence once evidence of the following approval/essential documents are in place:

1. REC approval
2. HRA approval
3. Host site confirmation of capacity and capability

All sites participating in the study will also be asked to provide a copy of the following:

1. Confirmation of participating site R&D approval

All participants who wish to enter the study will be screened and consented by the site Principal Investigator, one of the qualified clinicians involved in the study as Local Investigator or an affiliated Research Nurse.

Participants will be recruited from the study start date. Recruitment will last until 12 months after the first patient is recruited in each site.

Participants should be first recruited during the time period 0-24h following the index GA. Omission of recruitment during 0-24h time window does not exclude patients from eligibility and recruitment can still occur at 24-48h or later. However, such patients will be unable to retrospectively complete the earlier Brice questionnaire(s).

Patients will be approached by anaesthetists (PI and/or Local Investigators) during routine follow up of GA procedures in obstetric patients (between 0-24h and 24-48h following the index GA) and provided with information about the study. Consent for inclusion will be taken prior to questionnaire completion. Consent may be taken by Local Investigators or by designated Research Nurses.

9 Study procedures

9.1 Informed consent

Written, informed consent will be taken from all participants in the study. Information accompanying all study questionnaires will fully explain the purpose of the research and what the data will be used for. A separate Patient Information Sheet (PIS) will be given to each potential study participant, prior to recruitment.

Participants will be approached on the ward by Local Investigators during their post-operative hospital stay. Routine practice, as specified in national UK guidance [OAA/AAGBI 2013], is for a member of the anaesthetic team to approach patients after surgery to obtain feedback and exclude the occurrence of anaesthetic-related complications. Most frequently this clinical follow up occurs within 24 hours of surgery and whilst the patient is on a post-natal ward. Opportunity will be made of this routine visit to allow participants to be introduced to the study, time permitting and as appropriate.

Patients are under no obligation to enter the study and will be informed that they can withdraw at any time during the study, without having to give a reason. Because of the simple, non-interventional nature of the study, it is expected that most potential participants will be able to

decide rapidly whether or not they wish to enrol. However, the research team acknowledge that new mothers may be busy with their babies and may require more time to decide. Consent will be taken by an anaesthetic Local Investigator or designated Research Nurse who will have knowledge of the study and be able to answer any questions that may be asked.

If patients are too unwell to be included in the study during the first 24h following the index GA then they may be approached at a later stage for inclusion in subsequent follow up, with a note of the variance to standard recruitment protocol and reason for this.

9.2 Modified Brice Questionnaire

Screening for AAGA is being assessed in this study using the Brice Questionnaire, which has been adapted from the original published form [Brice 1970] in accordance with common usage [Avidan 2011]. Questions used in the modified Brice questionnaire are available in Appendix 2. Initial screening will be done by local investigator teams, who will be invited to contact the CI or DREAMY Research Team members with any queries regarding Brice response classification. All Local Investigators will be provided with training to ensure that responses are assessed in a consistent manner. In assessing whether a response should be assigned as “Brice positive”, investigators will be instructed to focus on memories of events that could occur only in the operating room during the anaesthetic and surgical periods. Participant reports of memories during the period between "going to sleep" and "waking up" will be taken as “Yes” answers to any of Q3, Q4 or Q5 or “Awareness” to Q6. Any such responses, indicating possible AAGA, require the Local Investigator to follow the Suspected AAGA follow up protocol (see section 9.3). If an investigator is in any doubt about whether the Brice Questionnaire responses constitute a possible AAGA event, then the responses should be discussed with the local PI and/or CI.

Final classification of Brice responses will be performed by the same expert panel responsible for making final AAGA classification decisions.

9.3 Suspected AAGA follow up protocol

Any patient with Brice questionnaire responses indicating possible memories during the anaesthetic episode will be provided with a secondary structured interview schedule/questionnaire to further detail the characteristics and psychological response to their experience (based upon questions in Appendix 4).

All suspected AAGA cases should be discussed with the local PI or CI. The local investigator or PI should upload the modified Brice CRF responses to the DREAMY REDCap Server as a matter of urgency (ideally on the same day as reported). An explanation of the subsequent DREAMY follow up procedures should be offered to the participant, alongside a choice of initial telephone/face-to-face structured interview schedule or paper questionnaire. The Local Investigator should notify the CI and/or DREAMY Research Team that they have identified a participant with suspected AAGA.

If the participant chooses a paper questionnaire, then this will be administered by the Local Investigator team whilst the participant is still in hospital. Responses are to be transferred according to arrangements with the DREAMY Research Team (to be couriered, collected by a member of the team or transmitted using secure NHS.net email).

If the participant chooses a structured interview schedule, then this can be conducted via telephone or face-to-face. Suspected AAGA interviews will be led by the CI or DREAMY Research Team at the earliest available opportunity. Any travel expenses incurred will be reimbursed to participants.

All Suspected AAGA structured interview schedules and questionnaires are adapted from those used in BAG-RECALL trial [Avidan 2011]) and feature categorical and free-text responses on the detail and nature of recalled events and experiences during anaesthesia, alongside self-reported perioperative context and post-operative psychological consequences.

All suspected AAGA patients will also be offered the PCL-5 PTSD checklist (Appendix 5) at day 30, 3, 6, 9 and 12 months following the index anaesthetic episode. The checklist will be administered via telephone by the DREAMY Research Team (although written forms or face-to-face will be provided if requested). During first administration of the PCL-5 checklist additional target information will be obtained using a structured and multi-dimensional questionnaire on the woman's self-reported mental health history, infant's health status and psychological experiences in the gravidic-puerperal cycle. Question domains have been derived from known risk factors for developing PTSD during the post-natal period [Andersen 2012] and will also be asked to the comparator sample of 300 non-AAGA patients collected during the early phase of the study (see Section 6.5).

An extended AAGA follow up will occur during the 3 month PTSD follow up episode, with a view to investigating the nature of local clinical follow up received by patients and how the AAGA episode has impacted on attitudes towards future anaesthetics and post-natal experience (see Appendix 7 for questions used).

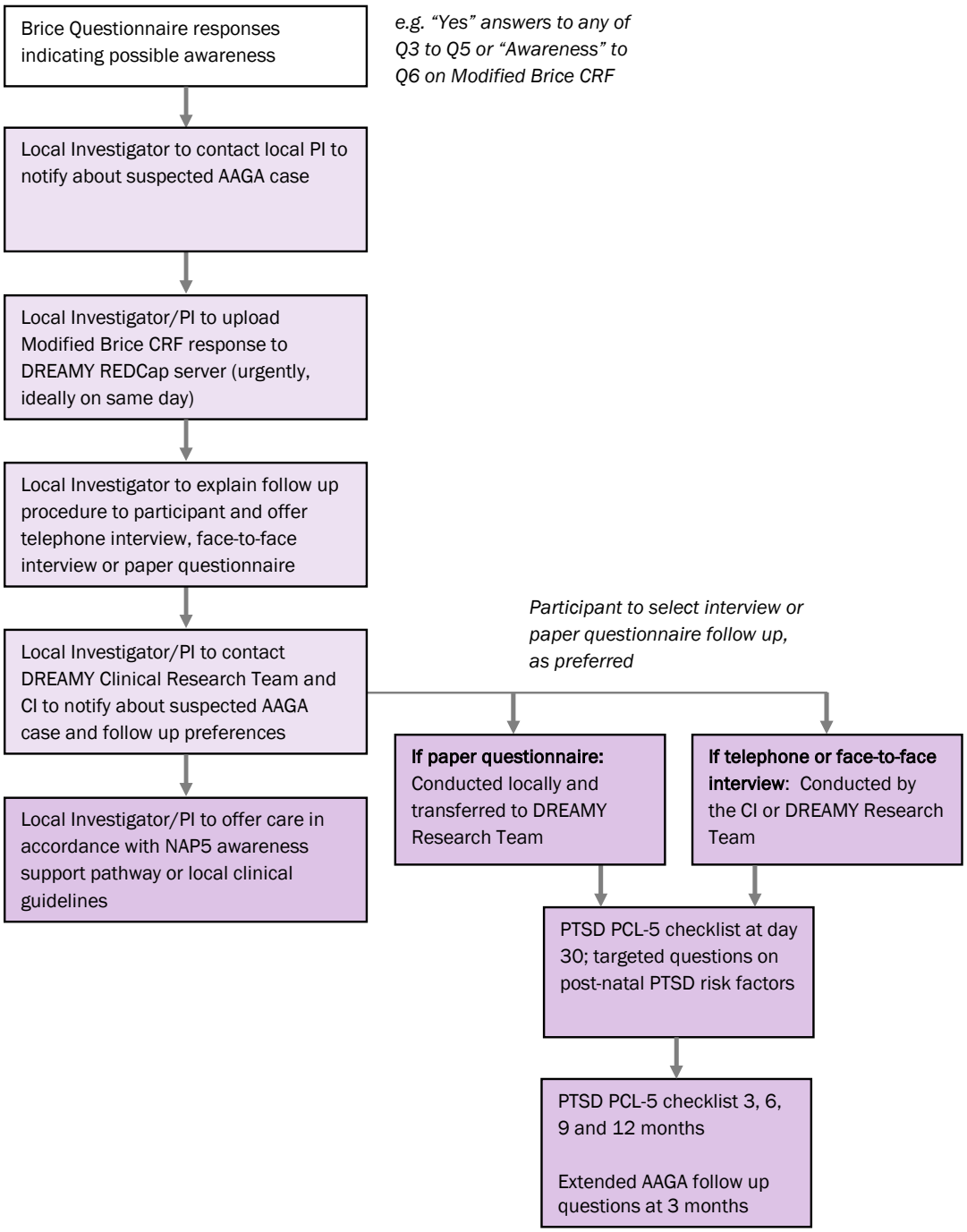

Figure 4. Suspected AAGA Follow Up flowchart

10 Data management and quality assurance

10.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

In order to facilitate follow up of patients at 30 days (i.e. post-hospital discharge) participant's name, contact details and relevant previous study questionnaire responses will be shared between the site of recruitment and by the DREAMY Research Team (Clinical Trial Assistants

(CTA)/Research Nurses at the St. George's Hospital Clinical Research Facility). Data will not be shared between recruitment sites. Confidential patient identifiers will be held for the minimal necessary period. Once 30 day Brice follow up is complete and no suspicion of AAGA is confirmed, patient identifiers may then be deleted from the database record. After data capture for the study has completed, all personal identifiable data will be deleted and the anonymised data transferred to a data safe haven approved by the Sponsor for final analysis and data storage. The electronic study data will be deleted confidentially after a specified time point (10 years after the end of the study).

10.2 Data collection tool

Case Report Forms have been designed by the CI and approved by the protocol authors. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all study personnel responsible for data collection, entry, handling and managing the database.

Data collection tools are used along the following schedule:

Timing	Data collection	Format	Responsible
0-24h	Modified Brice Questionnaire (repetition 1)	Written questionnaire	Local investigators
24-48h	Modified Brice Questionnaire (repetition 2)	Written questionnaire	Local investigators
Any time (ideally 0-48h)	Anaesthetic Episode data collection	Written CRF	Local investigators
Any time "Brice +ve" responses identified	Suspected AAGA Questionnaire	Telephone structured interview schedule (or face-to-face structured interview schedule or written questionnaire)	DREAMY Research Team (if identified at Day 30) or Local Investigators (if inpatient)
Day 30 (+/- 5 days)	Modified Brice Questionnaire (repetition 3)	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team

Day 30 (+/- 5 days)	If "Brice positive": PCL-5 Post-Traumatic Stress Checklist Post-natal PTSD risk factors questions	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team
3 months	If "Brice positive": PCL-5 Post-Traumatic Stress Checklist AAGA Extended follow up	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team
6 months	If "Brice positive": PCL-5 Post-Traumatic Stress Checklist	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team
9 months	If "Brice positive": PCL-5 Post-Traumatic Stress Checklist	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team
12 months	If "Brice positive": PCL-5 Post-Traumatic Stress Checklist	Telephone structured interview schedule (or written questionnaire)	DREAMY Research Team

10.3 Incidental findings

Any findings of relevance to ongoing clinical care will be shared with local care teams, provided participant consent is provided. Local clinical representatives in anaesthesia, obstetrics and midwifery will facilitate the further management and clinical care of participants in the study.

10.4 Data handling and analysis

All data collected, analysed and stored for DREAMY will remain strictly confidential. Data handling will comply with Good Clinical Practice guidelines, the Data Protection Act 1998 and the NHS code of confidentiality.

All data will be collected on paper data case report forms (CRFs). Identifiable patient data will be collected to facilitate follow up at 30 days and referral of any patients with AAGA or other incidental findings back to the local clinical care team.

CRF responses will be taken directly to a secure location accessible by the local Principal Investigator (or Local Investigator) who will enter the data from the paper data collection form onto a secure web-based portal for the study database. All information in paper format for the study will be held securely and treated as strictly confidential in accordance with NHS policies. Data will be entered electronically via a secure encrypted connection into an online portal hosted by St. George's University of London. The software used for data capture will be REDCap™ (Research Electronic Data Capture – http://www.project-redcap.org) [Harris 2009]. REDCap is a mature, secure web application for building and managing online surveys and databases. Access to the

REDCap data entry system will be protected by username/password and created during the Local Investigator registration process.

Confidential patient identifiers will be held for the minimal necessary period. Once 30 day Brice follow up is complete and no suspicion of AAGA is confirmed patient identifiers may then be deleted from the database record.

Adherence to the Sponsor SOP on Data Management JREOSOP0038 will be maintained.

11 Archiving arrangements

The study essential documents along with the study database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this study will be 10 years. This will include any study databases.

Each PI at any participating site will archive the study essential documents generated at the site for the agreed archiving period

12 Statistical design

12.1 Endpoints

12.1.1 Primary endpoints

The primary endpoint is the proportion of obstetric GA patients reporting AAGA in the included sample.

12.1.2 Secondary endpoints

The secondary endpoints are:

1. Descriptors of anaesthetic, surgical and patient factors associated with AAGA
2. 3, 6, 9 and 12 month results of the Post-Traumatic Stress Disorder Checklist (PCL-5), for patients with confirmed AAGA. This will be compared with PTSD incidence in the initial cohort of non-AAGA participants.
3. Qualitative description of the experience of AAGA undergone by obstetric patients.

12.2 Statistical analysis plan

12.2.1 Estimated sample size and expected recruitment

Aggregation of NHS hospital-level audit data collected by PLAN and data for Greater London from the Office for National Statistics [ONS 2014] and Health & Social Care Information Centre [HSCIC 2014] confirms an annual expected birth rate of approximately 150,000 per annum across the maternity units in the Greater London area. Direct data, collected by PLAN from these units, covering 209,982 deliveries indicates that 4,027 GAs were provided to facilitate maternal delivery over the same time period; this is equivalent to a GA proportion of 1.92% (95% CI 1.86% – 1.98%) for all deliveries.

Given the expected annual birth rate of approximately 150,000, we therefore expect approximately 2,880 GA deliveries (95% CI 2,685 – 3,075) over a given 12 month data collection period. Patients undergoing non-LSCS obstetric surgery under GA (e.g. manual removal of placenta) will also be eligible for inclusion: based upon the same audit data this is expected to increase the total number of eligible patients by a factor of 1.12 to 3,225 (95% CI 3008 – 3444) per annum.

We aim to recruit at least 70% of all eligible patients – equivalent to a point estimate of ~2250 included participants over 12 months. Some women will be ineligible to participate due to the inclusion criteria (e.g. must be English speaking). We also expect a proportion of eligible women to decline involvement and the total number of recruitment hospital sites to vary, hence the final included number of participants may be lower or higher than this point estimate.

This is a descriptive observational study with the intent of capturing data from as many eligible participants over a 12 month study period as possible. The power of the expected sample size to exclude the possibility of not detecting an incidence of "Brice positive" AAGA that is at least three times the incidence described in the overall surgical patient population (taken as 0.15% or 1:660 [Sandin 2000]) using an exact binomial test and one-sided α of 0.05 is 88%.

Analysis and post hoc power calculations will be taken at the 12 month threshold, with a view to potentially extending the study dependent upon the confidence interval width of the identified AAGA proportion and ability to make a statistically significant comparison between previously documented incidences for AAGA.

No formal estimate is made for the sample size of the baseline comparator group of non-AAGA patients who will be undergoing PTSD screening at 30 days. A lack of clear evidence regarding PTSD prevalence in patients receiving general anaesthesia for obstetric surgery would make such estimations speculative. Therefore, sample size has been preferentially determined by operational issues and consideration of sample size of studies identified in a previous systematic review of post-natal PTSD [Anderson 2012].

12.2.2 Primary endpoint analysis

The proportion of obstetric GA patients reporting AAGA will be expressed using binomial confidence intervals and compared with established values (see above for rectification of sample size).

There are three competing hypotheses. First, that the event proportion of Brice positivity in obstetrics is similar to that of the general population (i.e. ~1:660). If so, then we expect ~4 patients (binomial 95% CI 1 – 10). Second, that our incidence of Brice positivity will be similar to Paech's already reported incidence (i.e. ~1:152 [Paech 2008]). Then we expect ~15 (95% CI 8 – 25) patients. Third, that the ratio between "Brice positive" and spontaneous reporting as in the general population (i.e. 1:660 vs 1:19,000) is maintained for obstetric patients (i.e. ~1:19). Then we expect 118 patients (95% CI 98 – 141). These figures for each of the three possible outcomes will be compared using Fisher's exact test or chi-squared testing to yield a definitive answer as to which is the most likely hypothesis of the three.

Because we are administering the Brice questionnaire during 0-24h following the index GA (i.e. as soon as possible after GA recovery), we expect to obscure those cases who may otherwise report spontaneously. In other words, we do not expect by our methods to detect spontaneous reporting as such, as the questions will already have been asked. It is possible that some few patients may telephone in after their discharge to report that they now recall AAGA, perhaps triggered by the study, but even that would not fulfil the criterion for spontaneous reporting. We plan to class any such cases as "triggered reporting" and analyse them separately.

Subgroup analysis of the AAGA proportion will be conducted for type and urgency of surgical procedure (including emergency LSCS), de novo conversion from regional anaesthesia to GA and for GA inductions using propofol vs. thiopental.

12.2.3 Secondary endpoint analysis

For secondary outcomes of interest, data will be presented as a number or percentage; mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-parametric data, with 95% confidence intervals (CI). Significance of associations with anaesthetic, surgical and patient factors will be tested using relevant measures of correlation. If sufficient AAGA events are identified, then a multivariable regression model will be used to evaluate the independent association of specific anaesthetic episode variables with AAGA, with results expressed as odds ratios (ORs).

Post-Traumatic Stress Disorder Checklist (PCL-5) results will be expressed as a total symptom severity score (range = 0-80), obtained by summating the scores from each of the 20 checklist items. PCL-5 questions are grouped into 4 domains referring to different symptom criteria: 5 questions refer to symptoms of re-living (cluster B), 2 to avoidance behaviour (cluster C), 7 to emotional blunting (cluster D) and 6 to symptoms of hyper-excitability (cluster E). Symptoms are considered significant when the person scores 2 or more on the item. Women will be considered positive on the PCL-5 when they have at least 1 significant symptom for cluster B, at least 1 for cluster C, at least 2 cluster D items and 2 cluster E [Blevins 2015, National Centre for Posttraumatic Stress Disorder]. PTSD prevalence rates will be estimated for the entire sample and certain subgroups, including AAGA and non-AAGA patients. Results will be expressed with the respective 95% confidence intervals. Fischer's exact test will be used to test the homogeneity of prevalence rates in the subgroups.

Case descriptions of the experiences of AAGA undergone by patients with AAGA will be presented in anonymised format. The phase of anaesthesia/surgery when the AAGA event occurred, alongside possibility contributory, causal or mitigated factors, will be described where possible.

13 Direct access to source data

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

14 Ethics and regulatory requirements

Before any site can enrol patients into the study, the Principal Investigator must be granted written NHS R&D approval – confirmation of capacity and capability.

The site must conduct the study in compliance with the protocol, as agreed by the Sponsor and as given favourable opinion by the Research Ethics Committee (REC) and HRA.

The Chief Investigator will be provided (via the Sponsor) with file indices E.G. JREODOC0003 TMF index and JREODOC0004 ISF index for use with SOP JREOSOP0019 'Preparation and Maintenance of the TMF' The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary R&D approval. Refer to JREOSOP0011 'Management of Amendments'.

Within 90 days after the end of the study, the CI and Sponsor will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study. Refer to JREOSOP0015 'End of study declaration'.

The CI will supply an End of Study report of the clinical study to the REC within one year after the end of the study. The sponsor can provide JREODOC0059 End of Study report template.

The primary ethical issue in any obstetric study is to ensure the welfare of the mother and the baby take priority over any research aims. The psychosocial and physical vulnerability of mothers should always be considered. This study does not involve any physical intervention that could cause any harm or stress. The Brice questionnaire is short and has been designed with the intention that it does not present any significant risk or burden to the patient. However, the patient is under no obligation to participate and complete the questionnaires if they do not wish to.

One consideration of an adverse effect may be that by encouraging a patient to recall if they dreamed or not during the operation, then adverse memories may be triggered at a sensitive time. However, since this questionnaire has been used previously with no report of ill effects, we are confident that the risk of stress induced by the questions is low. In fact, it could certainly be considered advantageous to address the issue of awareness early, whilst a patient is still under the care of the hospital team, rather than to allow symptoms of illness, discomfort or adverse memories to go unexplored and unexplained or to emerge at a later time.

Patients who experience AAGA will benefit from a structured protocol for follow up and provision of support services by local clinical teams.

14.1 Definition of the End of Study

This is defined as the last data entry point.

14.2 Annual Progress Reports

The Chief Investigator will prepare the APR for non CTIMPs. It will be reviewed by the Sponsor and sent to the REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the Ethics Committee, and annually until the study is declared ended.

15 Finance

Funding provided by the OAA/NIAA Large project grant 2016 awarded to the principal applicant Peter Odor.

16 Insurance and indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

17 IP and development policy

Unless otherwise specified in agreements, the following guidelines shall apply: all Intellectual Property Rights and Know How (IP) related to the Protocol and the study are and shall remain the property of the Sponsor excluding:

1) pre-existing IP related to clinical procedures of any Hospital.

2) pre-existing IP related to analytical procedures of any external laboratory.

All contributors:

shall assign their rights in relation to all Intellectual Property Rights and all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake to treat such Know How as confidential information jointly owned between it and the Sponsor.

Nothing in this section shall be construed so as to prevent or hinder a medical professional from using Know How gained during the performance of the study in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of confidential information or the infringement of any Intellectual Property Right of the Sponsor.

18 Publication policy

Publication: “Any activity that discloses, outside of the circle of study investigators, any final or interim data or results of the study, or any details of the study methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the study have a responsibility to ensure that results of scientific interest arising from the study are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the study in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the study, data shall be consolidated over the duration of the study, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the study shall lie with the Sponsor in the first instance.

The DREAMY website will be used to provide free online access to study information. All publications will include “PLAN” as an authorship group, with PIs and Local Investigators individually named as collaborators. The CI and research development team will use lecture and webcast opportunities to publicise study results to healthcare professionals in anaesthesia,

obstetric surgery and critical care. Our lay representative will lead dissemination of important study findings to the public.

19 Statement of compliance

The study will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

20 List of Protocol appendices

Appendix 1 Protocol Amendment/Revision History (chronological order)

Appendix 2 Modified Brice questions

Appendix 3 Anaesthetic episode data collection parameters

Appendix 4 Structured follow-up questions for patients with Suspected AAGA

Appendix 5 PCL-5 PTSD checklist

Appendix 6 Post-natal PTSD risk factors questions

Appendix 7 AAGA Extended follow up questions

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Appendix 1. Protocol amendment / Revision history

Protocol Version and Date Protocol 1.0	New text Version submitted to HRA/REC

Appendix 2. Modified Brice questions

1. What is the last thing you remember before going to sleep?

Being in the pre-op area	☐	Seeing the operating room	☐
Being with family	☐	Hearing voices	☐
Feeling mask on face	☐	Smell of gas	☐
Burning or stinging in the IV line	☐		

Other (Free Text):

2. What is the first thing you remember after waking up?

Hearing voices	☐	Feeling breathing tube	☐
Feeling mask on face	☐	Feeling pain	☐
Seeing the operating room	☐	Being in the recovery room	☐
Being with family	☐	Being in intensive care	☐
Nothing	☐		

Other (Free Text):

3. Do you remember anything between going to sleep and waking up?

No:	☐		
Yes: Hearing voices	☐	Hearing events of the surgery	☐
Unable to move or breathe	☐	Anxiety/stress	☐
Feeling pain	☐	Sensation of breathing tube	☐
Feeling surgery without pain	☐		

Other (Free Text):

4. Did you dream during your procedure?

No:	☐	Yes:	☐

What about (Free Text):

5. Were your dreams disturbing to you?

No:	☐	Yes:	☐

6. What was the worst thing about your operation?

Anxiety	☐	Pain	☐
Recovery process	☐	Functional limitations	☐
Awareness	☐		

Appendix 3. Anaesthetic episode data collection parameters

Age: _____ years **Parity:** G____P____

Procedure:

LSCS ☐ MROP ☐

EUA ☐ Other_____

Urgency of surgery/LSCS:

Emergency/Cat. 1 ☐ Urgent/Cat. 2 ☐

Expedited/Cat. 3 ☐ Elective/Cat. 4 ☐

ASA: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Booking BMI (kg/m²): <18.5 ☐ 18.5-24.9 ☐ 25-29.9 ☐

30-34.9 ☐ >35 ☐

Anaesthesia times: Start ____hh: ____mm Finish ____hh: ____mm

Induction agents:

Thiopentone ☐ Dose_____mg

Propofol ☐ Dose_____mg

Fentanyl ☐ Dose_____mcg

Alfentanil ☐ Dose_____mcg

Other (e.g. Ketamine, Reminfentanil):

_____ Dose_____mg/mcg

De novo or conversion to GA: De novo ☐ Conversion ☐

Indication for GA:

Clinical urgency ☐ Failed regional block ☐

Maternal preference ☐ High spinal ☐

Regional block contraindicated ☐

Other: _____

Rapid sequence induction: Yes ☐ No ☐

Maintenance agent(s): tick all that apply

Sevoflurane ☐ Isoflurane ☐

Desflurane ☐ Nitrous oxide ☐

Propofol (TIVA) ☐ Remifentanil (TIVA) ☐

MAC: Lowest_____ Highest_____ Estimated median_____

Primary airway device:

Cuffed ETT ☐ Igel ☐

LMA Supreme ☐ LMA ☐

If a supraglottic airway device used, was this because of difficult intubation?:

Yes ☐ No ☐

Grade of laryngoscopy: 1 ☐ 2a ☐ 2b ☐ 3 ☐ 4 ☐

Difficult intubation: Yes ☐ No ☐

Please provide additional information where intubation was difficult, for example: How many attempts, use of bougie, change of laryngoscope:

Local/regional anaesthesia:

Spinal	☐	Epidural	☐
CSE	☐	TAP block	☐
Rectus sheath block	☐		

Neuromuscular blockade:

Suxamethonium	☐	Rocuronium	☐
Atracurium	☐	Other_____	

Nerve stimulator use: Yes ☐ No ☐

Reversal use: Neostigmine/glycopyrolate ☐ Sugammadex ☐

Depth of anaesthesia monitor use: BIS ☐ Other_____

Most senior anaesthetist present:

ST3-4	☐	ST5-7	☐
Associate specialist	☐	Staff grade	☐
Consultant	☐	CT1-2	☐

Location of extubation:

Theatre	☐	Critical care (Level 2 or 3)	☐
Recovery	☐		

Post operative destination:

Delivery suite/post natal ward	☐	Critical care (Level 2 or 3)	☐
Delivery suite HDU (midwifery-led)	☐	Other: _____	

Estimated blood loss:

0-499ml	☐	500-999ml	☐
1000-1999ml	☐	>2000ml	☐

Appendix 4. Structured follow-up questions for patients with Suspected AAGA

Part 1. When you completed our first questionnaire, you mentioned that you remembered something between going to sleep at the beginning of your surgery and waking at the end of your surgery. Do you still have memories of events that occurred during your surgery?

Yes ☐ No ☐

A. Can you describe when or how you started remembering it?

Recalled on waking ☐

Memory was there all the time but it took a while to realise what it was a memory of ☐

Memory emerged gradually/gradually pieced together ☐

Something triggered the memory ☐

If something triggered the memory, then do you know what that was?

B. When you remembered, did you tell someone or plan to tell someone about your experience?

C. If so, who did you tell? Why did you tell that particular person?

D. If not, why not?

E. If you told someone, how did they react?

Part 2. What do you remember?

Can you describe in your own words what you remember, what you thought and how you felt?

A. Did you hear anything? (What?)

Voices (gender) ☐ Specific words ☐

Music ☐

Other (Free Text):

B. How did you feel?

Calm ☐ Afraid ☐

Interested ☐ Helpless ☐

Reassured ☐ Trapped ☐

Confused ☐ Distressed ☐

Detached ☐ Surprised ☐

Other (Free Text):

C. What thoughts, if any, went through your mind at the time?

D. If you were you afraid or distressed at the time, what affected you most:

Unexpectedness of the awareness ☐ An experience of pain ☐

An experience of paralysis or inability to move ☐

An inability to communicate to those around you ☐

Fear that something had gone wrong ☐

Something else (please specify):

E. Did you experience any sensations?

Warmth	☐	Pressure	☐
Cold	☐	Pain	☐

Other (Free Text):

F. Did you try to move or speak? If yes, could you?

G. Did you try to open your eyes? If yes, could you?

H. What was your breathing like?

Normal	☐	Fast	☐
Laboured	☐	Unable to breath	☐

Other (Free Text):

I. Did you see anything?

Light	☐	Colours	☐
Shapes	☐	Specific image	☐

Other (Free Text):

Part 3. Did you go to the intensive care unit (may also be called the critical care unit or intensive treatment unit) after your surgery? If yes, did you still have the breathing tube in?

Did not go to intensive care	☐	Did go to intensive care	☐

Remember having a breathing tube in?: Yes ☐ No ☐ Not applicable ☐

B. When do you think your awareness experience occurred?

Before the start of the surgery	☐	During the surgery	☐
When waking up from the surgery	☐		

C. Do you think your awareness experience took place in the operating room or in the intensive care unit or both? Why do you think this?

Operating room	☐	During the surgery	☐

D. How long do you think the awareness experience lasted?

Part 4. Do memories of the event still trouble you now?

A. Do you sometimes feel that you are reliving the experience, or that it is happening to you again?

B. Do you have dreams or nightmares about the experience?

C. Do you feel anxious or fearful about something that you were not anxious about before?

D. Do you feel unusually upset or emotionally numb?

E. Have you felt any negative emotions because of your memories?

Fear	☐	Helplessness	☐
Anger	☐	Frustration	☐

Other (Free Text):

F. Do you avoid any situations as a result of your experiences?

G. Have your social life or relationships been affected?

H. Do you have problems sleeping? Have these changed since your experience?

I. Have you spoken to a health counsellor, GP, psychologist or other professional about these experiences?

Part 4. How would you feel about having an anaesthetic in the future?

A. Would you like to speak to a professional about your experiences?

B. Is it all right with you if we contact you again to talk to you about your experiences?

Yes, you may contact me again ☐

No, I would prefer NOT to be contacted ☐

Appendix 5. PCL-5 PTSD checklist

No.	Response	Not at all (0)	A little bit (1)	Moderately (2)	Quite a bit (3)	Extremely (4)
1	Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2	Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3	Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4	Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5	Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6	Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7	Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8	Trouble remembering important parts of the stressful experience experience?	0	1	2	3	4
9	Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10	Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4

11	Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12	Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13	Feeling distant or cut off from other people?	0	1	2	3	4
14	Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15	Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16	Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17	Being “superalert” or watchful or on guard?	0	1	2	3	4
18	Feeling jumpy or easily startled?	0	1	2	3	4
19	Having difficulty concentrating?	0	1	2	3	4
20	Trouble falling or staying asleep?	0	1	2	3	4

Adapted from Weathers FW, Litz BT, Keane TM, Palmier PA, Marx BP, Schnurr, PP. (2013). The PTSD Checklist for DSM-5 (PCL-5) – Standard [Measurement instrument]. Available from http://www.ptsd.va.gov/professional/ assessment/adult-sr/ptsd-checklist.asp

Appendix 6. Post-natal PTSD risk factors questions

1. Infant complications

A. Gestational age

≥ 37/40	☐	<37/40 (pre-term)	☐
Don't know	☐		

B. Perinatal outcome

Live birth	☐	Still birth	☐
Early neonatal death (<7/7)	☐		

C. Birth weight

≥ 2500g (≥ 5lb 8oz)	☐	1500-2499g	☐
<1500g (<3lb 5oz)	☐	Don't know	☐

D. Admission to neonatal ICU

No:	☐	Yes:	☐

2. Maternal mental wellbeing

A. Psychological disorder prior to or during index pregnancy

None:	☐	Depression:	☐
Anxiety trait or panic attacks:	☐	Previous PTSD:	☐

B. Postpartum depression

No:	☐	Yes:	☐

3. Maternal support

A. Please rate the quality of support you have received from healthcare professionals (e.g., hospital staff, midwife, GP). Please rate on a scale of 0 (no support) to 4 (excellent support).

No support (0)	A little support (1)	Moderate support (2)	Quite a bit of support (3)	Excellent support (4)

B. How much do friends and family support you?

No support (0)	A little support (1)	Moderate support (2)	Quite a bit of support (3)	Excellent support (4)

Appendix 7. AAGA Extended follow up questions

Part 1. Have you had any further memories, recollections or thoughts about your experience during the anaesthetic?

Part 2. Please think back to the time when your first remembered having an awareness experience.

Did you want to speak to a member of the anaesthetic team at your local hospital about your awareness experience?

Yes ☐ No ☐

Was the opportunity made available for you to speak a member of the anaesthetic team at your local hospital?

Face to face meeting:

Yes ☐ No ☐

Telephone discussion:

Yes ☐ No ☐

Other _____

If you had a meeting, then when did this take place?

Within 24 hours of reporting having awareness ☐

1-2 days after reporting awareness ☐

3-7 days after reporting awareness ☐

>7 days after reporting awareness ☐

Before hospital discharge ☐ After hospital discharge ☐

Did you feel that the local team listened to your story and experience?

Yes ☐ No ☐

Did anyone apologise or express regret to you about your experience?

Yes ☐ No ☐

Who else have you seen as part of your follow up for your awareness experience?

Please rank how helpful you found each specialist, relative to others (please rank as 1 the specialist that offered you the most emotional or practical support to enable you to understand and come to terms with your experience).

Anaesthetist ☐ How many meetings? _____ Rank _____

Clinical Psychologist ☐ How many meetings? _____ Rank _____

Psychiatrist ☐ How many meetings? _____ Rank _____

GP ☐ How many meetings? _____ Rank _____

Counsellor ☐ How many meetings? _____ Rank _____

Other _____ ☐ How many meetings? _____ Rank _____

If you haven't already then would you like to speak to any of the following:

Clinical Psychologist ☐ Psychiatrist ☐

GP ☐ Counsellor ☐

Did you receive any feedback regarding any local investigation that may have taken place to find the cause of your awareness incident?

Yes ☐ No ☐

How would you grade the quality of support you received following reporting your awareness event?

Very poor (0)	Poor (1)	Moderate (2)	Good (3)	Very good (4)

What aspects of your post-awareness support did you find particularly helpful?

What aspects of your post-awareness support did you not find helpful?

How might you improve post-awareness support for other patients?

Part 3. How do you feel now about having an anaesthetic again?

Have you received another general anaesthetic since your experience?

Yes ☐ No ☐

If so, then how many?

What was your experience around the subsequent general anaesthetics?

Part 4. Do you feel that your awareness experience has impacted upon your ability to care for your baby? If so, then how?