

# Acoustic CR Neuromodulation for adults with chronic subjective tonal tinnitus

Medtech innovation briefing

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# Summary

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"><li>• Evidence is based on 1 exploratory proof-of-concept randomised controlled trial, and 1 single-arm study reported as a conference abstract. Neither study reported outcomes beyond 6 months. Methodological limitations mean that results from these studies should be interpreted cautiously.</li><li>• The limited available evidence suggests that treatment with Acoustic CR Neuromodulation may improve patient-reported tinnitus symptoms compared with before treatment, and that it may improve tinnitus more than using a placebo.</li><li>• There is no evidence comparing Acoustic CR Neuromodulation with standard care for tinnitus, and no evidence that improvements in tinnitus symptoms are maintained in the long term.</li></ul>	<p><b>Adverse events and safety</b></p> <ul style="list-style-type: none"><li>• The randomised controlled trial of 63 patients (5 of whom received placebo) reported 8 mild or moderate adverse events related to treatment with Acoustic CR Neuromodulation.</li></ul>
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Cost and resource use	Technical factors
<ul style="list-style-type: none"> <li>• The current list price for an Acoustic CR Neuromodulation system is £1850 for the device and medical earphones, £20 for rechargeable batteries, and £1500 for the programming station.</li> <li>• There is no evidence available on whether Acoustic CR Neuromodulation would cost more or less than standard care. Currently offered treatments include hearing aids (£65–£85) and cognitive behavioural therapy (£157 per session, several sessions likely to be needed).</li> <li>• There is no published evidence reporting costs or resource use.</li> </ul>	<ul style="list-style-type: none"> <li>• The device is worn for between 4 and 6 hours a day over a course of 4–6 months of treatment (depending on the response to therapy).</li> <li>• The Acoustic CR Neuromodulation device must be programmed and fitted by a trained audiologist. The device needs reprogramming when the patient reports changes in their tinnitus frequency.</li> <li>• Acoustic CR Neuromodulation treatment is intended to be delivered alongside supporting tinnitus therapies such as counselling, sound enrichment, relaxation exercises and fitting of a hearing aid (if appropriate). The Acoustic CR Neuromodulation earphones cannot be worn at the same time as a hearing aid.</li> </ul>

## Introduction

Tinnitus causes people to perceive sounds, such as whistling and humming, intermittently or continuously, without external acoustic stimulation. In most cases tinnitus is subjective, meaning that only the person can hear the sound. In rare cases people experience objective tinnitus, which can be heard during a clinical examination and arises from sounds inside the ear such as muscle spasms or altered blood flow. Tinnitus is more common in people aged over 65, but it can affect people of all ages. Although it is more common in people with hearing loss or other ear problems, one third of people with tinnitus have no identifiable ear disorder. Its exact cause is not fully understood; in some cases it may be associated with damage to the cochlea or changes in brain activity.

Tonal tinnitus is sometimes described as 'ringing in the ears' and produces a continuous sound of a single tone. In different studies, tonal tinnitus was estimated to be present in

39% and 67% of people with tinnitus.

In the UK, around 6 million people (10% of the population) have some form of tinnitus, with about 600,000 (1%) experiencing it to an extent that it affects their quality of life. The impact of tinnitus varies, from little or no disruption of normal activities to its having a significant effect on day-to-day life. Tinnitus can cause problems such as trouble concentrating, trouble sleeping and depression. Very rarely, people can feel suicidal as a result of their tinnitus.

## Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

## About the technology

### CE marking

The Acoustic CR Neuromodulation device was CE marked as a Class IIa medical device on 3 February 2010. The name of the device on the declaration of conformity is the ANM Tinnitus Stimulator T30CR. The CE certificate was first awarded to ANM GmbH. Neurotherapies Reset GmbH now holds the CE certificate and the manufacturing licence. Throughout this document the technology is referred to as Acoustic Coordinated Reset (CR) Neuromodulation.

### Description

The Acoustic Coordinated Reset (CR) Neuromodulation system is a non-invasive device that produces sounds delivered to the patient through earphones. The technology is thought to act by disrupting synchronous brain activity that may cause tinnitus.

The technology comprises:

- a neurostimulator

- medical earphones
- a console
- a programming station.

The matchbox-sized neurostimulator device is programmed by an audiologist to deliver tones tailored to the individual person's tinnitus. The programming station includes a computer and software. The patient can use the console during their assessment to adjust parameters such as frequency and loudness. Once the device is programmed, the patient listens to the sounds through non-occluding earphones (earphones that enable people to hear external sounds) during their usual activities.

## Intended use

The Acoustic CR Neuromodulation device is intended to reduce tinnitus symptoms in adults aged 18 years or over with chronic tonal tinnitus through applying auditory stimuli. The device is programmed depending on the tinnitus frequency, and stimulation needs to be applied for several hours a day over weeks or months.

## Setting and intended user

The Acoustic CR Neuromodulation device should be fitted by a trained audiologist in an audiology clinic. The manufacturer provides training to clinicians before fitting the device. The audiologist uses the console and software developed by the manufacturer to programme the device to match the patient's tinnitus tones. The patient is then given a device and earphones to use for between 4 and 6 hours daily, tapering off over 4–6 months of treatment. People can use the device while going about their usual daily activities. During the course of treatment the tone of the tinnitus may change, and further consultations with an audiologist to reprogramme the device are likely to be needed.

## Current NHS options

There is currently no cure for tinnitus and treatment options have varying degrees of success. The evidence for the clinical effectiveness of treatments available on the NHS is limited (Hoare et al. 2012). Most tinnitus therapies focus on habituation of reaction or perception of the sound.

If hearing loss accompanies the tinnitus it may be appropriate to fit a hearing aid. This may

partially mask the tinnitus sound, distracting the patient away from tinnitus towards unrelated sounds, and reduce stress by improving communication. Patients may also use sound therapy or sound enrichment. This makes the tinnitus less noticeable by masking the unwanted sound with white noise or relaxing sounds.

Counselling or cognitive behavioural therapy (CBT) teaches people techniques to better cope with tinnitus and reduce their anxiety and depressed thoughts. Tinnitus retraining therapy is an intensive therapy that is not routinely commissioned in the NHS; nevertheless, most audiologists use elements of tinnitus retraining therapy such as a combination of sound therapy and counselling to help people focus away from the condition. In some cases drugs such as antidepressants or sedatives may be appropriate (Hobson et al. 2013).

A [Good Practice Guide](#) for the provision of tinnitus services, published by the Department of Health in 2009, recommends that patients should be referred to an audiology service in cases too severe to be managed with advice and information and those not caused by ear wax or infection (Department of Health 2009). The guide states that audiology services should offer tinnitus management through a variety of measures, including information and education, hearing aids, psychological support, relaxation therapy, CBT, sleep management, sound enrichment therapy, and tinnitus retraining therapy.

A national survey of tinnitus management in England (Hoare et al. 2012) reported that most patients in audiology departments receive an audiology-based intervention, such as a hearing aid or sound generator.

A tinnitus quality standard has been referred to NICE (see the [Library of NICE quality standards](#)).

NICE is not aware of other CE marked devices that have a similar function to the Acoustic CR Neuromodulation.

## Costs and use of the technology

The following are list prices provided by the device manufacturer for March 2014 (excluding VAT):

- Acoustic CR Neuromodulation device including medical earphones: £1850.

- Programming station: £1500.
- Rechargeable batteries: £20.
- Domes: £5.
- Wax guards: £6.

The manufacturer anticipates that these list prices would be reduced if the NHS were to purchase multiple units.

The expected life service of the Acoustic CR Neuromodulation device is 3 years. Each device is currently used for a single patient only (having been individually calibrated during treatment visits), but the manufacturer is investigating the device's reusability for multiple patients.

The programming station has an expected life service of 5 years and can be used for multiple devices. Annual calibration is recommended for each programming station. The medical earphones, domes and wax guards can be used multiple times for a single patient. Rechargeable batteries have an expected device life of 2 years, and are currently used for a single device. The manufacturer anticipates that a service contract would be negotiated for providing the system to NHS clinics. No costs are available for an NHS service contract, but the manufacturer anticipates that such a contract would include the following as a minimum:

- set up and initial training (5 days)
- annual calibration and annual quality assurance audits
- ongoing clinical support contract
- instruction manuals and information.

Currently, no NHS services offer Acoustic CR Neuromodulation. However, independent sector provider The Tinnitus Clinic offers treatment with the device and accepts NHS referrals for Acoustic CR Neuromodulation.

The following average national costs for NHS audiology services include interventions that are likely to be standard care for people with tinnitus (NHS reference costs 2012 to 2013):

- Fitting of hearing aids and counselling (assessment): £65 (AS1A).

- Fitting of hearing aids and counselling (fitting): £65 (AS1FA).
- Fitting of hearing aids and counselling (follow-up): £54 (AS1FU).
- Counselling and issue of aids for tinnitus: £84 (AS2).
- Hearing aid repairs: £26 (AS3X).
- Digital hearing aids: £85 (DHA1).

The cost to the NHS of fitting a hearing aid in an audiology clinic would include at least an assessment appointment, a digital hearing aid, fitting of the device, advice and counselling, a follow-up visit (possibly several), and possibly multiple repairs to the hearing aid. If people need hearing aids in both ears (binaural), the costs are likely to be substantially higher.

The average national cost for a single CBT session (not specifically for tinnitus) is £157 (AB11z). Several sessions are likely to be needed for tinnitus treatment.

The British Tinnitus Association offers sound enrichment devices for purchase by patients from £35 to £49.

The Acoustic CR Neuromodulation system is also available privately. The Tinnitus Clinic supplies a treatment package for purchase directly by patients which includes the device, medical earphones, rechargeable battery, battery charger, 1 fitting appointment, 5 recalibration appointments, counselling, and an information package for £4495 including VAT.

## Likely place in therapy

Acoustic CR Neuromodulation could be offered to adults with persistent subjective tonal tinnitus referred for treatment to an audiologist by their GP. An audiologist is needed to provide treatment with Acoustic CR Neuromodulation at an audiology clinic. An ear, nose and throat consultant may be needed to confirm suitability of treatment, and to rule out any need for medical or surgical intervention.

To enable the provision of Acoustic CR Neuromodulation, an NHS audiology clinic would need to purchase at least 1 programming station and training for all audiologists who would use the device. Each patient would need an Acoustic CR Neuromodulation device



with earphones, rechargeable batteries, domes and wax guards. It is anticipated that other facilities that are needed to provide Acoustic CR Neuromodulation would already be available in an NHS audiology clinic.

Acoustic CR Neuromodulation treatment is expected to be delivered alongside supporting tinnitus therapies such as habituation counselling, sound enrichment and relaxation exercises. In people for whom tinnitus is associated with hearing loss, a hearing aid may also be needed. Notably, hearing aids cannot be worn during treatment with Acoustic CR Neuromodulation (that is, the devices cannot be worn at the same time).

## Specialist commentator comments

One specialist commentator stated that the clinical significance of the results from Tass et al. (2012) is unconvincing. The outcome measure of loudness as measured on a visual analogue scale is not clinically relevant, and neither is the 4-point difference in Tinnitus Questionnaire scores between group 1 and placebo. Furthermore the adverse event rate in this study appeared unacceptably high. Further well-designed studies that are independent of the device manufacturer are needed, and publication of the RESET2 study would provide valuable evidence on this technology.

The specialist commentators stated that Acoustic CR Neuromodulation is not suitable for many people with tinnitus because they have atonal tinnitus, tinnitus that is of too high frequency for the device to deliver good quality sound stimuli, or they have too much hearing loss around the region of their tinnitus pitch to be able to hear all the stimuli. The specialist commentators considered the treatment to be suitable for approximately 20–25% of people assessed. It is not clear how people who need a hearing aid would manage treatment with Acoustic CR Neuromodulation as it cannot be used at the same time as a hearing aid.

The effective selection of patients is an important consideration. A specialist commentator stated that people with 1 or at most 2 identified tinnitus tones, constant tinnitus perception with little improvement over the previous 3 months, and hearing loss no greater than 35 dB hearing level (dBHL) average in the best ear would respond best to the treatment. Another specialist commentator noted that there was not enough evidence to support this treatment protocol, and that reliable pitch identification can be difficult.

The device appears expensive compared with other equally effective if not better tinnitus treatment strategies, including CBT. Acoustic CR Neuromodulation is currently delivered

(by a private provider) as a package including counselling and stress management; it is uncertain if NHS audiology services would offer the same level of service.

The current design of the device is suitable for a single use only.

Acoustic CR Neuromodulation was used for 9 months in the RESET2 study (Hoare et al. 2013), rather than the 4–6 months suggested by the manufacturer.

One specialist commentator suggested that 6 hours of clinical time with a senior audiologist and or hearing therapist would be needed to fit binaural hearing aids. Another specialist estimated that 2 visits lasting 2.5 hours in total would be needed for fitting binaural hearing aids. The patient may have a follow-up appointment or be followed up by telephone, depending on the department.

## Equality considerations

NICE is committed to promoting equality and eliminating discrimination. As a public authority NICE must also comply fully with legal obligations to promote race and disability equality and equality of opportunity between men and women; and to eliminate unlawful discrimination on the grounds of race, disability, age, sex and gender, sexual orientation, and religion or belief. This is in accordance with the NICE Equality Scheme.

Age is a protected characteristic defined in the Equality Act 2010. Treatment of tinnitus with this technology may allow older people with hearing problems caused by tinnitus to have a better quality of life and participate more in society.

## Patient and carer perspective

Any new treatment which alleviates the symptoms associated with tinnitus would be beneficial to patients and carers. Further information on the usability of the Acoustic CR Neuromodulation device would be helpful; if the device is difficult to use then this may affect patients' adherence to the treatment regime.

# Evidence review

## Clinical and technical evidence

### RESET trial

RESET was an exploratory, patient-blinded, randomised placebo-controlled trial (Tass et al. 2012; [NCT00927121](#)). In the study, 63 patients were treated at 2 sites in Germany, and randomised to 4 treatment groups and an active placebo group. The 4 intervention groups received different doses of Acoustic CR Neuromodulation delivered by a portable acoustic device with comfortable earphones for 4–6 hours per day (groups 1–3, using different sequences of sounds) or 1 hour per day (group 4). The treatment groups and outcomes are reported in tables 1 and 2. The main outcome measure was change in Tinnitus Questionnaire (TQ) and visual analogue scale (VAS) for annoyance and loudness after 12 weeks of treatment with Acoustic CR Neuromodulation. Whole-head electroencephalograms (EEGs) were recorded to look for changes in tinnitus-related activity.

Most of the outcomes of the RESET study were compared with baseline measurements rather than the placebo group. Results from the RESET study are reported in table 2.

Loudness and annoyance as measured by VAS after 12 weeks of treatment with Acoustic CR Neuromodulation was statistically significantly reduced in the active group 1 compared with placebo ( $p < 0.05$ ) while the patient was receiving stimulation. Improvement in annoyance as measured by VAS for the active group 3 was statistically significant ( $p < 0.05$ ) compared with placebo after the stimulation was turned off for 2.5 hours.

The mean difference in TQ scores after 12 weeks of treatment was  $-12.4$  (standard deviation [SD]  $\pm 8.9$ ) for group 1 and  $-8.4$  (SD  $\pm 7.1$ ) for the placebo group. The difference in TQ between the groups of 4.0 points was not compared statistically.

The authors conducted a post-hoc analysis (Tass et al. 2013) by pooling results into 'effective' and 'ineffective' stimulation groups. TQ scores for patients allocated to receive effective stimulation (groups 1 and 3 combined) were statistically significantly reduced compared with ineffective stimulation (groups 2, 4 and 5 combined) after 12 weeks of treatment ( $p = 0.0076$ ). Loudness and annoyance as measured by VAS were statistically

significantly reduced in the effective stimulation group compared with the ineffective group.

Fifteen mild to moderate adverse events and 2 serious adverse events were reported. Thirteen adverse events occurred during the blinded phase of the study and 2 occurred during the unblinded long-term extension phase. Eight of the adverse events were considered to be treatment related, of which 3 were associated with a transient increase of tinnitus loudness (although the authors did not report to which group the patients belonged). The 2 serious adverse events were not associated with the study treatment.

A further 6 articles were identified that related to the RESET study. Two of these were letters relating to the key paper by Tass and colleagues on the RESET study outlined below (Rucker and Antes 2013; Tass et al. 2013). In their letter, Tass and colleagues report additional analyses including analysis of covariance (ANCOVA) using baseline values for annoyance and loudness as measured by VAS, and TQ, as covariates between the groups. The authors reported statistically significant group differences for loudness and annoyance as measured by VAS ( $p < 0.05$ ) and TQ ( $p < 0.001$ ) in 'off-stimulation', although they did not explore which individual comparisons were statistically significant (Tass et al. 2013).

The remaining 4 articles used data from the RESET study to address other research questions (Adamchic et al. 2012a; Adamchic et al. 2012b; Adamchic et al. 2013; Silchenko et al. 2013). Adamchic et al. (2012a) looked at whether a change in tinnitus pitch correlated with a change in loudness and annoyance scores as measured by VAS; the authors also investigated whether changes in brain synchrony correlated with pitch change. Adamchic et al. (2012b) used loudness and annoyance scores as measured by VAS from the RESET trial to study whether they were valid measurements of tinnitus severity. Adamchic et al. (2013) compared EEG recordings from the RESET study from patients whose tinnitus responded well to neuromodulation against healthy controls. The authors studied whether the treatment shifted EEG patterns closer to normal physiological EEG patterns, or whether it was associated with substantially different, non-physiological patterns. Silchenko et al. (2013) considered the impact of Acoustic CR Neuromodulation on neural brain networks underlying the perception of tinnitus using EEG measurements before and after neuromodulation. This study used data from patients whose condition responded well to the treatment in the RESET study, and found that after treatment, the pathological interactions in the brain were diminished in 'good responders'.

**Table 1 Summary of the RESET trial: Tass et al. (2012)**

Study component	Description
Objectives/ hypotheses	To measure an improvement in tinnitus symptoms.
Study design	Randomised, single-blind, placebo-controlled trial (proof-of-concept).
Setting	Two treatment centres in Germany (start date reported as November 2011 in trial database; <a href="https://www.clinicaltrials.gov/ct2/show/study/NCT00927121">NCT00927121</a> ). Patients were treated for 12 weeks with different durations of treatment of Acoustic CR Neuromodulation and compared with an active placebo group.
Inclusion/ exclusion criteria	<p>The study included adults with chronic (<math>\geq 6</math> months) tonal, subjective tinnitus, and able to hear stimulation tones (hearing impairment up to 50 dB within frequency of 0.125–12.0 kHz).</p> <p>Patients were excluded if they suffered from Meniere's disease, auditory hallucinations, symptomatic hearing disorders, tinnitus due to temporomandibular joint disorders, brainstem diseases, psychiatric disorders or objective tinnitus.</p>
Primary outcomes	Tinnitus distress level measured by a German version of the TQ. Loudness and annoyance of tinnitus as measured using a VAS.
Statistical methods	<p>No formal sample size calculation reported. Patients were allocated to unequal groups including a small placebo group. ITT analysis was used. LOCF was used where data were missing, although no details of missing data were reported. Exploratory statistics reported and outcomes were compared mostly to baseline rather than placebo. Confidence intervals were not reported.</p> <p>Unusual methods were used to 'normalise' baseline differences and the unusual subgroup matching procedure. No adjustment was made to the p value cut-off for significance to correct for the increased risk of detecting a significant change when carrying out multiple testing.</p>

Participants	<p>Ninety nine patients from 8 centres were screened and 63 were randomised to 5 groups (2 treatment centres). Groups 1 (n=22), 2 (n=12), 3 (n=12) and 4 (n=12) received difference durations of treatment of Acoustic CR Neuromodulation delivered using a portable acoustic device and comfortable earphones. Group 5 (n=5) received placebo stimulation.</p> <p>Groups 1, 2 and 3 received stimulation for 4–6 hours daily (either continuously or split into sessions no shorter than 1 hour). Groups 4 and 5 received stimulation for a maximum of 1 hour each day. The pattern of sounds delivered to patients in groups 1–4 was based on a specific algorithm to match the patients' tinnitus tones. The authors reported that groups 1 and 3 received 'effective stimulation' and that groups 2, 4 and 5 received 'ineffective stimulation'. It is not clear whether this pooling was post-hoc.</p> <p>Patients were assessed at weeks 1, 4, 8, 12 and 16 (patients were blind to treatment allocated during this phase). After 12 weeks there was a 4-week pause in treatment. Patients were offered an optional unblinded long-term extension of the treatment during which they received the same stimulation pattern as that applied to group 1 in the blinded phase. During the long-term extension patients were assessed every 4 weeks for 24 weeks.</p>
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Results	<p>Change in VAS loudness and annoyance after 12 weeks of treatment for group 1 was statistically significant compared with placebo (<math>p &lt; 0.05</math>) for 'on-stimulation' (measured 15 minutes after beginning stimulation). Change in VAS annoyance for group 3 was statistically significant (<math>p &lt; 0.05</math>) compared with placebo for 'off-stimulation' (measured 2.5 hours after stopping stimulation).</p> <p>VAS loudness and annoyance reduced statistically significantly compared with baseline in groups 1 and 3 (<math>p \leq 0.01</math>) in the on- and off-stimulation conditions after 12 and 16 weeks respectively.</p> <p>VAS loudness/annoyance scores after 12 weeks of treatment did not reduce significantly compared with baseline in the placebo group.</p> <p>Mean TQ scores were significantly reduced compared with baseline in groups 1 (<math>p &lt; 0.0001</math>), 2 (<math>p &lt; 0.05</math>), 3 (<math>p &lt; 0.01</math>) and 4 (<math>p &lt; 0.01</math>) for weeks 12 and 16. There was no reduction in mean TQ scores compared with baseline for the placebo group. The authors did not compare reduction in TQ scored for the intervention groups with the placebo group, as would be expected. The difference between TQ mean scores for group 1 and placebo was 4.0 points (not compared statistically).</p> <p>The authors pooled the results from group 1 and 3 into an 'effective stimulation group' (<math>n = 34</math>) and pooled results from groups 2, 4 and 5 into an 'ineffective stimulation group' (<math>n = 29</math>). TQ scores were reduced in both groups after 12 weeks of treatment compared with baseline (<math>p &lt; 0.0001</math>). VAS loudness reduced in both groups (on-stimulation) (<math>p &lt; 0.001</math>) but only the effective group showed a significant reduction off-stimulation. VAS annoyance results showed a similar trend. The authors did not compare the differences between the groups.</p> <p>Following an unblinded 24-week long-term extension period during which Acoustic CR Neuromodulation was applied the authors report that 40% of patients showed an improvement in TQ of <math>\geq 15</math> points, 35% showed a TQ improvement of between 6 and 14 points, 23% were unchanged (<math>\pm 5</math> points), and 2% worsened by <math>\geq 6</math> points.</p> <p>VAS loudness and annoyance after 40 weeks were not reported.</p>
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<b>Conclusions</b>	Using Acoustic CR Neuromodulation for 12 weeks resulted in a statistically significant improvement in VAS annoyance and loudness and TQ scores compared with baseline measurements for patients allocated to receive effective stimulation. No statistically significant change from baseline was observed in the placebo group. Change in VAS loudness and annoyance for group 1 was statistically significant compared with placebo.
Abbreviations: CR, co-ordinated reset; ITT, intention to treat; LOCF, last observation carried forward; LTE, long-term extension; n, number of patients; TQ, Tinnitus Questionnaire; VAS, visual analogue scale.	

**Table 2 Summary of the RESET trial: Tass et al. (2012)**

	<b>Group 1<sup>a</sup></b>	<b>Group 2<sup>b</sup></b>	<b>Group 3<sup>c</sup></b>	<b>Group 4<sup>d</sup></b>	<b>Group 5<sup>e</sup> (placebo)</b>	<b>Analysis</b>
Randomised	n=22	n=12	n=12	n=12	n=5	
Efficacy	n=22	n=12	n=12	n=12	n=5	
VAS loudness (change from baseline [SD]) 'off stimulation' <sup>f</sup>	-21.8 (19.2) p<0.001*	-2.1 (21.7) p=0.844*	-25.8 (25.3) p=0.004*	-6.7 (15.3) p=0.297*	-9.0 (18.8) p=0.500*	
VAS loudness (change from baseline [SD]) 'on stimulation' <sup>g</sup>	-37.3 (24.7) p<0.001*	-21.3 (25.3) p=0.020*	-29.6 (30.0) p=0.008*	-18.8 (23.7) p=0.025*	-9.0 (18.8) p=0.500*	G1 significant reduction compared with placebo (p<0.05).



VAS annoyance (change from baseline [SD]) 'off stimulation' <sup>f</sup>	-18.0 (17.2) p<0.001*	-4.2 (24.6) p=0.611*	-28.8 (27.0) p=0.004*	-7.5 (16.7) p=0.281*	-2.0 (16.4) p=1.000*	G3 significant reduction compared with placebo (p<0.05).
VAS annoyance (change from baseline [SD]) 'on stimulation' <sup>g</sup>	-32.7 (23.2) p<0.001*	-22.1 (33.5) p=0.057*	-31.7 (33.3) p=0.010*	-18.8 (23.7) p=0.020*	-8.0 (13.0) p=0.500*	G1 significant reduction compared with placebo (p<0.05).
TQ score (change from baseline [SD])	-12.4 (8.9) p<0.001*	-5.2 (8.0) p=0.027*	-15.5 (15.1) p=0.007*	-8.6 (7.0) p=0.003*	-8.4 (7.1) p=0.125*	
Safety	15 mild to moderate AEs occurred in total: 13 AEs occurred during the blinded phase of the study and 2 AEs occurred during the long-term extension phase. Eight were judged to be related to the treatment, of which 3 were associated with a transient increase of tinnitus loudness. These 3 patients continued to the long-term extension phase of the study.					
Patients reporting serious adverse events	2 SAEs were reported (abdominal pregnancy and avascular necrosis of the femoral head; not associated with treatment).					

Abbreviations: AE, adverse event; EEG, electroencephalogram; n, number of patients; SAE, serious adverse event; SD, standard deviation; TQ, tinnitus questionnaire; VAS, visual analogue scale.

\* p values relate to a comparison with baseline measurements.

<sup>a</sup> G1: Patients received stimulation for 4–6 hours a day (4-tone sequence).

<sup>b</sup> G2: Patients received stimulation for 4–6 hours a day (4-tone sequence selected at random from 12 tones).

<sup>c</sup> G3: Patients received stimulation for 4–6 hours a day (4-tone sequence with the repetition rate controlled by EEG measurement).

<sup>d</sup> G4: Patients received stimulation for 1 hour a day (4 tones per sequence).

<sup>e</sup> G5: Patients received stimulation with a placebo tone for 1 hour a day.

<sup>f</sup> 'off stimulation': measurements were taken 2.5 hours after stopping Acoustic CR Neuromodulation.

<sup>g</sup> 'on stimulation': measurements were taken 15 minutes after starting Acoustic CR Neuromodulation.

## Wurzer and Weimann (2011)

Wurzer and Weimann presented data from a single-arm observational study conducted in Germany and published as an abstract at the 2011 Tinnitus Research Initiative Conference. Details of this study are reported in tables 3 and 4. No full text, peer-reviewed paper was available to accompany the abstract.

In the study, 70 patients with chronic tonal subjective tinnitus were treated with Acoustic CR Neuromodulation for at least 6 months. The authors report that 40% of participants showed at least a 15-point reduction in TQ score, and 30% of patients showed between a 6- and 14-point reduction. No statistical tests were reported in the abstract.

**Table 3 Summary of the observational study: Wurzer and Weimann (2011)**

Study component	Description
Objectives/ hypotheses	To measure an improvement in tinnitus symptoms (using the Tinnitus Questionnaire) in patients treated with Acoustic CR Neuromodulation.

Study design	Single-arm, observational study.
Setting	Specialised outpatient setting in Germany (no dates reported).
Inclusion/exclusion criteria	Patients with chronic tonal subjective tinnitus (0.2–10 kHz) with hearing loss <80 dB.
Primary outcomes	Change in TQ score from baseline following 6 months of treatment categorised as: 1) reduction of $\geq 15$ points, 2) reduction of 6–14 points, and 3) worsening of >6 points.
Statistical methods	Descriptive statistics reported only.
Participants	70 patients received treatment. No sample size calculation reported.
Results	40% of patients showed a reduction of at least 15 TQ points after 6 months of Acoustic CR Neuromodulation treatment. 30% of patients reported a reduction of between 6 and 14 TQ points, and 1 patient's condition worsened by more than 6 TQ points.
Conclusions	70% of patients had a reduction in TQ score of more than 6 points after 6 months of treatment with Acoustic CR Neuromodulation. This study was reported as a conference abstract only and therefore the results should be interpreted cautiously.
Abbreviations: CR, co-ordinated reset; n, number of patients; TQ, Tinnitus Questionnaire.	

**Table 4 Summary of the observational study: Wurzer and Weimann (2011)**

	<b>Acoustic CR Neuromodulation</b>
Included	Did not report drop-outs
Efficacy	n=70

Primary outcome: change in TQ score from baseline	40% of patients showed a reduction of $\geq 15$ TQ points. 30% of patients showed a reduction of 6–14 TQ points. 1 patient worsened by >6 TQ points
Safety	Not reported
Patients reporting serious adverse events	Not reported
Abbreviations: n, number of patients; TQ, Tinnitus Questionnaire.	

Two ongoing or in-development trials of Acoustic CR Neuromodulation for tinnitus were identified in the preparation of this briefing:

- [NCT01541969](#): Evaluation of the CR Neuromodulation Treatment for Tinnitus (RESET2) – This trial has been completed. Hoare and colleagues (2012) have published the protocol in a peer-reviewed journal.
- [NCT01435317](#): Acoustic Coordinated Reset (CR) Neuromodulation for the Treatment of Chronic Tonal Tinnitus ("RESET Real Life") (RRL) – This trial has completed recruitment. Although the manufacturer provided an unpublished interim report of the trial during the production of this briefing, data have not been included as the information has not yet been reported publically.

## Costs and resource consequences

No published evidence relating to the cost or resource consequences of using Acoustic CR Neuromodulation in the NHS was identified for this briefing.

For existing NHS audiology clinics to provide Acoustic CR Neuromodulation treatment, at least one programming station would need to be purchased as well as the neuromodulation device itself. Audiologists would need training, and appropriate calibration needs to be considered. The manufacturer offers training and calibration.

Acoustic CR Neuromodulation needs an initial assessment during which the device is programmed by a trained audiologist to match the patient's tinnitus tone. Multiple follow-up appointments are needed to reprogramme the device. There is uncertainty as to

how existing audiology services would manage the additional use of their resources.

Supporting therapies such as counselling, sound enrichment and relaxation exercises would be needed alongside Acoustic CR Neuromodulation. This technology would not replace hearing aids in people whose tinnitus is associated with hearing loss.

## Strengths and limitations of the evidence

The evidence discussed comes from one published proof-of-concept randomised controlled trial and one single-arm observational study reported as a conference proceeding.

The randomised controlled trial by Tass et al. (2012) has several strengths including blinding of patients, effective allocation concealment and low drop-out rates. These strengths reduce the risk of certain types of bias. The authors were clear that this study was the first to be conducted using human subjects and as such is proof-of-concept. Limitations include an unclear primary outcome description and the absence of a sample size calculation. The clinicians providing care were not blinded to the treatment allocation. Intervention groups were small and unequal, and the placebo group contained only 5 patients. A rationale for the choice of treatment regimens was not provided and the authors conducted unusual statistical analysis (such as a complex technique for normalising baseline differences). A key problem of the analysis of the trial was that most of the results were baseline controlled rather than compared with the placebo arm. In addition, post-hoc pooling of results into 'effective' and 'ineffective' stimulation groups may not be appropriate. Although the authors reported statistically significant findings, they did not explore whether these would be considered clinically significant. With these issues in mind, the results should be interpreted cautiously. The study was also funded by the device manufacturer and the authors reported conflicts of interest, which may be a source of bias.

In a journal letter Rucker et al. (2013) raised a number of concerns about the design, reporting and analysis. Tass et al. (2013) responded with a rebuttal letter to the editor.

The single-arm observational study by Wurzer and Weimann (2011) was reported as a conference abstract; it was not peer reviewed and provided limited information on the study. The results therefore should be interpreted with caution. In addition, the authors grouped and categorised TQ scores rather than reporting means or medians, and the abstract did not include any statistical comparisons. There is significant risk of bias in the

study due to the absence of a control group, blinding or allocation concealment.

Neither study looked at whether improvements in patient-reported tinnitus symptoms were maintained for more than 4 weeks after stopping treatment with Acoustic CR Neuromodulation. Long-term outcomes would be important for people with tinnitus.

## Relevance to NICE guidance programmes

The use of Acoustic CR Neuromodulation is not currently planned into any NICE guidance programme. [A quality standard on tinnitus has been referred to NICE.](#)

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## Search strategy and evidence selection

### Search strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2014

1. (Acoustic adj3 stimulation).ti,ab.
2. Acoustic co\*ordinated reset.ti,ab.
3. Acoustic CR.ti,ab.
4. (Acoustic adj3 neuromodulation).ti,ab.



5. (Acoustic adj3 desynchroni?ation).ti,ab.
6. acoustic stimulation/
7. tinnitus.mp,ti,ab.
8. tinnitus/
9. (Phantom auditory and (sound or sensation)).ti,ab.
10. pathological synch\*.ti,ab.
11. hyper?synch\*.ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6
13. 7 or 8 or 9 or 10 or 11
14. 12 and 13
15. exp animals/ not humans.sh.
16. 14 not 15
17. limit 16 to yr="2000 - 2014"

The following databases were searched:

- Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2014 (270 references retrieved).
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 19, 2014 (4 references retrieved).
- PsychINFO 1806 to February Week 2 2014 (13 references retrieved).
- Embase 1974 to 2014 February 19 (20 references retrieved).
- DARE (includes Cochrane Library, NHS EED, HTA, CRD; 24 references retrieved).

The above searches returned a total of 303 references after duplicate removal.

Abstract books from the Tinnitus Research Initiative (TRI) conferences held in 2010, 2011, 2012 and 2013 were searched for abstracts relating to the device of interest. Thirteen

relevant abstracts were identified, 2 of which contained data not published in the full text papers already identified (Toth et al. 2014; Wurzer and Weimann 2011).

## Evidence selection

Retrieved references were independently sifted by two researchers using the following criteria:

- Population: adults with chronic tonal subjective tinnitus.
- Intervention: Acoustic Coordinated Reset Neuromodulation.
- Comparator: standard care (including sound therapy, counselling, cognitive behavioural therapy, hearing aids and tinnitus retraining therapy) and placebo or no treatment.
- Outcomes: clinical and patient outcomes related to tinnitus (including relief from tinnitus, tinnitus annoyance, tinnitus loudness, psychological issues related to tinnitus, quality of life, risk of relapse, number of clinic visits and patient acceptability).

Ten papers were identified that were relevant to Acoustic CR Neuromodulation in tinnitus (based on title and abstract). One study reported outcomes relevant to this briefing document (Tass et al. 2012) (RESET trial). Four full text papers used data from the RESET trial but were not considered relevant to this briefing (Adamchic et al. 2012a; Adamchic et al. 2012b; Adamchic et al. 2013; Silchenko et al. 2013). One paper was a computer modelling study of coordinated reset neuromodulation (Tass and Popovych 2012). Two papers were editorial letters relating to the Tass et al. 2012 publication (Rucker and Antes 2013; Tass et al. 2013). One paper was a published protocol of the RESET2 trial ([NCT01541969](https://www.clinicaltrials.gov/ct2/show/study/NCT01541969)) (Hoare et al. 2013), and the last was a report from the National Institute for Health Research (NIHR) Horizon Scanning Centre (NIHR Horizon Scanning Centre, 2013). Neither of these reported data for inclusion in this document.

One TRI conference abstract was relevant to this briefing and contained data not already presented in full-text publications (Wurzer and Weimann 2011).

## About this briefing

Medtech innovation briefings summarise the published evidence and information available

for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

## Development of this briefing

This briefing was developed for NICE by Cedar. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

### Project team

Cedar External Assessment Centre

Medical Technologies Evaluation Programme, NICE

### Peer reviewers and contributors

- Dr Judith White, Researcher, Cedar
- Megan Dale, Researcher, Cedar
- Dr Grace Carolan-Rees, Director, Cedar

### Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Mr Tim Husband, Lead Audiologist, Novus Health
- Dr David Baguley, Consultant Clinical Scientist, Head Service: Audiology/Hearing Implants, Cambridge University Hospitals NHS Foundation Trust

- Dr Rudrapathy Palaniappan, Consultant in Audio-vestibular Medicine, Royal National Throat Nose and Ear Hospital, University College London Hospitals NHS Foundation Trust
- Dr Derek J Hoare, Senior Research Fellow (Tinnitus), National Institute for Health Research Nottingham Hearing

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