CSF rhinorrhoea after endonasal intervention to the anterior skull base (CRANIAL): proposal for a prospective multicentre observational cohort study

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CSF rhinorrhoea after endonasal intervention to the anterior skull base (CRANIAL): proposal for a prospective multicentre observational cohort study

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ABSTRACT

Background: The endonasal transphenoidal approach (TSA) has emerged as the preferred approach in order to treat pituitary adenoma and related sellar pathologies. The recently adopted expanded endonasal approach (EEA) has improved access to the ventral skull base whilst retaining the principles of minimally invasive surgery. Despite the advantages these approaches offer, cerebrospinal fluid (CSF) rhinorrhoea remains a common complication. There is currently a lack of comparative evidence to guide the best choice of skull base reconstruction, resulting in considerable heterogeneity of current practice. This study aims to determine: (1) the scope of the methods of skull base repair; and (2) the corresponding rates of postoperative CSF rhinorrhoea in contemporary neurosurgical practice in the UK and Ireland.

Methods: We will adopt a multicentre, prospective, observational cohort design. All neurological units in the UK and Ireland performing the relevant surgeries (TSA and EEA) will be eligible to participate. Eligible cases will be prospectively recruited over 6 months with 6 months of postoperative follow-up. Data points collected will include: demographics, tumour characteristics, operative data), and postoperative outcomes. Primary outcomes include skull base repair technique and CSF rhinorrhoea (biochemically confirmed and/or requiring intervention) rates. Pooled data will be analysed using descriptive statistics. All skull base repair methods used and CSF leak rates for TSA and EEA will be compared against rates listed in the literature.

Ethics and dissemination: Formal institutional ethical board review was not required owing to the nature of the study – this was confirmed with the Health Research Authority, UK.

Conclusions: The need for this multicentre, prospective, observational study is highlighted by the relative paucity of literature and the resultant lack of consensus on the topic. It is hoped that the results will give insight into contemporary practice in the UK and Ireland and will inform future studies.

Introduction

The endonasal transphenoidal approach (TSA) has emerged as the preferred approach in order to resect pituitary adenoma and related sellar pathologies owing to its superior effectiveness and safety profile when compared to transcranial approaches.1,2 This approach is defined by its purpose of accessing the sella turcica through the sphenoid bone. Whilst traditionally performed microscopically, recent technological advances have allowed the TSA to be performed with success endoscopically.1,3 Furthermore, building on these endoscopic techniques, the development of the expanded endonasal approach (EEA) has further improved access to the anterior skull base.4 This approach refers to a modified transsphenoidal approach (TSA) to the anterior skull base.5

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to accessing an area beyond the sella alone, bounded by the frontal sinus, cribriform plate, medial orbital wall, cavernous sinus, posterior clinoid processes, and clivus.5 The EEA is used for the surgical management of many pathologies including large pituitary adenomas, craniopharyngiomas, meningiomas, Rathke’s pouch cysts, clival chordomas and chondrosarcomas.7

Despite the advantages these approaches offer, cerebrospinal fluid (CSF) rhinorrhea remains a common complication and may lead to significant morbidity including prolonged hospital stay, headaches, pneumocephalus, and meningitis.6–8 CSF rhinorrhea occurs with the disruption of the tissue between the subarachnoid space and sinonasal cavity, namely the meninges, skull base, sinonasal mucosa.8 Arguably, therefore, the most important risk factor for the development of a CSF rhinorrhea is the method of reconstruction of the skull base5 (Figure 1). Other risk factors for postoperative CSF rhinorrhea include elevated BMI, prior cranial radiotherapy, prior cranial surgery, tumour size, local tumour infiltration, high-flow intraoperative CSF leak and surgeon experience.5,9–12 Commonly cited skull base repair methods include the use of fat or fascia grafts, nasoseptal flaps and lumbar drains.13 There is, however, a multitudinous array of techniques and combinations available, including direct dural closure (for example, with sutures), dural replacement (for example, Durepair or fascia lata), synthetic grafts (for example, TachoSil® Gelfoam®), butresses (for example, Titanium mesh or Medpor®), tissue glues (for example, Evicel® or Adherus®) and nasal packing (for example, ballooned catheters or Nasopore®).5,14

There is a suggestion that the use of nasoseptal flaps is particularly beneficial in the setting of large defects (>3cm) and/or high CSF flow.15,16 Similarly, a recent randomised controlled trial concluded that perioperative lumbar drain use decreased CSF rhinorrhea rates when combined with nasoseptal flap repair (in the context of dural defects >1cm² and high flow intra-op CSF leak).17 Overall, however, there is a lack of comparative evidence to guide the ideal choice of skull base reconstruction.13 This is the circumstance in both first and second attempts of leak repair, as well in both high and low CSF flow situations.17 Thus, there is considerable heterogeneity in current practice and is based mostly on surgeon preference.13 Similarly, there is marked variation in resultant CSF leak rates, estimated at up to 5% for TSA and up to 20% for EEA.5,6,11

To this end, this study aims to determine: (1) the scope of the methods of skull base repair; and (2) the corresponding rates of postoperative CSF rhinorrhea in contemporary neurosurgical practice in the UK and Ireland.

**Methods**

**Design**

We will adopt a multicentre, prospective, observational cohort study design.18 All neurosurgical units (NSUs) in the UK and Ireland performing the relevant surgeries (TSA and EEA) will be eligible to participate. The study will be registered as a quality improvement project on a local level, with registration in accordance with the local audit department and Caldicott guardian approvals if needed.

The project will be run through the Neurology and Neurosurgery Interest Group (NANSIG; https://nansig.org/) and British Neurosurgical Trainee Collaborative (BNTRC; https://www.bntrc.org.uk/) networks. Each participating centre will have an appointed consultant, trainee and junior doctor or student lead for the project. Consultant neurosurgeons will be contacted in advance and invited to join the project steering group by the central study team before local students and trainees are recruited. Local teams will be provided with supporting materials to facilitate the uniform set-up of the project, for example, project registration templates (Supplementary Appendix A) and explanatory figures/definitions (Supplementary Appendix B).

**Eligible patients**

Included cases will be patients of all ages undergoing TSA for sellar tumours and EEA for skull base tumours. Exclusion criteria include patients undergoing transcranial surgery and those with a history of preoperative CSF rhinorrhea.

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**Figure 1.** This image illustrates an example method by which the anterior skull base may be repaired following transsphenoidal surgery.
**Case recruitment**

As the study aim is to capture contemporary practice over the study period, stopping criteria will be time-based – with eligible cases being prospectively recruited over six months from the study launch date, and with six months of postoperative follow-up for each case. This time period was chosen for pragmatic reasons, allowing for trainees to support the study for its entire one-year duration. We estimated this would include sufficient patients for meaningful analysis.

**Data collection**

Data points collected will include: demographics, tumour characteristics, operative data, and postoperative outcomes (Table (1–5)). Baseline, operative and postoperative data points will be collected within 30 days of admission whilst follow-up outcomes will be collected within six months of surgery.

Pseudo-anonymised data will be collected locally and submitted to a secure web-based central database hosted by Castor Electronic Data Capture (https://www.castoredc.com/). Local data sources will include patient case files, multidisciplinary team discussions, theatre lists/logbooks and local registries/databases. Data will be collected by a member of the clinical team caring for the patient or member of the approved audit team. Importantly, the primary outcomes of the study will be: (1) methods of intraoperative skull base reconstruction used, and (2) postoperative CSF rhinorrhoea biochemically confirmed and/or requiring intervention (CSF diversion and/or operative repair). These primary outcomes will be compared with rates reported from the literature (Table 6). Secondary outcomes will be: (1) Intraoperative CSF leak; (2) operating time; (3) rates of other postoperative complications; and (4) length of hospital stay.

**Data accuracy**

All data points collected by medical students must be approved for accuracy by the local trainee or consultant lead before final submission into the Castor EDC system. Furthermore, specific data points must be discussed with the operating surgeon(s) before submission and this is highlighted by the Castor datasheet, for example, presence and grading of intra-op CSF leak, max diameter of skull base defect and exact methods of skull base repair used. Illustrations and clear definitions will be presented to support the accurate recognition of the various skull base repair techniques and facilitate standardised discussion (Supplementary Figures 1–3, Appendix B). The study procedure has been piloted in three NSUs – the National Hospital for Neurology and Neurosurgery (London), the John Radcliffe Hospital (Oxford) and Addenbrooke’s Hospital (Cambridge). Our pilot experience was formative in refining the data collection pro-forma and illustrated the feasibility and acceptability of the project process. Of note, adaptations to operative notes by surgeons (to explicitly display CRANIAL data points), impacted data collection efficiency and accuracy and will be encouraged going forward.

Local student and trainee leads must meet with the supervising consultant at the half-way mark (three months of case recruitment) for review of data collected, progress update and to troubleshoot any problems encountered. Additionally, the local student and trainee leads must meet with the supervising consultant again at the end of the case recruitment period (six months). Lastly, a final review meeting will occur at the end of data collection (at 12 months). This is a final review and sign off of data collected and marks the end of the local study.

Finally, data validation will be performed in all centres to audit data accuracy before data analysis. This will involve an independent data validator (who is not part of the local CRANIAL team) who is from the centre in which the data was collected. This is to facilitate working within the agreements set out by local audit/service evaluation processes and Caldicott guardian approval. 10% of the centre’s cases (selected randomly) will be reviewed, comparing the data submitted to raw data sources for accuracy. The target for data is accuracy is >95% with no case duplication. Conflicts between actual and submitted data will be resolved by discussion between the validator and local team, with oversight from a steering committee member. If data accuracy is <95%, the local team will then be asked to update all local data accordingly. A re-audit of 10% of the centre’s cases (selected randomly) will then be repeated. If the requested updating of data is not performed or data accuracy remains <95%, data from the respective centre will be analysed separately or excluded.

**Data analysis**

Pre-processing steps will include re-categorising free text entries into existing similar data categories and grouping free text entries into new data categories.

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**Table 1. Preoperative dataset to be collected via the online castor electronic data capture form.**

| No. | Variable | Definition | Metric type | Metric/Unit |
|-----|----------|------------|-------------|-------------|
| 1   | Age      |            | Discrete    | Years       |
| 2   | Biological sex |          | Nominal     | Male, Female |
| 3   | BMI >30? | Body mass index >30 (i.e. obese) | Nominal | Yes, No, Not available |
| 4a  | Visual loss at presentation? | Loss of visual acuity or visual field at presentation pre-op. | Nominal | Yes, No, Not available |
| 4b  | If yes to question 4a: Is the patient blind (binocular and < 6/60)? | Presence of blindness at presentation (both eyes and formally assessed) | Nominal | Yes, No, Not available |
| 5   | Preoperative anterior pituitary insufficiency requiring hydrocortisone? | | Nominal | Yes, No, Not available |
| 6   | Preoperative posterior pituitary insufficiency requiring desmopressin (DDAVP)/ Antidiuretic hormone (ADH)? | | Nominal | Yes, No, Not available |
| 7   | Tumour type? | | Nominal | Pituitary adenoma (functioning), Pituitary adenoma (non-functioning), Craniopharyngioma, Rathke’s Cleft Cyst, Meningioma, Chordoma, Other (please specify) |
| 8   | Tumour maximum diameter? (on radiology) | | Ordinal | <1 cm, >1 cm |
| 9   | Optional: Any other comments? (See help text for examples) | Help text: For example, preoperative CSF diversion (LPs, Lumbar drains) or pressure measurements (opening pressure, ICP), etc | Free text | Free text |
Table 2. Operative dataset to be collected via the online castor electronic data capture form.

| No. | Variable Definition | Metric type | Metric/Unit |
|-----|---------------------|-------------|-------------|
| **Category: Operative data** | | | |
| 10  | Approach for primary surgery | Nominal | Transsphenoidal approach, Expanded endoscopic endonasal approach |
| 11  | Method used for transsphenoidal approach | Nominal | Microscopic, Endoscopic, Both |
| 12  | Date of surgery? | Continuous | Date |
| 13  | Primary or revision surgery? | Nominal | Primary, Revision, Not available |
| 14  | History of sinonasal operations or disease? | Nominal | Yes, No, Not available |
| 14  | Maximum diameter of dural defect at surgery | Ordinal | <1cm, 1–3cm, >3cm, Not available |
| 15a | Neurosurgeon involved? | Nominal | Yes, No, Not available |
| 15b | If yes to question 14a: Grade of the primary operating neurosurgeon | Nominal | Consultant, Registrar |
| 16a | ENT surgeon involved? | Nominal | Yes, No, Not available |
| 16b | If yes to question 15a: Grade of the primary operating ENT surgeon | Nominal | Consultant, Registrar |
| 17  | Neuro-navigation used? | Nominal | Yes, No, Not available |
| 18  | Operative time (in minutes) | Discrete | Minutes |
| 19a | CSF leak detected during surgery? | Ordinal | Grade 0, Grade 1, Grade 2, Grade 3, Leak present but grade unknown. |
| 19b | If yes to question 19a: Method of CSF leak discovery in theatre | Nominal, free text | CSK leak observed without any adjuncts required, Valsalva manoeuvre, Intrathecal fluorescein, Not applicable (arachnoid breach was a planned and necessary part of the operation), Other (please specify) |
| 20a | Method(s) of CSF diversion utilised perioperatively | Nominal, free text | Lumbar drain, Other (please specify), None recorded |
| 20b | If yes to question 20a: When was this peri-operative lumbar drain placed? (Lumbar drains placed in response to post-operative rhinorrhoea are recorded in the ‘Postoperative’ form instead) | Nominal | Pre-procedure (before the patient was taken to theatre), Pre-procedure (in theatre, under the same GA but before skull base surgery begins), Immediately post-procedure (e.g. in theatre or under the same GA) as a prophylactic measure. |

(continued)
| No. | Variable                                                                 | Definition                                                                                     | Metric type        | Metric/Unit                                                                                   |
|-----|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------------------|
| 20c | If yes to question 20a: Type of drainage regime used                     | An example of an ‘other’ regime is when using Liquoguard                                         | Nominal, free text | Volume lead (state mls/hour), Pressure lead (state cmH2O level), Other (please specify)     |
| 20d | If yes to question 20a: For how many days was the drain kept in?        |                                                                                                | Discrete           | Days                                                                                        |
| 21a | Was dura closed directly as part of the repair?                         | Direct dural closure is where separated sections of the dura are approximated back together – for example by using sutures – such that total or near-total apposition is achieved. | Nominal            | Yes, No                                                                                     |
| 21b | If yes to question 21a: How was dura closed?                            |                                                                                                | Nominal, free text | Sutures, Clips, Other (please specify)                                                          |
| 22a | Dural replacement used in the repair?                                    | Dural replacement is a substitute material used specifically to reconstruct the dura – bridging gaps and adding structural integrity. This material can be endogenous tissue (e.g. nasal mucosa) or synthetic (e.g. Duragen). | Nominal            | Yes, No                                                                                     |
| 22b | If yes to question 22a: Type of dural replacement used?                 | An example of endogenous tissue is fascia lata being used to specifically reconstruct the dura | Nominal            | Durarepair®, Duragen™, Durafoam®, Endogenous tissue (please specify), Other (please specify) |
| 22c | If yes to question 22a: Under or overlay? (for dural replacement)       |                                                                                                | Nominal            | Underlay, Overlay, Combined, Not available                                                   |
| 23a | Vascularised flap used in the repair?                                    | A flap is tissue that is moved from a donor site to a recipient site with an intact vasculature. An example in the context of skull base repair is a nasoseptal flap. | Nominal            | Yes, No                                                                                     |
| 23b | If yes to question 23a: Type of vascularised flap used                  | For a flap to be pedicled, the blood supply to the flap tissue must be maintained through the original donor site vessels via a pedicle. | Nominal, free text | Pedicled Nasal Flap, Other (please specify)                                                   |
| 23c | If answer to question 23b ‘Pedicled Nasal Flap’: Where was the pedicled flap taken from? |                                                                                                | Nominal, free text | Nasoseptal, Middle Turbinate, Other (please specify)                                          |
| 24a | Graft (i.e. tissue graft or synthetic graft) used in the repair?         | A tissue graft is tissue that is moved from a donor site to a recipient site without its blood supply. For example fat, mucosa and bone grafts. A synthetic graft is a synthetic material usually in the form of sheets (e.g. Tachosil) or sponges (e.g. collagen sponges), which have been created as alternatives to traditional tissue grafts and thus avoid potential donor site morbidity. | Nominal            | Yes, No                                                                                     |
| 24b | If yes to question 24a: Which types of graft were used in the repair?    |                                                                                                | Nominal            | Tissue Graft, Synthetic Graft, Both                                                            |
| 24c | If answer to question 24a was ‘tissue’ or ‘both’: Material(s) used for the graft |                                                                                                | Nominal, free text | Bone (please specify), Fat (please specify), Mucosa (please specify), Periosteum (please specify), Fascia (please specify), Muscle (please specify), Other (please specify) |
| 24d |                                                                            |                                                                                                | Nominal, free text | (continued)                                                                                  |
With respect to primary study aims, the scope of the methods of skull base repair, will initially be described using descriptive statistics – exploring the incidence density of individual repair methods and repair method combinations within TSA/EEA and CSF leak grade subgroups. Corresponding rates of postoperative CSF rhinorrhoea will be presented as incidence percentages per TSA/EEA subgroups, operating time (will be presented as median and interquartile ranges for TSA and EEA subgroups) and length of hospital stay (will be presented as median and interquartile ranges for TSA and EEA subgroups).

### Ethics and dissemination

Formal institutional ethical board review was not required owing to the nature of the study (seeking to evaluate local services) and this was confirmed with the Health Research Authority, UK. Pseudo-anonymised data will be collected locally and submitted to a secure web-based central database hosted by Castor.
### Table 3. Postoperative dataset to be collected via the online castor electronic data capture form.

| No. | Variable                                                                 | Definition                                                                                                                                                                                                 | Metric type | Metric/Unit |
|-----|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|
|     | **Category: Postoperative data**                                        |                                                                                                                                            |             |             |
| 29  | Length of hospital stay after index surgery? (in days)                   | The index surgery is the main surgical event (e.g. resection of tumour) which was detailed in the 'operative' form (not to be confused with re-operation for surgical complications, which is captured in subsequent forms). | Discrete    | Days        |
| 30  | Postoperative conservative measure(s) utilised to prevent/ treat CSF leak? |                                                                                                                                               | Nominal, free text |             |
| 31  | Postoperative medical measure(s) utilised to prevent/ treat CSF leak?    |                                                                                                                                               | Nominal, free text |             |
| 32  | Were any of the following postoperative complications recorded?         |                                                                                                                                               | Nominal, free text |             |
| 33  | Did postoperative CSF rhinorrhoea occur during the index admission?     | The index admission refers to the admission episode for the operation in question (from arrival to discharge)                                                                                       | Nominal     | Yes, No     |
| 33a | After how many days postoperatively was the CSF rhinorrhoea reported?   |                                                                                                                                               | Discrete     | Days        |
| 33b | If yes to question 33a: How was the postoperative CSF rhinorrhoea confirmed? |                                                                                                                                               | Nominal, free text |             |
| 33c | If yes to question 33a: Did any episode of postoperative CSF rhinorrhoea require CSF diversion and/or operative repair (i.e. an intervention)? |                                                                                                                                               | Nominal     | Yes (please report a 'Return To Theatre'), No |

### Table 4. Follow-up dataset to be collected via the online castor electronic data capture form.

| No. | Variable                                                                 | Definition                                                                                                                                                                                                 | Metric type | Metric/Unit |
|-----|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|
|     | **Category: Follow-up**                                                 |                                                                                                                                            |             |             |
| 34a | Visual outcomes                                                         | Visual improvement with respect to acuity or visual field                                                                                   | Ordinal     | Normal vision, Improved from the initial presentation but not normal vision, Vision has remained stable from the initial presentation but the patient does not have normal vision and is not blind, Deteriorated from the initial presentation but not blind, Blind (binocular and < 6/60), Data not available |
| 34b | If yes to question 34a: How many weeks postoperative is this outcome reported? |                                                                                                                                               | Discrete    | Weeks       |
| 35a | Postoperative anterior pituitary insufficiency requiring hydrocortisone? | Patients with Cushing's disease are excluded from this particular question.                                                                  | Nominal     | Yes, No, Not available |

(continued)
Electronic Data Capture (https://www.castoredc.com/). Only anonymised data will be published and disseminated.

**Conclusions**

The heterogeneity of literature and a lack of consensus on the incidence and management of CSF rhinorrhoea following endonasal skull base procedures supports the need for this multicentre, prospective, observational study. It is hoped that the results will give insight into contemporary practice in the UK and Ireland. Additionally, this study aims to inform future studies and facilitate the establishment of national benchmarks for clinical practice. Finally, we hope that the established CRANIAL network of medical students, trainees and consultants will become a platform for future qualitative and quantitative studies aiming to consolidate evidence-based practice on this topic.

| No. | Variable | Definition | Metric type | Metric/Unit |
|-----|----------|------------|-------------|-------------|
| 35b | If yes to question 35a: How many weeks postoperative is this outcome reported? |  | Discrete | Weeks |
| 36a | Postoperative posterior pituitary insufficiency requiring desmopressin (DDAVP)? |  | Nominal | Yes, No, Not available |
| 36b | If yes to question 36a: How many weeks postoperative is this outcome reported? |  | Discrete | Weeks |
| 37a | Is the patient on testosterone replacement as a result of the index surgery? |  | Nominal | Yes, No, Not available |
| 37b | If yes to question 37a: How many weeks postoperative is this outcome reported? |  | Discrete | Weeks |
| 38a | Is the patient on thyroid replacement as a result of the index surgery? |  | Nominal | Yes, No, Not available |
| 38b | If yes to question 38a: How many weeks postoperative is this outcome reported? |  | Discrete | Weeks |
| 39a | Were any of the following postoperative complications recorded? (If not recorded in the initial ‘postoperative’ form) | If CSF rhinorrhoea was during the index admission, please record in the ‘postoperative’ form instead. Only record Epistaxis if required surgical intervention to treat. Major vascular complication refers to unintended damage to a major blood vessel (e.g. internal carotid artery). | Nominal, free text | Delayed CSF rhinorrhoea, Epistaxis (requiring surgical intervention), New focal neurological deficit, Meningitis/CNS infection, Residual or recurrent disease, Death, Other (please specify), None recorded |
| 39b | If answer to question 39a ‘CSF rhinorrhoea’: How many days after the index surgery is the postoperative CSF rhinorrhoea? |  | Discrete | Days |
| 39c | If answer to question 39a ‘CSF rhinorrhoea’: How was the postoperative CSF rhinorrhoea confirmed? |  | Nominal | Clinical assessment alone, Endonasal inspection using scope, Inspection + intrathecal fluorescein, Beta-2-transferrin, Significant pneumocephalus on CT Head/Head (e.g. for pneumocephalus), Intrathecal fluorescein, Other (please specify), Not available |
| 39d | If answer to question 39a ‘CSF rhinorrhoea’: Did any episode of postoperative CSF rhinorrhoea require CSF diversion and/or operative repair (i.e. an intervention)? |  | Nominal | Yes (please report a ‘Return To Theatre’), No, Not available |
| 39e | If answer to question 39a not ‘CSF rhinorrhoea’ or ‘None recorded’: How many weeks postoperative is the complication(s) reported? |  | Discrete | Weeks |
Table 5. Reintervention for CSF rhinorrhoea dataset to be collected via the online castor electronic data capture form.

| No. | Variable | Definition | Metric type | Metric/Unit |
|-----|----------|------------|-------------|-------------|
| 40  | How many days after the postoperative CSF rhinorrhoea was confirmed, did the intervention take place? | Discrete | Days |
| 41  | Date of surgery | Discrete | Date |
| 42  | Please denote whether this is the patient’s first (1), second (2), third (3), etc. return to theatre for postoperative rhinorrhoea management? | Discrete | Number |
| 43a | Method(s) of CSF diversion utilised postoperatively | Nominal, free text | Lumbar drain, Other (please specify), None recorded |
| 43b | If yes to question 20a: Type of drainage regime used | Nominal, free text | An example of an ‘other’ regime is when using Liquoguard |
| 43c | If yes to question 20a: For how many days was the drain kept in? | Discrete | Days |
| 44a | Was there a direct surgical approach for CSF leak repair? | Nominal | Yes, No |
| 44b | Which approach was used for direct repair? | Nominal, free text | Endonasal, Transcranial, Other (please specify) |
| 45-52 | Repair technique questions as per points 21 – 28 | Discrete | Minutes |
| 53  | Operative time? | Discrete | Bed rest (head of bed unspecified), Bed rest with the head of the bed flat, Bed rest with the head of the bed elevated, Advice to avoid heavy straining/stress (e.g. heavy lifting, sneezing), Other (please specify), None recorded |
| 54  | Postoperative conservative measure(s) utilised to prevent/treat CSF leak? | Nominal, free text | Stool softeners, Prophylactic antibiotics, Acetazolamide, Vaccines (eg. Pneumovax), Other (please specify), None recorded |
| 55  | Postoperative medical measure(s) utilised to prevent/treat CSF leak? | Nominal, free text | Currently, there is no established consensus for TSA or EEA. However, commonly cited methods include fat grafts, fascia grafts, nasoseptal flaps and lumbar drains. |

BMI: body mass index; CSF: cerebrospinal fluid; ENT: ear, nose and throat.

Table 6. Standards derived from literature against which primary outcomes will be compared.

| Surgical approach | Postoperative CSF leak | Skull base repair |
|-------------------|------------------------|------------------|
| Endonasal transphenoidal approach (TSA) | Up to 5\%\cite{11,19} | Currently, there is no established consensus for TSA or EEA. |
| Expanded endonasal approach (EEA) | Up to 20\%\cite{5} | However, commonly cited methods include fat grafts, fascia grafts, nasoseptal flaps and lumbar drains. |

Author contributions

Danyal Z. Khan: Study conception, study design, drafting manuscript, critical revisions of the manuscript; Soham Bandyopadhyay: Study conception, study design, drafting manuscript; Vikesh Patel: Study conception, study design, drafting manuscript; Benjamin Schroeder: Study design, critical revisions of the manuscript; Ivan Cabrilo: Study design, critical revisions of the manuscript; David Choi: Study design, critical revisions of the manuscript; Simon A. Cudlip: Study design, critical revisions of the manuscript; Rishi Sharma: Critical revisions of the manuscript; Georgios Solomou: Study design, critical revisions of the manuscript; James R. Tysome: Critical revisions of the manuscript; Hani J. Marcus: Study conception, study design, drafting of the manuscript, critical revisions of the manuscript; British Neurosurgical Trainee Research Collaborative (BNTRC): Study design; Neurology and Neurosurgery Interest Group (NANSIG): Study design; CRANIAL Steering Committee: Study design, drafting of the manuscript.

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