Title: Early phase trials of novel hearing therapeutics: avenues and opportunities

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Abstract

Novel hearing therapeutics are rapidly progressing along the innovation pathway and into the clinical trial domain. Because these trials are new to the hearing community, they come with challenges in terms of trial design, regulation and delivery. In this paper, we address the key scientific and operational issues and outline the opportunities for interdisciplinary and international collaboration these trials offer. Vital to the future successful implementation of these therapeutics is to evaluate their potential for adoption into healthcare systems, including consideration of their health economic value. This requires early engagement with all stakeholder groups along the hearing innovation pathway.

Keywords:

Hearing; aetiology; genetics; diagnosis; therapeutics; clinical trial

1.0 Introduction

Hearing loss represents the most common form of sensory dysfunction in humans and has been recognised as an area of significant unmet clinical need (Looi et al., 2015; Müller and Barr-Gillespie, 2015). 90% of hearing loss diagnoses relate to dysfunction of the inner ear and central auditory pathways (Müller and Barr-Gillespie, 2015; Yamasoba et al., 2013). In this type of hearing loss, scientific breakthroughs have enabled the identification of potential therapeutic targets. Between 2011 and 2015 alone, 34 patents were granted for new therapeutic and delivery approaches for inner ear disorders and a recent review identified 43 companies working in the field (Nguyen et al., 2017; Schilder et al., 2019). These novel approaches, which include a variety of drug, gene and cell therapies, are rapidly progressing along the translational pathway to the stage of clinical testing for safety and efficacy in humans (Schilder et al., 2018). Because these types of trials are new to the hearing community, they come with challenges in terms of trial design, regulation and delivery.

In this paper, we provide an overview of the key scientific issues, from understanding the pathophysiology of hearing disorders, diagnosing and monitoring patients, to developing and delivering therapeutics. We then discuss the challenges specific to clinical trials in this field, outlining the opportunities for interdisciplinary collaboration[1], which extend to the

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ABR: Auditory brainstem responses
AP: Action potential
ASSR: Auditory steady state response
COMET: Core Outcome Measures in Effectiveness Trials
CORE: Centre for Outcomes Research and Evaluation
COSMIN: Consensus-based Standards for the selection of health Measurement Instruments
CRO: Clinical research organisations
DOD: Department of Defence
BDNF: Brain derived neurotrophic factor
EEG: Electroencephalography
EPSRC: Engineering and physical sciences research council
HTA: health technology assessment
IHC: Inner hair cells
ISIET: International Society of Inner Ear Therapeutics
NIDCD: National Institute on Deafness and Other Communication Disorders
NIHR CRN: National Institute for Health Research Clinical Research Network
NGS: next generation sequencing
NT: neutrophin
NMDA: N-methyl-D-aspartate

adoption of novel hearing therapeutics into clinical practice. Based on a focused review of the key scientific and grey literature and consultations with experts in this field, we present the state of the science, identify gaps and propose solutions.

2.0 Genotyping and Phenotyping hearing loss

2.1 Aetiologies of hearing loss

Whilst most hearing disorders are sensorineural in nature, their underlying aetiologies are diverse, meaning that there will be no future single cure for hearing loss (Nakagawa, 2014; Okano, 2014; Yamasoba et al., 2013). Pathological dysfunctions include those of the stria vascularis (metabolic) or the basilar membrane (mechanical) with changes in the spiral ligament, as well as loss of sensory hair cells (sensory) or spiral ganglion nerve cells (neural) (Le et al., 2017; Yamasoba et al., 2013). Genetic predisposition, environmental factors (noise and ototoxic drug exposure), and combinations of the two determine the rate of development and severity of sensorineural hearing loss (SNHL). Such combinations include the increased risk of ototoxicity due to mitochondrial DNA mutations causing reduced clearance and thus higher serum levels of aminoglycosides (Gao et al., 2017; Qian and Guan, 2009).

Over the past decade our understanding of the genes, molecules and mechano-electrical processes that determine hearing and hearing loss has improved dramatically, enabling the detection of potential therapeutic targets. This includes the discovery of core components of the transduction process, such as transmembrane channel-like proteins (TMC1, TMC2, whirlin) (Ahmed et al., 2017), tip link filaments acting as gates for transduction channels (CDHR23, CDHR15, USH1 family) (Araya-Secchi et al., 2016; Emptoz et al., 2017; Libé-Philippot et al., 2017; Sakaguchi et al., 2009) and myosin motor proteins that play vital roles in hair cell function (MYO1A, MYO6) (Petit and Richardson, 2009). Our insight into the

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OHC: outer hair cells
PIHL: Pharmaceutical Interventions for Hearing Loss
PTA: Pure tone audiometry
RSV: Respiratory syncytial virus
SNHL: Sensorineural Hearing Loss
SP: Summating potentials
TEN: Threshold-equalising-noise

structures essential for cochlear cellular function such as tight junction proteins (TRIC and TJP2) (Kamitani et al., 2015; Kazmierczak et al., 2015; Mariano et al., 2011), associated proteins (including *Usp53*), synaptic transmission proteins (such as SLC17A8) (Ryu et al., 2016) as well as transmembrane channels (OTOF) (Hams et al., 2017) has also developed.

The signalling and transcription factors belonging to the *Notch* and *Wnt* pathways are key to regulating inner ear development and cell differentiation; mutations in the genes encoding these pathways are increasingly recognised as a cause of hearing loss, opening avenues for treatment (Li et al., 2015; Wu et al., 2016). Hearing is highly dependent on mitochondrial energy supply (Böttger and Schacht, 2013). Whole mitochondrial genome screens have allowed for the detection of specific mutations which are associated with ototoxic and non-syndromic hearing loss (Yano et al., 2014).

2.2 From Genotype to Phenotype

These genetic and molecular insights are not yet matched by similar advances in phenotyping hearing loss (Bitner-Glindzicz, 2002; Myint et al., 2016). This is in part due to the breadth of the field (with over 1,000 genes linked to polygenic forms of genetic hearing loss), as well as current gaps in phenotypic profiling ability. Many profiling efforts have focused on monogenic hearing loss. Audiometric profiles of Usher syndrome type III and DFNA10 patients followed over time have helped clinicians estimate and inform families about hearing loss progression rates (Plantinga et al., 2005; van Beelen et al., 2016). The AudioGene project captures hearing profiles of hundreds of patients with autosomal dominant, non-syndromic forms of hearing loss caused by known mutations. It uses machine learning to predict candidate genes based on these audiometric profiles, which allows for prioritisation of genetic screening in affected families (Hildebrand et al., 2009, 2008).

Next-generation sequencing (NGS) technology that allows for whole-genome sequencing at lower cost and greater efficiency has advanced the identification of hearing loss genes (Vona et al., 2015). Parallel sequencing of linked loci has replaced single gene sequencing, which is particularly important in the diagnosis of non-syndromic hearing loss which is most common in genetic sensorineural hearing loss. With NGS now widely available, research

focus has shifted into gene-disease associations via auditory phenotyping (Abou Tayoun et al., 2016).

3.0 Diagnosing hearing loss

3.1 Auditory tests

Precision medicine for hearing loss, which links underlying pathophysiology to targeted treatment, requires precision diagnosis, which is not yet offered by our current hearing tests (Rudman et al., 2018; Schilder et al., 2018).

Pure tone audiometry (PTA), the universal baseline hearing test, is a compound measure of hearing reflecting dysfunction of outer hair cells (OHCs); the test is much less sensitive to inner hair cell (IHC) loss and peripheral neuropathy (Lobarinas et al., 2013; Plack et al., 2016). Similarly otoacoustic emissions, particularly distortion produced otoacoustic emissions, are used to assess the integrity of OHCs that are critical to the sensitivity and frequency selectivity of the cochlea and speech discrimination (Rüttiger et al., 2017). The Threshold-Equalising-Noise (TEN) test, used in hearing aid fitting as an instrument for detecting cochlear dead regions, still needs to prove its usability in precision hearing medicine (Moore et al., 2004). Auditory brainstem responses (ABR) are commonplace in both clinical and research settings; using comparative electrophysiological measurement, they indicate firing of the auditory nerve (wave 1) and activation of brainstem pathways (Rüttiger et al., 2017). The threshold of ABRs induced upon defined sound stimuli can be used as a functional biomarker for loss of OHCs in defined cochlear regions; however, when OHCs are functioning, ABRs are unable to detect diffuse neuronal loss (Rüttiger et al., 2017).

Auditory steady-state response (ASSR) is an auditory evoked potential measured in a similar manner to ABRs, but in response to rapid stimuli. It represents phase locked discharging of the auditory nerve and cortex activation, but is again insensitive to auditory neuropathy. Importantly, both ABR and ASSR allow objective estimation of thresholds for those unable to take part in traditional behavioural testing. Speech in noise testing probably best reflects the hearing difficulties that prompt patients to present with hearing loss, but does not help identify underlying pathology (Guest et al., 2018). An illustration of the limitations of these hearing tests is in the diagnosis of ‘hidden hearing loss’, a term for hearing impairment in

people with normal PTA thresholds, and thought to be caused by dysfunction of the IHCs, auditory neurons and their synaptic connections (cochlear synaptopathy) (Bakay et al., 2018; Schaette and McAlpine, 2011). Speech in noise perception testing may help with its identification, and ABR wave 1 analysis provides some insight but is highly variable in humans, making interpretation challenging (Plack et al., 2016).

More precise diagnostic tests that are being used experimentally prior to their validation in larger cohorts include electrocochleography, giving insights into cochlear function, and compound action potentials and the cochlear microphonic detecting IHC dysfunction. The difference between waveform peaks generated by hair cells (summating potentials) and cochlear neurons (action potentials), known as the SP/AP ratio, indicates selective neural loss (particularly those with low spontaneous rates), and may help in the diagnosis of 'hidden hearing loss' (Liberman et al., 2016). Other tests being used experimentally include pupillometry as a measure of listening effort, and electroencephalography to reflect listening effort and central auditory processing (Marsella et al., 2017; Miles et al., 2017; Milner et al., 2018).

3.2 Imaging

Although the quality and resolution of current imaging techniques of the inner ear, including CT scanning and MRI, are improving in line with technological advances, these techniques do not yet have the resolution to identify the ultrastructural phenomena required for precision hearing medicine. This can be achieved with micro-optical coherence tomography, which has been used to show differentiation of cell types within the fixed guinea pig cochlea, but is limited at present by the high radiation doses required (Iyer et al., 2016).

Preclinical tests of iodine based compounds and gold or silver nanoparticles as contrast agents have been shown to improve image quality (Zou et al., 2015). For example, intratympanic administration of iohexol greatly enhanced image resolution in a temporal bone study (Abt et al., 2016).

As imaging resolution reaches the cellular level, the challenge will become its interpretation. Bioinformatic and machine learning approaches, similar to those used in ophthalmology,

will be crucial to integrating these complex multidimensional data into clinical practice (Burgansky-Eliash et al., 2005; Wong and Bressler, 2016).

3.3 Biomarkers

Many researchers are working on identifying molecular biomarkers for hearing disorders, both circulating and in the inner ear fluids, with most projects still at the preclinical stage (Y. H. Li et al., 2018; Rüttiger et al., 2017; Schmitt et al., 2018, 2017). Prestin, an OHC-specific protein, has been identified as an otologic peripheral circulating biomarker for OHC damage after acoustic trauma, chronic industrial noise exposure and cisplatin induced hearing loss (Hana and Bawi., 2018; Liba et al., 2017; Naples et al., 2018; Parham and Dyhrfjeld-Johnsen, 2016). In preclinical models of acoustic trauma, the severity of hearing loss and OHC death correlates with patterns of change in blood levels of prestin (Parham et al., 2019, 2014). If these findings could be validated clinically and be generally applicable as a surrogate marker of OHC survival, this biomarker could also be of great value in the monitoring for ototoxicity during drug treatments and hair cell regeneration in trials of regenerative therapeutics.

Other candidate biomarkers include circulating RNAs, which would offer high specificity, but require validation in humans before entering clinical use (Lee et al., 2018; Pang et al., 2016). Using preserved human temporal bones to investigate correlates of gene expression and audiometric profiles is a further avenue which could substantially advance inner ear biomarkers research (Bai et al., 1997; Fischel-Ghodsian et al., 1997; Markaryan et al., 2010).

Metabolomics and proteomics (measurement of complete cellular metabolic processes and protein expression) offer vast potential for biomarker discovery, but require access to inner ear cells and perilymph (Shew et al., 2018; Wong et al., 2018). This is a challenge that is already being overcome by the use of sampling during operations such as vestibular schwannoma resections and cochlear implantation (Edvardsson Rasmussen et al., 2018; Lysaght et al., 2011).

In cardiovascular disease for example, advances in data science have allowed linkage of extensive biological data (genomics, metabolomics, proteomics) on large numbers of people with equally extensive information on lifestyle, environmental factors and health records (Dale et al., 2017; Hemingway et al., 2017; Joshi et al., 2017; López-López et al., 2017). The

hearing loss field has yet to take advantage of these novel approaches and will benefit from fostering collaborations with the data science field.

3.4 Outcome Measures

Linked to improved diagnostic testing and biomarkers in reflecting the underlying pathophysiology of SNHL, as outlined above, is the choice of outcome measures for novel hearing therapeutics; what are the early signals of efficacy and how are functional changes in hearing best measured?

An example of the challenges faced in hearing outcomes is in age related hearing loss, where current hearing tests rely on patients' ability to comprehend instructions given by an audiologist, which can be challenging for older people with cognitive impairment and poses the question of whether the test is capturing deficiency in hearing or in cognition. Given the link between adult onset hearing loss and dementia, accurate testing to enable treatment selection and measurement of its outcomes is vital. Such tests should capture listening challenges (effort) and the effect of listening on cognitive resources, including electroencephalography (EEG) and pupillometry, and outcome measures should capture changes in these tests alongside changes in threshold testing (Piquado et al., 2010; Shen et al., 2016).

At the same time the field needs to consider how these measures relate to patients' experiences of changes in hearing. Current hearing tests performed in sound proof booths may not reflect or detect the subtle changes in hearing that patients may experience in challenging listening environments. A range of self-reported questionnaires are in use to quantify patients' hearing experiences and measure changes in hearing and tinnitus over time (Granberg et al., 2014; Hall et al., 2016).

There is also a need to achieve consensus and guidance on which outcome measures and accompanying instruments to use in trials in this emerging field. Such consensus would form the basis for a 'white paper' for industry, research institutions and regulatory agencies regarding the minimum package of clinical assessments to deliver proof of concept studies of novel hearing therapeutics. Initiatives like COMET (Core Outcome Measures in

Effectiveness Trials), COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) and CORE (Centre for Outcomes Research and Evaluation) recommend approaches to developing agreed standardised sets of outcomes across (late phase) clinical trials (COMET, 2019; CORE, 2019; COSMIN, 2019). Hall et al (2018) have applied COMET's methodology to develop a core outcome set for tinnitus (Hall et al., 2018).

4.0 Developing Novel Therapeutics

4.1.0 Tailored therapeutic approaches

More than 75 therapeutic programs covering a range of therapeutic targets, approaches and modalities and lead indications in hearing and balance are currently progressing along the translational pathway (Crowson et al., 2017; Schilder et al., 2018). Clinical trials of otoprotective, restorative and regenerative therapeutics are underway with several having completed Phase III (Schilder et al., 2019). Some approaches have yet to fulfil their promise, such as NMDA receptor antagonists and Kv3 ion channel modulators for the treatment of tinnitus, while others have succeeded, such as sodium thiosulfate as an otoprotectant against cisplatin induced hearing loss in children with hepatoblastoma (Auris Medical AG, 2015; Autifony, 2014; Brock et al., 2018, 2016). With age related hearing loss as the most common cause of SNHL and given its association with dementia, treatments which could regenerate hair cells, restore synapses and protect cochlear neurons would have the biggest impact on health beyond hearing capabilities (Livingston et al., 2017).

The below highlights several of the therapeutic approaches that have recently translated to trials.

4.1.1 Notch Pathway

Given their key roles in cell fate determination, Notch and Wnt pathways are prime targets for hair cell regeneration (Atkinson et al., 2015; Mizutari et al., 2013). Trials of gene and drug therapies aimed at regenerating hair cells have already begun, with modulation of the Notch pathway as the focus of two ongoing clinical trials. One uses a small molecule drug approach with transtympanic injections of a gamma secretase inhibitor to target Notch signalling; the other utilises a gene therapy approach surgically delivering Atonal (Hath1), a key determinant of cell fate in human inner ear hair cells, by a viral vector directly into the

inner ear (Novartis Pharmaceuticals, 2014; REGAIN, 2017). Trials of small molecule drugs manipulating Wnt pathways are also progressing (Frequency Therapeutics, 2018). Screens for potentially more efficacious modulators of this pathway are being developed (Zeng et al., 2018).

4.1.2 Neurotrophins

Cochlear synaptopathy as a target for therapeutics is being explored by various academic and biotech groups, but difficulties with diagnosis pose a translational challenge in this area (Hickox et al., 2017). There is increasing insight into the fate and function of cochlear neurons with age and with progressing hearing loss; neuroprotection and neuroregeneration therefore provide alternative therapeutic approaches. Neurotrophins (NTs), such as brain derived neurotrophic factor (BDNF), have been shown to stimulate neurite outgrowth of auditory nerve cells (Plontke et al., 2017; van Loon et al., 2013). A phase I trial of a gene construct which stimulates the overexpression of BDNF using electrophoresis in patients undergoing cochlear implantation is underway (Pinyon et al., 2018, 2014). Viral delivery systems of BDNF and other NTs are being tested preclinically (Budenz et al., 2015). The use of cochlear implants as a delivery device is very attractive; but is limited to those eligible for implantation and its effectiveness relies on retaining neuronal function.

4.1.3 Stem cells

Stem cells provide an attractive source of differentiable material and have multiple potential applications (Lenarz, 2017; Lustig and Akil, 2012; Mittal et al., 2017). Their use as an inner ear therapeutic has been stymied by limited understanding of specific signalling pathways necessary to determine cell fate, as well as challenges in verifying viable function within the resulting hair cell like structures (Takeda et al., 2018). Preclinical models have highlighted the potential of mesenchymal stem cell therapeutics in parallel with cochlear implant surgery via bio-hybrid electrodes (Roemer et al., 2016); nerve growth factors produced by these stem cells can enhance implant success. Feasibility and safety of this approach has recently been tested in a human trial (Roemer et al., 2016). Further work has highlighted the opportunity to modulate inner ear cell behaviour following local delivery of mesenchymal stromal cells (Schulze et al., 2018).

4.1.4 Gene therapies

Monogenic forms of hearing loss are potentially the most promising conditions for gene therapies (Lustig and Akil, 2012; Yoshimura et al., 2018). Restoration of hearing for Tmc1 mutant mice has been achieved recently via local delivery of synthetic adeno-associated viral vectors encoding Tmc1 (Nist-Lund et al., 2019). In murine models of Usher syndrome, local adeno-associated viral delivery of wild-type whirlin cDNA resulted in improved hearing and vestibular function (Isgrig et al., 2017). This offers promise for translation to human trials, particularly given on-going trials of gene therapy via retinal injection in patients with Usher syndrome type 1b related retinitis pigmentosa (Sanofi, 2012; UshTher, 2018). Otoferlin mutations are an important cause of inherited auditory neuropathy and are being explored for gene therapy in pre-clinical models; they are monogenic and leave the inner ear structure relatively intact making them a promising target for interventions (Michalski et al., 2017; Rodríguez-Ballesteros et al., 2008).

4.1.5 Challenges in developing novel therapeutics

Currently, potential therapeutics are tested in explant cultures and/or *in vivo* in small mammals. This poses not only logistical and ethical constraints, but importantly it is unknown how well positive results will translate to humans; some compounds proven efficacious in animal models have failed to fulfil their promise in human trials (Le Prell et al., 2016). Whilst difficulties in translating animal work are common across clinical research, they are particularly significant for the emerging hearing therapeutic field (Denayer et al., 2014; Frisina et al., 2018; Mak et al., 2014). These problems are compounded by difficulties in identifying endpoints for drug testing (Bognar et al., 2017; Posey Norris et al., 2014; Vasaikar et al., 2016).

While vertebrates offer the opportunity to study the in-depth effects of drugs on both cochlea structure and function, they are not suited to drug screening (Ou et al., 2010). *Drosophila melanogaster*, a screening tool for many therapeutic classes has been highlighted as a potential screening tool for hearing therapeutics and offers great potential (Christie and Eberl, 2014; T. Li et al., 2018; Wang et al., 2016; Yadav et al., 2016). The zebrafish has been identified as a valuable model for studying hair cell development and

function, and appears to be a useful screening tool for the identification of ototoxic drugs (Chiu et al., 2008). Cell culture would offer the opportunity to screen a wide variety of novel and existing compounds at a much lower time and economic cost, but inherent difficulties in culturing the cells of the organ of Corti make developing an appropriate model enormously challenging (Rivolta and Holley, 2002). Efforts to create such lines from stem cells have shown promise in generating spiral ganglion neurones that can be used for drug screening (Whitlon, 2017). This success has not yet been replicated with cochlea cells, although significant advances have been made, with several groups progressing towards having cultured hair cells or organoids (Jeong et al., 2018; Longworth-Mills et al., 2016; McLean et al., 2017).

Developing human cell models is limited by access to human inner ear tissue. Recently, vestibular tissue harvested during trans-labyrinthine acoustic neuroma surgery has been regenerated with some success and is a good option for testing regenerative therapeutics (Taylor et al., 2018, 2015).

4.2 Delivery of therapeutics to the inner ear

A key challenge in hearing loss trials is choice of delivery method. The decision will depend on the pharmacokinetic profile of the individual agent, and the balance of risks associated with delivery against the potential benefit of the treatment. Whilst some therapeutics currently undergoing clinical trials can be delivered orally (EU Clinical Trials Register, 2018), this mechanism of delivery is not always possible.

For small molecule delivery, systemic routes, or delivery via the middle ear have been in use clinically for some time. The efficacy of systemic administration however depends on both the pharmacokinetic properties of the molecule, and the underlying pathology. Molecules in current clinical use, such as corticosteroids, require high blood concentrations to overcome the tight junctions of the blood-perilymph barrier, increasing the chance of side effects (Jahnke, 1980; Salt and Plontke, 2009). Middle ear approaches include transtympanic injections of liquid or gel-form drugs, controlled release devices and surgical application of drugs to the round window niche (Borenstein, 2009; Gurman et al., 2015; Hütten et al., 2014; Liu et al., 2014; Plontke et al., 2014, 2006; Tandon et al., 2015). All rely on simple

diffusion through epithelial barriers, which is subject to inter-drug and inter-person variation, and leads to formation of concentration gradients, with variable concentrations reaching more apical regions of cochlea (W. Li et al., 2018; Liu et al., 2014; Salt et al., 2007; Salt and Plontke, 2018). Work is on-going in animal models to develop ways to overcome these problems, including magnetically targeted drug delivery and nanoparticles (Pyykkö et al., 2016, 2011; Shapiro et al., 2014).

Intracochlear drug delivery offers the best control of delivery, but comes with the highest risk to hearing, although the problem of base-apex gradient formation remains. Cochlear implant associated drug delivery presents a unique opportunity to develop this route for a subset of patients (Plontke et al., 2017). Options include coating implants with drugs or cells, incorporating catheters into the implant to allow controlled release or injecting drugs intracochlear at the time of surgery (Bas et al., 2016; Jolly et al., 2010; Roemer et al., 2016; Ye et al., 2007).

For gene and cell therapy, intracochlear routes are necessary, and round window, cochleostomy and canalostomy approaches have been developed in animals (Gehrke et al., 2016; György et al., 2017; Plontke et al., 2016; Suzuki et al., 2017; Yoshimura et al., 2018). The on-going phase I trial of intra-labyrinthine infusion of an adenoviral vector carrying Atonal is the first to use intracochlear delivery in humans (Novartis Pharmaceuticals, 2014; Peppi et al., 2018).

Translation of local delivery methods from animal models to human trials is challenging primarily due to differences in the size of the cochlea altering diffusion and excretion of agents. Computer modelling, currently used primarily to validate experimental data, may offer the only opportunity to gain insight into the intracochlear behaviour of therapeutics in humans and has potential to become a valuable translational tool (Plontke et al., 2007; Salt and Hirose, 2018).

5.0 Translating to clinical practice

5.1 Clinical trials capacity and capability

With novel hearing therapeutics progressing along the innovation pathway, it is vital that capacity and capability for delivering clinical trials is increased, by improving access to patient populations and their hearing data through patient registries as well as by building professional and clinical trials networks specialised in hearing research.

Development of successful patient registries and data repositories requires mapping-out patient populations and establishing collaborations with other medical specialties and professional organisations (Mandavia et al., 2017). This is particularly important considering that many people with or at risk of hearing loss, and therefore potentially eligible for hearing trials, are not 'on the radar of' existing hearing services. This includes people visiting memory and dementia clinics; patients treated with ototoxic medication, military staff and musicians exposed to occupational noise and individuals exposed to recreational noise (Lanvers-Kaminsky and Ciarimboli, 2017; Le Prell and Brungart, 2016; Le Prell and Clavier, 2017; Livingston et al., 2017).

To screen and monitor these large populations for hearing loss systematically, there is a need for alternatives to conventional sound-booth technologies with expensive audiometric equipment and highly trained personnel. This has been recognised by a range of companies developing and marketing novel strategies to bring hearing testing out of the booth and, often directly into the hands of the patients (Barczik and Serpanos, 2018; Yousuf Hussein et al., 2018). Early assessment of these technologies suggests that they may represent accurate, cost-effective and efficient tools for screening and follow-up. The use of high-quality sound attenuated insert earphones or circumaural earcups to compensate for the less than ideal sound environment is critical. (Barczik and Serpanos, 2018; Mahomed-Asmail et al., 2016). (Campbell et al., 2016; Rourke et al., 2016). Whilst these technologies are rapidly progressing, they do not yet allow for precision diagnosis, limiting their current applications in clinical and research settings.

Clinicians, scientists and industry have highlighted the importance of creating international registries and data repositories of systematically collected clinical hearing data, combined with biorepositories of blood samples and tissue specimens for future genomic, proteomic, and metabolomic analysis. Provided patient consent-to-contact is in place, these registries

allow for efficient patient identification and recruitment to so called registry-based clinical trials and provide an infrastructure for the collection of treatment and trial outcomes (Li et al., 2016). Ethical, governance and quality standards would need to be established among participating centres. These registries represent a long term investment for both patient and professional stakeholders; expectations regarding short term patient benefit need to be carefully managed.

5.2 Clinical trials and research networks for delivery of hearing trials

There is a need for clinical trials networks in the hearing field that will provide academic teams, biotech, pharma and Clinical Research Organisations (CROs) access to expert trial teams to deliver their hearing trials nationally and internationally. These expert teams with a track record of successful trial delivery, will play a vital role in the delivery to time and target of the rapidly increasing number of hearing trials and should share their expertise with the wider community, whilst offering guidance to newer teams. Collaboration with stakeholders including patients and advocacy groups will be essential for maximising trial recruitment.

Examples of successful international trial networks are SIOPEL, the International Childhood Liver Tumors Strategy Group, through which the trial of sodium thiosulfate in children receiving cisplatin for hepatoblastoma was successfully delivered across 52 centres in 12 countries. A similar global network, called ReSViNET, has been established to facilitate trials of new vaccines for Respiratory Syncytial Virus (RSV) infection as well as developing validated outcome measures in this field (Justicia-Grande et al., 2016; Mazur et al., 2018).

In the UK, The National Institute for Health Research Clinical Research Network (NIHR CRN) provides infrastructure and resources to support the rapid set-up and patient recruitment into clinical studies by streamlined approval processes, funding local research support staff and facilities, and linking NHS clinical research expertise across hospital sites. The NIHR CRN has placed a focus on the life sciences industry to help patients gain earlier access to breakthrough treatments: in the year 2016/17, the CRN brought 729 new commercial clinical trials to the UK and recruited more than 34,000 participants to life sciences industry research. A 2016 KPMG report on the impact and value of the NIHR CRN estimated that CRN

supported clinical research activity generated £2.4 billion of gross value added and almost UK 40,000 jobs. Additional impacts included improved transparency in pricing and more rapid uptake of treatments (KPMG, 2016). To build capacity for the growing NIHR CRN portfolio of hearing, tinnitus and balance studies, Audiology Champions and Trainee Speciality Leads have been appointed across the country; they signpost audiologists and ENT trainees to opportunities to develop as hearing researchers.

UK ENT trainees have recently united in INTEGRATE, a National ENT Trainee Research Collaborative conducting multicentre research within clinical training and NHS services (Smith et al., 2018). Our author group is working with INTEGRATE on a trainee led national prospective cohort study of adult patients presenting to the NHS with sudden onset SNHL. With trainees being the frontline staff managing these patients, this study will engage them in a better understanding of the condition and the patient pathways; as such paving the way for the successful delivery of upcoming trials of novel therapeutics for sudden onset SNHL.

5.3 Funding opportunities

Funding opportunities for hearing research have never been better. Support from: EU Research and Innovation Programmes, national public funders such as the National Institute on Deafness and Other Communication Disorders (NIDCD), the US Department of Defence (DoD) Hearing Center of Excellence, the NIHR, The UK Engineering and Physical Sciences Research Council (EPSRC), and charities like the Wellcome, Hearing Health Foundation, Action on Hearing Loss and Fondation Pour l'Audition have enabled major advances in the understanding of hearing loss and the development of innovative treatments.

At the same time biotech start-ups have benefitted from a sharp increase in funding; from 2007-12 to 2013-17, private funding rose from $86.4 million to $299.3 million, and public funding from $57 million to $469.7 million (Li, 2017). Recently large capital raised from private investors, pharmaceuticals and biotechnology companies as well as venture capitalists have recognised the growing investment opportunities in this field and are funding a pipeline of research into novel hearing therapeutics. The Cochlear Centre for Hearing and Public Health at the John Hopkins University is an excellent example of joint funding, including public, private and philanthropic support (Johns Hopkins Bloomberg

School of Public Health, 2018). Moving forward, to continue this funding trend, positive trial results will be needed to justify such investments in the longer term.

5.4 Adoption into clinical practice

If proven effective, novel hearing therapeutics are set to have a major impact on hearing services. It is therefore essential that the field starts thinking now about implementation and how these treatments can be of most value to patients. Lessons should be learned from other health fields, particularly Ophthalmology where anti-VEGF injections befell clinical services, and insufficient preparation by funders and providers led to inequalities in patient access, economic inefficiency and sub-optimal outcomes (Hollingworth et al., 2017; Shalaby et al., 2016). Crucial to implementation of these novel therapeutics, is to assess and evaluate their potential for adoption into healthcare systems (The Academy of Medical Sciences, 2018). This is determined by multiple interacting factors, each with their own intentions, including: “market makers” (discovery scientists, industry, investors) driving the uptake of novel therapeutics; “bodies of strategic constraint” (regulators, funders, guideline and policy makers) trying to impose order and cost-control; and “users” (patients and clinicians) extracting opportunities for treatment and ‘coping’ with potential service redistribution from secondary to primary care (May and Finch, 2009). Predicted cost-effectiveness represents another key factor within this arena, *influencing and influenced by* the decisions and perspectives of these agents (IJzerman et al., 2017; IJzerman and Steuten, 2011). Figure 1 introduces the core research components that must come together for the successful implementation of hearing innovations.

Figure 1

Our author team has constructed an early health economic model comparing novel regenerative hearing therapeutics with the current standard of care for people with age related hearing loss. Input data were derived from systematic literature searches and stakeholder expert opinion. We adopted a healthcare perspective of the UK National Health Service (NHS) and applied: headroom analysis to explore the maximum potential value; threshold analysis to search for the minimum effectiveness needed for the innovation to be cost-effective; and sensitivity and scenario analyses to evaluate relevant uncertainty. Figure

2 illustrates the key steps in our economic model development. Though this work focuses on regenerative hearing therapies for age related hearing loss, this model has the potential to serve as a framework for other hearing therapeutics and patient populations.

Figure 2

5.5 Moving forward, 'collaboration is the new competition'

Interdisciplinary discussion and cooperation involving stakeholders from each section of the innovation pathway are necessary in order to enable the latest developments in inner ear therapies to progress along the clinical pathway. The recently established International Society of Inner Ear Therapies (ISIET) will provide a forum for potential collaborators to share information and experiences as well as set standards.

Coordinated activities with The Pharmaceutical Interventions for Hearing Loss (PIHL) group also enables hearing stakeholders to discuss the latest advances in discovery science and clinical trials, as well as develop evidence-based standards for clinical research. The PIHL group, which is organised by the DOD's Hearing Centre of Excellence, is dedicated to disseminating the results of these discussions to the wider community.

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