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Clinical Equipoise in Sleep Surgery: Investigating Clinical Trial Targets

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Abstract

Objective. Surgical approaches for alleviating snoring and/or obstructive sleep apnea (OSA) have been questioned because of a lack of evidence from high-quality randomized controlled trials (RCTs). An ethical requirement for RCTs is that they must test questions where community equipoise (ie, uncertainty) exists as to the correct treatment. We aimed to measure perceived importance, community equipoise, and willingness to enroll patients in 5 potential trial targets among members of the Australian Society for Otolaryngology Head and Neck Surgery (ASOHNS).

Study Design, Setting, and Subjects. All ASOHNS members were surveyed using a multistage mail, email, Internet, and phone-based questionnaire.

Methods. Equipoise was measured for each of the scenarios using a bidirectional linear scale comparing 2 treatments. Responses were categorized into 1 of 3 groups: (A) preferred treatment 1, (B) completely undecided, and (C) preferred treatment 2. The resulting proportions are called equipoise ratios: A:B:C. Using tick boxes, the authors queried the general clinical importance and willingness to enroll patients for all scenarios.

Results. A total of 167 of 313 surgeons responded (53.4%). Three of the 5 trial scenarios exhibited evidence of community equipoise, but 2 scenarios, radiofrequency ablation plus uvulopalatopharyngoplasty (UPPP) versus UPPP alone and upper-airway reconstruction versus mandibular advancement splint (MAS), did not have strong support for enrolling patients. Informal feedback indicates one of these may be feasible in a smaller number of specifically trained surgeons.

Conclusion. We suggest 2 potential RCT targets: septoplasty and turbinate reduction versus conservative measures for snoring and airway reconstruction versus MAS for OSA, where importance, clinical equipoise, and willingness all exist.

Keywords

surgical choice, clinical equipoise, sleep apnea, snoring

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Obstructive sleep apnea (OSA) is a chronic condition associated with obesity and craniofacial abnormalities prevalent in about 5% of middle-aged adults, and it causes marked morbidity and mortality.[1-4] Recurring partial or complete occlusion of the upper airway during sleep is held in abeyance by the standard treatments for the condition: continuous positive airway pressure (CPAP) or dental appliance treatments, such as mandibular advancement splints (MAS).[5,6] However, poor treatment adherence limits disease alleviation,[7] a problem common to many nonimplantable medical devices. Effective surgical solutions to snoring and sleep apnea would not suffer from this adherence problem and may be a superior alternative.

However, the effectiveness and funding for upper airway surgery for snoring and sleep apnea have recently been questioned because of the paucity of high-quality randomized controlled trials (RCTs).[8,9] The lack of these trials does not automatically imply that surgical techniques do not work or that lower levels of clinical evidence are not instructive for

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clinical decisions that must be made immediately.[10] Regardless, in the medium to long term, high-quality clinical trials may be necessary to convince policy makers and nonsurgical clinicians[11] that surgery is a viable option in specified situations.

Unfortunately, clinical trials in surgery are technically difficult to undertake. There is a large body of evidence describing reasons for the relative lack of surgical trials, including difficulty in selecting an appropriate control group and difficulties in blinding and standardizing surgical technique between individual surgeons and centers over time.[12,13] Surgical trials are also expensive to execute, and without direct input and participation by a broad cross section of practicing surgeons, they are destined to fail in either execution or in translation to general ear, nose, and throat (ENT) practice.

Barriers to the individual surgeon's participation include time constraints, concerns about the trial's effects on the doctor-patient relationship, and a lack of interest in the proposed research questions.[13-15] A preference for one treatment over another may also dissuade surgeons from enrolling their patients. Furthermore, regardless of whether there is definitive evidence of effectiveness, such a trial can be considered unethical if one treatment is considered inferior by most practicing surgeons. For trials to proceed, a genuine state of uncertainty, or equipoise, must be demonstrated across the surgical community so that there is less than 70% agreement that one treatment is superior.[16]

A single surgeon may have individual equipoise, whereby he or she is uncertain as to the superiority of one treatment option over another. The wider surgical community can also demonstrate community equipoise, in which most are uncertain or whereby equal numbers favor each alternative treatment, with or without a middle group who are uncertain. Trials must address questions where there is significant community equipoise, not just on ethical grounds[16] but also for the additional pragmatic reason that surgeons will not refer their patients.

We need to identify viable trials in sleep surgery that are ethical, feasible, and widely supported by the clinical community because they address questions in which community equipoise exists. Hence, the aim of this study was to present 5 common clinical scenarios to all practicing ENT surgeons in Australia to gauge feasibility and interest in RCTs.

Methods

This study was approved by the University of Sydney human research ethics committee (11-2009/12114) and was supported by the Australian Society for Otolaryngology Head and Neck Surgery (ASOHNS). All members of the ASOHNS were surveyed to quantify attitudes toward 5 clinical scenarios. Surgeons were initially sent a postal questionnaire. For nonresponders, there were 4 phases of follow-up: mail (phase 1), email (phase 2), mail (phase 3), and phone (phase 4). We allowed respondents approximately 1 month before initiating the next data collection phase. The multiphase research technique has been shown to improve survey response rates.[17] Respondents who were not involved in sleep surgery were excluded from the analysis.

We presented 5 clinical scenarios each with 2 treatment solutions. The questionnaire was based on previous studies that have examined clinical equipoise and trial participation in surgery and oncology.[18-20] A copy of the questionnaire is available from the corresponding author.

- Scenario A: Septoplasty and turbinate reduction versus continuing conservative treatment in a patient who has had an inadequate response to nasal steroids. This patient has moderate-to-severe OSA with significant nasal flow limitation and cannot currently tolerate CPAP. The purpose is to make CPAP tolerable. (We have abbreviated this trial as Septo & Turb OSA vs Conservative.)
- Scenario B: Uvulopalatopharyngoplasty (UPPP) versus CPAP in patients with moderate-to-severe OSA (abbreviated as UPPP vs CPAP).
- Scenario C: Septoplasty and turbinate reduction versus watchful waiting/conservative measures in patients who present with simple snoring who do not complain of nasal blockage and in whom clinical observation/rhinomanometry reveals significant septal deviation (abbreviated as Septo & Turb vs Conservative).
- Scenario D: Is the addition of radiofrequency ablation of the tongue (±palate) in patients undergoing a UPPP procedure for OSA better than UPPP alone? (We have abbreviated this scenario as Radio & UPPP vs UPPP.)
- Scenario E: Multilevel stepwise upper airway reconstructive surgical protocol versus a mandibular advancement splint in patients with moderate-to-severe OSA with a patent nasal airway who cannot tolerate CPAP (abbreviated as Airway Recon vs MAS).

Scenarios A and B were considered a priori as pseudo-control questions for which we did not expect to observe community equipoise. Scenarios C, D, and E were selected because we suspected that they may be examples where significant community equipoise may exist.

Participants were first asked to quantify the importance of each clinical scenario (*extremely important*, *very important*, *somewhat important*, *not at all important*). We then calculated an Importance Ratio (Yes:No) by collapsing these 4 options into 2 categories. The "Yes, it is important" combined the responses of *extremely important* or *very important*. The "No, it is not important" option combined *somewhat important* or *not at all important*.

To investigate and quantify community equipoise, a bidirectional linear analogue scale with a treatment option anchored at either end was used.[21] The scale is centered on 0 to represent "completely undecided" and marked from 1 to 5 toward each end to represent increasing certainty in the best treatment approach (see the *x*-axes of **Figures 2-6** for what we presented to the participants).

Surgeon willingness to participate in each proposed trial was evaluated by way of a Willingness to Enroll Ratio (X:Y:Z),

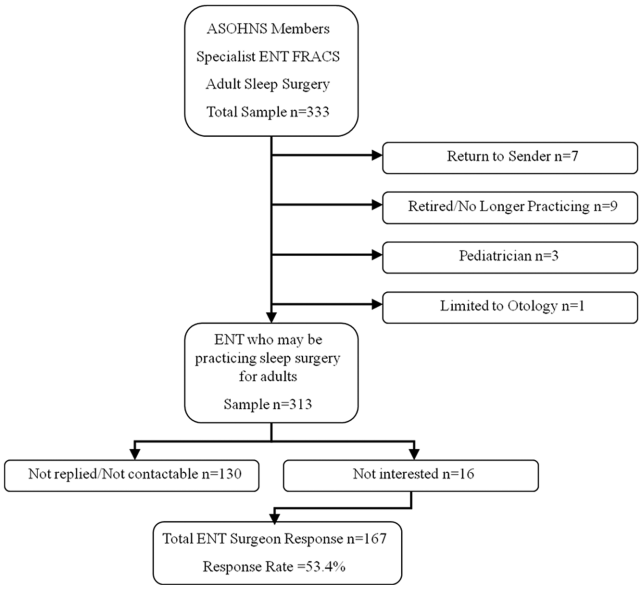

Figure 1. Response rate calculation from target population.

comprising the following: would take part in a randomized control trial (X), would take part in a nonrandomized follow-up study (Y), and would not take part (Z).

Surgeons were then asked a range of personal and clinical practice–related questions including age, gender, location of practice, and type of appointment. There was insufficient variation in these to investigate whether they might have been associated with treatment preferences or willingness to enroll in a way that would have been meaningful for our overarching aim: to build a comprehensive nationwide trials network.

Analysis

Community equipoise was determined by categorizing the surgeon responses' using the bidirectional linear analogue scale. Surgeon responses were plotted and categorized into 1 of 3 groups to quantify the equipoise ratio: (A) preferred treatment 1 (left-hand side of scale), (B) completely undecided, and (C) preferred treatment 2 (right-hand side of scale). The resulting proportions (A:B:C) are equipoise ratios and add to 100 because they are expressed as percentages, like a political opinion poll. For example, an equipoise ratio of 10:7:83 shows that 83% of respondents selected preferred treatment 2. No equipoise exists in this situation because more than 70% of respondents agree there is a superior option.[16] On the other hand, an equipoise ratio of 50:5:45 demonstrates community equipoise because there is substantial disagreement. The other possibility is predominantly individual equipoise, where an equipoise ratio similar to 10:75:15 is observed. In that case, a clear majority of surgeons have indicated they do not know which option is superior. Equipoise can be ethically inferred when less than 70% of clinicians agree that a particular treatment option is superior.[16]

We have also attempted to plot whether equipoise is related to willingness to enroll across the surgeon population. In the figures, the bars above each treatment preference option are given patterns to indicate the proportions of surgeons who would be willing to enroll patients. Although it may seem odd to some readers because this is a descriptive epidemiological study looking at whether trials will be supported by the professional ENT community, we have not included any inferential statistical testing.

Table 1. Characteristics of Respondents (N = 167)

Characteristic	n	%
Age, y		
<35	2	1.2
35-44	56	33.5
45-55	49	29.3
55-64	42	25.2
65+	18	10.8
Gender		
Male	155	92.8
Female	12	7.2
Location of practice		
Capital city	125	74.8
Other major urban area	30	18.0
Rural area	9	5.4
Other	3	1.8
Type of appointment		
Conjoint/academic staff	8	4.8
Visiting medical officer/ consultant	133	79.6
Staff specialist	7	4.2
Salaried university academic	3	1.8
Other	16	9.6
Hospital work		
Tertiary referral teaching hospital	57	34.1
District general hospital	10	6.0
Private hospital	95	56.9
Other	5	3.0

Results

We initially mailed the questionnaire to 333 members of ASOHNS. We then excluded from the denominator responses that were returned to sender or indicated that they were retired/no longer practicing, focused exclusively on pediatric cases, or told us that they never undertook surgery for the relief of snoring or sleep apnea (n = 20). This left 313 surgeons, of which 167 replied (response rate = 53.4%). The selection criteria and response rate are summarized in **Figure 1**. Personal and professional characteristics are shown in **Table 1**. The importance, equipoise ratios, and willingness to enroll patients for all scenarios are presented in **Table 2**. We have also plotted the combined clinical equipoise data with willingness to enroll in each separate uncertainty score bar for all of the scenarios in **Figures 2** to **6**. Marked community equipoise (less than 70% support for any treatment) was seen

Table 2. Clinical Importance, Equipoise Ratios, and Willingness to Enroll Patients in Clinical Trials for 5 Sleep Surgery Scenarios[a]

Clinical Scenario	Importance Ratio: Yes:No, %	Equipoise Ratio: A:B:C, %	Willingness to Enroll Ratio: X:Y:Z, %
A: Septo & Turb OSA vs Conservative	86:14	90:2:8	42:34:25
B: UPPP vs CPAP	54:46	11:7:82	37:23:40
C: Septo & Turb vs Conservative	43:57	45:14:41	49:19:31
D: Radio & UPPP vs UPPP	58:42	31:56:13	32:12:56
E: Airway Recon vs MAS	71:29	32:30:38	33:15:52

[a]Clinical scenarios are listed in full in the Methods section and under each of the relevant figures. The equipoise ratios list the percentage of surgeons who favored the left-hand treatment (A), neither treatment (B), and the right-hand treatment (C). The willingness to enroll ratio gives the percentage of surgeons who would be willing to enroll their patients in a randomized study (X) or a nonrandomized follow-up (Y) or who would not enroll a patient (Z).

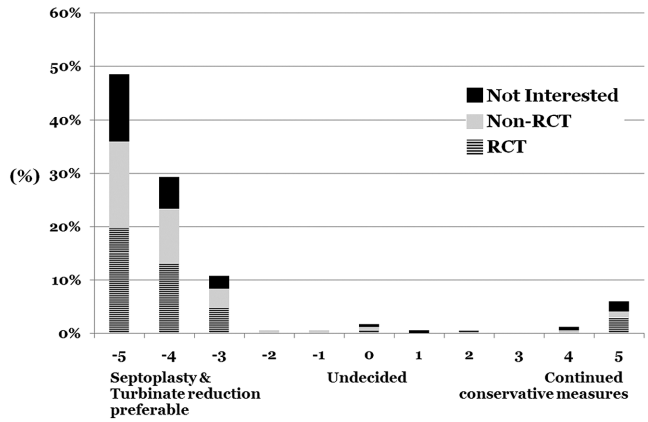

Figure 2. Surgeon willingness to enroll patients weighted to clinical uncertainty about scenario A. Willingness to enroll patients (in figure legend) is plotted with each bar of a clinical equipoise plot to show that the largest number of surgeons who would be willing to enroll their patients in trials are also those who have no treatment uncertainty. Respondents could select whether they would not enroll patients in any type of study (not interested), in non–randomized controlled trials (non-RCTs), or randomized controlled trials (RCTs).

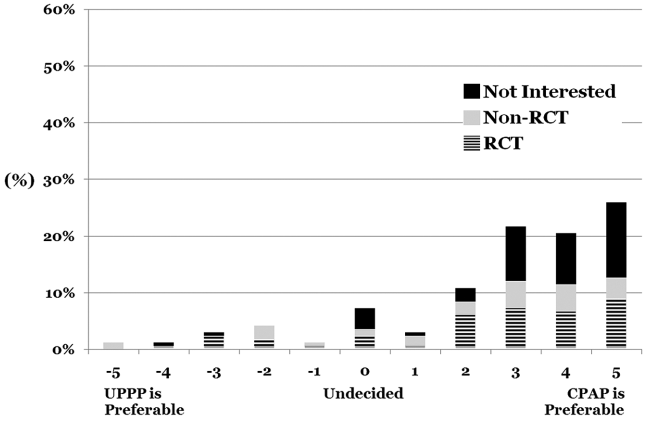

Figure 3. Willingness to enroll patients weighted to clinical uncertainty about scenario B. Willingness to enroll patients (in figure legend) is plotted with each bar of a clinical equipoise plot to show that the largest number of surgeons who would be willing to enroll their patients in trials are also those who have no treatment uncertainty. Respondents could select whether they would not enroll patients in any type of study (not interested), in non–randomized controlled trials (non-RCTs), or randomized controlled trials (RCTs).

in scenarios C (Septo & Turb vs Conservative), D (Radio & UPPP vs UPPP), and E (Airway Recon vs MAS). Interest (importance or willingness to enroll) in joining these trials was lower than in those scenarios where clinical equipoise did not exist. In addition, a snoring treatment scenario (C), where equipoise existed, was not regarded as important. This may indicate the lack of serious sequelae for snoring and could imply that funding for such a trial may be difficult to secure from public sources. Unwillingness to be involved in studies could also be caused by unfamiliarity with the techniques suggested, as was indicated to us verbally at conferences or informally by spontaneous notes helpfully returned with the questionnaire by the surgeons.

Discussion

Feasible trials in surgery are those that are perceived as important, unanswered (community equipoise), and will be supported (willingness to enroll patients). Three of the 5 sleep surgery trial targets we presented (C, D, and E) were regarded by surgeons as having equipoise (**Figures 4-6**). Despite this uncertainty, for 2 of the sleep apnea treatment scenarios (D, Radio & UPPP vs UPPP, and E, Airway Recon vs MAS), there was very low willingness to enroll patients in either trial. In the case in which the community as a whole was uncertain (C, Septo & Turb vs Conservative for snoring), surgeons were much more willing to be involved in a trial. The apparently low level of importance for that snoring scenario might indicate the relatively lower morbidity impact of snoring versus sleep apnea. Indirect community feedback suggested that scenario E might have suffered from low enrollment willingness due to a lack of familiarity with the techniques suggested. A trial might still be feasible in a smaller specifically trained subset of surgeons. Our survey thus suggests that 2 clinical trial targets are feasible (C, Septo & Turb vs Conservative for snoring; E, Airway Recon vs MAS for sleep apnea).

The mismatch between strong community equipoise on one hand and yet unwillingness to enroll patients in some scenarios seems counterintuitive. In scenario E, it is probably reflective of

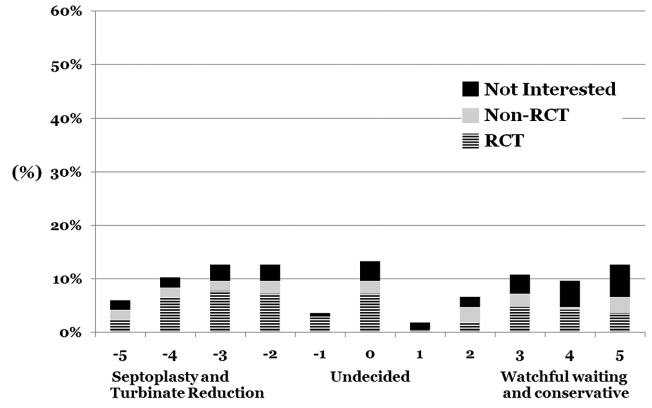

Figure 4. Willingness to enroll patients weighted to clinical uncertainty about scenario C. Clear community equipoise (ie, uncertainty when entire community's opinion is viewed) is seen in this scenario, with willingness to enroll distributed across the entire uncertainty spectrum. This combination suggests trial feasibility.

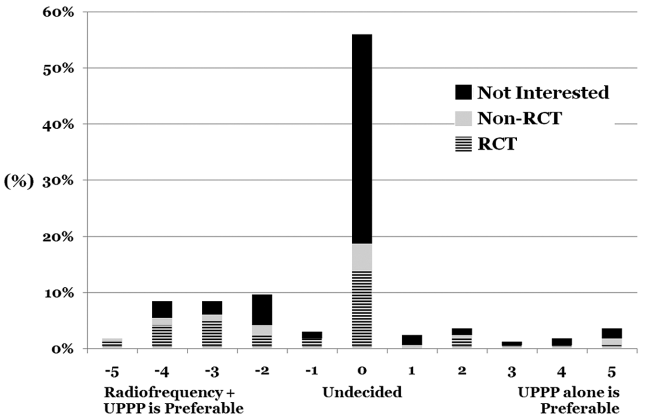

Figure 5. Willingness to enroll patients weighted to clinical uncertainty about scenario D. Clear individual and community equipoise (both personal and collective uncertainty) is seen in this scenario. However, 56% of surgeons are not willing to enroll their patients in any trial, suggesting low feasibility.

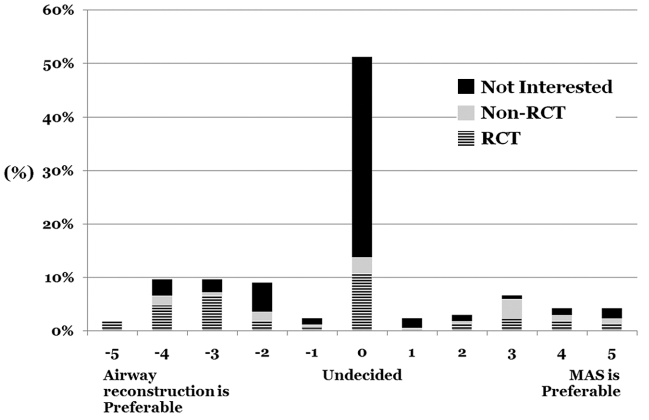

Figure 6. Willingness to enroll patients weighted to clinical uncertainty about scenario E. Clear individual and community equipoise (both personal and collective uncertainty) is seen in this scenario. However, the bulk of surgeons are not willing to enroll their patients, suggesting low trial feasibility. However, feedback from the clinical community suggests unfamiliarity with the technique drove the unwillingness. This trial may be feasible in a specifically trained subset of surgeons.

a lack of technical familiarity. However, we do not currently have an explanation for scenario D comparing UPPP with radiofrequency ablation in addition to UPPP suffering from this problem. Regardless of the cause, it would seem that if trials in scenarios D and E were to occur, they would need to be undertaken in an enthusiastic subsample of surgeons rather than the broad cross section we were testing for.

In scenario B, the lack of equipoise (82% in favor of CPAP over UPPP for OSA) and the relatively low level of interest in a randomized control trial (37%) are reflective of practice in Australia. Although there has been a very large rise in OSA diagnosis in the past 20 years, there has been a general flattening in the number of UPPP procedures billed to Medicare.[22-25] CPAP is felt by the surgical community to be superior both on this questionnaire and in practice.

Recent publications[11,26] have been less than favorable with respect to upper airway surgery for OSA, without truly reflecting on the potential improvement and benefits achievable with contemporary surgical protocols. The controversy associated with measuring success, on the spectrum from improvement to complete cure, is eloquently outlined by Weaver in a recent sleep medicine review article.[10] The "significant physiological and moreover clinical improvement offered by surgical therapy" is largely downplayed in the literature because of a "counter-productive" focus on Level I evidence and on the major disease severity index (the apnea hypopnea index) instead of wider patient-centered outcomes that improve as a result of disease severity reduction.

Some surgical procedures are so markedly successful that they do not require RCTs to confirm their effectiveness. For instance, maxillomandibular advancement (MMA) surgery is generally considered appropriate as phase 2 surgery in the well-documented Riley-Powell protocol or for patients who have failed device use and have correctable craniofacial anatomy.[26] That review identified the marked clinical and physiological improvements in OSA offered by MMA, and as Weaver[10] concludes, a randomized controlled trial of MMA versus CPAP would be near impossible to undertake. MMA is another example of a procedure in which no equipoise would be seen regarding its effectiveness in properly selected patients.

Feasibility studies for clinical trials are a new idea in sleep surgery. But they have been used previously to identify surgical and oncology trial targets. These studies provided data to focus clinical research efforts where they are most likely to be successful based on equipoise, feasibility, and clinical interest. Successful trials still require clinician support but also the support of patients willing to participate. Feasibility studies of potential trial targets should also consider the patient perspective. The importance of this was highlighted in a study that ascertained patient treatment preferences and willingness to participate in a number of surgical oncology trials. For these trials, only 19% to 31% of patients were willing to participate, and patients were significantly less likely to participate if they

had a strong preference against the treatment being trialled.[19] These considerations must be taken into account during the development of trials and the calculation of sample sizes.

Our survey does suffer from some weaknesses. The response rate of 53.4% was much lower than the attempted census that we had aimed for. However, with our intensive multiple follow-ups via mail, email, and phone combined with options to respond to the questionnaire via mail, email, phone, or Web portal, we are uncertain as to how to increase the response rate further. This might have been caused by not all members of the ASOHNS being sleep surgeons. Many clinicians surveyed may not have replied because sleep is not part of their practice. The nonrespondents are therefore more likely to be non–sleep focused, and our stated response rate is thus likely to be conservative. In addition, there are other surgical techniques of the head and neck area undertaken by clinicians who are not ASOHNS members, such as maxillofacial surgeons, whom we did not survey.

Conclusion

Our attempted census of all ASOHNS members to ascertain potential sleep trial targets has yielded 2 potential RCTs: septoplasty and turbinate reduction versus conservative measures for the alleviation of snoring and airway reconstruction versus MAS for sleep apnea. Significant equipoise exists as to optimal treatment for these conditions, and there are a sufficient number of surgeons who have indicated a willingness to enroll patients. Thus, a trial for primary snoring probably caused by a significant septal deviation comparing septoplasty plus turbinate reduction to watchful waiting/conservative measures is probably feasible, as might be a trial for treating moderate-to-severe OSA in patients who have already failed CPAP with multilevel stepwise upper airway reconstructive surgery compared with MAS. We may need to confirm that these are acceptable trials to patients, and they are unlikely to be feasible unless appropriately funded because of the largely private practice of the sleep surgery workforce in Australia.

Dedication

The article is dedicated to the memory of Dr Sam Robinson, who tragically died during the last stage of preparing this article. Undoubtedly the leading ENT-sleep surgeon/researcher in the southern hemisphere, his insight, experience, skill, and passion for airway reconstruction for patients with sleep apnea will be sorely missed.

Acknowledgments

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Author Contributions

Clarice J. Field, acquisition, analysis and interpretation of data, drafting of article, final approval of article; **Sam Robinson**, conception and design, interpretation of data, critical revision of article, final approval of article; **Stuart Mackay**, conception and design, interpretation of data, critical revision of article, final approval of article; **James D. Harrison**, interpretation of data, critical revision of article, final approval of article; **Nathaniel S. Marshall**, corresponding author, conception and design, acquisition, analysis, and interpretation of data, drafting of article, final approval of article.

Disclosures

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