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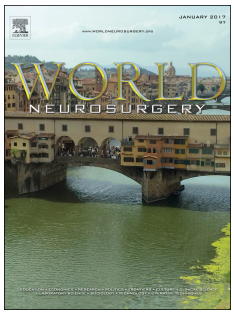

CSF rhinorrhoea after endonasal intervention to the skull base (CRANIAL).

CRANIAL Consortium, Danyal Z. Khan, Hani J. Marcus, Hugo Layard Horsfall, Soham Bandyopadhyay, Benjamin E. Schroeder, Vikesh Patel, Alice O'Donnell, Shahzada Ahmed, Andrew F. Alalade, Ahmad MS. Ali, Callum Allison, Sinan Al-Barazi, Rafid Al-Mahfoudh, Meriem Amarouche, Anuj Bahl, David Bennett, Raj Bhalla, Pragnesh Bhatt, Alexandros Boukas, Ivan Cabrilo, Annabel Chadwick, Yasir A. Chowdhury, David Choi, Simon A. Cudlip, Neil Donnelly, Neil L. Dorward, Graham Dow, Daniel M. Fountain, Joan Grieve, Anastasios Giamouriadis, Catherine Gilkes, Kanna Gnanalingham, Jane Halliday, Brendan Hanna, Caroline Hayhurst, Jonathan Hempenstall, Duncan Henderson, Kismet Hossain-Ibrahim, Theodore Hirst, Mark Hughes, Mohsen Javadpour, Alistair Jenkins, Mahmoud Kamel, Richard J. Mannion, Angelos G. Kolias, Habibullah Khan, Mohammad Saud Khan, Peter Lacy, Shumail Mahmood, Eleni Maratos, Andrew Martin, Nijaguna Mathad, Patrick McAleavey, Nigel Mendoza, Christopher P. Millward, Showkat Mirza, Sam Muquit, Daniel Murray, Paresh P. Naik, Ramesh Nair, Claire Nicholson, Alex Paluzzi, Omar Pathmanaban, Dimitris Paraskevopoulos, Jonathan Pollock, Nick Phillips. Rory J Piper, Bhaskar Ram, Iain Robertson, Elena Roman, Peter Ross, Thomas Santarius, Parag Sayal, Jonathan Shapey, Rishi Sharma, Simon Shaw, Alireza Shoakazemi, Saurabh Sinha, Georgios Solomou, Simon Stapleton, Patrick Statham, Benjamin Stew, Syed Shumon, Wai Cheong Soon, Nick Thomas, Georgios Tsermoulas, James R. Tysome, Adithya Varma, Philip Weir, Adam Williams, Mohamed Youssef

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CSF rhinorrhoea after endonasal intervention to the skull base (CRANIAL). Part 1: Multicentre pilot study

Authors list

CRANIAL Consortium

Danyal Z Khan, Hani J Marcus, Hugo Layard Horsfall, Soham Bandyopadhyay, Benjamin E Schroeder, Vikesh Patel, Alice O'Donnell, Shahzada Ahmed, Andrew F Alalade, Ahmad MS Ali, Callum Allison, Sinan Al-Barazi, Rafid Al-Mahfoudh, Meriem Amarouche, Anuj Bahl, David Bennett, Raj Bhalla, Pragnesh Bhatt, Alexandros Boukas, Ivan Cabrilo, Annabel Chadwick, Yasir A Chowdhury, David Choi, Simon A Cudlip, Neil Donnelly, Neil L Dorward, Graham Dow, Daniel M Fountain, Joan Grieve, Anastasios Giamouriadis, Catherine Gilkes, Kanna Gnanalingham, Jane Halliday, Brendan Hanna, Caroline Hayhurst, Jonathan Hempenstall, Duncan Henderson, Kismet Hossain-Ibrahim, Theodore Hirst, Mark Hughes, Mohsen Javadpour, Alistair Jenkins, Mahmoud Kamel, Richard J Mannion, Angelos G Kolias, Habibullah Khan, Mohammad Saud Khan, Peter Lacy, Shumail Mahmood, Eleni Maratos, Andrew Martin, Nijaguna Mathad, Patrick McAleavey, Nigel Mendoza, Christopher P Millward, Showkat Mirza, Sam Muquit, Daniel Murray, Paresh P Naik, Ramesh Nair, Claire Nicholson, Alex Paluzzi, Omar Pathmanaban, Dimitris Paraskevopoulos, Jonathan Pollock, Nick Phillips. Rory J Piper, Bhaskar Ram, Iain Robertson, Elena Roman, Peter Ross, Thomas Santarius, Parag Sayal, Jonathan Shapey, Rishi Sharma, Simon Shaw, Alireza Shoakazemi, Saurabh Sinha, Georgios Solomou, Simon Stapleton, Patrick Statham, Benjamin Stew, Syed Shumon, Wai Cheong Soon, Nick Thomas, Georgios Tsermoulas, James R Tysome, Adithya Varma, Philip Weir, Adam Williams, Mohamed Youssef.

Affiliations

See Supplementary File 1

Correspondence

Hani J Marcus
National Hospital for Neurology and Neurosurgery &
Wellcome / EPSRC Centre for Interventional and Surgical Sciences, University College London
United Kingdom
Email: hani.marcus@ucl.ac.uk

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CSF rhinorrhoea after endonasal intervention to the skull base (CRANIAL). Part 1: Multicentre pilot study

Abstract

Background:

CRANIAL (CSF Rhinorrhoea After Endonasal Intervention to the Skull Base) is a prospective, multicentre observational study seeking to determine: (1) the scope of skull base repair methods used; and (2) corresponding rates of postoperative CSF rhinorrhoea in endonasal transsphenoidal (TSA) expanded endonasal approaches (EEA) for skull base tumours. We sought to pilot the project - assessing the feasibility and acceptability by gathering preliminary data.

Methods:

A prospective, observational cohort pilot study was carried out at twelve tertiary UK neurosurgical units. Feedback regarding project positives and challenges were qualitatively analysed.

Results:

187 cases were included, 159 TSA (85%) and 28 EEA (15%). The most common pathologies included: pituitary adenomas (n=141/187), craniopharyngiomas (n=13/187) and skull-base meningiomas (n=4/187). The most common skull base repair techniques used were tissue glues (n=132/187, most commonly Tisseel®), grafts (n=94/187, most commonly fat autograft or Spongostan™) and vascularised flaps (n=51/187, most commonly nasoseptal). These repairs were most frequently supported by nasal packs (n=125/187) and lumbar drains (n=22/187). Biochemically-confirmed CSF rhinorrhoea occurred in 6/159 (3.8%) TSA and 2/28 (7.1%) EEA. Four TSA (3%) and two EEA (7%) cases required operative management for CSF rhinorrhoea (CSF diversion or direct repair). Qualitative feedback was largely positive (themes included: user-friendly and efficient data collection, strong support from senior team members) demonstrating acceptability.

Conclusions:

Our pilot experience highlights the acceptability and feasibility of CRANIAL. There is a precedent for multicentre dissemination of this project, in order to establish a benchmark of contemporary skull base neurosurgery practice, particularly with respect to EEA cases.

Introduction

The endonasal transsphenoidal approach (TSA) has developed into the approach of choice for resecting pituitary adenoma and the majority of sellar masses [1, 2]. More recently, the expanded endonasal approach (EEA) has bolstered endoscopic access to the skull base, allowing resection of many pathologies extending beyond the sella alone including large pituitary adenomas, craniopharyngiomas, Rathke's cleft cysts, meningiomas, and clival chordomas [3, 4]. Despite the benefits these minimally invasive approaches afford, cerebrospinal fluid (CSF) rhinorrhoea remains a frequent complication [5-7] with potentially serious consequences, including meningitis, pneumocephalus, low-pressure headaches and prolonged admission [6, 8, 9].

Arguably, the most important determinant for the development of CSF rhinorrhoea is the skull base repair technique used intraoperatively [4]. Other risk factors for postoperative CSF rhinorrhoea include prior cranial radiotherapy or surgery; tumour size and infiltration; high-flow intraoperative CSF leak, dural defect size, elevated body mass index (BMI) and surgeon experience [4, 5, 7, 10-12]. There is a vast array of options and combinations available for repairing the skull base, including direct closure of the dura using sutures or clips; dural reconstruction using autologous fascia or synthetic materials; vascularised flaps (for example, nasoseptal and turbinate flaps); avascular grafts (such as fat grafts), synthetic grafts; and tissue glues (for example, fibrin glues) [4, 12-15]. These repair constructs are often supported by buttresses (for example, septal bone or Titanium mesh), nasal packing (for example, Merocel® packs) and lumbar drains [4, 13, 14]. The choice of repair can be graded in response to numerous factors, such as tumour (type, size, hydrocephalus), defect (size, extent of intra-operative arachnoid breach), patient (BMI, sinonasal disease) and operation (approach, primary or revision) related factors [16, 17]. Previous observational studies suggest that there may be a role for nasoseptal flaps in the context of high-grade intra-operative CSF leak (high flow leaks with large dural defects) [18, 19]. Additionally, a recent randomised controlled trial suggests that perioperative lumbar drain use combined with nasoseptal flap repair (in the context of dural defects >1cm^2 and high flow intra-operative CSF leak), significantly decreases CSF rhinorrhoea rates [20]. However, overall, there is a lack of comparative evidence and consensus as to the optimal reconstruction technique – this is the case in high and low flow intra-operative CSF leaks, small and large dural defects, and primary and revision surgery [14, 16]. Resultantly, there is considerable heterogeneity in current skull base repair protocols (largely based on surgeon opinion) [14] with complimentary variations in CSF rhinorrhoea rates – generally up to 5% for TSA and generally up to 20% for EEA (although as high as 50% in some EEA case series) [4, 7, 8, 21-24].

CRANIAL (CSF Rhinorrhoea After Endonasal Intervention to the Skull Base) is a prospective, multicentre observational study seeking 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 & Ireland [25]. The project is a collaboration between three principle bodies: students and junior doctors via NANSIG (The Neurology and Neurosurgery Interest Group),

neurosurgical speciality trainees via the BNTRC (British Neurosurgical Trainee Research Collaborative) and skull base consultants (neurosurgery and ENT) via the CRANIAL Steering Committee. Thus far, 29 centres (of the 40 adult and paediatric neurosurgical centres in the UK & Ireland) have been recruited to join the project with each centre having a local team of consultants, trainees, junior doctors and medical students.

Before national dissemination, the project was piloted at selected centres. The utility of piloting multicentre studies before scaling is well established and includes: assessing protocol feasibility, logistical planning, refining data collection and recruitment instruments, and increasing the investment of key stakeholders [26]. The Consolidated Standards of Reporting Trials (CONSORT) statement has recently extended its guidelines to include feasibility projects – recognising their role in refining methodologies and processes prior to definitive multicentre studies [27]. In the context of previous BNTRC studies, reflection on pilot experiences has proved formative in streamlining recruitment, study set-up and data collection before expansion [28].

In this article, we aimed to assess the feasibility, acceptability and practicality of the proposed CRANIAL study. We present preliminary data collected and our experience, the successes and the challenges, in establishing a scalable version of the CRANIAL study.

Methods

Design

A multicentre, prospective, observational cohort study design was implemented across multiple tertiary academic neurosurgical units in 2 phases [29]. Phase 1 (01/11/2019 – 22/3/20) represented non-consecutive case recruitment at Addenbrooke's Hospital (Cambridge, UK), John Radcliffe Hospital (Oxford, UK), National Hospital for Neurology and Neurosurgery (London, UK) and Queen Elizabeth Hospital (Birmingham, UK) (Figure 1). Phase 2 (23/3/20 – 31/7/20) represented up-scaling of the study across 12 centres for consecutive case selection: Aberdeen Royal Infirmary (Aberdeen, UK), Addenbrooke's Hospital (Cambridge, UK), Beaumont Hospital (Dublin, Ireland), Greater Manchester Neurosciences Centre (Salford, UK), John Radcliffe Hospital (Oxford, UK), National Hospital for Neurology and Neurosurgery (London, UK), Royal Hallamshire Hospital (Sheffield, UK), Royal Victoria Hospital (Belfast, UK), Royal Victoria Infirmary (Newcastle-upon-Tyne, UK), Sheffield Children's Hospital (Sheffield, UK) and the Walton Centre (Liverpool, UK). The project was registered as a service evaluation at each centre – garnering approvals from audit departments (and Caldicott guardians when required). The local team consisted of consultant lead(s) with overall project responsibility, trainee lead(s) in charge of data collection and on occasion, student lead(s) for additional support. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used in the preparation of this section of the manuscript [30].

Eligible cases included patients of all ages undergoing TSA for sellar tumours and EEA for skull base tumours [29]. The TSA was defined as surgical access to the sella alone (transsphenoidal) whilst the EEA was defined as acquiring surgical access to an area beyond the sella (e.g. transtubercular, transclival) [25]. Exclusion criteria were: patients undergoing transcranial surgery and those with a history of preoperative CSF rhinorrhoea. Case selection was non-consecutive owing to pauses in collection for data proforma amendments and attaining extra approvals (for example, information governance approvals where requested).

Data collection

Data points collected were: patient demographics, tumour characteristics, operative data, and postoperative outcomes (Table 1) [25]. Of note, dural defects were recorded as <1cm, 1-3cm or >3cm[18], and intra-op CSF leak grade was recorded as Grade 0 (small leak without obvious diaphragmatic defect), Grade 1 (small leak with a small diaphragmatic defect), Grade 2 (moderate leak with obvious diaphragmatic defect) or Grade 3 (large leak typically created as a part of EEA) [17]. Primary outcomes were: (1) methods of intraoperative skull base reconstruction used; and (2) postoperative CSF rhinorrhoea requiring intervention (CSF diversion and/or operative repair).

Local teams submitted data to a secure web-based central database hosted by Castor Electronic Data Capture (https://www.castoredc.com/). All data were collected within 30 days of operation. Data points collected by medical students or junior trainees were confirmed with operating surgeons or

senior members of the team before final submission into the Castor EDC system [25]. To facilitate accurate and standardised discussion of skull base repair techniques, supportive materials were provided: skull base repair taxonomy, illustrations and clear definitions [25].

In addition to the above, qualitative data were collected from local pilot trainee leads with an open question “Tell us about your experience during the CRANIAL project – the positives and challenges”. This information, along with the procedural experience of the management committee overseeing the project, informed a set of iterative changes to the project.

Data validation

Data validation was performed in all three centres to audit quantitative data accuracy. This involved an independent data validator (who did not collect local data) who reviewed datasets for several enrolled cases, selected randomly. This data validator was from the hospital in which the data were collected. The targets for validation were: a secure and accurate record of Castor identification records with corresponding medical record numbers; no case/data duplication; and data accuracy is >95%.

Data analysis

Pooled quantitative data (from phase 1 and 2) were analysed using Microsoft Excel (Version 16.41) to present descriptive statistics. The data were utilised to create tables summarising demographic, tumour and operative characteristics. Tumour characteristics, intraoperative skull base repair technique and dural defect size with associated intraoperative CSF leak grade are graphically depicted. Six-month follow-up data were not available or complete in most cases owing to the recency of data collection and were excluded. Qualitative feedback from local pilot leads from the phase-1 centres was analysed in terms of content using NVivo software (version 12.6.0). Deductive coding was performed by an independent author (DZK). Codes were used to generate themes which in turn were organised into the following categories according to content analysis: 1) pilot positives and 2) pilot challenges.

Results

Data were collected on a total of 187 patients across the tertiary neurosurgical centres, between November 2019 and July 2020 inclusive (Figure 1). There were no duplicates in cases/data in the records audited for data validation. All centres fulfilled the >95% accuracy target per case.

Patient characteristics

The median age of patients within the study was 52 years (range: 7 – 84). There were 95 male patients and 92 female patients. At presentation, body mass index (BMI) was recorded in 182 patients (n=182/187, 97%). Fifty-five patients (n=55/182, 30%) had a BMI greater than 30 (TSA: 50/159, 31%; EEA: 5/28, 18%). The patient's vision at presentation was recorded in 185 patients (n=185/187, 99%). Visual loss (acuity and/or field deficits) was present in 107 patients (n=107/185, 58%) preoperatively (TSA: 89/159 56%; EEA: 18/28, 64%). Forty-four patients (n=44/187, 24%) presented with anterior pituitary deficiency requiring hydrocortisone preoperatively (TSA: 38/159, 24%; EEA: 6/28, 21%). 6 patients (n=6/187, 3%) had posterior pituitary deficiency requiring desmopressin preoperatively (TSA: 5/159, 3%; EEA: 1/28, 4%). Table 1 summarizes the information above.

The majority of tumours were pituitary adenomas (n=141/187, 75%) – mostly macroadenomas (n=132/141, 94%). There were 96 non-functioning pituitary adenomas (n=96/141, 68%) of which 95 were macroadenomas (n=95/96, 99%). Of the functioning pituitary adenomas (n=46/141, 33%), 30 were macroadenomas (n=30/46, 65%). The characteristics of the remaining tumours can be found in Table 2.

Operation characteristics

Operation characteristics are displayed in Table 1. The majority of cases utilised the TSA (n=159/187, 85%). Of the cases that utilised the TSA, 134 were done endoscopically (n=134/159, 84%) and 25 were done microscopically (n=25/159, 16%). The most common tumours operated on via TSA were non-functioning pituitary adenoma (92/159, 58%), functioning pituitary adenoma (45/159, 28%) and Rathke's cleft cysts (7/159, 4%) (Table 2). The EEA was used 28 times (n=28/187, 15%), with the most common tumours operated on being craniopharyngiomas (n=9/28, 32%), meningiomas (n=4/28, 14%) and non-functioning pituitary adenomas (n=4/28, 14%) (Table 2).

Intraoperative CSF leak and dural defects

There were 66 cases (n=66/187, 35%) of intraoperative CSF leak. In seven cases of intraoperative CSF leak (n=7/66, 11%), arachnoid breach was a planned and necessary part of the operation. Regarding TSA cases, CSF leak was present in 46 cases (n=46/159, 29%) with the following severity grades: Grade 1 CSF leak in 23 (n= 23/159, 14%), Grade 2 leak in 16 cases (n=16/159, 10%) and Grade 3 CSF leak in one case (n=3/159, 2%). In some cases (n=6/159, 4%), a CSF leak was detected by the operating surgeon, but the grade was unspecified. Regarding

EEA cases, the majority had an intraoperative CSF leak (n=20/28, 71%): Grade 1 CSF leak in 1 (n= 1/28, 4%), Grade 2 leak in three cases (n=3/28, 11%), Grade 3 CSF leak in eight case (n=8/28, 29%), and unspecified in eight cases (n=8/28, 29%). The majority of cases of intraoperative CSF leak (n= 48/66, 73%) were detected without any intraoperative adjuncts. For six cases (n=6/66, 9%), the Valsalva manoeuvre was performed to detect the CSF leak: all of these being TSA with low flow (Grade 1) leaks. Intrathecal fluorescein was used to detect a CSF leak (unspecified grade) in one case (n=1/66, 2%) in which TSA was utilised.

Intraoperative dural defect maximum diameter was recorded in 111 (n=113/159, 71%) of TSA cases. Among TSA cases, the maximum diameter of the intraoperative dural defect was recorded as <1cm in 41 cases (n= 41/111, 37%), 1-3cm in 70 cases (n= 70/111, 63%), and >3cm in no cases. Intraoperative dural defect maximum diameter was recorded in 19 (n=19/28, 68%) of EEA cases. Among EEA cases, the maximum diameter of the intraoperative dural defect was recorded as <1cm in four cases (n= 4/19, 21%), 1-3cm in 11 cases (n= 11/19, 58%), and >3cm in four cases (n= 4/19, 21%).

Skull base reconstruction and support

Skull base reconstruction included the use of dural repair, dural replacement, glues, haemostatic agents, grafts and pedicled flaps. Compiled EEA and TSA repair technique frequencies per pre-operative and operative risk factors for CSF leak are displayed in Table 3. Figures 2 and 3 demonstrate the heterogeneity of repair technique frequency per centre.

In TSA cases, the most commonly used method for intraoperative skull base repair was tissue glue (n=110/159, 69%): Tisseel® (n=35/110, 32%), Adherus® (n=30/110, 27%), Duraseal® (n=25/110, 23%), Bioglue® (n=9/110, 8%), and Evicel® (n=11/110, 10%). Grafts were used in 77 cases (n=77/159, 48%). The type of graft used was tissue (n=32/77, 42%), synthetic (n=31/77, 40%) or both (n=14/77, 18%). When a tissue graft was used, the materials used included fat (n=42/46, 91%), mucosa (n=3/46, 7%), fascia (n=2/46, 4%), bone (n=3/46, 7%), and muscle (n=1/46, 2%). The most common donor site for the tissue graft was the abdomen (n=40/42, 95%). A Spongostan™ synthetic graft was used in 40 cases (n=40/45, 89%), Tachosil® was used in four cases (n=4/45, 9%), and Gelfoam® was used once (n=1/45, 2%). Twenty-eight cases (n=28/159, 18%) utilised dural replacements (a substitute material used specifically to reconstruct the dura - bridging gaps and adding structural integrity) such as Duragen® (n=21/28, 75%), Duramend® (n=5/28, 18%), and endogenous tissue from the thigh (n=2/28, 7%). In no case was the dura closed directly using sutures or clips. Vascularised flaps were used in 30 cases (n=30/159, 19%) - with 22 (n=22/30, 73%) using a nasoseptal flap, six (n=6/30, 20%) using a sphenoid mucosa flap, one (n=1/30, 3%) using a mucoperichondrial flap, and one (n=1/30, 3%) using a middle turbinate flap. Lastly, several haemostatic agents (n=82/159, 52%) were used, such as Surgiflo® (n=30/82, 37%), Surgicel® (n=28/82, 34%), Fibrilar® (n=17/82, 21%), Floseal® (n=14/82, 17%), Lysosypt® (n=1/82, 1%) and Haemopatch® (n=1/82, 1%).

In terms of EEA cases, the most commonly used method for intraoperative skull base repair was tissue glue (n=22/28, 79%): Tisseel® (n=8/22, 36%), Evicel® (n=5/22, 23%), Adherus® (n=6/22, 27%), and Duraseal® (n=3/22, 14%). Grafts were used in 17 cases (n=17/28, 61%). The type of graft used was tissue (n=7/17, 41%), synthetic (n=6/17, 35%) or both (n=4/17, 24%). When a tissue graft was used, the materials used included fat (n=9/11, 82%), fascia (n=6/11, 55%), periosteum (n=1/11, 9%), and bone (n=1/11, 9%). A Spongostan™ synthetic graft was used in eight cases (n=8/10, 80%), and Tachosil® was used in two cases (n=2/10, 20%). Ten cases (n=10/28, 36%) utilised a dural replacement: Duragen® (n=7/10, 70%), Duraform ® (n=1/10, 10%), Tutoplast® Fascia Lata (n=1/10, 10%), and Fascia Lata (n=1/10, 10%). In no case was the dura closed directly using sutures or clips. Vascularised flaps were used commonly (n=21/28, 72%) - with 19 (n=19/21, 90%) using a nasoseptal flap, one (n=1/21, 5%) using a mucoperichondrial flap, and one (n=1/21, 5%) using a sphenoid mucosa flap. Finally, several haemostatic agents (n=21/28, 76%) were used such as Surgicel® (n=13/21, 62%), Surgiflo® (n=4/21, 19%), Floseal® (n=3/21, 14%) and Haemopatch® (n=1/21, 5%).

Support to the skull base reconstruction was provided by buttresses and/or nasal packing, which were not directly part of the skull base reconstruction but rather, provided external structural stability to the construct. For TSA, a buttress was used in 15 cases (n=15/159, 9%): bone was employed eight times (n=7/15, 47%), Spongostan™ was employed seven times (n=7/15, 47%), and Medpor® was employed once (n=1/15, 7%). Nasal packs were utilised in 99 cases (n=99/159, 63%) that utilised TSA. The types of nasal packs used were Nasopore® (n=77/99, 78%), Merocel® (n=18/99, 18%), and Bismuth Soaked Ribbon Gauze (n=8/99, 8%). Regarding EEA, a buttress was used in four cases (n=4/28, 17%): polyethylene (Medpor) was employed twice (n=2/4, 50%), bone was used once (n=1/4, 25%) and Spongostan was employed once (n=1/4, 25%). Similarly, nasal packs were utilised in 26 cases (n=26/28, 92%). The types of nasal packs used were Nasopore® (n=20/26, 77%), Merocel® (n=5/26, 19%), Bismuth Soaked Ribbon Gauze (n=2/26, 8%), Foley Cather (n=2/26, 8%), and Rapid Rhinos (n=2/26, 8%).

CSF diversion

A method of CSF diversion was utilised in 22 (n=22/187, 12%) cases: 21 cases (n=20/22, 91%) that utilised a lumbar drain (TSA: 11/159, 7%; EEA: 9/28, 32%), one case that utilised a ventriculoperitoneal shunt (TSA case), and one case that utilised an external ventricular drain (EEA case). Of the 20 lumbar drains, five were continuously clamped post-operatively and removed on day two post-operatively, so they in effect did not divert CSF. The 15 remaining lumbar drains remained in situ for a median of five days (range: 2-7 days); four days (range:2 - 6 days) for the TSA group and five days (range: 2 - 7 days) for the EEA group.

Postoperative management

The median length of patient stay was four days (range: 1 – 32 days) for the entire group, three days (range: 1 – 32 days) for the TSA group and 7.5 days (range: 1 – 20 days) for the EEA

group. Conservative measures to reduce the risk of CSF leak were not specified in 37 cases (n=37/187, 20%). The majority of patients (TSA: 123/159, 78%; EEA:19/28, 64%) were advised to avoid straining. Medical therapies to prevent or treat post-operative CSF leak were prescribed in 60 patients (n=60/187, 32%), including stool softeners (TSA: n= 37/159, 23%; EEA: n=4/28, 14%), prophylactic antibiotics (TSA: n=11/159, 7%; EEA= 8/28, 29%), acetazolamide (TSA: n=0/159, 0%; EEA= 1/28, 4%), and Pneumovax® (TSA: n=0/159, 0%; EEA= 2/28, 7%).

Postoperative complications

Overall, 36 patients (n=36/187, 19%) had postoperative complications. The most common complications were diabetes insipidus (TSA: 6/159, 4%; EEA: 7/28, 25%), post-operative CSF rhinorrhoea (see below) (TSA: 6/159, 4%; EEA: 2/28, 7%), and syndrome of inappropriate antidiuretic hormone secretion (TSA: 4/159, 3%; EEA: 1/28, 4%). Other complications involving cases that used TSA included meningitis (n=1/159, 1%), sellar abscess (n=1/159, 1%), pneumonia (n=1/159, 1%), mono-ocular blindness (n=1/159, 1%), unspecified hyponatraemia (n=1/159) and unspecified hypernatraemia (n=1/159, 1%). Among cases that used EEA, other complications included residual disease (n=1/28, 4%), meningitis (n=1/28, 4%), unspecified hyponatraemia (n=1/28, 4%) and unspecified hypernatraemia (n=1/28, 4%).

Postoperative CSF rhinorrhoea

Cases of postoperative CSF rhinorrhoea (n=8; TSA: 6/159, 3.8%; EEA: 2/28, 7.1%), took a median length of two days postoperatively to be reported (range: 1 – 17 days). Two of these cases were in individuals with BMI >30 (TSA: 1/6, 1/2 EEA). In terms of intra-operative CSF leak, four cases had no leak reported (TSA: 4/6, EEA 0/2), there were no cases with grade 1 leak, two cases were grade 2 leak (TSA: 2/6, EEA 0/2) and two cases were grade 3 leak (TSA: 0/6, EEA 2/2). Two TSA cases used CT scanning of the head (looking for pneumocephalus) as a diagnostic adjunct to beta-2-transferrin. Overall, six cases (TSA: 4/6, EEA 2/2) required a return to theatre for operative management (CSF diversion n=1, direct repair =1, both=4) (Table 4).

Qualitative feedback

Qualitative feedback was collected from four pilot leads in phase-1 of the study, informing improvements for phase-2. The content analysis generated 14 codes, refined into six themes (Supplementary Information 2). These themes were then categorised into ‘positives’ and ‘challenges’.

Three principal ‘positives’ were highlighted. Firstly, the data collection interface was complimented – the Castor software was described as “really simple to use, speeds up data collection and is enjoyable to use”, whilst the organisation of the data proforma (via logic trees) facilitated efficient data entry: “Not overwhelming the user with all the unnecessary questions (and only loading them if needed)” and the “flow is logical”. This collection process was complemented by electronic medical record systems at all pilot centres, allowing pilot leads to establish flexible routines: “15 minutes work a week” with “all electronic notes making the data collection very straight forward”. Additionally,

supportive materials provided to local teams were applauded for their utility (sample audit registration forms, study protocol, practical step-by-step guide and skull base methods explanatory diagrams). Comments included: “excellent diagrams explaining the technical nuance of skull base surgery” and “registration was easy because I had a template to follow”. Finally, pilot leads were generally met with receptiveness from senior colleagues – one pilot lead organised a meeting with senior operating members of the team who “amended her operation notes to specifically mention the things I need to collect data on”. This allowed efficient data collection and consistent data verification.

Indeed, local team engagement is crucial to the effective execution of the project. Lapses in this have the potential to present challenges – one pilot lead highlighted: “op notes contain limited information, often standardised text” and that it can be “difficult to get a hold of consultants or StR’s [specialist trainees] to check with them the data points that need to be checked with them or that weren’t clear”. Several approaches were adopted in response to this challenge – one pilot lead met with operating surgeons early-on to adapt operative notes to include additional CRANIAL data points (e.g. CSF leak grade, dural defect size) whilst another pilot lead compiled data points needing verification into a table for weekly verifications with operating surgeons. Moreover, the volume and complex nature of the data posed a challenge initially. There was heterogeneity in the definitions and categorisation for different skull base repair techniques across centres – to address this, a taxonomy diagram, definitions set and explanatory illustrations were generated as above [25]. Specific data points were adjusted and clarified based on feedback, for example, “size of skull base defect” was refined to “max diameter of dural defect” with categorical answer options (and a “not available” option for instances where this was difficult to ascertain). Concerns over future compliance with detailed follow-up data were raised – these data points were rationalised and many were made optional in order to capture primary outcomes without overloading data collectors. The final set of challenges were concerning the future of the project in the context of the COVID-19 pandemic and its impact on endonasal surgery. Guidance for a significant reduction in the amount of endonasal skull base cases was released just after the completion of pilot data collection. The pilot was then formally concluded and COVID-related data points were added to the data proforma for ongoing data collection (published elsewhere).

Discussion

Principal findings

This pilot study has demonstrated the acceptability and feasibility of the current CRANIAL protocol [29]. Acceptability is demonstrated through qualitative feedback from local pilot leads which was largely positive (user-friendly and efficient data collection, felt supported by central CRANIAL team and seniors). Challenges were addressed iteratively (production of supportive materials, adaptations of data proforma), again met positively by pilot leads. Moreover, feasibility is highlighted through the successful registration and execution of the study at 12 tertiary neurosurgical centres, with high-quality data collected on 187 patients.

As expected, the majority of these endonasal cases were pituitary adenomas (n=142/187, 76%) and the most common approach the TSA (n=159/187, 85%). Although our pilot sample is too small to conclude from, it is interesting to note the array of repair techniques used. The most common skull base repair techniques used were tissue glues (Tisseel®, Adherus®, Duraseal®, Bioglue®, and Evicel®) in 132/187 (71%) cases, and grafts (most commonly fat graft and Spongostan™) in 94/187 (50%) cases. These repairs were most frequently supported by nasal packs (Nasopore®, Merocel® and Bismuth Soaked Ribbon Gauze) in 125/187 (67%) cases. Interestingly, nasoseptal flaps were used in only 41/187 (22%) cases and lumbar drains were used in 22/187 (12%) cases. Adjuvant conservative and medical prevention of CSF rhinorrhoea were equally variable (most commonly laxatives and avoiding straining). Incidence of confirmed postoperative CSF rhinorrhoea was 6/159, (3.8%) of TSA cases and 2/28 (7.1%) of EEA cases. In all of these cases, the initial intraoperative skull base repair techniques were heterogeneous. Of note, four of these cases with postoperative CSF rhinorrhoea did not have intraoperative CSF leak detected, suggesting occult intraoperative leak. This is described in other case series', with some authors advocating for universal sellar repair or use of routine intrathecal fluorescein to address this [31, 32].

Findings in the context of literature

In our pilot analysis, the encountered postoperative CSF rhinorrhoea rates are in line with the array of rates cited in the literature. For TSA, the occurrence of CSF rhinorrhoea is generally between 2-5% [7, 8, 21, 22] but has been recorded as high as 10% via meta-analysis [33]. Occurrence in EEA is even more diverse (likely reflecting case-specific variations in exact approach) with rates generally ranging from 5%-20% but as high as 50% [4, 23, 24]. Risk factors for postoperative CSF rhinorrhoea include elevated BMI, intra-operative CSF leak (especially if high flow), prior cranial radiotherapy, prior skull base surgery, tumour size, local tumour infiltration, dural defect size and surgeon experience [4, 5, 7, 10-12, 34].

However, potentially the most important determinant for the development of CSF rhinorrhoea is related to skull base repair technique used intraoperatively [4, 17]. The heterogeneity in skull base repair techniques suggested in our pilot study is echoed in the literature, reflecting the general lack of comparative evidence to guide current practice [14]. Practically, many centres employ graded repair

protocols dependent factors such as dural defect size and CSF leak flow volume [35]. In our series, CSF diversion was used more in the context of tumours >1cm diameter, EEA, high-grade intraoperative CSF leak (Table 3). Similar patterns are noted for the use of vascularised flaps, dural replacement grafts, rigid buttresses and nasal packing on a basis of such CSF leak risk factors (Table 3).

Indeed, several non-comparative studies suggest that in the context of large skull base defects (>3cm) and/or high CSF flow (via the opening of the ventricle or arachnoid cistern), the use of nasoseptal flaps decreases resultant post-op CSF rhinorrhoea [18, 19, 24, 35]. Some authors advocate for graft-based reconstruction (fat, fascia and collagen sponge) in this context [36, 37] whilst others describe a multifaceted approach combining various techniques (e.g. fat, collagen sponge, rigid buttress and nasal packs) with or without lumbar drain for high flow leaks with large dural defects [17, 35]. The only Level 1 evidence supporting practice is a recent randomised controlled trial that found - in the context of dural defects >1cm^2 and high flow intra-op CSF leak repaired with a nasoseptal flap - that the use of perioperative lumbar drain significantly decreased post-op CSF rhinorrhoea rates ($p = 0.017$, odds ratio 3.0, 95% CI 1.2-7.6) [20]. For smaller defects and minor/no CSF leak: fat, fascia and avascular mucosal grafts are described [24, 37]. Other repair protocols support the use of collagen sponge and titanium mesh buttress for such cases [17]. More generally, some surgeons champion dural closure or dural replacements [38, 39] with others suggesting it has little impact in the context of nasoseptal flap use [40]. Similarly, high-level evidence for postoperative CSF leak repair is equally scarce, with lumbar drains and endonasal direct pedicled flap or graft repair frequently reported [41-43]. Evidently, there is widespread variability in skull base repair protocols - this is the circumstance in both high and low CSF flow situations, and in both prevention and repair CSF rhinorrhoea [14].

Limitations

There are several limitations to the study, calling for a tempered assessment of findings. Firstly, owing to the pilot nature of this study, results are of small sample size, particularly with respect to EEA. Cases were not necessarily collected consecutively and owing to recency of cases, follow-up is limited to the immediate postoperative period (the national project will include up to 6 months of follow-up per case). Data points are purely observational and across the context of multiple centres. Practically, data point verification was sometimes a challenge logistically for junior members of the team although ways to mitigate this have been presented and will be useful when scaling-up this project. One such data point was dural defect, which was not recorded in approximately 30% of cases and in the context of TSA was recorded to include sellar dura (a defect in which may not confer the same risk of postoperative CSF leak as dural/arachnoid defects elsewhere).

Conclusions

Our pilot experience highlights the acceptability, feasibility and scalability in the CRANIAL project procedures. Early results suggest heterogeneity in methods used for skull base repair. There is a clear precedent for establishing a benchmark of contemporary practice in skull base neurosurgery in the UK and Ireland via multicentre dissemination of this project.

Ethical approval

Formal institutional ethical board review and informed consent from human participants was not required owing to the nature of the study (seeking to evaluate local services as an observational study) and this was confirmed with the Health Research Authority, UK.

Consent

Not applicable, please see the ethical approval section.

Data availability

Data available upon request

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Figures

Figure 1: Study case flow chart

Figure 2: Correlogram highlight frequency of repair technique category use per centre for transsphenoidal cases

Figure 3: Correlogram highlight frequency of repair technique category use per centre for expanded endonasal cases

Tables

Table 1: Summary of patient demographics on admission and operation characteristics per approach subgroup. TSA = Trans-sphenoidal approach. EEA = expanded endonasal approach. ENT: ear, nose and throat,

Table 2: Number of cases with each type of tumour. TSA = Trans-sphenoidal approach. EEA = expanded endonasal approach.

Table 3: Repair technique categories by selected pre-operative and operative factors.

Table 4: Case series of patients with post-operative CSF rhinorrhoea that were confirmed or required intervention: baseline and tumour characteristics, intraoperative technique and recognition of post-operative CSF rhinorrhoea. BMI: body mass index; TSA: transsphenoidal; EEA: expanded endonasal endoscopic approach; NR: Not recorded; CSF: cerebrospinal fluid; NS: nasoseptal.

Supplementary Information

Supplementary information 1: Author affiliations

Supplementary Information 2: Summary of qualitative feedback from the pilot study leads – themes and component codes.

Tables:

*Table 1. Summary of patient demographics on admission and operation characteristics per approach subgroup. TSA = Trans-sphenoidal approach. EEA = expanded endonasal approach. ENT: ear, nose and throat. * the outlying TSA case which took 512 minutes was an invasive sinonasal cancer which had infiltrated the sella and required concomitant extra-cranial resection.*

Approach	*TSA*	EEA	**Total**
Total patients	159	28	187
Preoperative data			
Median Age (range)	51 years (10-84)	55 years (7-76)	52 years (7–84)
Males	81	14	95
Females	78	14	92
BMI > 30	50	5	55
BMI < 30	109	23	127
Preoperative Visual Loss	89	18	107
No Preoperative Visual Loss	70	9	78
Anterior pituitary deficiency requiring hydrocortisone	38	6	44
Posterior pituitary deficiency requiring desmopressin	5	1	6
Operative data			
Specilaity performing: Neurosurgery only	107	10	117
Specilaity performing: Neurosurgery and ENT	47	17	64
Specilaity performing: ENT only	5	1	6
Endoscopic technique	134	28	162
Microscopic endoscopic	25	-	25
Neuronavigation use	61	22	83
Median operation time (range)	89 minutes (30 – 512)*	192 minutes (64 – 433)	99 minutes (30 – 512)

Table 2: Number of cases with each type of tumour. TSA = Trans-sphenoidal approach. EEA = expanded endonasal approach.

Type of tumour	*TSA*	*EEA*	***Total***
Non-functioning pituitary adenoma	92	4	96
Functioning pituitary adenoma	45	1	46
Craniopharyngiomas	4	9	13
Meningiomas	0	4	4
Rathke's cleft cysts	7	0	7
Apoplexy	2	1	3
Chordomas	1	2	3
Arachnoid cysts	1	1	2
Dermoid cyst	0	1	1
Germinomas	1	0	1
Hypophysitis	1	0	1
Meningoencephalocele	0	1	1
Undefined neuroendocrine tumour	1	0	1
Melanoma metastasis	1	1	2
Prostate metastasis	1	0	1
Lung metastasis	0	1	1
Sinonasal carcinoma	0	1	1
Sinonasal endocrine tumour	1	0	1
Squamous cell carcinoma	0	1	1
Mucinous glands	1	0	1

Table 3: Repair technique categories by selected pre-operative and operative factors.

Category	Dural closure *N (% of category total)*	Dural replacement *N (% of category total)*	Tissue graft *N (% of category total)*	Synthetic graft *N (% of category total)*	Button technique *N (% of category total)*	Tissue glue *N (% of category total)*	Haemostatic agent *N (% of category total)*	Gasket sealing *N (% of category total)*	Buttress *N (% of category total)*	Pedicled flap *N (% of category total)*	Nasal packing *N (% of category total)*	CSF diversion *N (% of category total)*
BMI (if specified)												
<30 (n=126)	0 (0%)	25 (19.8%)	42 (33.3%)	38 (30.2%)	5 (4%)	85 (67.5%)	103 (81.7%)	3 (2.4%)	14 (11.1%)	39 (31%)	83 (65.9%)	4 (3.2%)
>30 (n=55)	0 (0%)	12 (21.8%)	15 (27.3%)	17 (30.9%)	2 (3.6%)	47 (85.5%)	39 (70.9%)	0 (0%)	5 (9.1%)	11 (20%)	37 (67.3%)	3 (5.5%)
Tumour diameter (if specified)												
<1cm (n=18)	0 (0%)	1 (5.6%)	4 (22.2%)	5 (27.8%)	0 (0%)	13 (72.2%)	13 (72.2%)	0 (0%)	2 (11.1%)	2 (11.1%)	10 (55.6%)	0 (0%)
>1cm (n=169)	0 (0%)	37 (21.9%)	54 (32%)	50 (29.6%)	7 (4.1%)	119 (70.4%)	133 (78.7%)	3 (1.8%)	17 (10.1%)	49 (29%)	115 (68%)	7 (4.1%)
Approach												
TSA (n=159)	0 (0%)	28 (17.6%)	47 (29.6%)	45 (28.3%)	7 (4.4%)	110 (69.2%)	121 (76.1%)	1 (0.6%)	15 (9.4%)	30 (18.9%)	99 (62.3%)	12 (7.5%)
EEA (n=28)	0 (0%)	10 (35.7%)	11 (39.3%)	10 (35.7%)	0 (0%)	22 (78.6%)	25 (89.3%)	2 (7.1%)	4 (14.3%)	21 (75%)	26 (92.9%)	10 (35.7%)
Intraoperative CSF leak grade (if specified)												
Grade 0 (n=121)	0 (0%)	18 (14.9%)	24 (19.8%)	33 (27.3%)	2 (1.7%)	74 (61.2%)	99 (81.8%)	1 (0.8%)	12 (9.9%)	17 (14%)	74 (61.2%)	2 (1.7%)
Grade 1 (n-24)	0 (0%)	5 (20.8%)	13 (54.2%)	8 (33.3%)	1 (4.2%)	22 (91.7%)	15 (62.5%)	0 (0%)	1 (4.2%)	6 (25%)	14 (58.3%)	1 (4.2%)
Grade 2 (n=19)	0 (0%)	3 (15.8%)	10 (52.6%)	5 (26.3%)	3 (15.8%)	18 (94.7%)	13 (68.4%)	0 (0%)	4 (21.1%)	10 (52.6%)	17 (89.5%)	1 (5.3%)
Grade 3 (n=9)	0 (0%)	4 (44.4%)	6 (66.7%)	3 (33.3%)	0 (0%)	9 (100%)	8 (88.9%)	0 (0%)	0 (0%)	8 (88.9%)	7 (77.8%)	2 (22.2%)

Table 4: Case series of patients with post-operative CSF rhinorrhoea that were confirmed or required intervention: baseline and tumour characteristics, intraoperative technique and recognition of post-operative CSF rhinorrhoea. BMI: body mass index; TSA: transsphenoidal; EEA: expanded endonasal endoscopic approach; NR: Not recorded; CSF: cerebrospinal fluid; NS: nasoseptal.

Case	Age, Sex	BMI >30	Tumour Type	Tumour diameter >1cm	Operative Approach	Dural Defect	Intra-op CSF Leak Grade	Intraoperative Repair	Post-op CSF Rhinorrhoea	Return to Theatre
1	38, male	Yes	Non-functioning pituitary adenoma	Yes	TSA	<1cm	0	Tisseel®, Nasopore®	2 days post-op (via beta-2 transferrin)	No (conservative management)
2	31, male	No	Dermoid cyst	Yes	EEA	1-3cm	3	Pedicled NS flap, Spongostan™, Tisseel®, Nasopore® + Merocel®	6 days post-op (via beta-2 transferrin)	Yes (direct repair)
3	60, female	No	Lung metastasis	Yes	EEA	NR	3	Duragen™, fascia lata graft, Nasopore®	2 days post-op (via beta-2 transferrin)	Yes (lumbar drain)
4	51, male	Yes	Non-functioning pituitary adenoma	Yes	TSA	1-3cm	0	Fat graft, Spongostan™, Duraseal, Surgiflo	1 day post-op (via beta-2 transferrin & CT head)	Yes (lumbar drain & direct repair)
5	10, female	No	Cranioph-aryngioma	Yes	TSA	1-3cm	2	NS flap, Tisseel, Surgicel, Spongostan, Nasopore	9 days post-op (via beta-2 transferrin)	Yes (lumbar drain & direct repair & VP Shunt)
6	30, male	No	Arachnoid cyst	Yes	TSA	1-3cm	2	Duragen, NS flap, Tisseel, Nasopore	17 days post-op (via beta-2 transferrin & CT head)	Yes (lumbar drain & direct repair)
7	76, male	No	Sinonasal carcinoma	Yes	TSA	>3cm	0	Mucoperichondrial flap, pericranial fascia graft, Tachosil, bone buttress, Sinofoam pack	1 day post-op (via clinical assessment alone)	Yes (lumbar drain & direct repair)
8	43, female	No	Non-functioning pituitary adenoma	Yes	TSA	<1cm	0	Surgiflo	2 days post-op (via beta-2 transferrin)	No (conservative management)

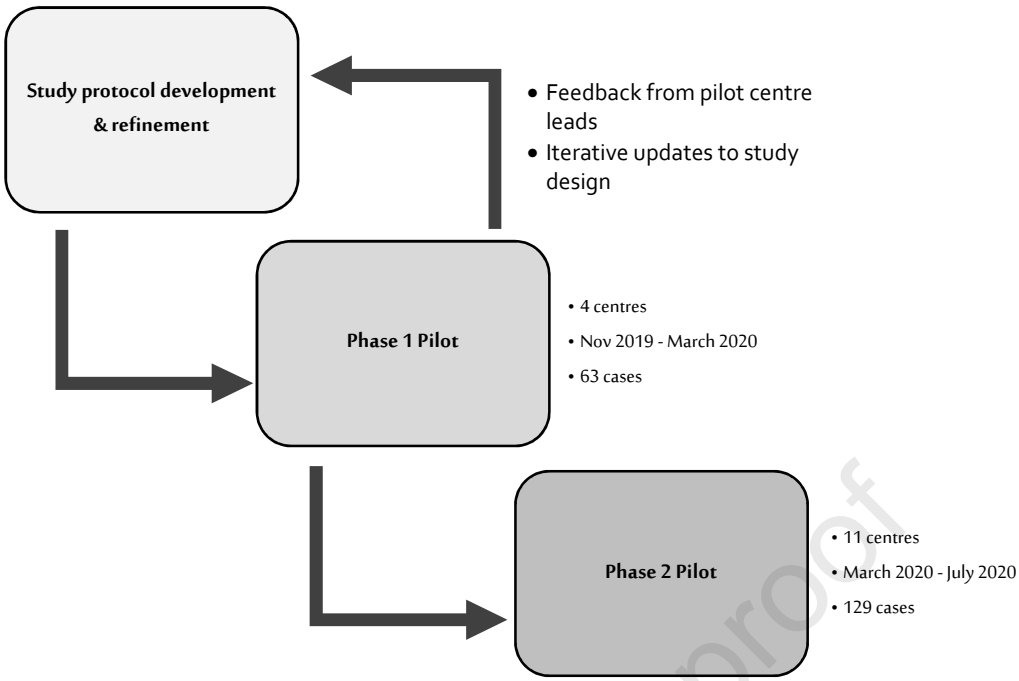

Figure 1: Pilot study process overview

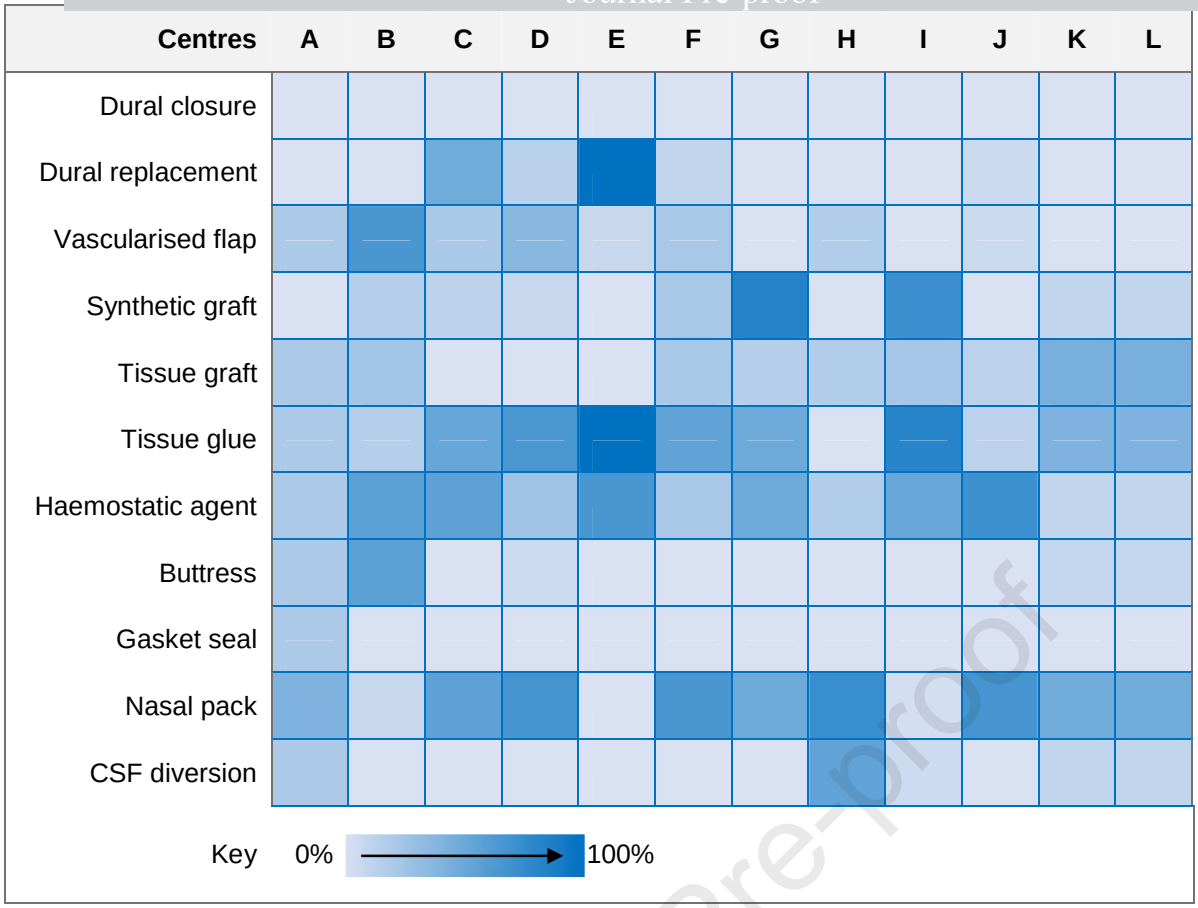

Figure 2: Correlogram highlight frequency of repair technique category use per centre for transsphenoidal cases

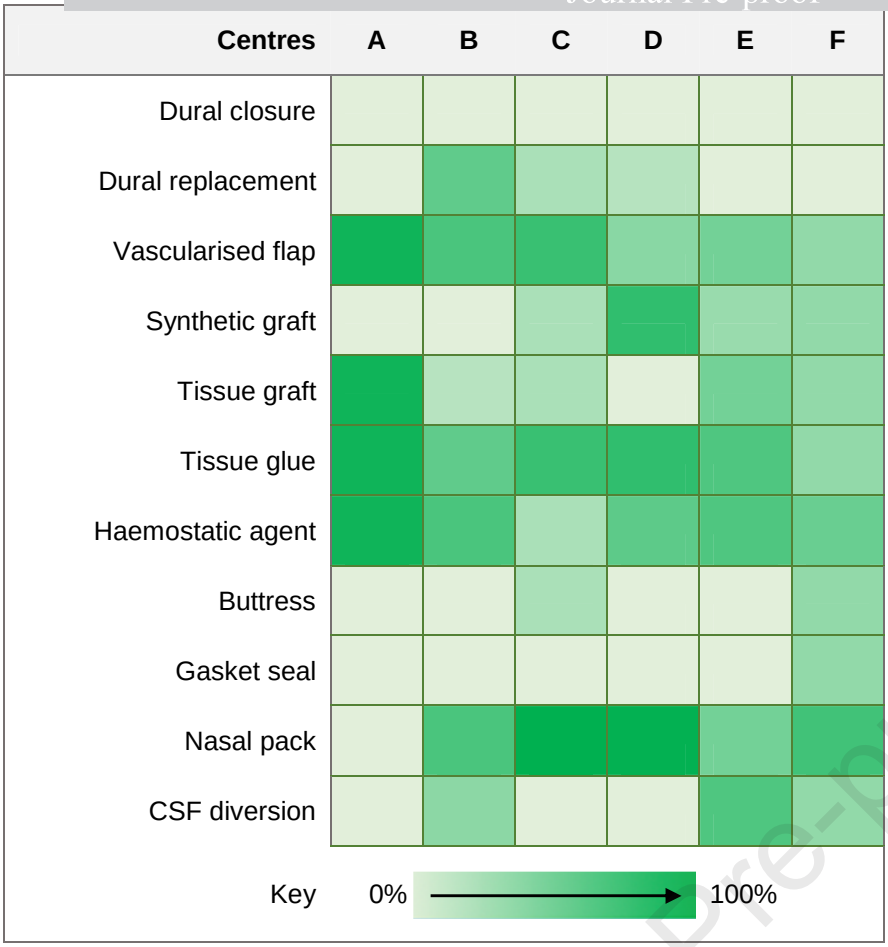

Figure 3: Correlogram highlighting frequency of repair technique category use per centre for expanded endonasal cases. Only centres with expanded endonasal cases were included.

Author affiliations & contributions

Danyal Z Khan, Wellcome / EPSRC Centre for Interventional and Surgical Sciences & National Hospital for Neurology and Neurosurgery, London, UK. Conceptualization, Resources, Data Curation, Formal analysis, Writing - Original Draft. Writing - Review & Editing

Hani J Marcus, Wellcome / EPSRC Centre for Interventional and Surgical Sciences & National Hospital for Neurology and Neurosurgery, London, UK Conceptualization, Formal analysis, Writing - Original Draft. Writing - Review & Editing, Supervision

Hugo Layard Horsfall, Wellcome / EPSRC Centre for Interventional and Surgical Sciences & National Hospital for Neurology and Neurosurgery, London, UK. Data Curation, Formal analysis,Formal analysis, Writing - Original Draft

Soham Bandyopadhyay, Medical Sciences Division, University of Oxford, Oxford, UK. Resources, Data Curation, Formal analysis, Writing - Original Draft. Writing - Review & Editing

Benjamin E Schroeder, School of Medicine, Cardiff University, Cardiff, UK. Formal analysis, Writing - Original Draft. Writing - Review & Editing.

Vikesh Patel, Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge University Hospitals Trust, Cambridge, UK. Resources, Data Curation. Formal analysis, Writing - Original Draft. Writing - Review & Editing.

Alice O'Donnell, Birmingham Medical School, University of Birmingham, Birmingham, UK. Writing - Original Draft. Writing - Review & Editing.

Shahzada Ahmed, Department of Ear, Nose & Throat (ENT), University Hospitals Birmingham NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Andrew F Alalade, Department of Neurosurgery, Lancashire Teaching Hospitals NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Ahmad MS Ali, Department of Neurosurgery, The Walton Centre, Liverpool, UK. Resources, Data Curation, Writing - Review & Editing.

Callum Allison, Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK. Resources, Data Curation, Writing - Review & Editing.

Sinan Al-Barazi, Department of Neurosurgery, King's College Hospital, London, UK. Writing - Review & Editing.

Rafid Al-Mahfoudh, Department of Neurosurgery, Hurstwood Park Neurosciences Centre and Royal Sussex County Hospital, UK. Resources, Writing - Review & Editing.

Meriem Amarouche, Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Anuj Bahl, Department of Neurosurgery, Hull University Teaching Hospitals, UK. Resources, Writing - Review & Editing.

David Bennett, Department of Neurosurgery, Ninewells Hospital, Dundee, UK. Resources, Writing - Review & Editing.

Raj Bhalla, Department of ENT, Salford Royal NHS Foundation Trust, Salford, UK. Resources, Writing - Review & Editing.

Pragnesh Bhatt, Department of Neurosurgery, Aberdeen Royal Infirmary, UK. Resources, Writing - Review & Editing.

Alexandros Boukas, Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, UK. Resources, Data Curation, Writing - Review & Editing.

Ivan Cabrilo, National Hospital for Neurology and Neurosurgery, London, UK. Resources, Data Curation, Writing - Review & Editing.

Annabel Chadwick, Department of Neurosurgery, Manchester Centre for Clinical Neurosciences, Salford Royal Trust, UK. Resources, Data Curation, Writing - Review & Editing.

Yasir A Chowdhury, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Conceptualisation, Resources, Data Curation, Writing - Review & Editing.

David Choi, National Hospital for Neurology and Neurosurgery, London, UK. Resources, Writing - Review & Editing.

Simon A Cudlip, Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Neil Donnelly, ENT Department, Cambridge University Hospitals Trust, UK. Resources, Writing - Review & Editing.

Neil L Dorward, National Hospital for Neurology and Neurosurgery, London, UK. Resources, Writing - Review & Editing.

Graham Dow, Department of Neurosurgery, Queen's Medical Centre Nottingham, Nottingham, UK. Resources, Writing - Review & Editing.

Daniel M Fountain, Department of Neurosurgery, Manchester Centre for Clinical Neurosciences, Salford Royal Trust, UK. Conceptualisation, Resources, Data Curation, Writing - Review & Editing.

Joan Grieve, National Hospital for Neurology and Neurosurgery, London, UK. Resources, Writing - Review & Editing.

Anastasios Giamouriadis, Department of Neurosurgery, Aberdeen Royal Infirmary, UK. Resources, Writing - Review & Editing.

Cath

Kanna Gnanalingham, Department of Neurosurgery, Manchester Centre for Clinical Neurosciences, Salford Royal Trust, UK. Resources, Writing - Review & Editing.

Jane Halliday, Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Brendan Hanna, Department of ENT, Royal Victoria Hospital, Belfast, UK. Resources, Writing - Review & Editing.

Caroline Hayhurst, Department of Neurosurgery, University Hospital of Wales, Cardiff, UK. Resources, Writing - Review & Editing.

Jonathan Hempenstall, Department of Neurosurgery, University Hospital Southampton, UK. Resources, Writing - Review & Editing.

Duncan Henderson, Department of Neurosurgery, Royal Hallamshire Hospital & Sheffield Children's Hospital, Sheffield, UK. Resources, Data Curation, Writing - Review & Editing.

Kismet Hossain-Ibrahim, Department of Neurosurgery, Ninewells Hospital, Dundee, UK. Resources, Writing - Review & Editing.

Theodore Hirst, Department of Neurosurgery, Royal Victoria Hospital, Belfast, UK. Resources, Data Curation. Writing - Review & Editing.

Mark Hughes, Department of Neurosurgery, The Western General Hospital, Edinburgh, UK. Resources, Writing - Review & Editing.

Mohsen Javadpour, Department of Neurosurgery, National Neurosurgical Centre, Beaumont Hospital, Ireland. Resources, Writing - Review & Editing.

Alistair Jenkins, Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK. Resources, Writing - Review & Editing.

Mahmoud Kamel, Department of Neurosurgery, Cork University Hospitals, Ireland. Resources, Writing - Review & Editing.

Richard J Mannion, Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge University Hospitals Trust, UK. Resources, Writing - Review & Editing.

Angelos G Kolias, Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge University Hospitals Trust, UK. Conceptualisation, Resources, Data Curation, Writing - Review & Editing.

Habibullah Khan, Department of ENT, Cork University Hospitals, Ireland. Resources, Writing - Review & Editing.

Mohammad Saud Khan, Department of Neurosurgery, Royal Hallamshire Hospital & Sheffield Children's Hospital, Sheffield, UK. Resources, Data Curation, Writing - Review & Editing.

Peter Lacy, Department of ENT, National Neurosurgical Centre, Beaumont Hospital, Ireland. Resources, Writing - Review & Editing.

Shumail Mahmood, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Resources, Data Curation, Writing - Review & Editing.

Eleni Maratos, Department of Neurosurgery, King's College Hospital, London, UK. Resources, Writing - Review & Editing.

Andrew Martin, Department of Neurosurgery, St George's University Hospitals Trust, London, UK. Resources, Writing - Review & Editing.

Nijaguna Mathad, Department of Neurosurgery, University Hospital Southampton, UK. Resources, Writing - Review & Editing.

Patrick McAleavey, Department of Neurosurgery, Royal Victoria Hospital, Belfast, UK. Resources, Data Curation, Writing - Review & Editing.

Nigel Mendoza, Department of Neurosurgery, Charing Cross Hospital, London, UK. Resources, Writing - Review & Editing.

Christopher Millward, Department of Neurosurgery, The Walton Centre, Liverpool, UK. Resources, Data Curation, Writing - Review & Editing.

Showkat Mirza, Department of ENT, Sheffield Teaching Hospitals, UK. Resources, Writing - Review & Editing.

Sam Muquit, Department of Neurosurgery, University Hospitals Plymouth, UK. Resources, Writing - Review & Editing.

Daniel Murray, Department of Neurosurgery, National Neurosurgical Centre, Beaumont Hospital, Ireland. Resources, Data Curation, Writing - Review & Editing.

Paresh P Naik, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Resources, Data Curation, Writing - Review & Editing.

Ramesh Nair, Department of Neurosurgery, Charing Cross Hospital, London, UK. Resources, Writing - Review & Editing.

Claire Nicholson, Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK. Resources, Writing - Review & Editing.

Alex Paluzzi, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Resources, Writing - Review & Editing.

Omar Pathmanaban, Department of Neurosurgery, Manchester Centre for Clinical Neurosciences, Salford Royal Trust, UK. Resources, Writing - Review & Editing.

Dimitris Paraskevopoulos, Department of Neurosurgery, Barts and The Royal London Hospital, UK. Resources, Writing - Review & Editing.

Jona

Rory J Piper, Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, UK. Resources, Writing - Review & Editing.

Bhaskar Ram, Department of ENT, Aberdeen Royal Infirmary, UK. Resources, Writing - Review & Editing.

Iain Robertson, Department of Neurosurgery, Queen's Medical Centre Nottingham, Nottingham, UK. Resources, Writing - Review & Editing.

Elena Roman, Department of Neurosurgery, National Neurosurgical Centre, Beaumont Hospital, Ireland. Resources, Data Curation, Writing - Review & Editing.

Peter Ross, Department of ENT, Ninewells Hospital, Dundee, UK. Resources, Writing - Review & Editing.

Thomas Santarius, Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge University Hospitals Trust, UK. Resources, Writing - Review & Editing.

Parag Sayal, National Hospital for Neurology and Neurosurgery, London, UK. Resources, Writing - Review & Editing.

Rishi Sharma, ENT Department, Cambridge University Hospitals Trust, UK. Resources, Writing - Review & Editing.

Simon Shaw, Department of Neurosurgery, Royal Stoke University Hospital, UK. Resources, Writing - Review & Editing.

Alireza Shoakazemi, Department of Neurosurgery, Barking, Havering & Redbridge University Hospitals, UK. Resources, Writing - Review & Editing.

Saurabh Sinha, Department of Neurosurgery, Royal Hallamshire Hospital & Sheffield Children's Hospital, Sheffield, UK. Resources, Writing - Review & Editing.

Georgios Solomou, School of Medicine, Keele University, Stoke-on-Trent, UK. Resources, Writing - Review & Editing.

Simon Stapleton, Department of Neurosurgery, St George's University Hospitals Trust, London, UK. Resources, Writing - Review & Editing.

Patrick Statham, Department of Neurosurgery, The Western General Hospital, Edinburgh, UK. Resources, Writing - Review & Editing.

Benjamin Stew, Department of ENT, University Hospital of Wales, Cardiff, UK. Resources, Writing - Review & Editing.

Syed Shumon, Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK. Resources, Data Curation, Writing - Review & Editing.

Wai Cheong Soon, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Resources, Data Curation, Writing - Review & Editing.

Nick Thomas, Department of Neurosurgery, King's College Hospital, London, UK. Resources, Writing - Review & Editing.

Georgios Tsermoulas, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK. Resources, Writing - Review & Editing.

James R Tysome, ENT Department, Cambridge University Hospitals Trust, UK. Resources, Writing - Review & Editing.

Adithya Varma, Department of Neurosurgery, Aberdeen Royal Infirmary, UK. Resources, Data Curation, Writing - Review & Editing.

Philip Weir, Department of Neurosurgery, Royal Victoria Hospital, Belfast, UK. Resources, Writing - Review & Editing.

Adam Williams, Department of Neurosurgery, Southmead Hospital Bristol, UK. Resources, Writing - Review & Editing.

Mohamed Youssef, Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK. Resources, Writing - Review & Editing.

Supplementary Information

Supplementary Information 2: Summary of qualitative feedback from the pilot study leads – themes and component codes.

Themes	***Codes***	***No. of pilot leads describing this code***	***No. of data points within code***
Positives			
User-friendly data collection process	Easy Castor software interface	4	5
	Logical data form	1	4
	Efficient data entry	4	6
	Routine establishment	2	3
The utility of supportive materials	The utility of supportive materials	3	4
Receptive senior engagement	Positive experience with seniors	4	5
Challenges			
High volume, complex data points	Difficult taxonomy	4	6
	Unclear/complex data points	3	6
	Follow up data - compliance	1	1
Need for teamwork and senior buy-in	Data verification challenges	2	2
	Amount of data points	1	1
	Difficult offsite data collection	1	1
Pandemic related concerns	COVID-19 impact on case availability	1	2
	COVID-19 data collection	1	1

CSF rhinorrhoea after endonasal intervention to the skull base (CRANIAL). Part 1: Multicentre pilot study

Abbreviations

CRANIAL: CSF Rhinorrhoea After Endonasal Intervention to the Skull Base

CSF: Cerebrospinal fluid

TSA: Transsphenoidal approach

EEA: Expanded endoscopic endonasal approach

CI: Confidence interval

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: