Designing and Conducting a Double-Blind Randomized Placebo-Controlled Trial of a Novel Sound Therapy for Tinnitus: A Commentary on Medical Device Trials in ENT and Audiology

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Abstract

Study results for an early-phase trial evaluating a novel sound therapy for tinnitus (the T30 neurostimulator) were made publicly available in May 2015 via the Clinical Trials.gov Identifier: NCT01541969. There was no evidence for a clinically meaningful difference between active intervention and placebo groups enrolled, but this null finding still leaves open the question of clinical efficacy. Here we share our experience and discuss four specific learning experiences relating to the design and conduct of future clinical trials of this type: i) The device fitting procedure should follow manufacturer documentation for normal conditions of clinical use and may even need to be more fully documented (EU Directive 93/42/EEC); ii) Acceptable tolerance limits should be clearly established for deciding when and how any device recalibration may be required; iii) A monitoring plan and documented monitoring of progress of the clinical investigation at all sites are essential (ISO14155). Monitoring includes competence in device fitting and compliance with the study-specific device fitting procedure; and iv) Choice of comparator is important, and the challenge in selecting an appropriate medical device placebo must be carefully considered.

ABBREVIATIONS

CIP: Clinical Investigation Plan; IQR: Interquartile range; NIHR: National Institute for Health Research; NICE: National Institute for Health and Clinical Excellence

INTRODUCTION

There are widespread pressures from patients and clinicians for interventions that are effective in alleviating the symptoms and impact of chronic tinnitus. Many medical devices are currently sold for chronic tinnitus by a number of manufacturers, some of whom make persuasive claims about therapeutic benefit. The T30 neurostimulator which forms the basis of acoustic coordinated reset neuromodulation therapy can be described as one of those products [1,2]. It was CE marked as a Class IIa medical device in February 2010 [3] and delivers a randomized sequence of four ‘phase resetting’ tones that are claimed to generate a lasting desynchronization of pathological brain rhythms. The evidence for claims about clinical efficacy from the initial proof-of-concept trial [1] has been critically scrutinized by a number of independent organisations. In March 2013, the National Institute for Health Research (NIHR) Horizon Scanning Centre [4] reported that “much more research is needed to know for sure how well it works” pp. 5, while in June 2014 a National Institute for Health and Clinical Excellence (NICE) Medtech innovative briefing [3] stated that “methodological limitations mean that results from
these studies should be interpreted cautiously” pp. 1. The German Cochrane Centre expressed a similar call for further evidence [5]. One observational study of a clinical sample has been conducted since the time of these independent reports [2], but evaluation was not conducted under controlled conditions required for a clinical investigation to establish efficacy. We also note that a number of the authors [2] have a conflict of interest with the manufacturer or distributor, as in [1]. In this context, the findings of our independent double-blind randomized placebo-controlled trial were keenly anticipated by a number of stakeholders.

METHODS

A protocol of the trial was published in Trials in 2013 [6]. Informed consent was obtained for all 100 participants fitted with the device. Study results were made publicly available in May 2015 (ClinicalTrials.gov Identifier: NCT01541969). The primary outcome was a group difference in the change in tinnitus measured using the Tinnitus Handicap Questionnaire [7] from baseline to 12 weeks post-fitting. Although the mean change over time showed a small improvement, the magnitude of this change and the difference between groups were relatively small given the large between-subject variance. This statistical null finding still leaves open the question of clinical efficacy. From a scientific perspective, we have since highlighted some uncertainty about the responsiveness of Tinnitus Handicap Questionnaire [8] and this warrants further investigation. On ClinicalTrials.gov, we also declared four limitations and caveats to the interpretation of the clinical findings. There was insufficient space to explain these in detail and so here we add to the literature by sharing details of those lessons learned and making recommendations that are generally applicable to designing and conducting future medical device trials in ENT/Audiology.

RESULTS

Device fitting procedure

Medical devices for hearing loss and tinnitus often require complex fitting prescriptions where decisions are guided by individual patient characteristics and by clinical experience. The Directive 93/42/EEC (Table 1) states that “Each device must be accompanied by the information needed to use if safely and properly, taking account of the training and knowledge of the potential users”, Annex 1 section 13.1. The manufacturer documentation for fitting the T30 neurostimulator was not made available to the Chief and Principal Investigators at any point during the trial. Thus, while the Clinical Investigation Plan was approved by an ethics committee, it did not define the procedure to be used for fitting. The published protocol [6] did go some way to describe the device fitting procedure, but only in general terms.

The Directive 93/42/EEC states that “Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device”, Annex X section 2.3.3. A detailed step-by-step device fitting procedure was created during the study-specific training for all qualified audiologists and was guided by the clinical experience of the Principal Audiologist at the funding organisation. A manufacturer representative also participated in the hands-on audiology training on device fitting. Training included guidance on how to improve the reliability of individual pitch matching [9] and the study-specific device fitting procedure was informed directly from the content of the training. Although this procedure was authorized by the funder, it later came to light that it did not comply with the

Table 1: Brief overview of the scope and content of regulatory and good practices standards relevant to clinical trials of medical devices.

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<td>Intended to harmonize the laws relating to medical devices within the European Union.</td>
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<td>Presents the legal definition of a medical device and obliges the manufacturer to maintain a ‘technical file’ for the medical device.</td>
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<td>For all CE-marked devices, the manufacturer must issue and keep on file ‘declarations of conformity’. A declaration of conformity states the characteristics and performance of the medical device under normal conditions of use including the evaluation of the side-effects.</td>
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<td>For clinical investigations, Article 15 and Annex X lay down the rules to be followed. These are consistent with the international standard (ISO14155).</td>
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<td><strong>Scope</strong></td>
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<td><strong>Clinical investigation planning</strong></td>
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manufacturer’s documentation which specified that the patient should operate the pitch matching controls on the console, not the audiologist. The study team acknowledge that the manufacturer instructions were not adhered to, but the study-specific device fitting procedure was undertaken in good faith, on the understandings that the funder and manufacturer provided training that adequately reflected normal conditions of use in the clinic. This was not considered by the Sponsor to have affected participant safety or the scientific integrity of the trial and the ethics committee was informed of this discrepancy (Table 1).

Acceptable tolerance limits for shifts in pitch matching across participant visits

A specialist commentator for the Medtech innovative briefing [3] noted that “reliable pitch identification can be difficult” pp. 8. The Horizon Scanning report [4] noted that “further study of how accurately patients are able to match their tinnitus to a sound frequency may be valuable in optimising the use of this therapy” pp. 4. Prescription of the T30 Neurostimulator relies on a precise estimate of individual dominant tinnitus pitch so that the sound algorithm can be tailored to optimally promote asynchronous spontaneous activity [10]. The manufacturer’s device fitting software seeks to achieve this by roving a pure tone up or down in frequency until the participant judges that the tone matches the pitch of their tinnitus. Nine enrolled and randomized participants were subsequently excluded before receiving an intervention because they were unable match the pitch (Figure 1). For those who were able to match the pitch of their tinnitus to an external sound, tinnitus pitch matching was repeated at each visit and when there was a change in the pitch value, the sound algorithm was adjusted accordingly [6]. The study team received no explicit manufacturer’s guidance on what were the acceptable boundaries of measurement error and so the trial was conducted on the basis that pitch match was acceptable (i.e. changes in pitch were clinically meaningful, and the prescription was adjusted accordingly) (Figure 1).

Site monitoring of trial personnel

The International Standard ISO14155 recommends documented training records and monitoring visits (Table 1). While the Clinical Investigation Plan approved by the ethics committee stated that device fitting would be performed by a “specially trained audiologist”, it did not define the process of training or monitoring. The published trial protocol [6] did not elucidate these matters either. The funder is the sole UK distributor of the T30 neurostimulator, and when the trial was contracted the company had experience of managing only a small number of patients with the device. Their Principal Audiologist was informally designated responsible for monitoring of competence in device fitting and monitoring of compliance with the study-specific device fitting procedure. He did conduct at least one informal monitoring visit at each recruiting site after study opening and was available to respond to email and telephone queries throughout the trial, but this was not adequately documented.

Evidence for the choice of sound stimulation algorithm used in the active placebo device

We anticipated the optimal active placebo would mimic the acoustic sensation of the intervention without affecting tinnitus or inducing the therapeutic desynchronization of cortical activity. The earlier proof-of-concept trial [1] reported exploratory outcomes comparing the device to baseline not to placebo, and the placebo group itself was small [3]. Before our first participant was enrolled, the device inventor conducted a small preparatory study in 10 people with chronic tonal tinnitus in order to identify the ‘best’ placebo acoustic stimulation [Tass, personal communication]. Four different placebo algorithms were explored; a low-frequency (0.5-4 kHz) four-tone stimulation sequence and three variants of a pseudorandom selection of tone frequencies. Acute effect on tinnitus was measured using Visual Analogue Scales of tinnitus loudness and annoyance, while acute effects on cortical activity were measured using electroencephalographic measures of oscillatory brain power in low frequency (delta) power band. On the basis of the findings, we were recommended the low-frequency placebo stimulation. This development was submitted by Tass and colleagues as an abstract to the 2014 Tinnitus Research Initiative conference [11], but the poster was not presented.

DISCUSSION AND CONCLUSIONS

We have explained four specific experiences in the conduct of NCT01541969. Each experience lends itself to a more general recommendation, compliant with the European Commission Directive 93/42/EEC and international standard (ISO14155):

- If detailed written fitting instructions are to be made available for a medical device, the challenge is to ensure that there is an adequate step-by-step procedure for dealing with every patient profile and scenario. In this context, rarely do published trial protocols or study findings in ENT/Audiology make detailed descriptions of how the device is to be fitted and programmed [e.g. 1], even though such trials may be reported according to CONSORT guidelines. We recommend that before a trial commences, all trial-related procedures and practices comply with manufacturer documentation and are sufficiently documented to ensure that any other investigator could perform the investigation according to this documentation and likely obtain more or less the same results.

- Numerous sound therapy devices for tinnitus rely on a precise estimate of individual dominant tinnitus pitch so that the sound algorithm can be tailored to optimally therapeutic benefit. Although tinnitus pitch matching generates an objective numerical value, there is a body of independent evidence that individual’s pitch estimates can be unreliable between assessment sessions [10]. We recommend that “for important clinical decision making, acceptable tolerance limits should be clearly established and stated as part of the patient assessment and therapy procedure” [12] pp 16. Tolerance limits apply to any device recalibration process.

- The ISO14155 standard requires descriptions of the study-specific training and of the monitoring plan. Before a trial commences, a documented process for monitoring clinical competencies should be put in place and the resources to implement this should be adequately costed into the trial. It is not possible to determine retrospectively the impact on the scientific...
integrity of the data. Nevertheless, analysis confirmed that the center had no influence on the outcomes. Analysis included a covariate to account for ‘center’ (one center had one research audiologist and the other center had four research audiologists).

- Features of any active placebo need to be carefully considered. For sound therapy devices, this could be a device that looks identical, but generates a non-therapeutic sound. Publication of any supporting preparatory studies would not only support the choice of a placebo, but would also support open scientific scrutiny. Appropriate placebos in medical device trials are difficult to create in a way that maintains subject blinding.

ACKNOWLEDGEMENTS
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Conflict of Interest

DAH and DJH were awarded a grant from The Tinnitus Clinic (Brook Henderson Group, Reading, UK) to conduct this trial in partnership with the device manufacturer at the time, Adaptive Neuromodulation GmbH (ANM), Köln, Germany). This grant only part-funded the trial-related work because not all contracted payments were made.

REFERENCES


