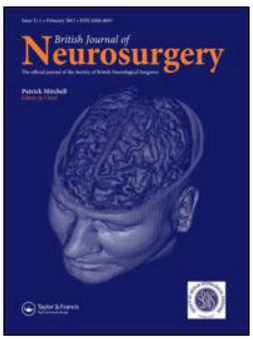

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ORIGINAL ARTICLE

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 transsphenoidal 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 neurosurgical 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.

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Cerebrospinal fluid; CSF; CSF leak; skull base tumours; neuroendoscopy; pituitary surgery

Introduction

The endonasal transsphenoidal 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

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Supplemental data for this article can be accessed here.

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.[5]

Despite the advantages these approaches offer, cerebrospinal fluid (CSF) rhinorrhoea remains a common complication and may lead to significant morbidity including prolonged hospital stay, headaches, pneumocephalus, and meningitis.[6–8] CSF rhinorrhoea 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 rhinorrhoea is the method of reconstruction of the skull base[5] (Figure 1). Other risk factors for postoperative CSF rhinorrhoea 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®), buttresses (for example, Titanium mesh or Medpor®), tissue glues (for example, Eviceal® 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 rhinorrhoea rates when combined with nasoseptal flap repair (in the context of dural defects >1cm^2 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.[13] 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 rhinorrhoea 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 rhinorrhoea.

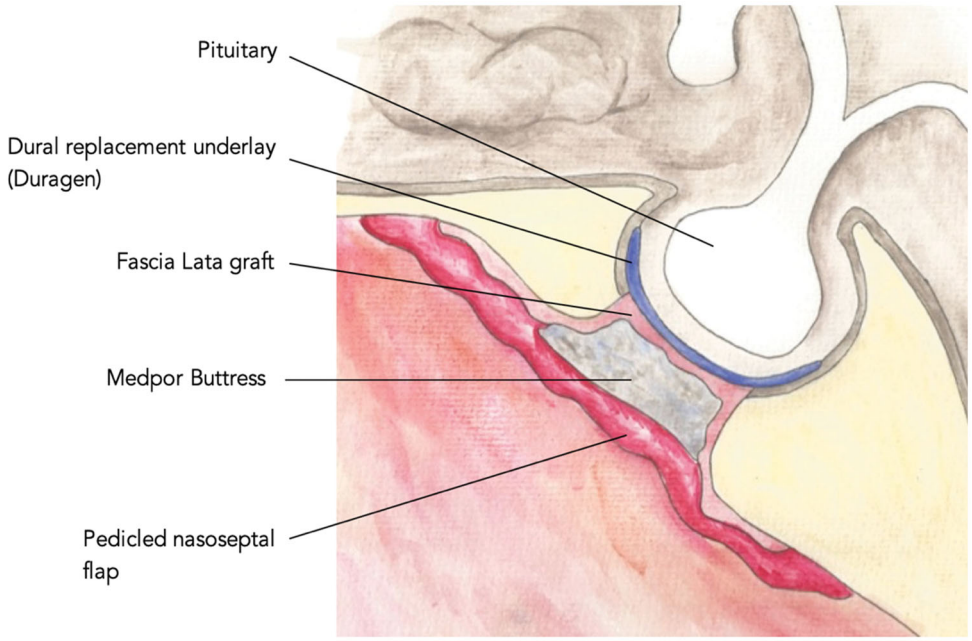

Figure 1. This image illustrates an example method by which the anterior skull base may be repaired following transsphenoidal surgery.

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,[20] 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 proforma 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.

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

No.	Variable	Definition	Metric type	Metric/Unit
Category: Preoperative data				
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, free text	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	The operative approach used for surgery to the previously specified tumour. The transsphenoidal (transsellar) approach is defined by its purpose of accessing the sella turcica through the sphenoid bone. The expanded endoscopic endonasal approach refers to accessing an area beyond the sella alone – bounded by the frontal sinus, cribriform plate, medial orbital wall, cavernous sinus, and clivus.	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	Based on Ref.[15]	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)	Time from incision/procedure start to close/ procedure finish	Discrete	Minutes
19a	CSF leak detected during surgery?	Grade 0 (None). Grade 1 (Small leak without obvious diaphragmatic defect). Grade 2 (Moderate leak with obvious diaphragmatic defect). Grade 3 (Large leak with large diaphragmatic/ dural defect and/or opening of the 3rd ventricle). Leak present but grade unknown.[20]	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	If cerebrospinal leakage was detected intraoperatively, how was it observed or found?	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	CSF diversion refers to allowing the flow of CSF through an alternative passage (e.g. out of the body through a drain).	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*)

Table 2. 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 cmH20 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*)

Table 2. Continued.

No.	Variable	Definition	Metric type	Metric/Unit
	If answer to question 24a was 'tissue' or 'both': Name of synthetic grafts used			Spongestan®, Tachosil®, Gelfoam®, Other (please specify)
24e	If yes to question 24a: Was the buttonhole technique used?	Creation of a bilayer graft (often two grafts stitched together), with one layer squeezed through the dural defect to act as an underlay and the other layer as an overlay on the dural defect.[22]	Nominal	Yes, No
25a	Buttress used in the repair?	A buttress is a material used to stabilise and support the skull base repair materials.	Nominal	Yes, No
25b	If yes to question 25a: Was the gasket seal technique used?	The gasket seal technique refers to the use of an overlay graft that is countersunk into the skull base defect with a rigid buttress to create a watertight seal against the bony margins of the defect.[23]	Nominal	Yes, No
25c	If yes to question 25a: Material(s) used for buttress		Nominal, free text	Bone, Titanium Mesh, Polyethylene e.g. Medpor®, Other (please specify)
26a	Tissue glue used in the repair?	Tissue glue is a liquid monomer, which rapidly polymerizes on contact with living tissues to form a hard-acrylic plastic. An example is Tisseel.	Nominal	Yes, No
26b	If yes to question 26a: Tissue glue(s) used?		Nominal, free text	Evicel®, Tisseal®, Adherus®, Duraseal®, Other (please specify)
27a	Use of nasal pack following repair?	Nasal packing refers to using a material to occupy a nasal space and provide structural support through its local pressure effects. They can also be coated with substances (e.g. bismuth) to augment particular qualities (e.g. haemostasis).	Nominal, free text	Bismuth Soaked Ribbon Gauze, Foley Catheter, Nasopore®, Other (please specify)
27b	If yes to question 27a: Type of nasal pack used		Nominal	Yes, No
27c	If yes to question 27a: Was this nasal pack removed?		Nominal	Yes, No (absorbable nasal pack)
27d	If yes to question 27c: How many days was the nasal pack kept in for?		Discrete	Days
28	Other repair methods used (If any)		Free text	Free text

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 and per repair method used. CSF rhinorrhoea rates for individual centres will not be presented separately. Multivariable logistic regression models will be used to assess the impact of baseline characteristics and skull base repair methods used on postoperative CSF rhinorrhoea. Odds ratios and 95% confidence intervals will be reported. Sub-group analysis will be performed where possible.

Descriptive statistics will be used to summarise baseline characteristics (demographic and operative data points) and surgical outcomes. This includes study secondary outcomes of *rates of other postoperative complications* (will be presented as incidence percentage for TSA and 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.[21] 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	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 straining/stress (e.g. heavy lifting, sneezing), Other (please specify), None recorded
31	Postoperative medical measure(s) utilised to prevent/ treat CSF leak?		Nominal, free text	Stool softeners, Prophylactic antibiotics, Acetazolamide, Vaccines (eg. Pneumovax), Other (please specify), None recorded
32	Were any of the following postoperative complications recorded?		Nominal, free text	Epistaxis (requiring surgical intervention), Cranial Nerve Injury, Major blood vessel injury (carotids, anterior cerebrals), Meningitis/CNS infection, Residual or recurrent disease, Death, Other (please specify), None recorded
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	Clinical assessment alone, Endonasal inspection using scope, Inspection + intrathecal fluorescein, Beta-2-transferrin, CT Head (e.g. for pneumocephalus), Other (please specify), Not available
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*)

Table 4. Continued.

No.	Variable	Definition	Metric type	Metric/Unit
		Therefore please select 'Not applicable' if this is the case.		
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 HeadCT 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

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.

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
Category: Return To Theatre				
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	CSF diversion refers to allowing the flow of CSF through an alternative passage (e.g. out of the body through a drain). Postoperative includes immediately after surgical closure (whilst in theatres) and onwards.	Nominal, free text	Lumbar drain, Other (please specify), None recorded
43b	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 ml/hour), Pressure lead (state cmH20 level), Other (please specify)
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*			
53	Operative time?		Discrete	Minutes
54	Postoperative conservative measure(s) utilised to prevent/treat CSF leak?		Nominal, free text	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
55	Postoperative medical measure(s) utilised to prevent/treat CSF leak?		Nominal, free text	Stool softeners, Prophylactic antibiotics, Acetazolamide, Vaccines (eg. Pneumovax), Other (please specify), None recorded

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 transsphenoidal approach (TSA)	Up to 5%[6,11,19]	Currently, there is no established consensus for TSA or EEA. However, commonly cited methods include fat grafts, fascia grafts, nasoseptal flaps and lumbar drains.[13]
Expanded endonasal approach (EEA)	Up to 20%[5]	

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; Neil Donnelly: Critical revisions of the manuscript; Neil Dorward: Study design, critical revisions of the manuscript; Daniel M. Fountain: Study design, critical revisions of the manuscript; Joan Grieve: Study design, critical revisions of the manuscript; Jane Halliday: Study design, critical revisions of the manuscript; Angelos G. Kolias: Study design, critical revisions of the manuscript; Richard J. Mannion: Study design, critical revisions of the manuscript; Alice O'Donnell: Study design, critical revisions of the manuscript; Nick Phillips: Study design, critical revisions of the manuscript; Rory J. Piper: Study design, critical revisions of the manuscript; Bhavna Ramachandran: Study design; Thomas Santarius: Study design, critical revisions of the manuscript; Parag Sayal: 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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