Skull Base Registries: A Roadmap

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Abstract

Hospitals, payors, and patients increasingly expect us to report our outcomes in more detail and to justify our treatment decisions and costs. Although there are many stakeholders in surgical outcomes, physicians must take the lead role in defining how outcomes are assessed. Skull base lesions interact with surrounding anatomy to produce a complex spectrum of presentations and surgical challenges, requiring a wide variety of surgical approaches. Moreover, many skull base lesions are relatively rare. These factors and others often preclude the use of prospective randomized clinical trials, thus necessitating alternate methods of scientific inquiry. In this paper, we propose a roadmap for implementing a skull base registry, along with expected benefits and challenges.

Keywords
- skull base
- registry
- multicenter study
- patient reported outcomes
- quality of life
- database

Introduction

Before the age of the operating microscope, outcomes for skull base lesions were often poor. At the dawn of the microsurgical era, skull base surgeons focused on building the following fundamentals: anatomy, approaches, and techniques. As experience accumulated over the ensuing decades, attention was directed to the indications and goals of surgery, particularly balancing aggressive treatment with functional preservation, with an increased emphasis on patient-centered quality of life including vision, olfaction, hearing, and cranial nerve function.[1–4] While this has often led to better outcomes, hospitals, payors, and patients increasingly expect us to report our outcomes in more detail and to justify our treatment decisions and costs. Although there are many stakeholders in surgical outcomes, physicians must take the lead role in defining how outcomes are assessed, as they have the most intimate knowledge of clinical behavior. The outcomes data that are collected should facilitate the development of evidence-based "best practices" and "care pathways" that optimize outcomes and costs, while at the same time preserving our freedom to innovate.[5,6] Such an effort requires consensus which may be challenging in the field of skull base surgery due to various institutional-related preferences and schools of thought.

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Because of the density of critical neurovascular structures within the skull base, lesions here may interact with surrounding anatomy to produce a complex spectrum of presentations and surgical challenges. As a result, a wide variety of surgical approaches are required to address these variations, perhaps more than any other area of human anatomy. Moreover, skull base lesions are significantly less common than other neurological conditions such as disc herniations or stroke. These factors often preclude application of the ultimate tool of evidence-based medicine: the prospective randomized clinical trial. In this paper, we propose a roadmap for implementing a skull base registry, along with the expected benefits and challenges.

Sources of Skull Base Clinical Evidence

Randomized Controlled Trials

Randomized controlled trials (RCTs) are the gold standard and the most rigorous and robust research method for determining whether a cause–effect relationship exists between an intervention and an outcome. Proper randomization ensures that comparison groups are similar in all aspects except for the intervention. This improves the probability that any difference in outcome between groups is caused by the difference in intervention rather than other important factors that influence outcome, some of which may still be unknown. Blinding the patient and treatment team can also reduce bias. This can usually be done for medication-based interventions but not surgical interventions.

Challenges of Surgical Randomized Controlled Trials

There are several practical issues that create challenges for any surgical RCT including recruitment, surgeon and patient preferences, surgeon skill set, rare or infrequent outcomes, and follow-up. These issues are magnified in the field of skull base surgery, given the relative rarity of pathologies, multispecialty care, steep surgical learning curves, and relative lack of standardized outcome measures. A predetermined timeframe for prospective recruitment of subjects into an RCT is a major challenge in this heterogenous group of relatively rare benign and malignant pathologies (►**Table 1**).

The principle of equivalency between two interventions, until proven otherwise, is a necessity in RCT design. However, it also removes the surgeon's expertise from the decision-making process which could hamper the patient's trust in the surgeon's decision-making ability and authority over their care.[7] In addition to recruitment, outcomes of surgical trials are deeply dependent on the surgeons participating in the study. A surgeon's particular preference, skill set, and experience are elements of bias and may jeopardize the validity of a surgical outcomes trial, since they may directly impact their decision to participate in the trial or to enroll particular patients.

Multi-institutional study design could mitigate some of these recruitment challenges and make study findings more generalizable. On the other hand, strategies to reduce surgeon-related outcome biases such as "expertise-based design" (patients are only randomized to surgeons who are well trained in all of the procedures in question) or "randomized-surgeon design" (patients are randomized to different surgeons who are experts on the specific procedure being studied) are much more difficult to execute in a large multicenter trial. The high cost associated with multicenter RCTs is also a significant limiting factor.

Another challenge related to RCTs in skull base surgery is the rarity of the event being studied (e.g., mortality), as many skull base pathologies are benign or indolent. When the outcome is rare, the assessment of an intervention's benefit usually requires a very large sample size. A method to overcome the challenge of rare events is to use composite end points which capture patients who experience any one of several events (e.g., reoperation, hospital readmission, and death). This requires a very important assumption that the effect of each of the components will be similar, and patients will attach similar importance to each component.[8] In other words, the validity of composite outcomes is dependent on the similarity of importance to patients, frequency, and relative risks across components.[9] When studying

Table 1 Incidence of skull base tumors

Type of tumor	Incidence (per 100,000)	Reference	
Metastasis	18	Laigle-Donadey et al, 2005[31]	
Pituitary adenoma	5.1	Daly et al, 2020[32]	
Meningioma	2	Louis et al, 2016[33]	8 cases per 100,000 including all intracranial meningiomas
Vestibular schwannoma	1	Fisher et al, 2014[34]	
SCC (sinonasal)	0.4	Sanghvi et al, 2014[35]	
Craniopharyngioma	0.2	Momin et al, 2021[36]	
Esthesioneuroblastoma	0.04	Thompson, 2009[37]	
Chordoma	0.033	Bakker et al, 2018[38]	0.088 case per 1,000,000 including skull base, spine and sacrum
Chondrosarcoma	0.02	Dibas et al, 2020[39]	

Abbreviation: SCC, squamous cell carcinoma.

intervention for benign conditions, long-term follow-up is necessary to prove the long-term benefits that justify the upfront surgical risks. The issue of inadequate follow-up has been a significant criticism of RCT's such as Aruba and COSS.[10,11]

Skull Base Surgery Randomized Controlled Trials

Surgical RCTs in the field of skull base surgery are very challenging to execute for the reasons discussed above. The majority of the current RCT literature in skull base surgery is focused on perioperative management including anesthesia-related issues, use of antibiotics, pain control, and postoperative care. There are only a few studies focused on approach-related outcomes, and there are no studies assessing treatment and tumor-specific outcomes. Relevant RCTs in the field of skull base surgery are summarized in the ►**Table 2**.

A PubMed search for the terms "skull base surgery" reveals a slow increase in the number of publications until the early 2000's with under 300 publications per year. This trend was followed by a significant increase in the number of publications in the past two decades with over 1,500 publications per year in the last 2 years (►**Fig. 1**). When the search results are filtered for "Meta-Analysis," "Review," and "Systematic Review" we observe similar trend in the increase of publication from 36 articles in 2000 to 203 articles in 2021 (►**Fig. 2**). Nevertheless, these types of articles that represent levels of evidence 2 and 3, according to the Oxford Centre for Evidence-Based Medicine,[12] only comprise 13% of the publications in "skull base surgery" in 2021. Interestingly, a similar trend is not observed in level 1 of evidence. When the results are filtered for "Clinical Trial" and "Randomized Controlled Trial" (►**Fig. 3**), the number of trials published from 2000 to 2022 is variable ranging from 3 to 18 per year representing an even smaller fraction of the available literature in skull base surgery.

Personal, Institutional, and Multi-Institutional Series

The main body of literature in skull base surgery is comprised of levels 3 to 5 of evidence. The best quality of work among this group is a result of pathology-specific case series or series reporting the use of a particular approach or technique. Personal and institutional series are more common but usually have a limited number of patients due to the paucity of skull base tumors. They also have limited generalizability, given the participation of a single surgeon or few surgeons.

Despite the challenges in coordination and heterogeneity in care protocols, multi-institutional efforts have been able to study larger cohorts for more common skull base tumors such as pituitary adenomas and meningiomas. The Transsphenoidal Extent of Resection (TRANNSSPHER) study is one example of a prospective multicenter effort to compare outcomes between microscopic and endoscopic resection of nonfunctioning pituitary adenomas in adults. Surgeons performing more than 30 transsphenoidal operations at centers with more than 200 cases overall were eligible to participate in this study with the rate of gross total resection as the primary endpoint. Ultimately, it included 15 surgeons from seven centers and 259 unique patients. The study demonstrated with level-3 evidence that there was no significant difference in gross total resection rate or volume of tumor resection between the two surgical techniques. However, it was not able to be completed due to the retirement of two participating surgeons on the microscopic resection arm and the failure to recruit replacements for them.[13]

Similar effort coordinated 40 sites to gather outcomes of 987 patients with tuberculum sellae meningiomas operated through transcranial and transsphenoidal approaches. The study, which was presented as an abstract, showed that use of the transsphenoidal approach for tuberculum sellae meningiomas is increasing and is associated with better visual outcomes and decreased recurrence rates after gross total resection. However, CSF leak rates after transsphenoidal approach remain high.[14,15] An example of a modern multi-institutional prospective data registry that could be particularly instructive for future registries is the CORISCA initiative for sinonasal malignancies. This incorporates tumor biobanking in a centralized site, oncologic outcomes, and QOL metrics[16]

Administrative Database Studies

The past decade has witnessed an increasing use of administrative databases in the surgical literature to study larger groups of patients. Although the large sample sizes can be enticing to both authors and readers, one must be cautious interpreting the findings with this approach as the content and curation of these database are often lacking which limits their scientific applications. While they offer large numbers, they lack many important details. A common criticism of these studies is "Garbage in, garbage out."

The NIS database is a part of the Healthcare Cost and Utilization Project, dating back to 1988. It contains diagnosis and procedure codes, patient demographics, total charges, length of stay, discharge status, and hospital characteristics. It samples 20% of discharges from U.S. community hospitals with the goal of reporting national estimates. Only inpatient morbidity and mortality is studied, and readmissions are not tracked secondary to the lack of availability of patient identifiers. The database was redesigned in 2012 to improve the margin of error, but there is still concern that the data are curated solely by nonclinicians and hospital billing. There is no information in this database regarding specifics of presentation, conditions, treatments, or outcomes beyond the index hospital stay.

The surveillance, epidemiology, and end results (SEER) cancer database began collecting data in 1973 in geographic regions chosen to mimic the general population.[17] Initially, Caucasian patients represented a high proportion of the patients, although, over time, it was expanded and adjusted to better reflect ethnic and racial diversity. It currently represents 48% of the U.S. population. Data collected include patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and survival. In addition to lack of clinician involvement in data curation, another concern is the lack of central pathology review, and the lack of policies on how malignant central nervous system (CNS) tumors are reported. Reporting of surgery, radiation therapy,

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Table 2 Randomized controlled trials in skull base surgery

Article Title	Authors	Publication year	Study question	Study design	No. of patients	Number of institutions	Period of the study	Conclusion
Prophylactic Nimodipine Treatment for Cochlear and Facial Nerve Preservation after Vestibular Schwannoma Surgery: A Randomized Multicenter Phase III Trial	Scheller et al[40]	2016	Does prophylactic nimodipine and hydroxyethyl starch treatment have a beneficial effect on facial and cochlear nerve preservation following vestibular schwannoma surgery?	Prospective, open-label, 2-arm, randomized, multicenter (Phase III)	112	7	2010–2013 (37 months)	There were no statistically significant effects of the treatment
Recovery after Prolonged Anesthesia for Acoustic Neuroma Surgery: Desflurane Versus Isoflurane	Boisson-Bertrand et al[41]	2006	Does desflurane provide similar anesthesia cardiovascular profile but better recovery profile than isoflurane in vestibular schwannoma surgery?	Prospective, open-label, 2-arm, randomized, single center	33	1	NA	Desflurane is associated with similar operating conditions and faster postoperative recovery
Effect of Corticosteroids on Facial Function after Cerebellopontine Angle Tumor Removal: A Double-Blind Study versus Placebo	Bozorg Grayeli et al[42]	2015	Does corticosteroids administered intra- and postoperatively has any effect on the occurrence of facial palsy after a cerebellopontine angle tumor resection?	Prospective, double-blinded, 4-arm, randomized, multicenter	310	5	2006–2010	Steroids did not affect the facial function at postoperative days 1, 8 and 30 in patients with small or large tumors
The Effect of Nasoseptal Flap Elevation on Post-Operative Olfaction and Sinonasal Quality of Life: A Prospective Double-Blinded Randomized Controlled Trial	Chou et al[43]	2021	Does the nasoseptal flap use and side has any impact on binarial and uninarial olfaction and sinonasal quality of life (QOL)?	Prospective, double-blinded, 2-arm, randomized, single center	31	1	2014–2017 (30 months)	The use or side of nasoseptal flap during EEA for sellar pathology does not have a significant effect on olfaction or rhinologic QOL
A Prospective Randomized Trial Comparing Topical Intranasal Lidocaine and Levobupivacaine in Patients Undergoing Endoscopic Binostril Transnasal Transsphenoidal Resection of Pituitary Tumors	Konay et al[44]	2021	Does long acting local anesthetic levobupivacaine would provide superior hemodynamic stability and postoperative analgesia compared with lidocaine in endoscopic transnasal transsphenoidal surgery?	Prospective, double-blinded, 2-arm, randomized, single center	48	1	2015–2016 (11 months)	Preoperative intranasal packing with 1.5% lidocaine or 0.5% levobupivacaine provide similar hemodynamic stability throughout endoscopic transnasal transsphenoidal surgery.Lidocaine may be more advantageous for hemodynamic stability during extubation
Randomized, double-blinded, placebo-controlled trial comparing two multimodal opioid-minimizing pain management	Shepherd et al[45]	2018	Does multimodal opioid-minimizing pain regimen yields satisfactory postoperative pain control and does intravenous ibuprofen improved	Prospective, double-blinded, 2-arm, randomized, single center	62	1	2015–2016 (13 months)	Multimodal opioid-minimizing pain-management protocols resulted in acceptable pain control following transsphenoidal surgery. IV ibuprofen

Table 2 (*Continued*)

Article Title	Authors	Publication year	Study question	Study design	No. of patients	Number of institutions	Period of the study	Conclusion
regimens following transsphenoidal surgery			postoperative pain scores and reduced opioid use?					resulted in significantly improved pain scores and significantly decreased opioid use compared with placebo
Does lumbar drainage reduce postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery? A prospective, randomized controlled trial	Zwagerman et al[46]	2019	Does lumbar drainage reduce postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery?	Prospective, open-label, 2-arm, randomized, single center	170	1	2011–2015 (49 months)	Perioperative lumbar drain used in the context of endoscopic endonasal intradural surgery in patients with high CSF leak risk significantly reduced the rate of postoperative CSF leaks
Assessment of Opioid Use and Analgesic Requirements After Endoscopic Sinus Surgery: A Randomized Clinical Trial	Ayoub et al[47]	2021	Do different analgesic regimens prescribed after endoscopic sinus surgery affect the degree of postoperative pain experienced and number of opioids consumed?	Prospective, open-label, 2-arm, randomized, multicenter	100	6	2019–2020 (12 months)	Most patients could be treated postoperatively using a nonopioid regimen of either acetaminophen alone or acetaminophen and ibuprofen. Ibuprofen as a second-line therapy did not reduce overall narcotic consumption, but the overall narcotic use was low in both groups
Hydrocortisone Dose and Postoperative Diabetes Insipidus in Patients Undergoing Transsphenoidal Pituitary Surgery: A Prospective Randomized Controlled Study	Rajaratnam et al[48]	2003	Does different dosing in postoperative steroid replacement protocol have any impact on postoperative diabetes insipidus?	Prospective, open-label, 3-arm, randomized, single center	114	1	NA	Low dose hydrocortisone protocol reduces the incidence of postoperative diabetes insipidus when compared with the conventional dose perioperative hydrocortisone replacement protocol
Effects of Nasal Lavage with and without Mupirocin after Endoscopic Endonasal Skull Base Surgery: A Randomized, Controlled Study	Ng et al[49]	2019	Does nasal lavage with mupirocin after endoscopic endonasal skull base surgery improve outcomes?	Prospective, open-label, 2-arm, randomized, multicenter	20	1	2016–2017 (12 months)	Nasal lavage with mupirocin seems to yield better outcomes regarding patients' symptoms and endoscopic findings
Effect of Omega-3 Supplementation in Patients With Smell Dysfunction Following Endoscopic Sellar and Parasellar Tumor Resection: A Multicenter Prospective Randomized Controlled Trial	Yan et al[50]	2020	Does omega-3 supplementation following endoscopic skull base tumor resection have any impact on smell outcomes?	Prospective, open-label, 2-arm, randomized, multicenter	110	3	2014–2018 (44 months)	Omega-3 supplementation appears to be protective for the olfactory system during the healing period in patients who undergo endoscopic resection of sellar and parasellar masses

(*Continued*)

Table 2 (*Continued*)

Article Title	Authors	Publication year	Study question	Study design	No. of patients	Number of institutions	Period of the study	Conclusion
Effects of Nasal Irrigation after Endoscopic Transsphenoidal Resection in Patients with Pituitary Adenomas: A Randomized Controlled Trial	Xu et al[51]	2021	Does nasal irrigation reduce or prevent nasal complications after endoscopic transsphenoidal pituitary adenoma resection?	Prospective, open-label, 2-arm, randomized, single center	60	1	2019 (9 months)	Nasal irrigation helps reduce the incidence of complications such as epistaxis and nasal adhesions in the early postoperative period, however, it did not reduce the incidence of sphenoid sinusitis
Olfactory Outcomes following Endoscopic Pituitary Surgery with or without Septal Flap Reconstruction: A Randomized Controlled Trial	Tam et al[52]	2013	Does the nasoseptal flap have any impact on postoperative olfactory function in the setting of endoscopic transsphenoidal pituitary surgery?	Prospective, open-label, 2-arm, randomized, single center	20	1	2010–2011 (11 months)	Endoscopic pituitary surgery results in decreased olfaction with or without deploying a septal flap, however, use of the nasoseptal flap for reconstruction can worsen hyposmia at least 6 months after surgery
Real-time Hemodynamic Effects of 1:100,000 and 1:200,000 Injectable Epinephrine and Placement of Topical 1:1000 Epinephrine Pledgets in Patients Undergoing Endoscopic Sinus and Skull-Base Surgery: A Randomized, Prospective Study	Ahmed et al[53]	2020	Does the use of different concentrations of epinephrine in endoscopic sinus/skull base surgery have different hemodynamic response?	Prospective, open-label, 2-arm, randomized, single center	28	1	2018 (8 months)	There is no difference in changes in hemodynamic parameters between injecting epinephrine 1:100,000 compared with 1:200,000 during endoscopic sinonasal surgery
Long-Term Olfaction Outcomes in Transnasal Endoscopic Skull-Base Surgery: A Prospective Cohort Study Comparing Electrocautery and Cold Knife Upper Septal Limb Incision Techniques	Puccinelli et al[54]	2019	Does cold knife upper septal limb incision techniquei provide better long-term olfactory outcome compared with monopolar cautery?	Prospective, open-label, 2-arm, randomized, single center	22	1	2016–2017 (18 months)	There was no significant change in patient UPSIT scores 1 year after transnasal skull-base approaches, and no short-term or long-term differences between cold knife and cautery upper septal limb incision techniques
Effectiveness of Dietary Diabetes Insipidus Bundle on the Severity of Postoperative Fluid Imbalance in Pituitary Region Tumors: A Randomized Controlled Trial	Koundal et al[55]	2021	Does dietary diabetes insipidus bundle have any impact on the severity of postoperative fluid imbalance in pituitary region tumors?	Prospective, double-blinded, 2-arm, randomized, single center	50	1	2018–2019 (6 months)	Dietary diabetes insipidus bundle among operated pituitary patients was able to flatten the DI trend with significant benefits in polyuria, hypernatraemia, vasopressin requirement and hospital stay

Journal of Neurological Surgery–Part B Vol. 83 No. B6/2022

Table 2 (*Continued*)

Article Title	Authors	Publication year	Study question	Study design	No. of patients	Number of institutions	Period of the study	Conclusion
Impact of the Modality of Mechanical Ventilation On Bleeding during Pituitary Surgery: A Single Blinded Randomized Trial	Le Guen et al[56]	2019	Does ventilation mode impact intraoperative bleeding during pituitary surgery?	Prospective, single-blinded, 2-arm, randomized, single center	86	1	2013–2015 (20 months)	Ventilation mode does not influence intraoperative bleeding during transsphenoidal pituitary surgery
Postoperative Oral Antibiotics and Sinonasal Outcomes Following Endoscopic Transsphenoidal Surgery for Pituitary Tumors Study: A Multicenter, Prospective, Randomized, Double-Blinded, Placebo-Controlled Study	Little et al[13]	2021	Does postoperative oral antibiotics result in superior sinonasal quality of life compared with placebo among patients who undergo endoscopic endonasal transsphenoidal pituitary surgery?	Prospective, double-blinded, 2-arm, randomized, multicenter	113	3	2016–2019 (39 months)	Postoperative prophylactic oral antibiotics did not result in superior sinonasal quality of life compared with placebo among patients who underwent standard endoscopic transsphenoidal surgery
Safety and Efficacy of TachoSil (Absorbable Fibrin Sealant Patch) Compared with Current Practice for the Prevention of Cerebrospinal Fluid Leaks in Patients Undergoing Skull Base Surgery: A Randomized Controlled Trial	George et al[57]	2017	Does Absorbable Fibrin Sealant Patch provide superior dural sealing over current practice after craniotomy for skull base surgery?	Prospective, open-label, 2-arm, randomized, multicenter	726	35	2011–2013 (26 months)	There was no difference in postoperative CSF leak or clinically evident pseudomeningocele within 7 weeks after surgery
The Efficacy of Postoperative Ondansetron (Zofran) Orally Disintegrating Tablets for Preventing Nausea and Vomiting After Acoustic Neuroma Surgery	Hartsell et al[58]	2005	Does Ondansetron reduce both the frequency and severity of postoperative nausea and vomiting in patients undergoing craniotomy for acoustic neuroma resection?	Prospective, double-blinded, 2-arm, randomized, single center	60	1	2000–2002 (27 months)	Postoperative treatment with ondansetron in an orally disintegrating tablet formulation was associated with less frequent rescue therapy as compared with placebo on the first postoperative day
The Inhibitory Effect of Intravenous Lidocaine Infusion on Tinnitus after Translabyrinthine Removal of Vestibular Schwannoma: A Double-Blind, Placebo-Controlled, Crossover Study	Baguley et al[59]	2005	Does intravenous infusion of lidocaine improve tinnitus in individuals who had previously undergone translabyrinthine excision of a vestibular schwannoma?	Prospective, double-blinded, 2-arm, randomized, single center	12	1	NA	Intravenous infusion of lidocaine has a statistically significant inhibitory effect on tinnitus in patients who have previously undergone translabyrinthine removal of a vestibular schwannoma
Withholding Perioperative Steroids in Patients Undergoing Transsphenoidal Resection for Pituitary Disease: Randomized Prospective Clinical Trial to Assess Safety	Sterl et al[60]	2019	Is it safe to withholding glucocorticoids in patients undergoing transsphenoidal surgery for pituitary tumors?	Prospective, open-label, 2-arm, randomized, single center	36	1	2012–2015	Perioperative steroids can be safely withheld in patients with an intact hypothalamic-pituitary-adrenal axis undergoing transsphenoidal surgery

Abbreviations: CSF, cerebrospinal fluid; EEA, endoscopic endonasal approach; IV, intravenous; NA, not available; QOL, quality of life; UPSIT, University of Pennsylvania Smell Identification Test.

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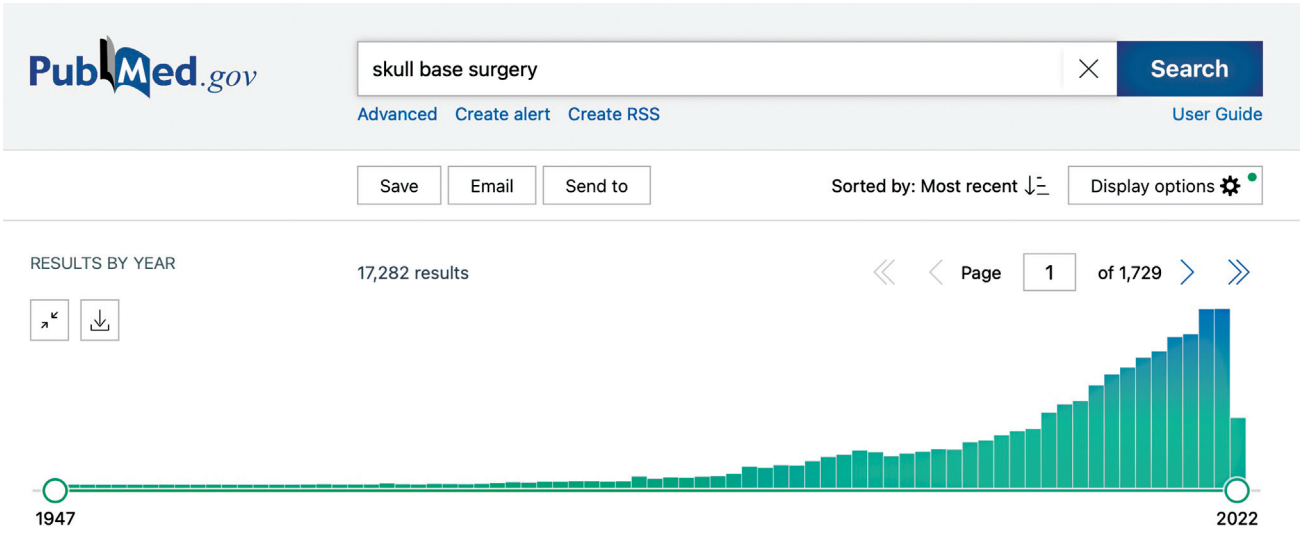

Fig. 1 The number of skull base surgery publications each year, with accelerated growth in th past two decades.

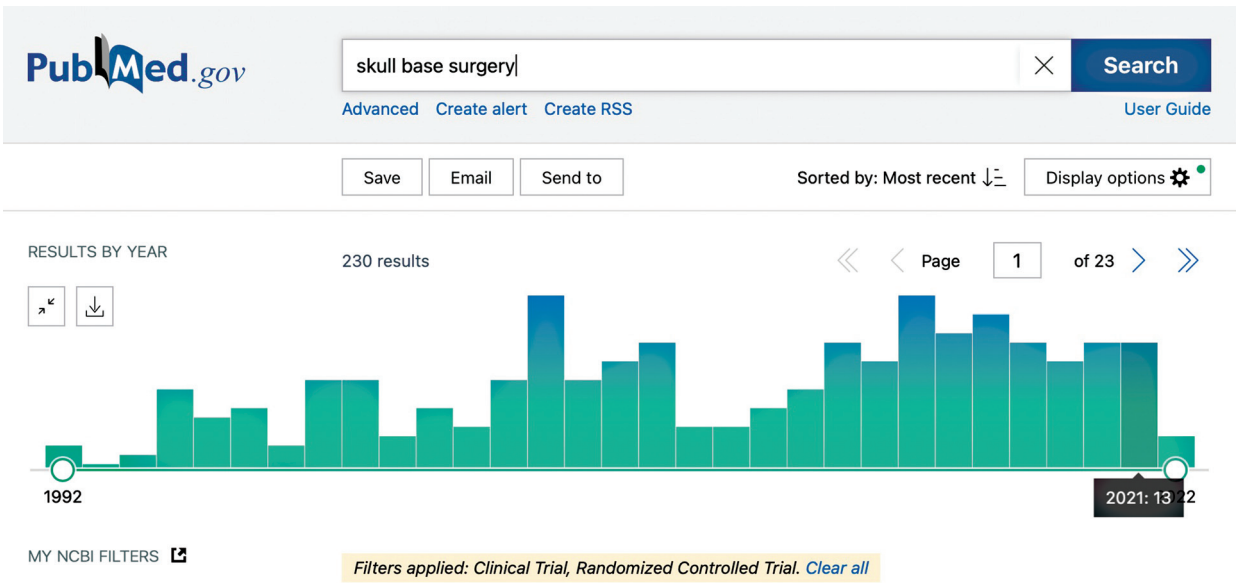

Fig. 2 Number of publications each year for randomized clinical trials related to skull base surgery.

and chemotherapy lack important details that may impact outcomes and thus significantly limit the usefulness of any conclusions derived from this database.

As a clinical database, the American College of Surgeons—National Surgical Quality Improvement Project (ACS-NSQIP) is superior to administrative databases with respect to accuracy. However, the use of databases such as ACS-NSQIP to address the important questions of our specialty is difficult because it was not constructed with input from skull base surgeons, hence there is a lack of relevant disease-specific variables.

Roadmap toward a Skull Base Registry

Although registries cannot match the power of RCTs to address head-to-head comparisons, they facilitate accrual of relatively rare cases into a series that demonstrates the spectrum of disease behavior, practice patterns, and treatment responses. These are usually designed by physicians with expertise in the conditions and their treatments, so appropriate disease-specific variables are much more likely to be included than in administrative databases. Registries may allow quick identification of a subgroup of patients that can be recruited into an RCT. For example, skull base chordomas cases, which have very limited treatment options, could be quickly identified when a promising new intervention becomes available, accelerating enrollment into the RCT.

Learning from Previous Registries

There are several prospective surgical registries that have been developed by neurosurgeons. The largest are the Quality Outcomes Database (QOD) which includes

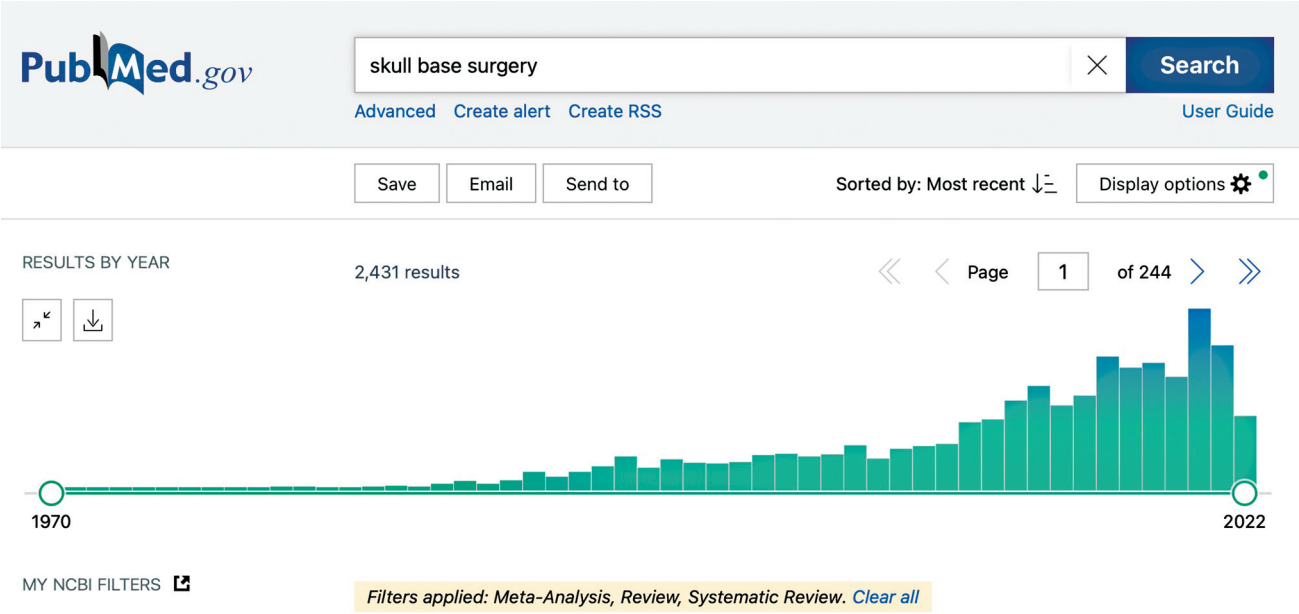

Fig. 3 Number of publications each year for meta-analyses and systemic reviews related to skull base surgery.

degenerative spine conditions, brain tumors, and neurovascular diseases; the Stereotactic Radiosurgery (SRS) registry, and Registry for the Advancement of Deep Brain Stimulation in Parkinson's Disease (RAD-PD). The American Spine Registry (ASR) is a collaborative effort between neurosurgery and orthopaedic surgery which seeks to expand enrollment volume compared with QOD, although with more limited follow-up. These registries represent broad geographical regions across North America and have structured administration, coordination, and auditing to ensure completeness and accuracy. They are designed to track the outcomes of neurosurgical procedures and place them on an evidence-based footing that can withstand the scrutiny of all stakeholders. The data from these large registries can also be used to guide clinical decision-making and cost-effectiveness initiatives. Although the spine registry is the largest, the tumor registry is most relevant to this discussion. This registry contains six categories, including intracranial metastasis, high-grade glioma, low-grade glioma, meningioma, pituitary tumor, and other intracranial tumors. These categories are divided and tracked based on general anatomical location, rather than disease type or invasion of surrounding anatomical structures, factors that are vital in clinical decision-making for the skull base surgeon. The outcomes measured in the QOD Tumor Registry include LOS, discharge disposition, inpatient complications, and patient-reported outcomes (PROs). This registry a good starting point for a national registry for intracranial tumor and sets a good model for organization, auditing, and oversight for maintaining a quality high-volume database. However, it is limited in its clinical decision-making utility, as it fails to account for determinants of extent of surgical resection and neurological outcome in patients with complex skull base lesions. Given the nature of skull base lesions, details of anatomical involvement, disease pathology, as well as anatomical approach, are important determinants of outcome and factors pertinent to research investigations.[18] Tracking lesions in such detail would involve the development of numerous data collection schemes up front at the time of registry development.

Mayo Clinic describes a system across their multicity hospital system, Mayo Clinic Enterprise Neurosurgery Registry. The database includes categories of cranial, spine, peripheral nerve, and revision surgeries. The cranial category subdivides lesions by broad anatomical region, not specific pathology or anatomical detail. In this registry, the electronic health record (EHR) is directly linked to the central database, allowing data to be automatically pulled from the EHR and recorded in the database. This facilitates efficiency by minimizing the need for manual chart review and manual entry into the database. This system allows integration of computerized adaptive testing (CT) questionnaires and their automated scores assessing patient reported outcomes to be input directly into the EHR. The registry involves a multidisciplinary team for technical support, administration, and clinical oversight to monitor for clinical relevance and completeness in data collection, somewhat like the QOD registries. Designated teams at each clinical site aim to increase patient enrollment in the online patient portal where patients would participate in the CT survey questionnaires. Alternatively, patients would complete questionnaires electronically on arrival for their in-person initial clinic visit and at designated time intervals following any surgical intervention. This model at Mayo was also expanded to include the creation of a "dashboard report," summarizing provider productivity, total cost, and charges from a given provider or clinical site, providing an example of how large and detailed registries can be utilized to analyze and streamline health care costs.[19]

Building Consensus

> "Not everything that can be counted counts, and not everything that counts can be counted."

Perhaps the most difficult part of laying the groundwork for a registry, particularly one that includes a wide variety of pathologies and treatment strategies, is building consensus on what data to collect at each phase of the patient's timeline. We must first characterize the patient's condition at the time of diagnosis and at future points in time that are determined by a protocol or by clinical events. This typically involves grading scales and classification schemes, both objective and patient reported. Commonly used indicators of overall health include age, comorbidities, the Karnofsky Performance Status, American Society of Anesthesiologists (ASA) Class,[20] and quality of life instruments such as the Euroqol Five-Dimensional Questionnaire (EQ-5D). But it is usually also necessary to characterize the status of the lesion, including anatomical involvement, radiographic features, and disease-specific symptoms that have a significant impact on the anatomical approach, extent of maximal safe resection, and associated morbidities.[2,21–25] Clearly, radiologic assessments will play an extremely important role in a successful skull base registry, but these are still lacking in some areas. In particular, our increasing ability to visualize cranial nerve involvement will hopefully lead to a consensus on classification systems for perineural spread of skull base lesions that have clinical or prognostic significance.[26]

The Knosp classification scheme for cavernous sinus invasion by pituitary lesions is an example of an attempt to create clinically meaningful categories of anatomical involvement, which has been shown to be related to the extent of surgical resection achieved.[27] ►**Table 3** lists common skull base lesions and the anatomical classification scales that attempt to describe them with concise uniform scoring systems. There are some lesions presented in this table that do not have widely accepted scales for characterization.

There are several objective scales for neurological function that may be relevant to a skull base registry. The Gardner–Robertson Scale and American Academy of Otolaryngology—Head and Neck Surgery hearing test[28,29] combine pure-tone averages and speech discrimination to define categories of auditory nerve function that are clinically relevant to patients harboring a vestibular schwannoma. The House–Brackmann[30] facial paralysis scale is widely used to report facial nerve weakness. However, there are not widely adopted objective scales in place for reporting and measuring all relevant neurological deficits encountered in skull base surgery. The objective scales found in our search of the literature are represented in ►**Table 4**. This illustrates

Table 3 Anatomical classification scales for skull base tumors

Anatomical classification scales				
Skull base region	**Pathology described**	**Classification system**	**Anatomical reference point**	**Scale**
Anterior fossa				
	Pituitary lesions	Knosp et al (1993)[61]	Intracavernous ICA involvement	5 grades, range: 0–4
		Wilson ("Hardy-Wilson Scale"; 1979)[62]	Sellar destruction (grade), with extent of suprasellar extension (stage)	4 grades, range I–IV, 6 stages, range: 0, A–E.
		Micko et al ("Modified Knosp"; 2015)[63]	Intracavernous ICA, delineating superior and inferior cavernous sinus invasion	6 grades: 0–4, with A/B for grade 3
	Optic pathway gliomas	Dodge et al (1958)[64]	Optic nerve, chiasm, hypothalamus	3, range: stages 1–3
		Taylor et al ("Modified Dodge classification"; 2008)[65]	Optic nerve, chiasm, hypothalamus, leptomeningeal dissemination	12
	Craniopharyngioma			
		Yasargil et al (1990)[66]	Sellar, diaphragm, ventricle	6, range: types A–F
		Fan et al (2021)[67]	Sellar, diaphragm, subarachnoid, pars tuberalis	3, Tumor origin in the third ventricle (T), stalk (S) and subdiaphragmatic intrasellar space (Q)
		Kassam et al (2008)[68]	Infundibulum, ventricle	4, range: types I–IV
		Jamshidi et al (2018)[69]	Diaphragm, Infundibulum, ventricle. The expanded Kassam scale to include 0 (infradiaphragma)	5, range: types 0–IV

Table 3 (*Continued*)

Anatomical classification scales				
Skull base region	**Pathology described**	**Classification system**	**Anatomical reference point**	**Scale**
	Rathke's cleft cyst	Potts et al (2011)[70]	Sella, suprasellar	Sellar, suprasellar, both
	Planum sphenoidale and tuberculum sella meningioma			
		Magill et al (2018)[71]	Tumor score (size), Canal score (invasion of optic canal), artery score (relationship to ICA, ACA)	7, range: 0–6
		Mortazavi et al (2016)[72]	Size, optic canal, vascular invasion, brain invasion, previous surgery, previous radiation	11, range: 0–3 (class I), 4–7 (class II), 8–11 (class III)
	Olfactory groove meningioma	N/A		
	Olfactory neuroblastoma (esthesioneuroblastoma)	Kadish et al (1976)[73]	Nasal cavity, paranasal sinuses, other	A, B, C
	Anterior clinoidal meningiomas			
		Xu et al (2020)[51]	Point of origin on the anterior clinoid process and pattern of extension	5: range: I, IIa, IIb, III, IV
Middle fossa		Al-Mefty (1990)[74]	Point of origin relative to carotid cistern and optic foramen	3: range: I–III
		Pamir et al (2008)[75]	Modification of Al-Mefty's classification system, adding tumor diameter	6: range: IA/B, IIA/B, IIIA/B
		Goel (2000)[76]	relationship with ipsilateral and contralateral ICAs, with composite score also based on size and visual impairment	9: range: 2–10
		Nakamura et al (2006)[77]	Invasion of cavernous sinus	2: range: 1–2
		Nanda et al (2016)[78]	relationship with ipsilateral and contralateral ICAs, cavernous sinus, and optic canal	10: range: 1–10 (group 1: <5, group 2 >5)
	Sphenoid wing meningioma, generally accepted lat/middle/med boundaries			
	Medial sphenoid wing meningioma	Wang et al (2020)[79]	Any arterial involvement, cavernous sinus involvement, bone invasion	10, range: 1–10
	Cholesteatoma			
		N/A		
	trigeminal schwannoma			
		Lesoin et al (1986)[80]	Origin: root, ganglion, branches	3, range: types I–III
		Jefferson (1953)[81]	Origin: root, ganglion, branches, posterior and middle fossa involvement	3 (types A–C)
		Yoshida and Kawase (1999)[82]	Posterior or middle fossa, extracranial involvement	6, posterior fossa tumor in the subdural space (P), middle fossa tumor in the interdural space (M), extracra- nial tumor in the epidural space (E), and combinations of these (MP, ME, MPE)

(*Continued*)

Table 3 (*Continued*)

Anatomical classification scales				
Skull base region	**Pathology described**	**Classification system**	**Anatomical reference point**	**Scale**
	Facial nerve schwannoma			
		N/A		
	Vestibular schwannoma	Koos et al (1998)[83]	IAC, brainstem compression	4 grades: range: I–IV
		Samii et al ("Hannover Classification System"; 1997)[84]	IAC, brainstem compression, cerebellopontine cistern, fourth ventricular compressiom	6, range: T1–T4 with T3a/b and T4a/b
Posterior fossa	Epidermoid			
		Bayatli et al (2022)[85]	Cistern, cerebellomedullary, cerebellopontine, prepontine/premedular	9, range: 1a-c–3a-c
	Endolymphatic sac tumors			
		n/a		
	Glomus tumors	Jenkins and Fisch (1981)[86]	Petrous anatomy and size determining subtype for intracranial masses	5 grades: type A–D, D2, and D2
		Jackson and Glasscock (1982)[87]	Petrous anatomy and size	4 grades, range: types I–IV
		Borba et al (2010)[88]	Petrous anatomy and carotid canal, extradural and intradural involvement	11, range: type A-D with subtypes
	Chondroma/ chondrosarcoma			
		N/A		
	Chordoma			
		Brito et al ("Sekhar Grading System for Cranial Chordomas"; 2018)[89]	Size, site, vascular involvement, intradural invasion, regrowth after prior treatment	24, range: 2–25
	Posterior petrous meningiomas			
		Desgeorges et al (1995)[90]	Petrous apex, IAC, posterior petrous	3, range: type A, M, and P
		Zhou et al (2009)[91]	Compression of cerebellum, cranial nerve involvement, combined involvement	3, type I–III
	Petroclival meningioma			
		Sekhar et al (1990)[92]	Region of clivus	3, range: upper, middle, lower clivus
		Panigrahi et al (2015)[93]	IAC, petrous apex, jugular tubercle	5, range: 1–5
	Foramen magnum meningioma			
		Bruneau and George (2010)[94]	Intradural/extradural or both, relationship to vertebral artery, dural insertion, posterolateral or anterolateral extradural involvement	No distinct grades

Abbreviations: IAC, internal auditory canal; ICA, internal carotid artery; N/A, not available; ACA: anterior cerebral artery.

Table 4 Objective functional measures of neurological function

Objective functional outcome measures			
Scale	**Publication**	**Function measured**	**Reported measure**
Gardner-Robertson Hearing Scale	Gardner and Robertson (1988)[95]	Hearing	Pure tone average (measured in dB)
Snellen Acuity	Snellen (1862)[96]	Visual acuity	Minimal angle of resolution (MAR) (scored as a fraction of distance from chart/smallest line read)
Early Treatment Diabetic Retinopathy Study (ETDRS) Charts	Kaiser (2009)[97]	Visual acuity	Minimal angle of resolution (MAR) (scored in logarithm of minimal angle of resolution, "logMAR")
Visual Field Index (HVFI)	Bengtsson and Heijl (2008)[98]	Visual fields	VFI (reported as a % of normal full VF)
German Ophthalmological Society Score	Fahlbusch and Schott (2002)[99]	Visual fields and acuity	Composite Score using tables
House–Brackman	House and Brackmann (1985)[30]	Facial nerve palsy	Full motor to total CNV II palsy (grade I–VI)
Ocular Motor Nerve Palsy Scale	Zhou et al (2018)[91]	Oculomotor, trochlear, abducens nerve palsy	Motor palsy of ocular movement (detailed multi-part scoring system for each cranial nerve involved)
Abducens Nerve Palsy Score	Holmes et al (2001)[100]	Abducens new palsy	Abduction deficit: 0 to −5
University of Pennsylvania Smell Identification Test (UPSIT)	Doty et al (1984)[101]	Olfaction	Scored based on multiple choice answers to scratch and sniff test
NIH Odor Identification	Dalton et al (2013)[102]	Olfaction	Scored based on correct pairing of scratch and sniff odors with representative pictures
Motor Scale for Trigeminal Nerve	N/A	–	–
Sensory Scale for Trigeminal Nerve	N/A	–	–
Lower Cranial Nerve Function	N/A		

Abbreviations: N/A, not available; NIH, National Institute of Health.

several gaps in assessment, including the lack of scales that measure the motor and sensory function of the trigeminal nerve, as well as lower cranial nerve function. On the other hand, there are two widely used scales for trigeminal nerve pain.

Subjective, patient-reported outcome measures (PROMs) that may relate to specific symptoms, such the visual analogue pain scale (VAS), or general quality of life, such as the EQ-5D, collect important information about the impact of disease that may not be captured by the clinician during office visits. Nondisease-specific measures also allow ranking the impact of interventions in various medical subspecialties on quality of life which could have implications in a healthcare rationing environment. Several relevant patient reported scales and outcome measures are represented in ►**Table 5**.

After arriving at a consensus on how to characterize lesions, we must agree how on how to characterize the treatment that is delivered. At a minimum, this should include details of what approach(es) was used, extent of resection, texture of the lesion, technique used to address the lesion, preservation of neurovascular structures, blood loss, duration of surgery, and complications. For malignancies, this should also include details on histopathologic findings, adjuvant therapies, recurrence and survival. For radiosurgery, this should include dose and the treated isodose line, and for fractionated radiation, the treatment volume, total dose, and number of fractions. Ideally, the various costs associated with the treatment should be collected, though this can often be difficult to define due to the complexities of hospital charging algorithms for various payors.

Finally, there should be consensus on how to measure outcomes at various points in time. Typically, assessments used to describe the patient's condition at baseline should be repeated during follow-up evaluations. There will also be a need to collect new data that measures complications of the treatment, such as a postoperative cerebrospinal fluid leak or delayed radiation effects. We must carefully assess whether the classification schemes we employ capture all the important aspects of the conditions that we are assessing. In some cases, we may need to devise new assessments.

Implementation

Before final implementation of a data collection system, bylaws regulating the use of the data should be established. In some cases, each institution may own their own data, but may be required to obtain approval from the registry before publishing their institutional series. Guidelines regarding authorship for registry papers should also be discussed

Table 5 Patient reported outcome measures

	Subjective outcome measures	
Scale	**Publication**	**Function measured**
Patient-Reported Outcomes Measurement Information System (PROMIS)	Fries and Cella (2005)[103]	General physical, mental, and social health
Neurology Quality of Life (Neuro-QoL)	Cella et al (2011)[104]	General physical, mental, and social effects of neurological conditions
Five Level Euroqol Five Dimensional Questionnaire (EQ-5D-5L)	Ravens-Sieberer et al (2010)[105]	5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression
Short Form-36	Brazier et al (1992)[106]	Perception of overall health
Barrow Neurological Institute Pain Intensity Score	Rogers et al (2000)[107]	Facial pain (score I-V)
Barrow Neurological Institute Facial Numbness Score	Rogers et al (2000)[107]	Facial numbness (score I-IV)
Anterior Skull Base Questionnaire (ASBQ)	Gil et al (2003)[108]	Performance, physical function, vitality, pain, specific symptoms, and impact on emotions specifically in the setting of anterior skull base tumor resection
Skull Base Inventory (SBI)	de Almeida et al (2012)[109]	Social, emotional, physical, cognitive, family, financial, spiritual, endocrine, nasal, neurologic, and visual function
SNOT-22	Piccirillo et al (2002)[110]	Sinonasal symptoms
ASK-Nasal 12	Gravbrot et al (2018)[111]	Sinonasal specific symptoms
Endoscopic Endonasal Sinus and Skull Base Surgery Questionnaire (EES-Q)	Ten Dam et al (2017)[112]	Physical, psychological, social function
The Karnofsky Performance Scale (KPS)	Karnofsky and Burchenal (1949)[113]	Ability to carry out activities of daily living
Functional assessment of cancer therapy-Brain (FACT-Br)	Weitzner et al (1995)[114]	Physical well-being, social/family well-being, emotional wellbeing, functional well-being
Meningioma Quality of Life (MQOL)	Baba et al (2021)[115]	Symptoms, vitality, cognition, family, social, emotional, anxiety, functional, physical
Suprasellar Meningioma Patient Reported Outcomes (SMPRO)	Khalafallah et al (2021)[23] et al (2021)	Based on PROMIS-29 with disease specific features
Penn Acoustic Neuroma QOL	Shaffer et al (2010)[116]	Hearing, vestibular, facial symptoms, headache, emotional wellbeing, cognition
Dizziness Handicap Inventory (DHI)	Jacobson et al (1990)[117]	Vestibular symptoms, physical, emotional, functional
Activities Specific Balance Confidence (ABC)	Powell et al (1995)[118]	Confidence in balance in various scenarios
Glasgow Benefit Inventory (GBI)	Robinson et al (1996)[119]	Assessing benefit of an intervention in activity, emotion, social
Acromegaly QOL (AcroQOL)	Webb et al (2002)[120]	Disease specific symptoms, social, emotion, physical
Cushing QOL	Webb et al (2008)[121]	Disease specific symptoms, social, emotion, physical

and agreed on before data collection begins. Some journals limit the number of authors that can appear on a paper which creates additional logistical challenges for large collaborative studies. Finally, operational costs should be clearly understood and funding sources secured. Funding may come from grants, industry, professional societies, and participating institutions, each of which must be sustained through ongoing effort.

Once consensus has been achieved to determine what information should be collected, the next step is to build a functional repository to hold the actual data to be analyzed. There are several existing options which are commonly

employed to collect and store data. Data from multi-institutional clinical studies are typically stored in an online database such as REDCap (Nashville, Tennessee, United States) which provide web-based forms that can be built and deployed according to a protocol. Alternatively, personal database files built using software such as Microsoft Access or Filemaker Pro can be used. The most accessible, though rudimentary, method is to use a spreadsheet with columns for each data element and rows for each observation event. As long as the same data elements are collected, data from each of these systems can be combined for later analysis.

There are varying costs, security considerations, and backup strategies associated with each of these types of repositories. In an age when security breaches are reported on a daily basis, simple password protection to protect acquired data are inadequate. Advanced encryption and two-factor authentication should be considered to protect clinical data and to remain compliant with institutional regulations. Additionally, data redundancy and a sound backup strategy should be a consideration with any future registry, giving cloud-based systems, such as REDCap or other similar solutions, a significant advantage over spreadsheet files or standalone databases which can be more easily deleted, overwritten, or corrupted.

The most labor intensive and expensive aspect of building a registry is usually data collection which often involves directing personnel to abstract data from clinical records and enter it into a database. This person also serves as a semi-independent third party who may obtain more truthful answers from patients during follow-up interviews since some patients may minimize their symptoms to avoid disappointing their doctors. Traditionally, patient-reported data has been collected on forms that are filled out during clinic visits or through a telephone interview. Although telephone interviews generally produce high quality data, they are labor intensive and thus more costly. More recent alternatives include tablet entry in the clinic or hospital setting, though the patient may not be present for such visits during the desired time point in the protocol. Finally, web-based forms linked to a patient portal can be solicited with emails, or outcome data can be entered into a dedicated phone application.

Conclusion

Skull base lesions can be difficult to study because they vary significantly in presentation, anatomical involvement, and treatment approaches. Moreover, there is still no consensus on how to characterize these lesions, the interventions used to treat them and assessments of outcomes. Many of these lesions are rare, making it difficult to collect sufficient numbers for each type of presentation and treatment approach. Despite these difficulties, the value of skull base procedures will need to be proven in the current climate of rationing and cost reduction. Therefore, we should combine our data in skull base registries that make it easier for us to learn from our collective experiences. Increasingly, machine learning will be used to predict outcomes and augment decision-making, and a registry is our best option for creating the quantity and quality of data that will make this possible. Even so, it may take decades to accumulate enough data to answer certain questions. There are significant challenges, but the rewards will justify our efforts. We should begin as soon as possible.

Conflict of Interest
None declared.

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