An assessment of the clinical acceptability of direct acoustic cochlear implantation for adults with advanced otosclerosis in the United Kingdom

Running head: Acceptability of DACI for Otosclerosis in the UK

Pádraig Thomas Kitterick PhD[1,2] , Guna Reddy-Kolanu BMBS[3], David Baguley PhD[2], Jeremey Lavy FRCS[4], Peter Monksfield FRCS[5], Rupan Banga PhD[5], Jaydip Ray PhD[6], Ad Snik PhD[7], Gerard M. O' Donoghue FRCS[1,2,8]

[1] National Institute for Health Research Nottingham Hearing Biomedical Research Unit, Ropewalk House, Nottingham, United Kingdom

[2] Otology and Hearing group, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, United Kingdom

[3] Royal United Hospitals Bath NHS Foundation Trust, Bath, United Kingdom

[4] Department of Otolaryngology, The Royal National Throat Nose and Ear Hospital, London, United Kingdom

[5] Department of Otolaryngology, University Hospitals Birmingham, United Kingdom

[6] Department of Otolaryngology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom

[7] Department of Otorhinolaryngology, Radboud University Medical Center, Nijmegen, The Netherlands

[8] Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, United Kingdom

Address correspondence to: Pádraig Kitterick
National Institute for Health Research Nottingham Hearing Biomedical Research Unit
Ropewalk House, 113 The Ropewalk, Nottingham, NG1 5DU, United Kingdom
Telephone: 00441158232626, Fax: 00441158232615
Email: padraig.kitterick@nottingham.ac.uk

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Introduction

Permanent conductive hearing loss can result from otosclerosis, a disease in which abnormal bone growth may impede the movement of the stapes bone and impair cochlear function. Examinations of temporal bones suggest that the disease presents bilaterally in approximately 70-80% of cases (Hueb et al., 1991; Menger & Tange, 2003). Temporal bone studies have estimated a prevalence for otosclerosis of between 2.5% (Declau et al, 2001) and 8.3% (Altman et al, 1967). These estimates represent the combined sum of both symptomatic (clinical otosclerosis) and asymptomatic (histologic otosclerosis) cases. The proportion of these cases that correspond to clinical otosclerosis, where the disease actually interferes with hearing function, has been estimated to be between 12% (Altman et al, 1967) and 15% (Guild, 1944). These data therefore suggest that the prevalence of clinical otosclerosis in the population lies between 0.3% and 1.2%. It is estimated that sensorineural hearing loss also arises in about 10% of clinical otosclerosis cases (Browning & Gatehouse, 1992; Ramsay & Linthicum, 1994) and accounts for approximately 5-6% of cases at large cochlear implant centres (Tange R., personal communication, 2016), which if accurate would correspond to a prevalence for mixed losses arising from otosclerosis of 0.1% or lower.

Several treatment options are available for adults with a bilateral mixed hearing loss of a mild, moderate, or severe degree. If the hearing loss is mild, a conventional acoustic hearing aid can be sufficient to overcome the conductive and sensorineural components. A hearing aid may also be beneficial for a moderate-to-severe loss provided the aid can overcome the conductive component while still providing sufficient residual amplification to aid the sensorineural component. The conductive component of the loss may also be addressed by performing stapes surgery where a prosthesis is placed to restore the function of the fixed stapes bone. The sensorineural component may then be more readily aided using an acoustic

hearing aid. In cases where an acoustic hearing aid cannot provide sufficient amplification or is not tolerated (e.g. ear infections) or surgical correction is not appropriate, a bone-anchored hearing device (BAHD) may be used to deliver acoustical energy to the cochlea via bone conduction (Tjellström & Håkansson, 1995). In cases of moderate-to-severe loss where both acoustic and bone-anchored hearing aids are unsuccessful or contraindicated, a middle-ear implant may also be considered.

In the United Kingdom (UK), the treatment options for individuals with a severe-to-profound mixed hearing loss are limited. The severity of the loss means that an acoustic hearing aid alone is unlikely to provide benefit without surgical intervention to address the conductive component. The rate of successful stapes surgery in this patient group has been estimated to be approximately 60% (defined as the closure of the air-bone gap to <10 dB) and lower than that observed in patients with mild or moderate losses (Kisilevsky et al, 2010). The capacity of a BAHD device to provide benefit in these patients is also limited by its ability to provide sufficient energy transfer to the cochlea to overcome the sensorineural component of the loss. The introduction of more powerful BAHDs has expanded the candidacy range but aiding those with more severe sensorineural losses is still restricted by feedback (Bosman et al, 2006). Although individuals with bone-conduction thresholds between 60-90 dB HL are therefore unlikely to be aided satisfactorily by either acoustic or bone-anchored hearing aids, they also do not meet current UK candidacy criteria for cochlear implantation (NICE, 2009).

The Direct Acoustic Cochlear Implant (DACI) was developed to address this gap in treatment options for individuals with a severe-to-profound mixed hearing loss (Häusler et al., 2008). The DACI is an active implantable device which is composed of two parts. The wholly-implanted part comprises a receiver-stimulator and a fixation system that couples an artificial

incus to a conventional stapes prosthesis (Fig. 1). The external part comprises a speech processor that converts incoming sound into a digital signal that is transmitted to the implanted part via a radio-frequency coil. The receiver-stimulator decodes that digital signal and drives the actuator accordingly via a mechanical piston. By stimulating the intracochlear fluids directly, the DACI bypasses any existing conduction problems in the middle ear and can deliver acoustical energy directly to the cochlear perilymph of sufficient power to aid severe-to-profound sensorineural losses.

Lenarz et al. (2013) conducted a case series study of the safety and efficacy of the DACI in 15 patients with a severe-to-profound mixed hearing loss defined as bone-conduction thresholds poorer than 30 dB HL from 0.5 to 4 kHz and an air-bone gap of at least 30 dB at 3 or more test frequencies. On average, implantation of the device did not impair air- or bone-conduction thresholds, with bone-conduction thresholds improving at 0.75, 1, and 1.5 kHz post-operatively. The DACI also improved sound-field thresholds measured from 250 Hz to 8 kHz. Among those patients who used a hearing aid pre-operatively, the DACI improved sound-field thresholds, sentence recognition, and word recognition in quiet. The results of this preliminary study suggest that the DACI may be efficacious in patients with a severe-to-profound mixed hearing loss and with moderate bone-conduction thresholds (Busch et al., 2013).

Direct acoustic cochlear implantation is not currently provided in the UK. Evidence from a well-designed prospective evaluation of effectiveness that compared DACI to usual care would be required to support its provision. However, there is uncertainty over which comparator intervention(s) should be used to represent usual care. There is also uncertainty over the audiometric definition of the patient group whose needs are unmet by usual care and

who would therefore be included in the future trial. Finally, there is uncertainty over whether clinicians in the UK would support such a trial. A study was therefore conducted to address these areas of uncertainty and to inform the design of the future trial.

Materials and Methods

An online survey was constructed using the Survey Monkey™ software. The patient group of interest was defined in accordance with the indications for the Codacs™ DACI manufactured by Cochlear Ltd., Sydney, Australia (Cochlear 2013) as follows: (a) Otosclerosis; (b) Bone conduction (BC) thresholds of 55 dB or worse; (c) Air conduction thresholds in the severe-to-profound range; (d) Receive insufficient benefit from conventional hearing aids. It was also clarified that these patients should be assumed to be otherwise healthy and that they fall outside the candidacy guidelines for cochlear implantation in the UK following guidance from the National Institute for Health and Care Excellence (NICE 2009).

An initial question asked about the professional group to which respondents belonged (ENT, Audiologist, Hearing therapist, Other) as this survey sought to explore the routine practice and views of the various professional groups responsible for the care of these patients. Respondents were then asked to consider a vignette that described the patient group of interest and indicate the preferred treatment option for these patients (Fig. 2). The treatment options were given as: ‘No intervention’, ‘Audiological / speech-language therapy’, ‘Amplification with hearing aids’, ‘Combination of amplification and audiological / speech-language therapy’, ‘Other (please specify)’, and ‘I don't know’. Respondents to the survey were also asked to indicate the important outcomes to assess when measuring clinical benefit in the patient group of interest. The available outcome domains were specified based on a

review of those assessed in previous clinical studies of DACI (Busch et al 2013; Lenarz et al 2013) and are listed in Table 1.

Finally, respondents were reminded of the characteristics of the patient group of interest before being asked three questions about the clinical appropriateness of the DACI device, whether respondents would be willing to refer these patients into a trial of the DACI device, and at what stage in their treatment would they be willing to refer. For the latter, the options given were: 'Even before initial stapes surgery', 'Only after stapes surgery', 'Only after revision stapes surgery', 'Other (please specify)', and 'I don't know'. The DACI device was not described by name but rather as a device which: (a) Couples directly to the perilymph of the cochlea via a conventional stapes prosthesis; (b) Is capable of delivering sufficient gain to aid bone conduction thresholds of 55 dB or worse; (c) Involves the surgical placement of a receiver/stimulator similar to that of a cochlear implant; and (d) Involves the use of a behind-the-ear sound processor similar to that used with a cochlear implant.

A consensus process was conducted to identify inclusion criteria for a future trial of direct acoustic cochlear implantation. An initial face-to-face meeting of experts in otosclerosis was held at which attendees were presented with information on the surgical considerations and audiological management by clinical professionals who have experience with providing DACI. A facilitated discussion was then held around three topics: 'Which patients do not benefit from current treatment options in the UK?', 'Who are potential candidates for DACI?', and 'What factors should guide the design of a future trial and would it be feasible?' A transcript of the resulting discussions was analysed and used to generate statements around which a potential consensus could be reached. Two rounds of an online survey were conducted. In the first round, respondents were asked to state their level of agreement with

each of the resulting statements on a five-point Likert scale from 'Strongly disagree' to 'Strongly agree'. In the second round, respondents were shown the level of agreement that had been expressed in round 1 and asked to reconsider their response in light of that information. Consensus was considered to have been reached on a particular statement if at least 80% of respondents agreed with it.

The survey and consensus exercise were advertised through national professional bodies: ENT UK for otolaryngologists, and both the British Academy of Audiology and British Society of Audiology for audiologists. Invitations to participate were also sent directly to clinicians working at major referral centres for otosclerosis in the UK.

Results

Thirty-two clinical professionals completed the online survey comprising nine ENT specialists, 22 audiologists, and one hearing therapist. All had experience of managing patients with advanced otosclerosis within the UK National Health Service (NHS). Of those, 30 provided responses to the question about the preferred management options for patients with advanced otosclerosis (Fig. 2). All but two (93%; 95% CI 78.7 to 98.2) indicated that their preferred management would include amplification via conventional acoustic hearing aids with 11 (37%; 95% 21.9 to 54.5) also indicating that they would recommend hearing therapy in addition to amplification. Only two respondents suggested alternative treatment options, which were the provision of a bone anchored hearing device and cochlear implantation.

Respondents' choices for the most important outcome to assess when measuring treatment benefit are shown in Table 1. No outcome domain was chosen by a statistical majority of

150 respondents either as the most or second most important outcome. The most frequently
151 chosen outcome across either response option was self-reported quality of life, with 55% of
152 respondents (95% CI 37.5 to 71.6) selecting it as either the most or second most important
153 outcome to assess treatment benefit.
154
155 When asked about whether DACI would be an appropriate treatment option for the patient
156 group of interest, 25 of the 29 respondents (86%; 95% 69.4 to 94.5) indicated that it was,
157 with the remainder selecting 'I do not know'. None indicated that it was inappropriate. All
158 those who considered it appropriate also indicated a willingness to refer their patients into a
159 future trial. However, there was variability in when respondents would be willing to refer
160 patients with 9 (38%; 95% 21.2 to 57.3) willing to do so even before stapes surgery had been
161 attempted and 8 (33%; 95% 18.0 to 53.3) willing only after stapes surgery had been carried
162 out. One respondent indicated that they might be willing to refer before stapes surgery but
163 only if further evidence for the effectiveness of the DACI was available. Three respondents
164 listed other criteria for referral, which were: (1) only after revision stapes surgery; (2) only
165 after discussion with the patient; and (3) only after full investigation of non-surgical aiding
166 options.
167
168 Nineteen clinical professionals participated in the consensus exercise. An analysis of the
169 transcript of the face-to-face facilitated discussion identified sixteen statements around which
170 consensus was considered possible. Table 2 lists these statements along with the levels of
171 agreement after one and two rounds of voting. The consensus was that stapes surgery, either
172 with or without a hearing aid, is the best available treatment for advanced otosclerosis and a
173 hearing aid trial is recommended prior to surgery, if that patient is willing. Bone-anchored
174 hearing devices are an option for some patients and a headband trial would always

recommended, but the limit of candidacy for these devices is considered to be BC thresholds at 50 dB HL. Bone-anchored hearing devices are considered to be not powerful enough for patients whose BC thresholds are greater than 55 dB HL.

The consensus was that there is a lack of clear alternative treatment options for those who have already received the best available treatment, who are outside criteria for both bone conduction hearing devices and cochlear implantation, and who still receive insufficient benefit from their hearing aids. These patients would therefore be referred for an implantable intervention such as a DACI as long as the odds of the patient receiving additional benefit over their hearing aids were favourable and similar to those expected for benefit from a cochlear implant. The consensus was also that further trials are needed and that would be supported by clinical professionals involved in the management of these patients.

Discussion

It is perhaps as informative to examine the statements that did not reach the required level of agreement as it is to identify where consensus was reached. The survey responses suggest that stapes surgery would still be offered to some patients with an air-bone gap as small as 20 dB. The willingness of respondents to carry out stapes surgery even when benefit could be limited due to poor cochlear function could reflect the fact that pre-operative bone conduction levels may under-estimate the actual benefit achievable from stapes surgery (Shea et al., 1999). However, the observed consensus on the need for favourable odds of improvement to warrant referral for a DACI suggests that there will be a lower limit of cochlear function beyond which clinicians will not be willing to refer patients. It is therefore important for future studies to characterise the relationship between pre-operative speech perception and the odds of a favourable outcome following the provision of a DACI device. Such an

approach can be used to define candidacy criteria based on the likelihood that the patient will improve following the intervention (UKCISG, 2004). However, studies should also consider the size of change that would be considered meaningful from clinical and patient perspectives.

It would also seem logical to assume that there will be an upper limit for the speech perception abilities of these patients beyond which DACI would either been seen as unnecessary or inappropriate. However, consensus was not reached on a statement that restricted referral to those with speech discrimination up to 50% correct, a threshold that has previously been used to define insufficient benefit from acoustic hearing aids in patients with more profound losses (NICE 2009). The failure to reach consensus on this point could reflect a belief that the threshold for referral should be more or less restrictive, but it could also be that respondents believed 'insufficient benefit from hearing aids' cannot be defined adequately or reliably in terms of a fixed threshold on a test of speech perception conducted in the artificial environment of an audiology testing booth. In the absence of an agreed threshold, such a judgement could be based on patient self-report of benefit in real life situations following the confirmed completion of a hearing aid trial.

The failure to reach a consensus on whether clinicians were willing to refer for a DACI where a conductive component remained suggests that referral would be conditional on the outcome of stapes surgery in those patients where surgery would be recommended. However, the group failed to reach consensus on a general statement indicating that stapes surgery would be required before referral for a DACI could be recommended. This result is compatible with the fact that the needs of patients for whom stapes surgery is not recommended were considered to be unmet by the available treatment options. Their apparent willingness to refer

some patients for a DACI even without having conducted stapes surgery could also have reflected their views on the needs of patients with losses that are predominantly sensorineural in origin. The current study did not ask about such patients as it fell outside the current labelling of the device at the time the study was conducted (Cochlear, 2013).

The current study aimed to inform the design of a future trial of DACI in the UK, including identifying the target patient population for whom the intervention is appropriate and needed. Table 3 lists proposed inclusion and exclusion criteria for a trial based on an analysis of the statements upon which the respondents reached consensus. The results of the current practice survey and the consensus exercise both suggest that the trial design needs to account for two groups: (1) those for whom stapes surgery is recommended where referral for a DACI would only be supported after that surgery has been conducted; (2) those for whom stapes surgery would not be clinically appropriate and for whom referral would be supported without prior surgical intervention. In both cases, the comparator to the DACI should be a trial of an acoustic hearing aid in combination with hearing therapy. Respondents' views on important outcome domains suggest that the primary end-point for the trial should be an assessment of quality of life. Previous early-phase evaluations of the DACI have used a well-established measure of the impact of listening difficulties on everyday life (the Abbreviated Profile of Hearing Aid Benefit (APHAB); Cox & Alexander, 1995) and have suggest that outcomes could be assessed as early as three months after the intervention is provided (Lenarz et al., 2013). The resulting trial design is shown in Figure 3.

Prior to conducting such a trial, a feasibility study would be required to assess such practical issues as the learning curves of surgeons, the structure of the clinical pathway following provision of a DACI, and the nature and content of post-operative rehabilitation that would

be required. The willingness of patients to accept both randomization and the intervention itself would also need to be confirmed. Should a randomized controlled trial be unacceptable to patients or not be feasible to conduct, alternative approaches such as the creation of a matched control group from existing patients populations using propensity score matching could be considered (McCulloch et al., 2009). In that approach, patients are drawn from a control group based on their similarity to a smaller group of patients who receive the treatment on factors that could influence outcome.

The current study identified quality of life as the outcome domain most frequently chosen by respondents. This result is one of two key pieces of information that are necessary to determine the required sample size for the future trial (Williamson et al 2012). The other is the smallest difference on that outcome that could be considered to be clinically important and is referred to as the minimal clinically-important difference (MCID) (Gatchel et al 2010). While the most important outcome domain can be identified through the use of surveys and consensus techniques (Sinha et al 2011), as demonstrated in the current study, the MCID is determined by relating the change in outcome to whether the patient perceived a change or not. The size of the change in outcome among those reporting no change in their hearing provides an estimate of the minimally-important difference (Jaeschke et al 1989). Further work would be required to identify an instrument that measures those aspects of quality of life that are relevant to the specific patients of interest (Buchbinder et al., 2011). Early-phase studies have already suggested that the APHAB is sensitive to the reductions in everyday listening difficulty that occur following the provision of a DACI (Lenarz et al., 2013).

The current study suggests that there is a patient population for whom there is a lack of treatment options and for whom direct stimulation of the cochlea via the implantation of an

auditory prosthesis is considered an appropriate intervention. There appears to be strong support amongst the clinical professionals who manage the care of these patients to conduct a clinical trial to evaluate the effectiveness of this novel intervention. A feasibility study is now necessary to determine how many patients would be required for that future trial, whether those patients could be recruited within a reasonable timeframe, and whether the proposed trial design would be acceptable to patients.

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Figure captions

Figure 1: A photograph of the implanted component of a direct acoustic cochlear implant system (left) and a computer rendering of the fixation system (right) used to attach the mechanical actuator (5) to a conventional stapes prosthesis. 1: Removable magnet; 2: Receiver coil; 3: implant electronics; 4: lead assembly; 5: actuator; 6: rod; 7: artificial incus. Reproduced from the surgical instructions for use (Cochlear, 2013).

Figure 2: The clinical vignette used to assess the preferred management option for the target patient group with advanced otosclerosis.

Figure 1

Click here to download Figure (TIFF, PDF, Word Doc, PPT, or EPS files are acceptable) Figure 1.tiff

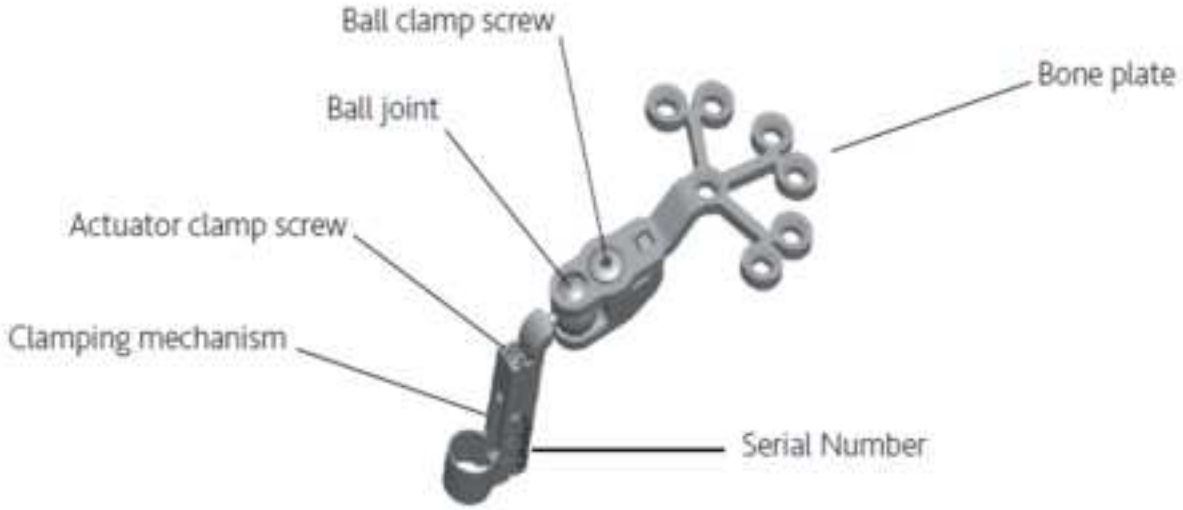

Figure 2

An otherwise healthy patient with otosclerosis currently wears two hearing aids. They have had stapes surgery which closed the air-bone gap to less than 10 dB. Their post-operative audiogram is shown on the right. However, they still report receiving insufficient benefit from their hearing aids.

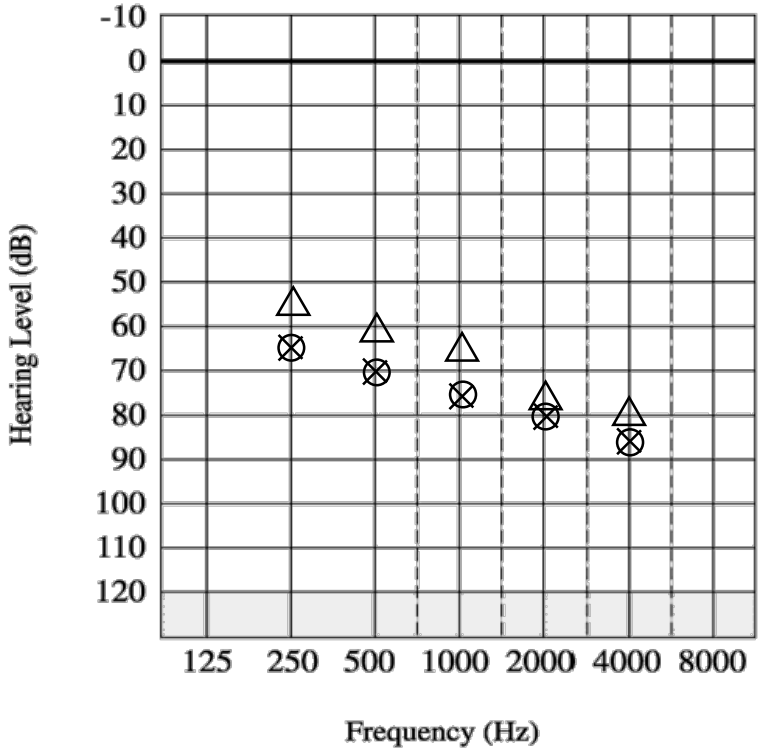

Figure 3

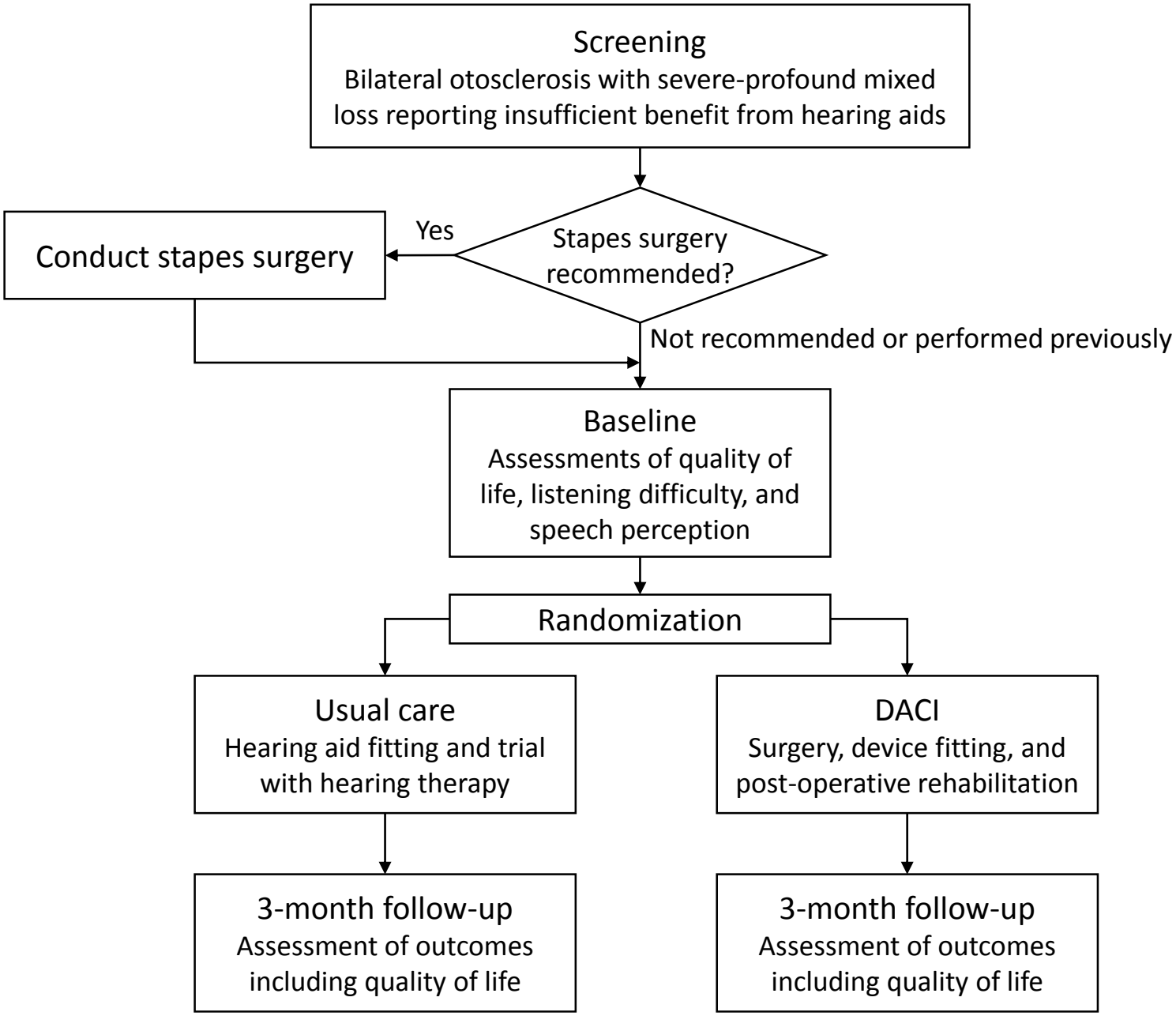
Screening
Bilateral otosclerosis with severe-profound mixed loss reporting insufficient benefit from hearing aids
Stapes surgery recommended?
Yes
Conduct stapes surgery
Not recommended or performed previously
Baseline
Assessments of quality of life, listening difficulty, and speech perception
Randomization
Usual care
Hearing aid fitting and trial with hearing therapy
DACI
Surgery, device fitting, and post-operative rehabilitation
3-month follow-up
Assessment of outcomes including quality of life
3-month follow-up
Assessment of outcomes including quality of life

Table 1: Respondents choices for the most important outcome to assess when measuring treatment benefit in adults with advanced otosclerosis. The outcome domains have been sorted based on the proportion of respondents who identified them as the 'most important' outcome to measure to assess treatment effect. The values in parentheses represent the number of respondents.

Outcome domain	*Most important*	*2nd most important*	*Total*
Quality of life reported by the patient	38% (11)	17% (5)	55% (16)
Ability to understand speech in quiet listening conditions	17% (5)	21% (6)	38% (11)
Ability to understand speech in noisy listening conditions	17% (5)	14% (4)	31% (9)
Level of listening difficulty reported by the patient	14% (4)	17% (5)	31% (9)
I don't know	7% (2)	0% (0)	7% (2)
Ability to localise sounds (tell where they are coming from)	3% (1)	0% (0)	3% (1)
Level of effort required to listen reported by the patient	3% (1)	10% (3)	14% (4)
Sensitivity to sound (e.g. pure-tone/soundfield audiometry)	0% (0)	7% (2)	7% (2)
Other	0% (0)	0% (0)	0% (0)

Table 2

Table 2: Level of agreement across 19 participants in the consensus process with 16 statements generated from the initial open round.

Statement	*Round 1*	*Round 2*
I would always recommend a hearing aid trial to patients with advanced otosclerosis before stapes surgery, as long as the patient is willing.	**93%**	**95%**
For otosclerosis patients with BC thresholds worse than 55 dB but who are also outside of CI criteria, either a hearing aid alone or in combination with stapes surgery is the best treatment that is currently available.	**93%**	**95%**
I would not recommend stapes surgery for cases of advanced otosclerosis with sloping high-frequency loss because the risks would outweigh the potential benefits to speech perception.	36%	16%
I would not recommend stapes surgery to patients with advanced otosclerosis if their speech discrimination is worse than 30% correct.	57%	37%
There is currently a lack of treatment options for otosclerosis patients with BC thresholds worse than 55 dB, who are outside of CI criteria, and who still struggle with HAs after receiving stapes surgery or if surgery is not recommended.	79%	**89%**
For patients whose BC thresholds are worse than 55 dB and who are not close to CI criteria, I would not recommend stapes surgery if their air-bone gap is less than 20 dB.	64%	63%
I would consider a bone-anchored hearing device for a patient with otosclerosis if their BC thresholds are better than 55 dB.	71%	74%
Patients with otosclerosis whose BC thresholds are 50 dB are approaching the limits of what a bone-anchored hearing device can aid.	**86%**	**89%**
I would always recommend a headband trial before surgery to provide a bone-anchored hearing device.	**93%**	**89%**
The acoustic gain of a bone-anchored hearing device is insufficient for otosclerosis patients with BC thresholds worse than 55 dB.	**86%**	**89%**
I would always recommend stapes surgery to patients with advanced otosclerosis before referring them for a new implantable intervention.	64%	68%
I would not refer otosclerosis patients whose needs are currently unmet by currently-available treatments for a new implantable intervention if their speech discrimination is better than 50% correct.	57%	26%
I would refer otosclerosis patients whose needs are currently unmet by currently-available treatments for a new implantable intervention, as long as there is at least an 80% chance of the patient receiving additional benefit.	71%	**89%**
I would refer otosclerosis patients whose needs are currently unmet by currently-available treatments for a new implantable intervention even if a conductive component remained, as long as I am sure that their previous stapes surgery was done competently.	64%	68%
Clinical trials are needed to evaluate new treatments for otosclerosis patients whose needs are currently unmet by currently-available treatments.	**100%**	**100%**
I would support clinical trials to evaluate treatments for otosclerosis patients whose needs are currently unmet by currently-available treatments.	**100%**	**100%**

Table 3: Suggested inclusion and exclusion criteria for a trial of DACI in the United Kingdom.

Inclusion criteria
Bilateral severe-to-profound hearing loss defined as average AC thresholds > 70 dB HL[1]
Bilateral otosclerosis
BC thresholds worse than 55 dB HL
Where recommended, has undergone stapes surgery that closed the air-bone gap to within 10 dB[2]
Completed a hearing aid trial
Exclusion criteria
Reports receiving sufficient benefit from acoustic hearing aids
Simultaneously satisfies both of the following criteria:[3] 1. A score of less than 50% on Bamford–Kowal–Bench (BKB) sentence testing at a sound intensity of 70 dB SPL 2. AC thresholds >90 dB HL at 2 and 4 kHz

[1] Following definition of categories of hearing loss from British Society of Audiology (2011)
[2] Following definition of a resolved conductive component from Kisilevsky et al (2010)
[3] Following guidance on the candidacy criteria for cochlear implantation from NICE (2009)