PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploring the experiences and challenges for patients undergoing cranioplasty: A mixed-methods study Protocol
AUTHORS	Mee, Harry; Clement, Clare; Anwar, Fahim; Whiting, Gemma; Timofeev, Ivan; Helmy, Adel; Hutchinson, Peter; Kolias, Angelos

VERSION 1 – REVIEW

REVIEWER	Mitchell , Kerry-Ann The Ohio State University
REVIEW RETURNED	07-Mar-2021

GENERAL COMMENTS	With increasing advances in neurosurgery and neurocritical care, adult patients with severe brain injury and strokes are having increased rates of survival following decompressive craniectomy. As secondary skull reconstruction, i.e. cranioplasty, becomes more common, it is important to examine the impact of the surgery on quality of life. Neuroplastic Surgery is a new subspecialty aimed at developing novel strategies and techniques through multidisciplinary collaboration to improve outcomes of adult patients with neurocranial soft tissue and bony defects. The authors present a very timely study protocol, with the goal to evaluate the impact of cranial reconstruction from patients, families, and healthcare professionals' perspective. A limitation to the proposed study is the lack of a validated instrument specific to cranioplasty patients. The importance of patient reported outcomes (PRO) is widely recognized as a critical aspect of studies examining health related quality of life (HRQoL). To my knowledge, there is no specific patient reported outcome measure (PROM) for utilization in adult cranioplasty patients. This is a shortcoming of the current study protocol, given that the authors will need to use ad hoc instruments to obtain feedback from patients. The QOLIBRI questionnaire is a valid HRQoL instrument specifically developed for traumatic brain injury (TBI) patients. However, it does not cover domains specific to cranioplasty, such as appearance, factors related to the cranial implant materials, scarring, and etcetera. While it is a useful tool for the purposes of this study protocol, this further highlights the need for rigorously developed and validated PROMs for use in patients before and after cranioplasty. This should be discussed as well. Another aspect that is not addressed in the protocol is the impact of other neurological comorbidities on cranioplasty outcomes. For example, patients with TBI and strokes may have accompanying hydrocephalus or epilepsy managed with cranially embedded neurotechnological devices. These may impact cranioplasty surgery, risks of complications, and patients' perception of health.

	Purposeful sampling should be performed to include patients from these subgroups as well. Despite these limitations, this is a well-designed study, and the results will undoubtedly be invaluable to neurosurgeons, neuroplastic surgeons, and other healthcare practitioners working with patients with skull defects before and after reconstruction. A few minor suggested edits: - In the second paragraph of the introduction, the authors mention cranioplasty “aid in the prevention of falls”. How does cranioplasty prevent falls? Did they mean “protect the brain in the event of a fall? - There are a number of studies suggesting cranioplasty helps to restore intracranial physiology. In the second paragraph of the Introduction, would suggest citing Mitchell et al for restored intracranial pressure dynamics after cranioplasty. - There are a number of grammatically and syntax errors throughout. Would recommend editing overall with this in mind. For example, in the first sentence of the abstract and conclusion, “cranioplasty” does not need the modifiers “a” and “the”, and can simply be started with “Cranioplasty”. Citations: Mitchell, KS et al. First-In-Human Experience with Integration of Wireless Intracranial Pressure Monitoring Device within a Customized Cranial Implant Operative Neurosurgery, Volume 19, Issue 3, September 2020, Pages 341–350

REVIEWER	Schwalb, Jason Henry Ford Medical Group, Neurosurgery
REVIEW RETURNED	02-May-2021

GENERAL COMMENTS	This is an important study that addresses an important question. The authors should discuss number of patients to be studied. What %age of patients with cranial defects after TBI or stroke do they expect to be consentable? Is there anything in the literature to estimate this %age?

REVIEWER	Guan, Junwen West China Hospital of Medicine, Neurosurgery
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	Thank you for the opportunity to review the protocol, which I read with interest. To date, there is very little literature on the patients cranioplasty process impacts patients rehabilitation and social reintegration. For instance, little is known about how the temporal hollowing, an underreported complication following cranioplasty, may impact the rehabilitation and social reintegration. Understanding the process would help clinical practice. I have some suggestions： (1) I suggest uniform training should be provided to all Health care professionals. (2) Because the patients and their relatives will be asked to complete questionnaire. In the exclusion criteria, I suggest adding patients who are unable to communicate. Overall, I consider this project very important and support its implementation.

REVIEWER	Staudt, Michael Oakland University William Beaumont School of Medicine, Neurosurgery
REVIEW RETURNED	15-May-2021

GENERAL COMMENTS	The authors present a study protocol to evaluate the views and experiences of patients and their relatives regarding cranioplasty surgery. The authors attempt to bridge the gap of knowledge and present the views or challenges from the perspective of patients, relatives and healthcare professionals. This is a mixed-methods study that utilizes semi-structured interviews, notes, diaries and questionnaires co collect data. Data will be analyzed thematically using “Interpretive Phenomenological Analysis”. This study proposes to explore a multi-dimensional view of recovery, rehabilitation and social reintegration. 1. One of the inclusion criteria is that patients must be able to provide their own consent. Patients who have experienced a TBI or stroke necessitating decompressive craniectomy are often cognitively impaired and unable to provide their own consent, and certainly this would seem to limit the study population. How do the authors anticipate this will impact enrollment? 2. Patient recruitment is somewhat unclear. The study design seems to be a mix of prospective and retrospective enrollment, given that patients are eligible if they are awaiting or have already received a cranioplasty. It is mentioned that recruitment will occur in a variety of settings but is not specific. Will patients be identified through coding? The UK Cranial Reconstruction Registry should be explained for those unfamiliar. 3. Many readers will be unfamiliar with the proposed tools of data collection. As such, the data analysis tools should be included in this protocol, such as the QOLIBRI. If interviews are semi-structured, the structured portions should be explicitly stated. 4. The overall protocol is vague. Beyond the use of QOLIBRI, which is the sole validated metric, there is no clear structure to the study. The methods of triangulation and interpretive phenomenological analysis need to be explicitly defined, with examples given beyond a singular reference. What does it mean to “read and re-read” patient accounts? Who are interpreting these accounts and what qualifications are required? What and who decides if on-going discussions are being held with the research team? 5. “Triangulation strategies will be used, allowing the mixed methods of data sources to be brought together, allowing a more comprehensive, more complete picture to emerge from the study” (page 9, lines 38-39) – these strategies need to be more explicitly defined. How exactly will the mixed qualitative data be collated? 6. Thematic analysis using deductive and inductive coding needs to be similarly defined. “Data will be compared across and within groups” (page 9, line 16) – which groups are being referred to? At what time points? 7. “For all interviews and focus groups if the participant is becoming increasingly distressed or upset, then the interview or focus group will be stopped” (page 10, lines 14-16) – in these

	circumstances, are the data excluded? Are patients allowed to withdraw from the study? 8. “Patients post craniectomy may also be reluctant to engage in rehabilitation due to altered cosmetic appearance” (page 10, lines 56-57) – is there any evidence to support this claim? Is it reluctance to participate, or physical/mental barriers from their neurological insult? 9. The “novel external cosmetic cranioplasty” should be explained in more detail. What is it exactly? Which patients will be offered it, and how is that decided? 10. Experiences change throughout rehabilitation and recovery. Will there be an attempt to explore longitudinal views and experiences following cranioplasty? Especially as it has been demonstrated that cranioplasty improves motor and cognitive function (see 10.1002/brb3.1106), having these data would enhance the results. 11. The protocol would benefit from a flowchart depicting patient identification, data collection, timelines and study endpoints.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. The impact of other neurological comorbidities on cranioplasty outcomes: Given the nature of an IPA study, there will be opportunities to explore this in the interviews. However, it will be difficult to cover all potential comorbidities given the small sample size expected and we have explained this in the study limitations.
2. Lack of validated instrument specific to cranioplasty: We agree, and the hope will be that this will be a first step in the development of such measure, we have outlined this in the future directions section.
3. Grammatical and syntax errors: Editing of these has been completed.
4. Mitchell et al citation: We have included this as a reference.

Reviewer 2

1. What age of patients with cranial defects after TBI or stroke do they expect to be consent able? This is a study of adults aged 16 and over, if the patient has capacity following their brain injury for consenting, we hope to be able to approach them.
2. Is there anything in the literature to estimate this %age? This is a very valid point, but not well researched.
3. The authors should discuss number of patients to be studied. Study numbers are discussed in the protocol for both the IPA and thematic analysis studies.

Reviewer 3

1. I suggest uniform training should be provided to all Health care professionals. We agree that a wider education around cranioplasty should be available for HCP’s. For this study, HM will be the sole data collector and HM and CC will analyse the data.
2. Because the patients and their relatives will be asked to complete questionnaire. In the exclusion criteria, I suggest adding patients who are unable to communicate. We agree this should be flagged. We have added this to the study limitations as the protocol has already gone through an ethics review, we cannot change the specific study exclusion criteria, but will ensure it is addressed.

Reviewer 4

1. Limitation with patients providing own consent: We agree, this is a limiting factor, but given the nature of an IPA study, in-depth interviews of a few patients can be insightful. A further limitation here is the generalisability of an IPA study, which is also addressed in the protocol.
2. Patient recruitment is somewhat unclear: We have explained this further in the revised manuscript. Essentially, using purposive sampling, appropriate patients will be individually approached from a variety of known settings, such as outpatient clinics and rehabilitation units.
3. Many readers will be unfamiliar with the proposed tools of data collection: We have extensively re-written these sections, hopefully making the data collection tools and methods clearer.
4. The overall protocol is vague: We have better defined the research methods used and how they will interlink with each other.
5. Triangulation strategies: We have further outlined the type of triangulation adapted and how the main data sets will be collected and analysed.
6. Thematic analysis using deductive and inductive coding needs to be similarly defined: As for the whole section around data collection and analysis, we hope to have made this much clearer.
7. "For all interviews and focus groups if the participant is becoming increasingly distressed or upset, then the interview or focus group will be stopped" in these circumstances, are the data excluded: This would be at the wishes of the patients.
8. "Patients post craniectomy may also be reluctant to engage in rehabilitation due to altered cosmetic appearance" – is there any evidence to support this claim? Is it reluctance to participate, or physical/mental barriers from their neurological insult? We have made it clear that is one of the hypotheses and is something I am exploring as part of this study.
9. The "novel external cosmetic cranioplasty" should be explained in more detail. What is it exactly? Which patients will be offered it, and how is that decided? We have explained further in the protocol that this in development and we hope to use the views of patients both on the design and potential application for further development. All patients will be asked about it, we will show them the prototype while we are discussing cosmesis in general, but at this stage it is not ready for clinical application.
10. Experiences change throughout rehabilitation and recovery. Will there be an attempt to explore longitudinal views and experiences following cranioplasty? We totally agree that longitudinal evaluation is very important. It is not possible to follow up the same patient over a long period of time in this study, however, different patients will be interviewed regardless of time point from cranioplasty and so individual views will be captured at different time points. We hope this work will aid in the development of a longitudinal study in the future and we have outlined this in the future directions section.
11. The protocol would benefit from a flowchart: We have included a flow chart now for clarity.

We hope the reviewers points have be adequately addressed and are now reflected in the manuscript. If there is anything further, please don't hesitate to contact Dr Harry Mee.

Many thanks

VERSION 2 – REVIEW

REVIEWER	Mitchell , Kerry-Ann The Ohio State University
REVIEW RETURNED	17-Dec-2021

GENERAL COMMENTS	This is a timely, well designed study to evaluate patient reported outcomes for patients undergoing cranioplasty.