

**THE CONDITIONS FOR ADOPTION OF STEM
CELL THERAPIES FOR HEARING**

**THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF MEDICINE (MD)**

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Abstract

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Title: The Conditions for Adoption of stem cell therapies for hearing

Objectives:

Hearing impairment is commonly due to degeneration and death of hair cells and or their associated spiral ganglion neuron as a result of noise trauma, infection, ototoxic drugs, metabolic disorders, ageing and the inability to replace lost or damaged hair cells by regeneration or cell division. The use of stem cells offers new and powerful strategies for future tissue development and engineering. Cell replacement therapy potentially could have a massive impact on health during the coming decades. This research thesis focus on the translational process required to move stem cell therapy from the laboratory to clinical use, as novel treatment of deafness and as an alternative to current treatment modalities. This research aims to inform and enable the adoption process for such a therapy.

Methods: Three main questions

1- What is the current evidence on the performance of stem cells as a potential treatment for deafness?

Literature search and systematic review on the current scientific evidence for stem cell therapy.

2- What does the clinical community require to adopt stem cells therapy?

Approach the expert clinical community via a structured questionnaire, to study their awareness and attitudes towards stem cell therapy

3- What is the service requirement needed to adopt stem cell therapies?

Analysis of the current position for stem cell therapy from the developer, commissioner and potential adaptors perspectives, particularly with respect to the maturity and applicability of this therapy. This includes analysis of the socio-economic status of this putative therapy.

Conclusion:

There is a clear therapeutic and economic opportunity to move cell based therapy for hearing from the laboratory into the clinic. Key potential adaptors need to be persuaded of the utility of such a therapy by the communication of its biological plausibility, and it is for researchers, developers and suppliers to take the initiative on this.

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CHAPTER 1

Introduction:

The sense of hearing is very vital to our function and interaction with the environment. Hearing depends on the function of specialised sensory cells in the cochlea of the inner ear, the hair cells. These hair cells are mechano-electrical transducers that generate action potential in the auditory nerve that leads to hearing. Damage or loss of these cochlear hair cells leads to many types of congenital and acquired hearing loss.

The incidence of congenital deafness is about 1 in 1000 children and a further 1 in 1000 children become deaf before adulthood, 4 in 10000 children are born profoundly deaf (1-3). Acquired hearing loss is rising as the ageing population is increasing and it is estimated that 1 in 3 adults over the age of 65 have some form of hearing loss (4). According to World Health Organisation figures there are more than 250 million affected worldwide (5).

The permanence of hearing loss is due to the very limited regenerative capacity of the inner ear sensory epithelia. In humans hearing impairment is, in most cases, due to degeneration and death of hair cells and their associated spiral ganglion neurones (6) as a result of noise trauma, infection, ototoxic drugs, metabolic disorders and ageing, and the inability to replace lost or damaged hair cells by regeneration or cell division.

Current conventional treatment of deafness includes hearing aids, cochlear implants, BAHA's, and surgical procedures to restore conductive hearing loss.

The use of stem cells offers new and powerful strategies for future tissue development and engineering. Cell replacement therapy has the potential to have a massive impact on human health during the coming decades. Stem cells represent a big hope to treatment of many degenerative and neurological conditions such as DM, Parkinson's disease, Alzheimer's disease, cardiac disease and deafness.

Aim:

This research MD project will discuss the current knowledge of stem cell therapies and its potential future therapeutic use in the management of deafness. We will be researching the evidence from the clinical and reimbursement sides of the potential use of stem cell therapies in the treatment of deafness. This will include:

- A systematic review (and status evaluation against the Warren framework), Chapter 2.
- Translation process and study questionnaire.
- Financial aspects of the future potential use of stem cell therapies (value-based pricing).

Methods:

The social and economic demand for therapeutic treatment for hearing loss is enormous. Over the past decade there has been remarkable progress in the research of stem cell therapy and the time has now come to move this research into the clinical part where millions of people could be benefited.

There is a clear therapeutic opportunity from a clinician's point of view to move the cell-based therapy from the laboratory to the clinical side. We are persuaded by the scientific evidence and discovery that has been made, and the mileage in stem cell therapy, that this is the right time for the pharmaceutical and biotechnology companies to take the initiative in this field.

As clinicians in Otolaryngology there is a clear clinical requirement to have a novel treatment for deafness based on the clinical evidence and reimbursement evidence to use a stem cell therapy.

Clinical evidence:

Literature searches over the past decade have shown that stem cells could be used to replace inner ear damaged or lost hair cells and associated spiral ganglion neurones, which represent about 80% of the causes of sensorineural hearing loss. Thus, there is great potential for treatment of deafness due to age (presbycusis, noise-induced deafness and deafness due to ototoxic therapy). Hair cells could be generated *in vivo* from embryonic stem cells, from adult inner ear stem cells as well as from neural stem cells. These are pluripotent stem cells that have the ability to develop into many of the human inner ear cells types.

- The ability of stem cells to divide and differentiate into specialised cell types make them an ideal candidate for cell replacement therapy and tissue repair (7).
- Embryonic stem cells hold significant potential for regenerative medicine due to their capacity to differentiate into different cell and tissue types (8), which could be differentiated into spiral ganglion neurones, a source for cell replacement to the auditory nerve.
- Inner ear progenitors have been generated from murine embryonic stem cells *in vitro* (9). A sub-population of these progenitors are developed after differentiation *in vitro* exhibits hair cell phenotype, which are very important for the generation and maturation of hair cells (10,11). This involves a process of transcription of markers Math 1 and Brn 3.1 and up-regulation of structural hair cell proteins such as myosin VIIA, parvalbumin 3 and espin.
- Stem cells isolated from the inner ear appeared to differentiate more completely into hair cells than the neural stem cells.
- Neural stem cells, which have the ability to differentiate into many neuronal cell types, have been successfully grafted into the drug-injured mouse inner ear. They have survived for several weeks and expressed markers of mature cells types (12,13).
- High proliferative capacity stem cells were isolated from adult mice vestibular sensory epithelium (14) using sphere formation assay (14,15); these are pluripo-

tent and self-renewing cells that have the ability to form clonal free floating colonies called spheres. These sphere-forming cells are capable of differentiating into a variety of different cell types such as supporting and hair cells (16,17,18,19).

- Different methods have been used to deliver cells into the deafened cochlea; such as direct transplantation into the cochlea (20,21), delivery into the scala media (22) and scala tympani (23,24,25).

Reimbursement evidence:

Current therapeutic treatments for sensorineural hearing loss are hearing aids and, for severe to profound deafness, cochlear implants. In the UK the estimated cost for a hearing aid is about £420 per patient (ENT Department, Leicester Royal Infirmary cost) (26), and DOH Budget is £200 million annually. The global market for hearing aids is probably worth £5.5 billion. The estimated cost of cochlear implantation in the first three years is around £70000 to include assessment, surgery and follow up (27), and for BAHA it is £7000 per patient which is only the cost of surgery and processor.

A study of the opinion of the clinical community and the current practice in the UK health system and whether stem cells would be a better alternative to conventional therapy, and The adoption of the new treatment such as stem cells may cause some resistance to change, a learning curve for clinicians to be able to take the new treatment forwards. Ethical and religious criticism against the use of embryonic stem cell remains a controversial issue.

Method: A structured questionnaire to approach the ENT clinical community in the UK through the Royal College of Surgeons and ENT-UK

There are about 9 million people in the UK with deafness. The burden of hearing loss can lead to serious social and economic problems, reduced physical and psychological well-being, low education, isolation, and depression.

The NHS faces huge bills every year which is centrally controlled. According to NICE (27), there are approximately 613,000 people older than 16 years of age with severe to profound deafness in England and Wales. In the UK around 3% of people older than 50 years of age and 8% of those older than 70 years of age have severe to profound hearing loss. NICE report in January 2009 recommends a simultaneous bilateral cochlear implantation for people with severe to profound deafness who do not receive adequate benefit from hearing aids. These are children and adults who are blind or have other disabilities that increase their reliance on auditory stimuli. Approximately 40% of children who are deaf and 45% of people younger than 60 years of age have additional difficulties. The cost of a cochlear implant device would be roughly £50000 for bilateral cochlear implantation devices only, which depends on the supplier, and there are other costs of surgery and rehabilitation. This figure would not be cost effective for the NHS and, therefore, would not recommend bilateral implantation for adults.

Method: Review of the socio-economic cost and of current conventional treatment of deafness in the UK healthcare system.

CHAPTER 2:

Systematic Review (and status evaluation against the Warren framework)

Aim

This chapter presents a systematic review which follows the standards for gathering, analysing and reporting evidence, and the status application of the potential stem cell therapies against the Warren (28) framework algorithm to assess this from a commissioner perspective.

In this chapter we apply the Warren algorithm together with a review of the state of the art – working the scientific literature from the perspective of practice to identify the status of stem cell therapies to treat deafness and the development steps necessary to enable their future potential use and adoption by a clinical commissioner – we are essentially attempting to match the potential treatment of a disease, the clinical need, to a putative therapy/emerging technology. As we have seen earlier in the introduction there has been considerable work in the science base.

This systematic review aims at reducing a large amount of information to a digestible size in order to identify key challenges associated with use of future potential stem cell therapies to treat deafness, in particular for sensorineural type hearing loss (SNHL), and to help in determining the consistency of challenges quoted in different publications to further extrapolate the key issues for SNHL. It has further enabled the combination of information from individual publications with a broader perspective in comparison to a single analysis from the medical and health care literature, to present the disease of hearing loss and in particular sensorineural hearing loss (SNHL), along with its background, epidemiology, classification, cell therapeutic rationale and approach.

Methodology:

This section reports the method employed to gain insights from the literature studied. A systematic review of literature is considered the least biased and most rational fundamental scientific activity to organise, evaluate and integrate research evidence from amongst the expanding medical and health care literature (29). Being a formalised and thorough method of investigation it assists in integrating valid information to provide a basis for rational decision making. It also improves the reliability and accuracy of recommendations.

Search Strategy:

Electronic database searches formed the basis of the literature search and, therefore, the following databases were searched with appropriate keywords and search engines used are Pub med, Medline Science direct ISI web of science, Cochrane library ISI Science Citation Index. An electronic search was then run on the databases to extract any further applicable studies from these papers. The reference lists of all included publications were scanned during data abstraction for any additional papers meeting the research criteria.

Generic translation reviews and studies were integrated provided relevant issues were discussed and inferences of value could be drawn with respect to cell-based hearing therapies. Generic reviews focusing on scientific and commercial issues facing regenerative medicine were also included to enable identification of challenges which might relate to hearing loss at present or in the future as therapies get closer to reality.

Only publications focusing on the above general criteria were included; consequently contributing to enhancing an understanding of key challenges facing translation of cellular products.

Hearing Loss Definition:

Hearing loss (HL) is full or partial diminution in the ability to perceive or understand sound. It is a clinically heterogeneous disorder, with variations in aetiology, age of onset, severity of the disease and site of lesion (30).

Epidemiology:

Hearing impairment is the most common chronic disabling sensory disorder in humans (31). Severe to profound HL affects 1 in 1000 newborns children, another 17 in 1000 children before they reach adulthood, and 50% of people older than 75 years will manifest HL of at least 25 decibels (dB) (32,33). Due to increased life expectancy and the resultant increment in ageing population the prevalence of acquired hearing loss is rising. Hearing impairment, both acquired and congenital, in most cases is a direct consequence of loss and/or damage to cochlea hair-cells or their connected neurones. SNHL, which affects the inner and outer hair cells and the sensory epithelia in the organ of Corti of the inner ear, is the most common form of HL. Approximately 60% of HL has a genetic basis and a substantial proportion of it is non-syndromic, the majority of which is inherited in an autosomal recessive mode (34,35).

Classification & Aetiology:

In this chapter we discuss the classification and aetiology of adult hearing loss.

Hearing loss in children will be discussed in more details in chapter 5

Hearing loss can be categorised into three basic types according to the site of auditory system damage:

- Conductive hearing loss (CHL)
- Sensorineural hearing loss (SNHL)
- Mixed hearing loss.

Conductive hearing loss (CHL):

This occurs when sound is not conducted efficiently through the external auditory canal to the tympanic membrane and ossicles of the middle ear. It is generally secondary to lesions in this pathway from the external auditory meatus to the middle ear. Some causes of conductive loss may be due to external ear canal occlusion by wax or a foreign body, infections of the canal called otitis externa which can be viral, bacterial or fungal. Other causes include perforation of the tympanic membrane, trauma that can lead to disruption of the ossicular chain mechanism that leads to a defect in sound transmission normally from the tympanic membrane to the stapes footplate and the oval window, through the cochlea to the nerve path.

Tympanosclerosis:

Fixation of the ossicular chain due to deposition of calcium and other materials over the ossicles or the tympanic membrane, results in limitation of vibration of the chain and the impairment of sound waves to be transmitted.

Otosclerosis:

Fixation of the stapes footplate is an autosomal dominant condition with incomplete penetration, also called otospongiosis, due to deposition of premature otospongiotic bones in the area of fissula ante fenestrum in the anterior part of the oval window. Theories behind its causes are that it may be due to endocrine, metabolic, infective, vascular, or auto-immune causes. It affects females twice as much as males and is characterised by:

- Slow progressive conductive hearing loss
- Tinnitus in more than 75% of patients
- Vertigo can occur in up to 25% of patients.
- It typically occurs in middle-aged ladies and may be related to hormonal changes. In particular symptoms are more severe during pregnancy and during the

menstrual cycle. It is bilateral in 70% of cases and more than 50% of patients have a family history of otosclerosis.

In children the most common cause of conductive hearing loss is due to otitis media with effusion (glue ears): This will be discussed in chapter 5

Chronic suppurative otitis media (CSOM), with or without cholesteatoma, is another cause of conductive hearing loss. CSOM without cholesteatoma is characterised by chronic ear discharge with a tympanic membrane perforation and hearing loss which is usually conductive in nature but a sensorineural component may co-exist. It has a prevalence of 0.6% in the adult population. Common causative pathogens are bacterial infection secondary to *Pseudomonas aeruginosa*, *Staph.aureus*, and *Proteus* species.

Cholesteatoma with chronic suppurative otitis media is a serious condition.

Cholesteatoma can be defined as a skin (or keratin) in the wrong place, i.e. in the middle ear. It has an incidence of 6 cases per 100000 of population; with a slightly higher figure for children. It can be congenital or acquired. Congenital cholesteatoma results from an abnormal focus of embryonic squamous epithelium in the middle ear space.

Acquired cholesteatoma results from evolution of retraction pockets or perforations in the tympanic membrane.

Pathophysiology of acquired cholesteatoma is due to impairment of the normal migratory mechanism of the squamous epithelium of the external ear canal. Migration will be misdirected producing accumulation of keratin within it. Super-added infection stimulates the activation of osteoclast cells and the release of lytic enzymes which leads to bone destruction and expansion of the cholesteatoma sac. Treatment of cholesteatoma is usually by surgery to remove and drill out the diseased bone and creating a bony cavity in the mastoid bone that requires regular follow-up for cleaning.

Treatment of the perforated tympanic membrane is by an operation called tympanoplasty to graft the perforation with or without ossiculoplasty to reconstruct the ossicular chain mechanism that requires some form of prosthesis which may be titanium

or part of remodelled ossicles, bones of the middle ear, to bridge or replace the gap in the ossicular chain.

Sensorineural Hearing Loss (SNHL):

SNHL develops due to loss of cochlea hair cells or their associated neurones. Lost hair cells are neither replaced by cell division nor regeneration from endogenous cells present in the inner ear epithelium rendering SNHL an irreversible condition. There is little mortality risk factor associated with SNHL, a non-fatal disease, but there is a very high disability factor (37,38), which makes this disorder a good potential candidate for a novel RM based therapeutic modality. Sensorineural hearing loss may be congenital or acquired.

Congenital hearing loss will be discussed in chapter 5.

Acquired hearing loss:

Commonest causes of acquired deafness are presbycusis, noise-induced hearing loss and ototoxicity.

1. Presbycusis:

Age-related or degenerative hearing loss due to degeneration and loss of spiral ganglion cells as well as hair cells. Usually affects people in their sixth decade. About 30-35% of adults between the ages of 65 and 75 years of age have a hearing loss. It is estimated that 40-50% of people 75 years of age and older have a hearing loss (39). Deafness is progressive, bilateral and symmetrical and affects the higher frequencies.

Types:

a) Sensory presbycusis: Degeneration or loss of sensory hair cells and supporting cells in the organ of Corti. Because of the tonotopic organisation of the cochlea, this process originates in the basal turn of the cochlea and slowly progresses toward the apex. These affect the high-frequency thresholds, which begins after middle age.

b) Neural presbycusis: Atrophy of nerve cells in the cochlea and central neural pathways, usually affects first order neurones. Atrophy occurs throughout the cochlea with the basilar region only slightly more predisposed than the remainder of the cochlea so it will affect most of the speech frequencies.

c) Strial (metabolic) presbycusis :Results from atrophy of the stria vascularis that normally maintains chemical and bioelectric balance and metabolic health of the cochlea.

May be assisted by modification to blood or O₂ supply of stria vascularis, not direct stem cell therapy.

d) Cochlear conductive (indeterminate) presbycusis: Due to thickening and stiffening of the basilar membrane of the cochlea. The thickening is more severe in the basal turn of the cochlea where the basilar membrane is narrow.

2. Noise-induced hearing loss:

Damage to the inner ear caused by exposure to loud noise. There is a relationship between the volume of sound and its duration. Eight hours of exposure to a sound level of 85dbA over several years usually causes damage, and louder sounds cause damage in a shorter time.

On exposure to loud noise the cochlea will be affected and there will be a temporary threshold shift that will recover after a rest period. If the loud stimulus continues there will be irreversible damage to the cochlea where the outer hair cells of the basal turn of the cochlea are affected first, thus causing high frequency hearing loss. This is due to the tonotopic organisation of the cochlea, and then the inner hair cells are affected leading to damage of other frequencies of sounds. Hearing loss is greatest at 3-6 KHz, because of the resonance of the external ear canal and also the protective mechanism of the acoustic reflex. As mentioned before, damage to hair cells cannot be replaced as there is no regeneration to these cells once damaged in humans.

In the UK the Control of Noise at Work Act of 2005 (40), set the safe minimum of noise exposure an employee may be exposed, safest time and the requirement by the employers to implement at work. It sets two levels of actions:

- a) At 80DbA noise levels for 8 hours employers are responsible for:
 - Regular hearing tests
 - Decreasing noise exposure at source
 - Education for employees
 - Providing hearing protection, whether an employee would use them or not
- b) At 85DbA for 8 hours employers are responsible for:
 - Ensuring employees are wearing and using their hearing protection devices
 - Decreasing noise exposure at source
 - Regular noise monitoring
 - Regular hearing tests
 - Education for an employee

Mammalian inner ears lose their regenerative capacity. This may well be due to structural specialisations of the organ of Corti. The adult mammalian organ of Corti completely lacks regenerative potential (41).

3. Ototoxicity:

Damage to the cochlea and vestibular system of the inner ear can occur due to the use of ototoxic medications in particular Gentamicin, Streptomycin, other aminoglycosides and cisplatin. These medications have narrow therapeutic index and can enter the perilymph and then the endolymph of the cochlea causing sensorineural hearing loss due to damage of the outer hair cells of the basal turn of the cochlea and later the inner hair cells.

Ototoxicity has now been identified to be genetically associated with mutation of the gene A1555 G mitochondrial on 12S Ribosomal RNA.

4. Other causes of SNHL:

- Viral and bacterial infections of the inner ears, meningitis
- Auto-immune diseases
- Trauma including barotrauma and acoustic trauma, and perilymph fistula
- Idiopathic causes.

The recent developments of stem cell offer great promise but experience in other areas of medicine has demonstrated that advancing from animal studies into human trials using human embryonic stem cells as a therapeutic candidate can be very difficult. Problems arise due to a host of concerns such as ethical issues associated with the use of a product derived from a human embryo (42).

From a clinical aspect the use of stem cells would represent great hope in treating deafness, particularly sensorineural type deafness due to presbycusis; although other type varieties of aetiology may also benefit from the new technology. However, there are great challenges to their use and to applying this using the Warren algorithm:

Patients' factors are due to their age. People are usually elderly who may well have other comorbidities that limit their fitness for surgery. Surgery to introduce stem cells into the cochlea is very difficult and also there are ethical issues around the use of stem cells. Stem cell availability and whether it is biologically plausible for their use are very important factors that determine their potential future use.

Clinicians should be able to diagnose the type of deafness and the cause of hearing loss as early as possible as this would determine patient selection and success for treatment.

It is extremely viable to try and marry clinical need with emerging putative technology and identify potential gaps that need bridging into each step of the process that apply to the use of stem cell therapies.

Sensorineural hearing loss (SNHL) cannot be compensated by endogenous repair mechanisms and may eventually lead to permanent deafness. It is an increasingly significant

health problem with wide psychosocial (43) and economic (44,45) implications. Current technology based treatment regimes neither replicate the complex native biological system nor furnish a full, permanent solution (46, 47). This opportunity has driven the development of potential cell therapies with the promise to replace degenerated inner hair cells in SNHL and ultimately reverse the natural progression of the disease (48).

In the early 1990's it was demonstrated by research groups that the avian cochlea hair cells, receptors for auditory perception, undergo structural and functional regeneration following noise-induced damage or aminoglycoside treatment (49,50). Such events lead to apoptosis and death of the hair cells, loss of cochlea ganglion cells and structural damage to the tectorial membrane thereby disrupting normal auditory input. The dying hair cells induce the neighbouring supporting cells to undergo regeneration to substitute the lost hair cells in the avian model either by their direct trans-differentiation or mitotic proliferation. Concurrently some of the supporting cells synthesise new tectorial membrane and the peripheral cochlear nerve processes detach from the basal surfaces of the dying hair cells awaiting the differentiation of new hair cells to reinstate synaptic contacts (51,52). Further, recent studies have identified stem cells in the inner ear of mice. They have demonstrated cell survival and differentiation and also shown positive expression of characteristic markers when exogenous stem cells were transplanted in experimental animal models (53,54). Although mammalian cochlea hair cells undergo apoptosis in response to ageing, noise damage and/or ototoxic medication, the supporting cells do not possess the ability to undergo regeneration, unlike the avian model. Such permanent loss of hair cells extends to variable levels of spiral ganglion cell loss which can also impact the success of therapeutic electronic devices such as cochlear implants. As the regenerative biology of the auditory system is being unfolded the time is ripe to be attentive to the problems of repeatedly realising therapeutic cell populations under robust bioprocesses which can be ultimately employed under good manufacturing practice (GMP) compliant conditions suitable for cost effective mass treatment (55). This together, with a suitable delivery technique (56) to implant the cells in the inner ear, is a key step in translating this promising therapy into the clinic and, subsequently, to the broader patient population. In parallel with such work in fundamental and applied

science there is also a requirement to create in a timely way the enabling clinical and necessary commercial infrastructure that will further allow the realisation of these therapies (57). Establishing viable business models for the components of this infrastructure will be another major challenge.

Therefore, building upon the current developments in stem cell research for SNHL, this study research attempts to look at the most significant challenges that must be addressed to deliver a cost effective clinical treatment regime. Individual problems with their solutions are integrated to reveal how these challenges can be met to allow the realisation of such a therapy.

Scientific Background:

All hearing sensations are derived from the output of a surprisingly small number of sensory cells - fewer than 15,000 per inner ear. SNHL is mainly attributed to the loss of these cells, therefore, a biological approach encompassing replacement of damaged cells by a functioning cell population holds tremendous potential. Hence, the premise of a cell based therapy will be to replace the dead or diseased cells, both hair cells and their supporting cells, with a functioning cell type which would integrate into the damaged auditory epithelium in order to re-establish the neuronal pathways and restore hearing.

The potential of this approach is reinforced by the progress accomplished in the repair of nervous and visual sensory systems by the restoration of diseased cells (58,59,60).

Embryonic stem cells hold significant potential for regenerative medicine due to their capacity to differentiate into many different cell and tissue types, including, in particular, spiral ganglion neurones, a source for cell replacement following cell loss in the auditory nerve. Inner ear progenitors have been generated from murine embryonic stem cells *in vitro* and a subpopulation of these progenitors after differentiation *in vitro* exhibit a hair cell phenotype with the potential to allow the generation and maturation of hair cells.

The recent detection of progenitor cells in the mammalian adult inner ear having the capacity to differentiate into hair cells as well as the finding that murine embryonic (54), adult inner-ear (53) and neural stem cells (59) can be differentiated into hair cells further consolidates the potential of such therapy.

Stem cells isolated from the inner ear appear to differentiate more completely into hair cells than neural stem cells. Neural stem cells, which have the ability to differentiate into many neuronal cell types, have been successfully grafted into a drug-injured mouse inner ear. They subsequently survived for several weeks and expressed markers of mature cell types. High proliferative capacity stem cells have been isolated from an adult mouse vestibular sensory epithelium (20) using a sphere formation assay. These are pluripotent and self-renewing cells that have the ability to form clonal free floating colonies called spheres. These sphere-forming cells are capable of differentiating into a variety of different cell types such as supporting and hair cells. A number of different methods have been used to deliver cells into the deafened cochlea, including direct transplantation into the cochlea, delivery into the scala media, and scala tympani with a variable survival time for the cells after injection of an average of five weeks. The inner ear progenitors generated from murine embryonic stem cells express hair cell specific genetic markers and, on further differentiation, the cells express characteristic transcription regulators involved in the generation and maturation of hair cells, *Math1* and *Brn3.1*, along with structural hair cell proteins, myosin VIIA, parvalbumin 3 and *espin*, thereby demonstrating hair cell phenotype. Further, the genetically labelled selectively enriched murine inner ear progenitors express hair cell specific markers in the developing sensory epithelium of the otic vesicle when grafted into the inner ear of chick embryos. This establishes that the murine progenitor cell derivatives respond to local cues that ensure avian hair cell growth and differentiation. Also, a number of cell therapy studies have successfully demonstrated delivery and survival of cells in the damaged inner ear.

These transplanted cells preserved existing hearing function by replacing primarily degenerated/lost sensory hair cells and spiral ganglion cells (61,62,63).

Recent work by two of the leading research groups is summarised as follows. Rivolta et al. (42) examines the potential application of neural crest stem cells for the treatment of deafness. This population shares a similar developmental origin with the cells of the otic placode, the molecular machinery controlling their maturation and differentiation is comparable and they can produce related sensory neurones. Their exploration and application to hearing conditions could facilitate the development of a clinically viable, cell-based therapy. Heller et al (14). have explored the conundrum of inner ear stem cells, which are present in the inner ear sensory epithelia of non-mammalian vertebrates, giving these ears the ability to functionally recover even from repetitive ototoxic insults. Despite the inability of the mammalian inner ear to regenerate lost hair cells there is evidence for cells with regenerative capacity can be isolated from vestibular sensory epithelia and from the neonatal cochlea. A longer life paired with a lifetime of ototoxic insults causes a steady increase of the number of patients worldwide who await novel treatments for hearing loss

Current modalities of treatment include Hearing aids, cochlear implants and bone anchored hearing aids. These treatments option will be discussed in details in chapter 5

Scientific Challenges:

The current research has established differentiation of stem cell populations towards inner ear hair cell lineage using otic inducers and environmental cues that reflect the hair cell development pathway. These cell populations are capable of replacing diseased cells . Therefore, to transform a progenitor cell population into a viable replacement cellular product, it is imperative that the progenitor cell expansion and differentiation processes are robust and reproducible without batch to batch variation (64) and yield clinically a relevant number of (65) functional and genetically stable inner ear hair cells.

- Cell processing and differentiation: Currently there is no well-defined or preferred cell source and differentiation protocol to facilitate the development of an appropriate cell based therapy for SNHL. Lack of definitive criteria for

the measurement of functional performance and appropriate cell sources that can be differentiated and expanded to clinically relevant numbers expressing validated biological markers (66,67) are the initial hurdles to be crossed before realisation of a classic cell based therapy for hearing loss. Further, integration and engraftment of the grafted cells post transplantation at the native site without immunological rejection has to be taken into account.

Cell culture and population expansion are critical steps of bio-processing required to generate sufficient cells for the therapy. Continued and sequential passaging can have detrimental effects on cells including loss of “stemness” which is dependent on cell

Scientific challenges for a new cell based hearing therapy:

- Isolation, expansion & controlled differentiation of applicable progenitor cell types
- Improve process capability on an appropriate culture platform cell sourcing & processing
- Imaging & electrophysiological profiling
- *In vivo* testing in animal models to assay physiological hearing function
- Tailored minimally invasive delivery technique & prognostic imaging
- Functional testing by audiometry to measure sensitivity of hearing implantation & pre-clinical studies source, culture duration, and culture and differentiation processes (68,69,70) and the number of cells ultimately required for a therapeutic intervention. Therefore, it will be necessary to design capable processes of producing stable cell populations thereby resulting in improved survival and function of cells both *in vitro* and *in vivo* (71). In this direction, automation of the cell culture process can improve process capability by removing the operator and reducing or eliminating other sources of variation and further allowing scale

up and/or out (72). Directing the efforts towards such systems is a significant step; however, a prior crucial step is to distinguish and delineate cytokine and growth factor supplementation strategies, to encourage development of consistent and stable inner ear hair cell populations at laboratory bench scale.

1. Cell Delivery: Another challenge relates to the very limited space in the scala media (the whole cochlea is 35 mm long spiralled about 2.7 times upon itself) where the cells have to be transplanted. It requires development of novel surgical delivery techniques before such a therapy can be translated from a promising experimental modality to clinical reality (73,74). A minimally invasive transplantation procedure to access inner ear necessitates direct microsurgical access to deliver cell populations (75). The efficacy of such a delivery technique depends upon the adequate engraftment, survival and functioning of the applied cells at the target site. This is controlled by the molecular mechanisms involved in their homing and the balance between mass transfer and metabolic demand at the graft site. This means that molecular and genetic strategies together with precise cell delivery tools have to be devised to enhance engraftment. Direct delivery to the inner ear via the endolymphatic sac, the non-sensory component of the endolymph filled membranous labyrinth, has significant potential therapeutic advantage due to the presence of a blood–labyrinth barrier which is anatomically and functionally similar to the blood–brain barrier (76,77). Here the transplanted cells will have ready access to the target tissue in the inner ear (the hair cells) and their synaptic regions but will be prevented from migrating to other areas. Also, no variation in pressure has been noted between the endolymph and perilymph after injection of up to 2 μ l of artificial endolymph as evidenced by mechanical compliance examination of the endolymphatic compartments (94). In fact, a 0.5 μ L of cell injection in the scala media depicted no significant morphological damage (78).
2. Measuring efficacy of cell therapy: Such a therapy must also necessarily be evaluated by comparison with the incumbent treatment regimes and standard of care available. In terms of SNHL, there is a possibility that the terminal thera-

peutic strategy might be a combination product of cell and gene therapy coupled with a pharmaceutical and/or an electronic device depending upon the efficacy of individual regimes. Therefore, logical and statistically significant animal and clinical studies with valid endpoints replicating the clinical problem and demonstrating efficacy and cost effectiveness with respect to the incumbent technologies need to be detailed. Also, data from such trials has to be carefully interpreted by using clinically valid assessment criteria in the form of audiometric testing to reflect individual patient needs and applying cell types with a defined dose and delivery method.

3. Cell Imaging: Direct assessment of cell engraftment, survival and integration into the host ear requires precise and specific non-invasive imaging techniques (79) with high spatial resolution to establish whether cells engraft (80) at their target. Such imaging tools will allow improvement of implantation techniques as well as assessment of the patient in the follow up process to determine both cellular viability and function with time (81,82). Nuclear imaging techniques, such as direct cellular radio-labelling (PET and SPECT) and reporter genes, give high sensitivity with quantification and visualisation of cellular function at particular locations. Magnetic resonance imaging gives good spatial resolution, and optical techniques allow tracking of cells (83,84). Therefore, the ultimate objective of complete functional monitoring of the repair process will require a combination approach with multiple imaging modalities and output integration to monitor inner ear hair cell engraftment.
4. Translational Challenges: The transition of proof of concept studies for cellular products derived from insights in the laboratory to enabling technologies for scale up and/or out is a complex issue. These include characteristic biomarker validation for stability and potency, design of phased clinical trials for safety and efficacy, release tests of the final formulation for adequacy, decision algorithms for clinical assessment and multivariate statistical analysis for functional assays, and cellular profiling to ultimately produce pure, safe and efficacious high volume clinical products that satisfy the regulatory framework.

Translational challenges will be discussed in further detail in Chapter 3, which especially looks at the translational process of cell based therapies, a study of the clinical ear, nose and throat community in the UK.

This necessitates active participation of practicing clinicians, the key gatekeepers, in the conception, development, evaluation and informed use of such novel therapeutic regimes.

Work by the author Khalid Ali et al. and colleagues (85), to date has explored the ENT community’s perspective on such therapies. This work now turns to examine the development steps necessary to secure adoption using the recently published Warren algorithm as an analogue of the clinical commissioners’ approach.

The Warren Algorithm (28) below has been developed to allow commissioners to make yes/no decisions on funding from a clinical perspective; we have used it here to structure a review of technology maturity and to identify some of the key issues from a developer’s perspective. This algorithm would allow maturity and applicability of regenerative medicine to be judged by public health preferential.

Cell-based therapy products.		
B ox	Description	Outcome
A	License for given indication (stage and first- or second-line treatment, as well as pathology)?	If Yes: fund routinely If No: go to Box B
B	Convention that the treatment is used for given indication although licensed for something else, or compelling Phase III trial result in a peer reviewed journal paper?	If Yes: fund routinely If No: go to Box C

- | | | |
|---|--|--|
| C | Formal UK trial (any phase) investigating use in given indication and currently recruiting? | If Yes: in trial only
If No: go to Box D |
| D | Has the product ever been subject to formal clinical research as shown by listing on Clinicaltrials.gov for example? | If Yes: go to Box E
If No: not currently |
| E | Is it patient's only treatment option? | If Yes: go to Box F
If No: not currently |
| F | Is it a common disease (e.g., osteoarthritis/ordinary breast cancer/prostate cancer)? | If Yes: go to Box O
If No: go to Box G |
| G | Is it a very rare disease? | If Yes: go to Box H
If No: go to Box K |
| H | Is it biologically plausible that the treatment might work? | If Yes: go to Box I
If No: not currently |
| I | Is there any evidence that it is efficacious? | If Yes: go to Box J
If No: not currently |
| J | Is it safe, in the context of the severity of the disease? | If Yes: yes as a one-off
If No: not currently |

- | | | |
|---|--|--|
| K | Is there a Phase II trial recruiting or in follow-up abroad? | If Yes: yes as a one-off
If No: go to Box L |
| L | Is it biologically plausible that the treatment might work? | If Yes: go to Box M
If No: not currently |
| M | Is there any evidence that it is efficacious? | If Yes: go to Box N
If No: not currently |
| N | Is it safe, in the context of the severity of the disease? | If Yes: yes as one-off
If No: not currently |
| O | Is there a Phase III trial recruiting or in follow-up abroad? | If Yes: yes as one-off
If No: go to Box P |
| P | Is it biologically plausible that the treatment might work? | If Yes: go to Box Q
If No: not currently |
| Q | Is it likely to be efficacious (e.g., ASCO abstract/paper reporting Phase II trial)? | If Yes: go to Box R
If No: not currently |
| R | Is it safe? | If Yes: yes as one-off
If No: not currently |

Cell based therapy Warren algorithm

This algorithm has been produced to help evaluate new tests and treatments rapidly and so being able to decide whether they should be funded or not when ill members enquire about them in the BUPA healthcare system clinical setting. This has been produced and populated using information which is easily and quickly available in the public domain. The information available from this algorithm would represent sources of information that can be utilised to gather information on the new test or treatment and to understand its context in the current best care, including available resources of clinical trials, UKCRN portfolio, Pubmed, British National Formulary, Cancer research UK website and others. This process is rapid and robust relying on a focus on clinical outcomes relevant to patients care. Warren et al. published two algorithms, one for interventional procedures and the second one for a new cell-based therapy.

The cell based algorithm above assists public health professionals to judge the maturity and applicability of regenerative medicine. Such algorithms are produced to help evaluate new tests and treatments rapidly in order to decide whether they should be funded by an independent healthcare provider. This process is rapid and robust relying on a focus on clinical outcomes relevant to patients' care.

Commissioners need to be able pragmatically to identify RMs which are safe and which will, when delivered in the context of an appropriate care pathway, avoid premature death and reduce morbidity for patients. This application will demonstrate that thinking of RM's as those that cause organs or tissues to regrow, or support them while they do that, alongside the use of one of a suite of health technology appraisal algorithms, will facilitate the process of distinguishing between those which are useful and those which are not (yet). Consideration of their cost effectiveness or cost utility can then be layered onto this, see for example the headroom method (86,87).

BUPA's HTA algorithms have been developed to structure the rapid appraisal of tests, interventional procedures and medicines. They focus on peer reviewed clinical evidence in the public domain about the achievement of outcomes that matter to patients, and the

length of time for which those outcomes are sustained. Literature searching and critical appraisal skills are key to their use, rather than detailed knowledge of any clinical speciality. An explanation of how to use them has been published previously (28).

Appraisals have shown that the IP and medicines algorithms were appropriate for use for cell-free RM's: the IP algorithm is appropriate for those that need surgical siting, and the medicines one for those that don't. However, these two are inadequate for cell-based therapies as neither deal with the issues of whether the cells have been ethically sourced and properly handled. In response to these problems the cell-based therapies algorithm was derived from the medicines algorithm, by the addition of a question (D) on whether the product had ever been subject to research logged on clinicaltrials.gov. An entry there implies that an Institutional Review Board/ Research Ethics Committee have reassured itself on a range of issues including those of ethical sourcing and proper handling. Such a proxy question is necessary because there is not a rapid method of answering the underlying question to facilitate a fast assessment. Also, in two of the three divisions of the algorithm (common diseases, and neither common nor very rare diseases) this question is also a shortcut to testing plausibility, if there is investment of effort and money in formal research, it must be plausible that such a treatment might work. If the shortcut fails, the algorithm then asks the overt question "is it biologically plausible it might work?"

The algorithm has common initial questions and then divides into three parallel streams by prevalence of disease. Common diseases use questions O-R and require the most mature evidence. Rare diseases use questions H-J and require the least mature evidence. The balance use questions K-N requiring middle mature evidence. From a developer's perspective the algorithm can be viewed as some key components, in particular distinguishing disease and patient population's maturity and accumulation of evidence.

A key lesson of the application of the algorithm (and incidentally of the headroom method) is that it is important to determine as closely as possible the patient group that can benefit from treatment; too broad a claim or license leads to poor value for money for commissioners of health care and disappointed patients if the treatment is used for

wider groups that do not have any capacity to benefit from it.

The application of the Warren algorithm together with a review of the state of the art – working the scientific literature from the perspective of practice to identify the status of stem cell therapies to treat deafness and the development steps necessary to enable their future potential use and adoption by a clinical commissioner – we are essentially attempting to match the potential treatment of a disease, the clinical need, to a putative therapy/emerging technology. As we have seen earlier in the introduction there has been considerable work in the science base. The table shows each step in the algorithm, the data sources and data collected and the outcome. The process to collect data has been analogous to that used in a systematic review.

In order to assist the developer we have divided the algorithm into three main subdivisions distinguishing maturity of evidence, disease and patients and accumulation of evidence as presented in tables 1-3. Each table shows the step in the algorithm, the data sources and data collected and the outcome. The process to collect data has been analogous to that used in a systematic review

Results & Discussion:

The first sub-division (Table 1) is related to the maturity of the evidence for stem cell therapies as a potential treatment for deafness. Applying steps A-D of the algorithm shows there is no licence available for stem cell therapies for deafness (Step A). The next steps, B and C, consider whether there is a convention that a treatment is used (off-label use) or whether there is or has been a phase III trial as the response again shows there is no mature evidence.

	Description	Outcome	Our response
A	Licence for given indication (stage and 1st or 2nd line treatment, as well as pathology)?	If Yes: Fund Routinely If No: Go to Box B	<i>No licence available</i>
B	Convention that the treatment is used for given indication although licensed for something else, or compelling phase III trial result in a peer reviewed journal paper?	If Yes: Fund Routinely If No: Go to Box C	<i>No off-label treatment is available yet nor is there a published phase III trial result. Data bases searched Clinicaltrials.gov and Pub Med.</i>
C	Formal UK trial (any phase) investigating use in given indication and currently recruiting?	If Yes: In trial only If No: Go to Box D	<i>We are not aware of any formal current UK trial investigating possible use of stem cell therapies for deafness. Web search of clinicaltrials.gov. Confirmed by private communication with Marcelo Rivolta(University Of Sheffield).</i>
D	Has the product ever been subject to formal clinical research as shown by listing on e.g. Clinicaltrials.gov?	If Yes: Go to Box E If No: Not Currently	<i>A Phase I safety trial commenced in the US in Feb 2012 using paediatric patients own cord blood stem cells to treat post-natal sensorineural hearing loss http://beyondthedish.wordpress.com/2012/02/21/new-clinicals-trials-use-umbilical-cord-blood-stem-cells-to-treat-neurological-conditions-and-hearing-loss/ (88).</i>

Table 1: Testing the maturity of evidence

As the introduction has shown there have been significant and promising advances in the development and understanding of stem cell therapies for the treatment of deafness over the past two decades but there also have been surgical challenges to deliver cells into the inner ear. The published demonstration of the potential to resolve both (89) has finally led to a safety trial, the first step in the accumulation of evidence of potential clinical utility in man.

Table 2 below presents sub-division two of the application of the Warren algorithm (steps E-G) that related to the diseases and patient, to stem cell therapies for hearing.

E	Is it patient's only treatment option?	If Yes: Go to Box F If No: Not Currently	<i>No, see below.</i>
<i>Current conventional treatment of deafness includes hearing aids, cochlear implants, Bone-Anchored hearing aids and surgical procedures to restore conductive hearing loss.</i>			
F	Is it a common disease (e.g. OA / ordinary breast ca / prostate ca) ?	If Yes: Go to Box O If No: Go to Box G	<i>Yes, see below.</i>
<p><i>Yes, very common in the aging population (presbycusis) and one of the most common industrial and occupational hazardous diseases. 250 million people are affected worldwide. In the developed world there are an estimated 90 million suffering from moderate to severe sensorineural hearing loss. Hearing loss may be due to congenital or acquired causes.</i></p> <p><i>Hearing impairment is largely due to degeneration and death of hair cells and their associated spiral ganglion neurons, due to noise trauma, infection, ototoxic drugs, metabolic disorders and ageing and the inability to replace lost or damaged hair cells by regeneration or cell division.</i></p>			

G	Is it a very rare disease?	If Yes: Go to Box H If No: Go to Box K	<i>Yes, there are rare variants, see below.</i>
<p><i>There are very rare genetic disorders that are associated with severe forms of deafness. Genetic hearing loss can be syndromic or non-syndromic.</i></p> <p><i>Syndromic causes are either autosomal recessive such as Pendred’s syndrome, Usher’s syndrome, Jervell-Lange-Neilson syndrome and Refsum’s syndrome or due to the autosomal dominant mode of inheritance such as Waardenburg’s syndrome, Treacher-Collins syndrome, Pierre-Robin, Crouzon’s and Apert syndromes.</i></p> <p><i>Non-syndromic causes represent about 70% of hereditary hearing loss. Connexin 26, GJB2, was the first non-syndromic sensorineural deafness to be discovered on chromosome 13. A1555G mitochondrial mutation has been found to be associated with aminoglycoside toxicity due to mutation in the 12S ribosomal RNA.</i></p>			

Table 2: The disease and patients

Application of the algorithm clearly captures that there are alternative current incumbent treatments for deafness including hearing aids and cochlear implants as well as surgery to reconstruct the hearing mechanism in some forms of conductive deafness. These treatments are costly and they are not without complications. Deafness is a very common disease especially in the growing, ageing population; especially in the developed world due to the advancement in health care systems. This highlights deafness also occurs in the younger population.

Table 3 below represents sub-division three (steps H-R) of the algorithm related to the accumulation of the evidence to support the potential use of stem cell therapies to treat deafness. As the table shows, critical steps from a clinical commissioner’s perspective are an increasing body of evidence to show biological plausibility; in particular the maturity of outcomes in animal models as a precursor to clinical trials – this taking of the order of 20 years to secure and then the necessary effort to move from animal evidence

to first in man paediatric trials, this taking at least from the publication in 2008 to the start of trial recruiting in 2012. Significantly in this instance early treatment is necessary to allow early language and speech development. The table also shows the additional steps necessary to satisfy, to accumulate and to secure routine clinical use.

H	Is it biologically plausible that the treatment might work?	If Yes: Go to Box I If No: Not currently	<i>See below</i>
<p><i>There has been accumulating evidence that stem cells therapies could be used to treat deafness in animal models.</i></p> <p><i>Embryonic stem cells hold significant potential for regenerative medicine due to their capacity to differentiate into many different cell and tissue types; including, in particular, spiral ganglion neurons, a source for cell replacement following cell loss in the auditory nerve. Inner ear progenitors have been generated from murine embryonic stem cells in vitro, and a sub-population of these progenitors after differentiation in vitro exhibit a hair cell phenotype, with the potential to allow the generation and maturation of hair cells. Stem cells isolated from the inner ear appear to differentiate more completely into hair cells than neural stem cells. Neural stem cells, which have the ability to differentiate into many neuronal cell types, have been successfully grafted into a drug-injured mouse inner ear. They subsequently survived for several weeks and expressed markers of mature cell types. High proliferative capacity stem cells have been isolated from an adult mouse vestibular sensory epithelium using a sphere formation assay. These are pluripotent and self-renewing cells that have the ability to form clonal free floating colonies called spheres. These sphere forming cells are capable of differentiating into a variety of different cell types such as supporting and hair cells.</i></p> <p><i>Importantly the paper (89), that triggered the US trial demonstrated both the promise of efficacy and overcame surgical issues by systemic delivery of cells rather than direct implantation of cells in the inner. This been known as a bottleneck for many years.</i></p>			

Table 3i: Accumulation of evidence – a key step

I	Is there any evidence that it is efficacious?	If Yes: Go to Box J If No: Not Currently	<i>No, not known</i>
J	Is it safe, in the context of the severity of the disease?	If Yes: Yes as a one-off If No: Not currently	<i>Not known</i>
K	Is there a phase II trial recruiting or in follow-up abroad?	If Yes: Yes as a one-off If No: Go to Box L	<i>No, not aware of any</i>
L	Is it biologically plausible that the treatment might work?	If Yes: Go to Box M If No: Not currently	<i>Equivalent to H above</i>
M	Is there any evidence that it is efficacious?	If Yes: Go to Box N If No: Not currently	<i>Not known yet.</i>

O	Is there a phase III trial recruiting / in follow-up abroad?	If Yes: Yes as one off If No: Go to Box P	<i>No, not aware of any</i>
P	Is it biologically plausible that the treatment might work?	If Yes: Go to Box Q If No: Not currently	<i>Equivalent to H above</i>
Q	Is it likely to be efficacious? (e.g. ASCO abstract / paper reporting phase II trial) ?	If Yes: Go to Box R If No: Not currently	<i>Not known, no trials yet.</i>
R	Is it safe, in the context of the severity of the disease?	If Yes: Yes as one off If No: Not currently	<i>Not currently available, not known</i>

Table 3ii: Accumulation of evidence – outstanding data

The analysis shows that critical steps from a clinical commissioner’s perspective are an increasing body of evidence to show biological plausibility; in particular the maturity of outcomes in animal models as a precursor to clinical trials – this taking of the order of 20 years to secure and then the necessary effort to move from animal evidence to first in man paediatric trials, this taking at least from the publication in 2008 to the start of trial recruiting in 2012. Significantly in this instance early treatment is necessary to allow early language and speech development. The table also shows the additional steps necessary to satisfy, to accumulate, to secure routine clinical use. It is important for a developer to recognise that H (L and P) is the most important question from the developer’s perspective – it is the question that the commissioner is using to test potential. It is important also to recognise that if the cause of the disease is known it is much more likely that this question can be answered satisfactorily because of the increased likelihood of being able to describe the mode of action. This kind of thinking will guide the

developer in making initial application and technology choices and in the direction of the accumulation of the necessary evidence.

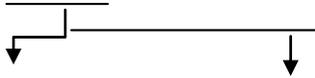
This discussion also highlights that, subsequent to applying the algorithm, the commissioner has to take into account the cost-effectiveness of the putative therapy with respect to the incumbent solutions and the trajectories of other technologies to the market place. This consideration should also take account of the behaviour of the clinical specialism, for example an increased willingness to apply stem cells as an adjuvant to a cochlear implant rather than alone (85).

Conclusion:

Despite the existence of significant markets, high costs to health service providers, the clear advances in stem cell therapy research in the laboratory and the requirement for a novel treatment for deafness, there has been slow engagement of clinicians, researchers and pharmaceutical and biotechnology companies in stem cell therapies. This application of the Warren algorithm to the use of stem cell treatments for deafness has shown it to be a comprehensive tool to systematically evaluate the maturity of the technology from a clinical commissioner's perspective and to identify critical steps from a developer's perspective, in particular the accumulation of biological plausibility and its communication in a manner acceptable to a clinical and regulatory audience to permit clinical trials. This in turn has highlighted the importance of animal models to the clinical audience; these are particularly problematic in this instance because of difficulties of replicating human deafness and stem cell treatments in animals.

Flow Chart of the Warren algorithm

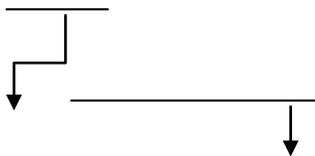
A Licence for given indication (stage and 1st or 2nd line treatment, as well as pathology)?



Y (Fund Routinely) N



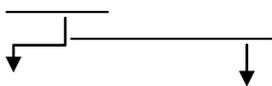
B Convention that the treatment is used for given indication although licensed for something else, or compelling phase III trial result in a peer reviewed journal paper?



Y (Fund Routinely) N



C Formal UK trial (any phase) investigating use in given indication and currently recruiting?

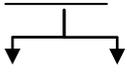


Y (In trial only) N



Has the product ever been subject to formal clinical research as shown by listing on e.g. clinical trials.gov?

D

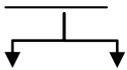


Y N



Is it the patient's only treatment option?

E

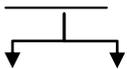


Y N (Not currently)



Is it a common disease (e.g. OA/ordinary breast CA/prostate CA)?

F

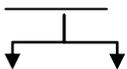


Y N



Is it a very rare disease?

G



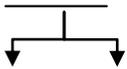
Y

N



Is it biologically plausible that the treatment might work?

H



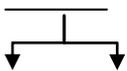
Y

N (Not currently)



Is there any evidence that it is efficacious?

I



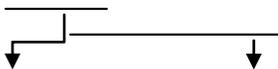
Y

N (Not currently)



Is it safe, in the context of the severity of disease?

J

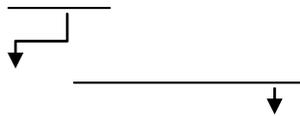


Y (As a one-off)

N (Not currently)

Is there a phase II trial recruiting or in follow up abroad?

K



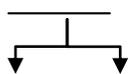
Y (As a one-off)

N



Is it biologically plausible that the treatment might work?

L



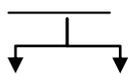
Y

N (Not currently)



Is there any evidence that it is efficacious?

M



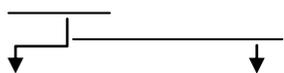
Y

N (Not currently)



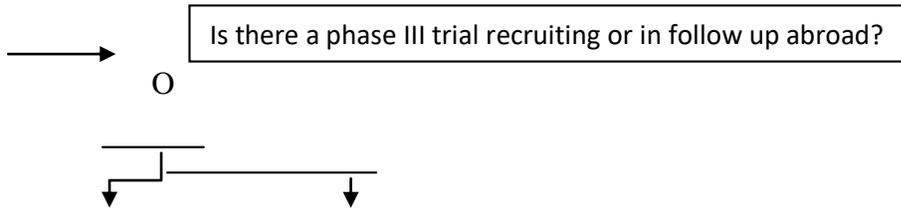
Is it safe, in the context of the severity of disease?

N



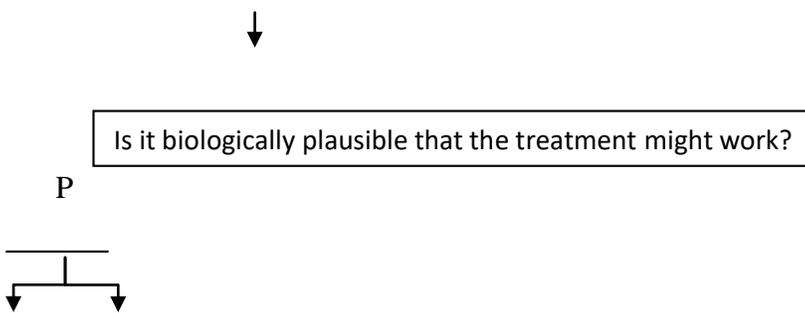
Y (As a one-off)

N (Not currently)



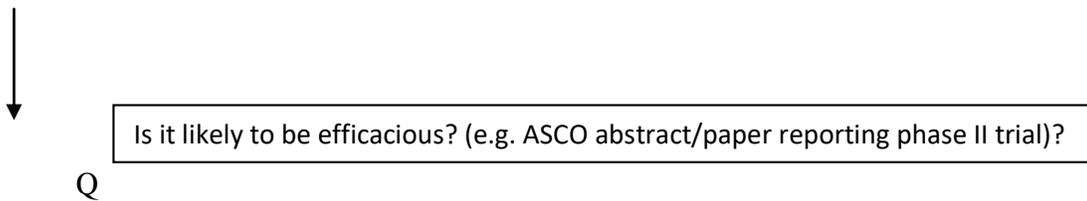
Y (As a one-off)

N



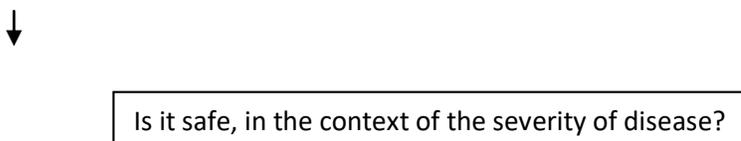
Y

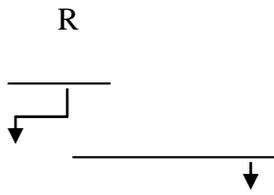
N (Not currently)



Y

N (Not currently)





Y (As a one-off)

N (Not currently)

CHAPTER 3:

Translation process and study questionnaire:

Aim:

The aim of this chapter is to look at the translational process to potentially move stem cell therapy from the laboratory to the clinical stages as a future potential treatment of hearing loss. In particular authors conducted a study to explore the clinical community's perspective on the use of stem cells in the treatment of hearing disorders to help define what is required to help this process and alignment. The study also aims to inform and enable the adoption process for such therapies by including understanding the awareness of and attitudes towards stem cell therapy for hearing loss amongst ENT surgeons, physicians, audiologists and scientists

Background:

Definition of the Knowledge translation:

The exchange, synthesis and ethically sound application of knowledge within a complex system of interactions among researchers and users to accelerate the capture of the benefits of research through improved health, more effective services and products, and a strengthened healthcare system (90).

World Health Organisation (91) defined the knowledge translation as the synthesis, exchange and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people's health. Knowledge translation (KT) is a complex and multi-dimensional concept that demands a comprehensive understanding of its mechanisms, methods and measurements as well as of its influencing factors at the individual and contextual levels - and the interaction between both those levels. KT is the effective and timely incorporation of evidence-based information into the practice of healthcare professionals in such a way as to affect optimal healthcare outcomes and maximise the potential of the healthcare system.

A prominent characteristic of KT, as indicated by CIHR (92), is that it encompasses all steps between the creation of new knowledge and its application to yield beneficial outcomes for society. Essentially, KT is an interactive process underpinned by effective exchanges between researchers who create new knowledge and those who use it. As stated by CIHR, bringing users and creators of knowledge together during all stages of the research cycle is fundamental to successful KT. Continuing dialogues, interactions, and partnerships within and between different groups of knowledge creators and users for all stages of the research process are integral parts of KT. Examples of different interactive groups are as follows:

- Researchers within and across research disciplines
- Policymakers, planners, and managers throughout the healthcare, public-health, and health public-policy systems
- Healthcare providers in formal and informal systems of care
- General public, patient groups, and those who help to shape their views and/or represent their interests, including the media, educators, non-governmental organisations, and the voluntary sector
- The private sector, including venture capital firms, manufacturers, and distributors.

Characteristically, KT is an interactive process that requires on-going collaboration amongst relevant parties, and includes multiple activities. It is a non-linear process involving all steps between the creation of new knowledge and its application, which needs multi-directional communication and diverse knowledge-user groups. KT is user- and context-specific, impact-oriented and it is an interdisciplinary process.

In the healthcare field KT is used to represent a process of moving what we have learnt through research to the actual applications of such knowledge in a variety of practice settings and circumstances. In varieties of medical specialities, the interest in KT (and other concepts about moving research-based knowledge into practice) appears to coincide with the growing engagement in the evidence-based practice (EBP) approach, in

which practitioners make practice decisions based on the integration of the research evidence with clinical expertise and the patient's unique values and circumstances (93). However, despite a strong endorsement for evidence-based practice in different healthcare fields, the use of research for practice continues to be lacking (94,95,96,97)

Model of Knowledge Translation:

Canadian Institute for Health Research (CIHR) (2005) proposed a global KT model based on a research cycle that could be used as a conceptual guide for the overall KT process. CIHR identified six opportunities within the research cycle at which the interactions, communications, and partnerships that will help facilitate KT could occur. Those opportunities are the following:

- KT1: Defining research questions and methodologies
- KT2: Conducting research (as in the case of participatory research)
- KT3: Publishing research findings in plain language and accessible formats
- KT4: Placing research findings in the context of other knowledge and sociocultural norms
- KT5: Making decisions and taking action informed by research findings
- KT6: Influencing subsequent rounds of research based on the impacts of knowledge use

Figure 1 below shows a graphical model in which the six opportunities listed here were superimposed on CIHR's depiction of the knowledge cycle.

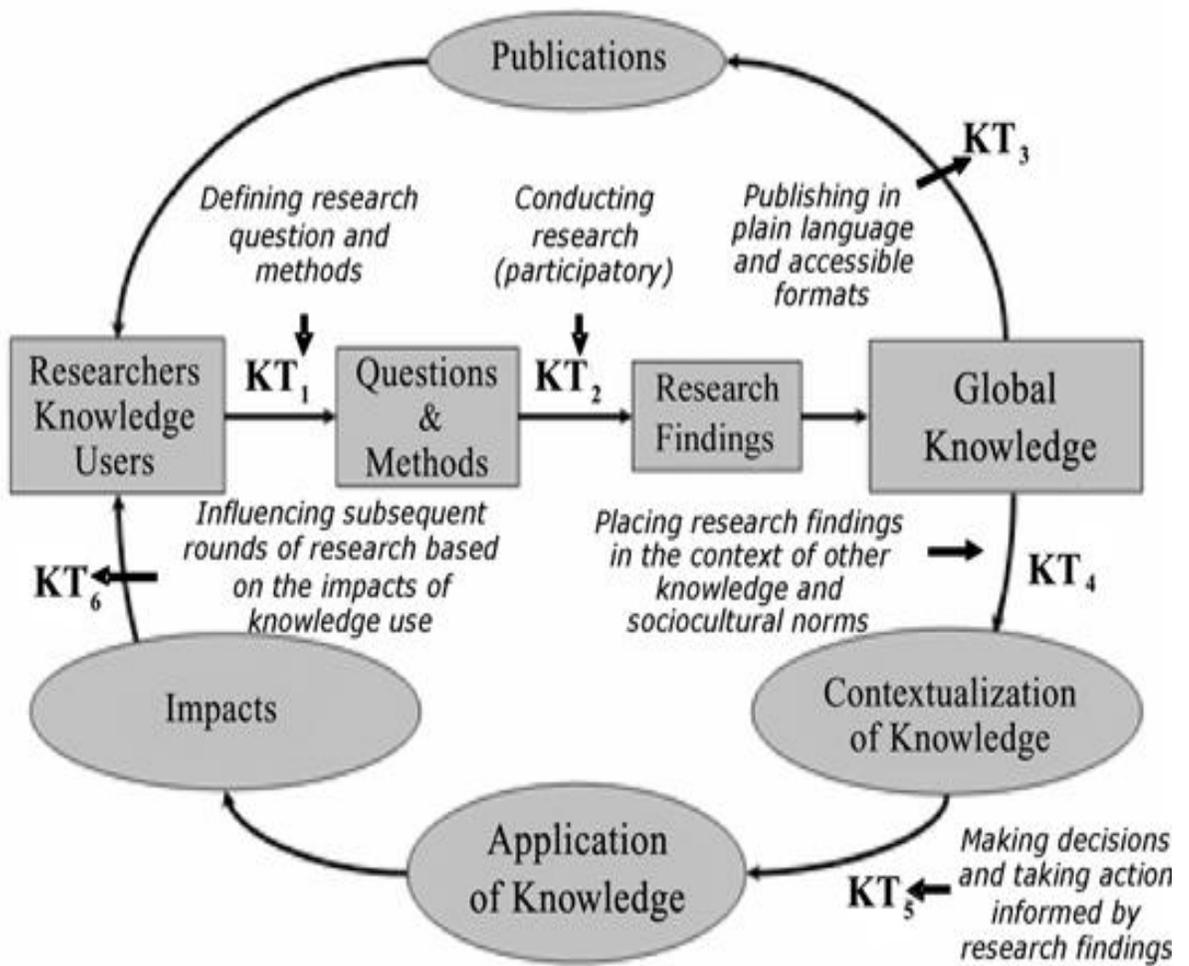


Figure 1. CIHR research cycle superimposed by the six opportunities to facilitate KT

The Ottawa Model of Research Use (OMRU) (98), Figure 2, is an interactive model developed (99) and includes six key elements:

1. Evidence-based innovation
2. Potential adopters
3. The practice environment
4. Implementation of intervention
5. Adoption of the intervention
6. Outcome resulting from implementation of the intervention

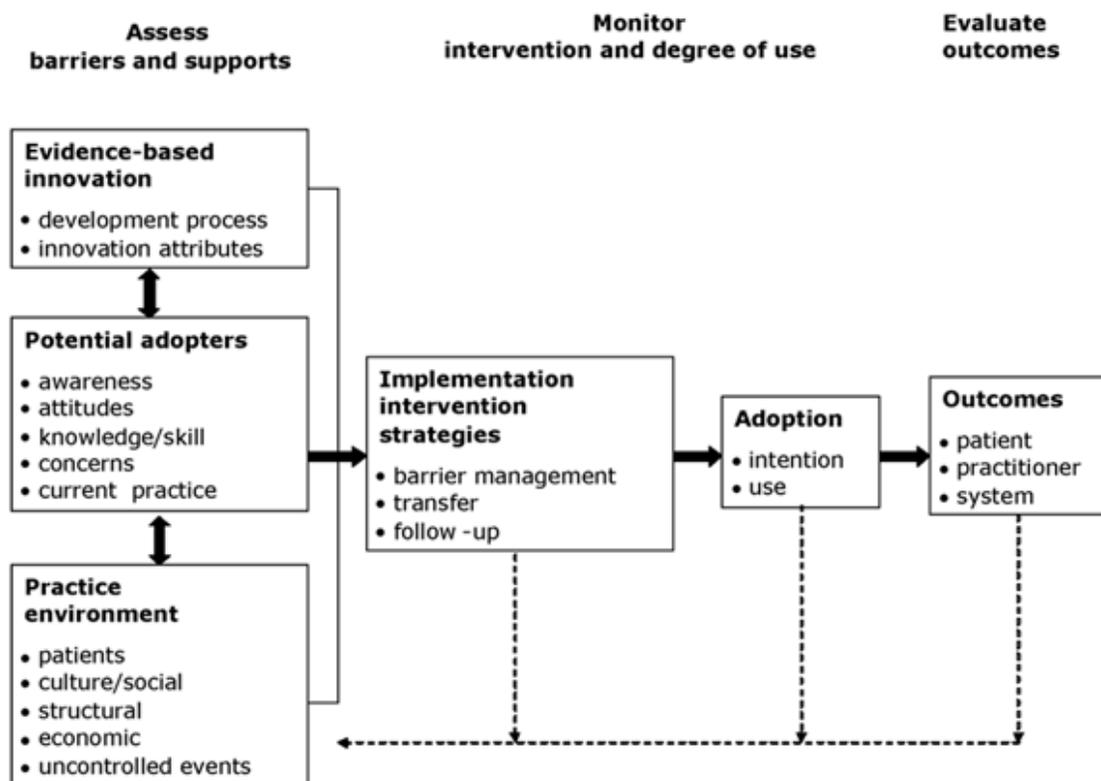


Figure 2.The Ottawa Model of Research Use

The use of specific strategies to implement research-based recommendations seems necessary to promote practice changes and that more intensive efforts are generally more successful. It is of vital importance to indicate the need to conduct studies to eval-

uate two or more interventions in a specific setting to clarify the circumstances likely to modify the effectiveness of such interventions.

Regenerative medicine technologies are now maturing and giving clearer indications of where they are likely to give clinical impact. Ultimately securing this clinical impact will require the clinical community to embrace the technologies as a key part of their adoption process - this will require that approaches match clinicians' requirements. Consequently an essential step in the translational process is the alignment of the expectations of the clinical community with the direction of the scientific research community. Our study explores the clinical community's perspective on the use of stem cells in the treatment of hearing disorders to help define what is required to help this alignment. In this study brief systematic review of the causes and types of deafness, and current treatment available with hearing aids or cochlear implants, are discussed using and implementing the first two key elements of the Ottawa model that is the evidence-based innovation and potential adopters in the possible use of stem cell therapies as a potential treatment for hearing loss. In particular this study aims to inform and enable the adoption process for such therapies by including understanding the awareness of and attitudes towards stem cell therapy for hearing loss amongst ENT surgeons, physicians, audiologists and scientists. Unless the perspectives of these key stakeholders are taken into account in the translation and adoption process there will be little likelihood of the uptake of a successful therapy.

According to the Ottawa Model of translational research it is vital for any translational process to look at the potential adopters. Adoption of the new treatment such as stem cells will require the opinion of the clinical community as there may be a resistance to change; a learning curve for a clinician to be able to take the new treatment forwards.

Methods:

A questionnaire has been developed that has allowed the clinical community to be approached in order to investigate their awareness, attitude and understanding of the current evidence, knowledge and the potential use of stem cell therapies to treat hearing loss. The study was performed in two stages:

1. The first stage was a pilot study to test the questionnaire. The first questionnaire consisting of 16 items was sent electronically to all ear, nose and throat doctors in the Trent Regional Health Authority and also hard copies were circulated to all ear, nose and throat doctors at the University Hospitals of Leicester at different levels of training from the very junior status to consultant level. The data was collected and analysed from the pilot study and the results showed that further questions needed to be added to the questionnaire which led us to modify the original questionnaire.

Further modification to the questionnaire was made after discussion and involvement of the University of Sheffield research department in stem cells.

2. In the second stage of the study, and with the support of ENT UK, a modified questionnaire which consisted of 22 items (see below) was sent to 400 clinical members of the ear, nose and throat community in the UK and 129 responses were secured. ENT UK (123) is the result of 5 years amalgamation in 2008 between the British Association of Otorhinolaryngologists – Head and Neck Surgeons and the British Academic Conference in Otolaryngology. Its objectives are “The advancement for the public benefit of education, training and research in the fields of otorhinolaryngology – head and neck surgery; the relief of patients suffering from diseases in the ear, nose and throat and related areas.” In particular it aims to improve the care available to patients suffering from conditions of the ear, nose, throat, head and neck and represent the specialty at the Royal Colleges of Surgeons and to Government bodies. It represents over 1,300 medical practitioners, including surgeons and trainees at different level of training, as well as allied specialties.

The Questionnaire:

1. How would you rate your knowledge of stem cell therapies as a potential treatment for hearing loss?
2. Do you agree that new treatment is needed for hearing loss replacing current conventional treatment with hearing aids?
3. Do you think that stem cell therapies would take away the current surgical skills you have learned through your career?
4. Do you believe that stem cell therapies would compromise surgical training?
5. Have you been asked by your patients whether there is any new treatment for deafness?
6. Would you feel comfortable answering or give advice to your patient if you were asked about new treatments for deafness?
7. Have you been asked by your patients about stem cell therapies as a new treatment of deafness?
8. Would you feel comfortable answering or give advice to a patient if you were asked about stem cell therapies as new treatment of deafness?
9. Do you think that stem cell therapies would be a good adjuvant treatment with a cochlear implant?
10. Do you think that stem cell therapies would be an alternative treatment to a cochlear implant?
11. The literature shows good promise/evidence of the ability of stem cells to help regenerate lost or damaged hair cells in the laboratory (for example the work of Rivolta and his group at Sheffield University, and Heller and his group at Stanford University). Are you aware of such literature and the evidence it contains?
12. Do you think that stem cell therapies give rise to ethical and religious issues?
13. Do you agree that stem cell therapies will help reduce social isolation and the psychology of the deaf population?
14. Will stem cell therapies save money for the NHS?
15. Do you agree that the new treatment will help the economy by getting more people back to work quickly and decreasing unemployment?

16. Would you encourage and support the transitional or translational process of taking stem cell therapy from the laboratory through clinical trials to ultimate adoption to healthcare benefit?
17. Do you agree that biotechnology and pharmaceutical companies should be investing more money to develop and manufacture such new a therapy?
18. Do you agree that the Government should spend money to support and encourage biotechnology companies to invest in such stem cell therapy?
19. Would you support the UK taking a leading role and competing with other global markets in health management and therapy?
20. Would you support and encourage the UK to take the lead in stem cell therapy for hearing loss?
21. Would you like to add any comments?

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Name or Email address

Speciality:..... Sub-speciality:.....

Consultant SAS SPR ST SHO FY

Audiologist Grade (years' of experience):.....

Scientist Grade (years' of experience):.....

Respondents were asked to choose one of four possible answers to each question:

A- Yes

B- No

C- Maybe

D- Don't Know

The modified questionnaire which consisted of 22 itemised questions, plus two items for participation and CPD points, was sent via ENT UK(100) using an electronic method, the “Survey Monkey” (101). An e-mail invitation was sent requesting the completion of the questionnaire and an upload of the response information electronically.

The questionnaire was subdivided into eight categories to reflect the need and focus of answers as in the following:

- Stem Cell therapies for hearing loss
- Stem Cell therapies for hearing loss and Surgical Skills / Training
- Stem Cell therapies for hearing loss - Advice to patients
- Stem Cell therapies for hearing loss and Cochlear Implants
- Stem Cell therapies for hearing loss - Ethical and Social issues
- Stem Cell therapies for hearing loss - Economic Issues
- Stem Cell therapies for hearing loss - Translational Research
- Stem Cell therapies for hearing loss - UK position

Below is a detailed response to answers to each question and also a percentage to each answer:

Filter Responses to each item question

Stem Cell therapies for hearing loss

1. How would you rate your knowledge of Stem Cell therapies as a potential treatment for Hearing Loss			
		Response Percent	Results Count
answered question			127
skipped question			2
1- None		30.7%	39
2- Little		56.7%	72
3- Adequate		10.2%	13
4- Very good		2.4%	3

2. Do you agree that new treatment is needed for hearing loss, replacing current conventional treatment with hearing aids			
answered question			128
skipped question			1

2. Do you agree that new treatment is needed for hearing loss, replacing current conventional treatment with hearing aids			
		Response Percent	Response Count
1- Yes		64.1%	82
2- No		3.9%	5
3- Maybe		30.5%	39
4- Don't Know		1.6%	2

Stem Cell therapies for hearing loss and Surgical Skills / Training

3. Do you think that Stem Cell therapies would take away the current surgical skills you have learned through your career			
		Response Percent	Response Count
	answered question		126
	skipped question		3
1- Yes		0.0%	0
2- NO		80.2%	101

3. Do you think that Stem Cell therapies would take away the current surgical skills you have learned through your career

3- Maybe		13.5%	17
4- Don't know		6.3%	8

4. Do you believe that Stem Cell therapies would compromise surgical training

answered question			127
skipped question			2
		Response Percent	Response Count
1- Yes		1.6%	2
2- No		81.1%	103
3- Maybe		9.4%	12
4- Don't Know		7.9%	10

Stem Cell therapies for hearing loss - Advice to patients

5. Have you been asked by your patients whether there is any new treatment for deafness			
		Response Percent	Response Count
answered question			127
skipped question			2
1- Yes		68.5%	87
2- No		29.1%	37
3- Maybe		2.4%	3
4- Don't Know		0.0%	0

6. Would you feel comfortable answering or give advice to your patient if you were asked about new treatment for deafness			
		Response Percent	Response Count
answered question			128
skipped question			1

6. Would you feel comfortable answering or give advice to your patient if you were asked about new treatment for deafness

1- Yes	55.5%	71
2- No	23.4%	30
3- Maybe	18.8%	24
4- Don't Know	2.3%	3

7. Have you been asked by your patients about Stem Cell therapies as a new treatment of deafness

	Response Percent	Response Count
answered question		127
skipped question		2
1- Yes	11.0%	14
2- No	89.0%	113
3- Maybe	0.0%	0
4- Don't Know	0.0%	0

8. Would you feel comfortable answering or give advice to your patient if you were asked about Stem Cell therapies as new treatment of deafness

		Response Percent	Response Count
	answered question		127
	skipped question		2
1- Yes		28.3%	36
2- No		50.4%	64
3- Maybe		17.3%	22
4- Don't Know		3.9%	5

Stem Cell therapies for hearing loss and Cochlear Implants

9. Do you think that Stem Cell therapies would be a good adjuvant treatment with a Cochlear implant

	answered question	125
	skipped question	4

9. Do you think that Stem Cell therapies would be a good adjuvant treatment with a Cochlear implant

	Response Percent	Response Count
1- Yes	20.0%	25
2- No	4.0%	5
3- Maybe	40.0%	50
4- Don't Know	36.0%	45

10. Do you think that Stem Cell therapies would be an alternative treatment to a Cochlear implant

	Response Percent	Response Count
answered question		126
skipped question		3
1- Yes	11.9%	15
2- No	7.9%	10
3- Maybe	53.2%	67

10. Do you think that Stem Cell therapies would be an alternative treatment to a Cochlear implant

4- Don't Know		27.0%	34
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11. The literature shows good promise/evidence of the ability of Stem Cells to help regenerate lost or damaged hair cells in the laboratory (for example the work of Rivolta and his group at Sheffield University, and Heller and his group at Stanford University). Are you aware of such literature and the evidence it contains?

		Response Percent	Response Count
	answered question		125
	skipped question		4
1- Yes		29.6%	37
2- No		61.6%	77
3- Maybe		8.8%	11
4- Don't Know		0.0%	0

Stem Cell therapies for hearing loss - Ethical and Social issues

12. Do you think that Stem Cell therapies give rise to ethical and religious issues			
		Response Percent	Response Count
answered question			125
skipped question			4
1- Yes		42.4%	53
2- No		34.4%	43
3- Maybe		20.8%	26
4- Don't Know		2.4%	3

13. Do you agree that Stem Cell therapies will help reduce social isolation and the psychology of the deaf population

answered question			126
skipped question			3

13. Do you agree that Stem Cell therapies will help reduce social isolation and the psychology of the deaf population			
		Response Percent	Response Count
1- yes		33.3%	42
2- No		7.1%	9
3- Maybe		48.4%	61
4- Don't Know		11.1%	14

Stem Cell therapies for hearing loss - Economic Issues

14. Do you think that Stem Cell therapies would save money for the NHS			
		Response Percent	Response Count
answered question			124
skipped question			5
1- Yes		7.3%	9
2- No		33.1%	41

14. Do you think that Stem Cell therapies would save money for the NHS

3- Maybe	21.0%	26
4- Don't Know	38.7%	48

15. Do you agree that the new treatment will help the economy by getting more people back to work quickly, and decreasing unemployment

answered question		124
skipped question		5
	Response Percent	Response Count
1- Yes	12.1%	15
2- No	32.3%	40
3- Maybe	38.7%	48
4- Don't Know	16.9%	21

Stem Cell therapies for hearing loss - Translational Research

16. Would you encourage and support the transitional or translational process of taking Stem Cell therapy from the lab through clinical trials to ultimate adoption to health care benefit

	answered question	124	
	skipped question	5	
		Response Percent	Response Count
1- Yes		78.2%	97
2- No		2.4%	3
3- Maybe		14.5%	18
4- Don't Know		4.8%	6

17. Do you agree that biotechnology and pharmaceutical companies should be investing more money to develop and manufacture Stem Cell therapy

	answered question	124
	skipped question	5

17. Do you agree that biotechnology and pharmaceutical companies should be investing more money to develop and manufacture Stem Cell therapy

	Response Percent	Response Count
1- Yes	59.7%	74
2- No	4.0%	5
3- Maybe	21.0%	26
4- Don't Know	15.3%	19

18. Do you agree that the government should spend money to support and encourage biotechnology companies to invest in such Stem Cell therapy

answered question		125
skipped question		4
	Response Percent	Response Count
1- Yes	54.4%	68
2- No	12.8%	16
3- Maybe	22.4%	28

18. Do you agree that the government should spend money to support and encourage biotechnology companies to invest in such Stem Cell therapy

4- Don't Know		10.4%	13
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Stem Cell therapies for hearing loss - UK position

19. Would you support the UK taking a leading role and competing with other global markets in health management and therapy

		Response Percent	Response Count
	answered question		123
	skipped question		6
1- Yes		78.9%	97
2- No		4.9%	6
3- Maybe		13.8%	17
4- Don't Know		2.4%	3

20. Would you support and encourage the UK to take the lead in Stem Cell therapy for hearing loss.

		Response Percent	Response Count
answered question			123
skipped question			6
1- Yes		78.0%	96
2- No		4.9%	6
3- Maybe		14.6%	18
4- Don't Know		2.4%	3

21. Would you like to add any comments

answered question		27
skipped question		102
		Response Count

21. Would you like to add any comments

 Show replies

27

22. What is your level of experience and specialty, You may tick more than one box

	answered question	skipped question	Response Percent	Response Count
Consultant			69.6%	87
SAS (non training post)			4.0%	5
SPR (in training)			22.4%	28
SHO			3.2%	4
Audiologist			0.0%	0
Scientist			1.6%	2
Otorhinolaryngologist			33.6%	42
Other specialty			1.6%	2

Thank you for participating in this ENT.UK approved survey on Stem Cell Therapies for Hearing Loss

23. Your Details for CPD			
	answered question		118
	skipped question		11
		Response Percent	Response Count
 Show repliesName		100.0%	118
 Show repliesGMC Number		98.3%	116

24. How do you rate the quality of this survey?	
answered question	116
skipped question	13

Statistical analysis:

The data was analyzed using the SPSS package (Version 18). Statistical analysis consisted of a descriptive analysis of all items in the questionnaire. Principle component analysis with Varimax rotation of items 2-19 of the questionnaire was used to identify high loading factors indicating related questions. Non-parametric analysis of the questionnaire items using independent sample Kruskal-Wallis test sought to establish whether the results differed by type of respondent, where a significant difference is > 0.05 .

Results:

The total number of questionnaires sent out was 400 and the total respondents were 129, representing a response rate of $>30\%$. When asked whether the respondent had any knowledge of stem cell therapies as a potential treatment for hearing loss, 57% answered that they had little knowledge and 30% had no knowledge at all. Figure 1 shows that 64% of the respondents felt that a new treatment is needed for hearing loss replacing the current treatment of deafness with hearing aids. Importantly for adoption 80% did not feel that a new therapy would take away current surgical skills or compromise surgical training. 11% of respondents have been asked by their patients about the use of stem cells as a new treatment for deafness and 28% of the respondents felt comfortable in answering or giving advice to patients when asked about stem cell therapies.

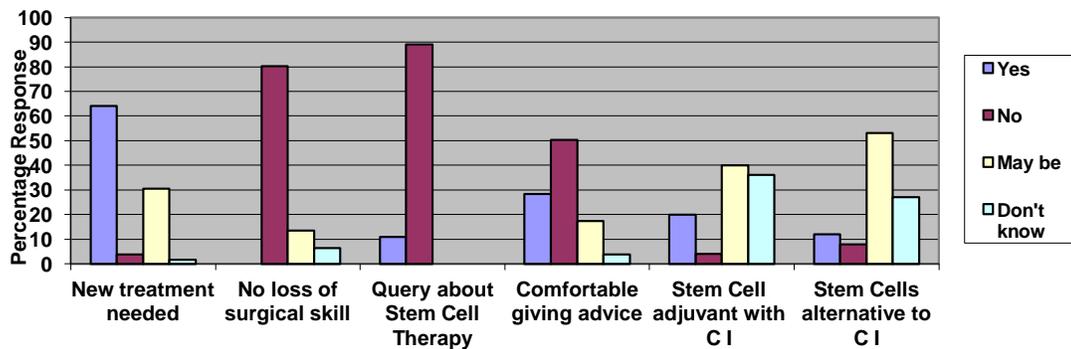


Figure 1. Response to questions 2-10 – Approach, education and training

When asked about whether stem cell therapies would be a good adjuvant treatment with a cochlear implant (CI) 20% responded positively. 40% felt stem cell treatments may be a good adjuvant with CI. When asked whether stem cells will be an alternative treatment to a cochlear implant only some 12% responded positively and 53% answered may be.

When asked whether respondents were aware of any literature showing evidence of the promise of stem cell therapies (see Figure 2) about 30% answered positively but 62% were not aware of any such literature. Figure 2 also shows that 42% think that stem cell therapies will give rise to ethical and religious issues.

33% of respondents felt that stem cell therapies will help reduce social isolation through enhanced social interaction and improved communication of the deaf population with 48% of respondents feeling they may help. 39% of respondents were unsure whether future stem cell therapies would save any money to the NHS or help the economy by getting more people back to work quickly and decreasing unemployment (see also Figure 2)

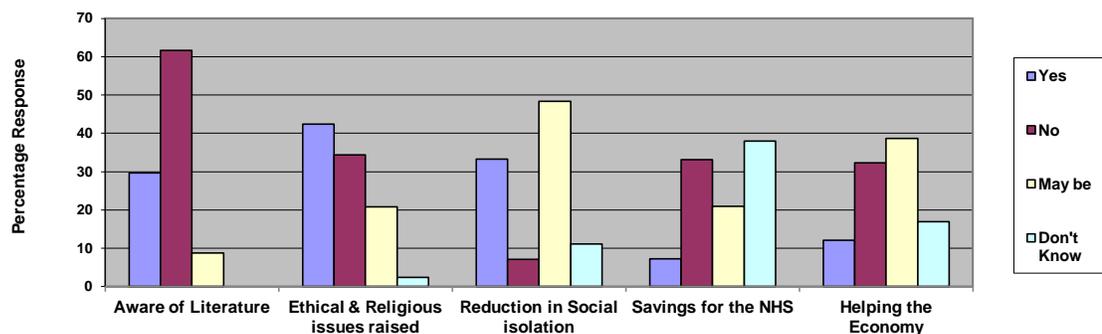


Figure 2: Responses to questions 11-15 – Literature, Ethical and Social issues

Figure 3 shows that more than 78% of respondents (97 out of the 124 who answered this question) would encourage and support the translational process of taking stem cell therapies from the lab through clinical trials to ultimate adoption to healthcare benefit. Some 60% agree that the biotechnology and pharmaceutical companies should be in-

vesting more money to develop and manufacture stem cell therapies and that this should be supported by the Government (55% of respondents). Figure 3 shows that more than 78% of respondents would support the UK taking a leading role and competing with other global markets in health management and therapy, and the same percentage would also support and encourage the UK to take the lead in stem cell therapies for hearing loss.

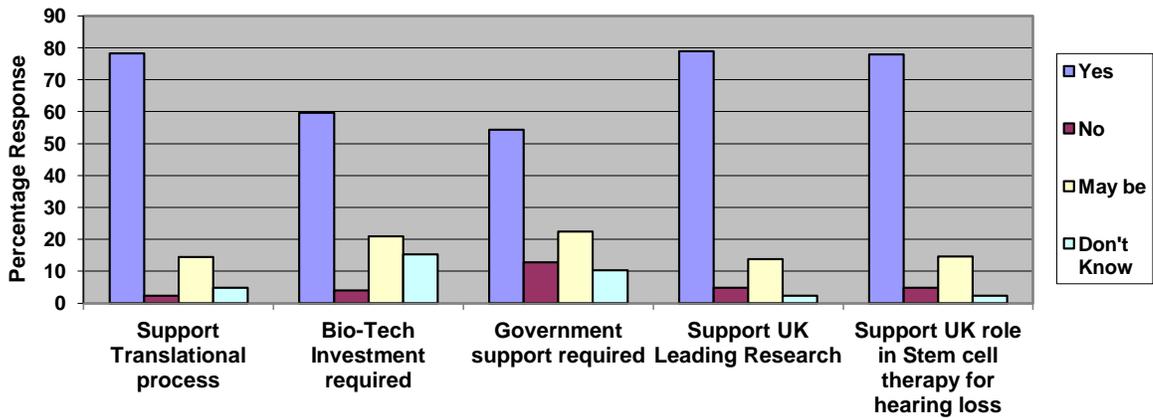


Figure 3. Responses to questions 16-20 – The UK and clinical translation

Principle component analysis with Varimax rotation of items 2-19 of the questionnaire was used to identify high loading factors that categorise related questions. Four factors were identified that accounted for 22%, 14%, 11% and 9% of the common variance as is shown in Table 1.

Factor Interpretation	Variance accounted for	Items
Economic and Social	22%	save_money (14), economy_work (15), govt_spend (18), isolate_psy (13)
Advice to Patients	14%	pts_advice (8), pts_comfs (6), pts_asks (5), pts_asked (7), aware lit (11)
Clinical Trials And Pharma	11%	clin_trials (16), pharma (17), cochlear_adjuv (9)
Surgery	9%	surgical_skills (3), surgical compromise (4)

Table 1. Factors identified using principal components analysis

The first factor had four items loaded high, and these are questions 14, 15, 18 and 13 which represent a category of questions that relate to economic and social factors. The second factor had five items loaded high, questions 8, 6, 5, 7 and 11 which represent a category of items that relate to questions and advice given to patients regarding stem cell therapies and awareness among the clinical community in respect to this therapy. The third factor had three items loaded high together, questions 9, 16 and 17, representing a third category of questions that relate to support of clinical trials in stem cell therapy and agreement among respondents that the biotechnology and pharmaceutical companies should invest more to develop and manufacture such a new therapy. The fourth factor had two items loaded high, questions 3 and 4 representing the fourth category related to surgical training.

Non-parametric analysis of the questionnaire items using the independent sample Kruskal-Wallis test (this compares the medians of two or more samples to determine if the samples have come from different populations) was used to see whether the results differed by type of respondent – i.e. to see whether there is any significant difference

(0.05) in responses between respondent groups; in particular between consultants and other groups. The test shows that there is a significant difference between the consultants and other professionals in response to question 3 (0.018) and question 4 (0.00). These are related to surgical training and skills. This means that consultants did not feel, with the availability of stem cell therapies, that there will be a compromise to levels of current surgical training, nor will there be a threat of losing current surgical skills. There was also a significant difference between consultants and other respondents (0.05) in the response to question 13 relating to the perception of ethical issues. The test also showed significant differences (0.019), (0.038) and (0.034) for questions 16, 8, and 7 respectively. This shows that the consultant group felt more comfortable answering or giving advice to their patients when asked about potential stem cell therapies as compared to other respondent groups in training or not in training.

Discussion:

There is clear indication that the knowledge of stem cell therapies within the clinical community needs to be increased as, while many were clearly enthusiastic about the potential, the majority of the clinicians completing the questionnaire (87%) indicated they had no, or very little, knowledge regarding the potential use of stem cell therapies to treat deafness. The study also shows that there is common agreement among respondents (>90%) that there is a requirement for a new treatment for deafness replacing current conventional treatment with hearing aids.

Clearly stem cell therapies would require additional surgical skills training with regard to the injection and transplantation procedures required to deliver these cells into the human cochlea but, importantly, the majority of the clinical community did not feel any threat to their current surgical skills or any compromise to surgical training.

Equally significantly this study shows that patients are curious to know about whether there are new treatments for deafness and in particular whether stem cell therapies may be used in the future to treat deafness. Indeed, patients frequently ask about such therapies and are disappointed to learn they are still in the laboratory (102). The willingness

of doctors to respond to patients varies widely between those who felt comfortable answering their patients' questions and discussing the opportunity to those who did not. Alarminglly this study clearly shows that while 87% of respondents have no knowledge or very little knowledge of stem cell therapies; despite this about 30% of respondents indicated they felt comfortable in answering their patients' questions.

Participants were unsure as to whether future stem cell therapies would work better as an adjuvant treatment with a cochlear implant or as a treatment replacing a cochlear implant. Clearly a cochlear implant needs viable neurones to function effectively. Stem cell therapies delivering such viable neurones would assist a cochlear implant to function efficiently. Ultimately stem cell therapies may be available commercially that are able to replace cochlear implants. Future therapies are likely to be a combination therapy of stem cells, gene therapies and cochlear implant and such a combination therapy may have to be customised to the particular cellular ailment of the individual patient (103). The interactions of the expectations of the clinical community with time and the regulatory and reimbursement barriers to be surmounted must be carefully considered by both the scientific and commercial communities to ensure that acceptable therapies are delivered at an acceptable cost. Such considerations much echo the concerns of respondents on ethical and religious issues.

Participants were unsure if the new treatment would help reduce social isolation and improve the psychology of the deaf population and whether it would be a cost effective treatment that would save money to the NHS. Deafness can lead to reduced physical and psychological well-being, social withdrawal, isolation, loneliness and depression (104) and, in consequence, the NHS faces significant costs. The global hearing aid market is approximately £5 billion, assists people only with residual hearing and there are limitations to their benefits.

There is a very clear indication that the majority of the clinical community (78%) who have responded to this questionnaire would support and encourage current and future studies of stem cell therapies; especially the translational process to move from the laboratory to the clinic; and would also support the UK in taking a leading role in this

field and investing in this technology by supporting pharmaceutical and biotechnology companies.

Despite the existence of significant markets massive annual bills to health service providers, the clear advances in stem cell therapy research in the laboratory and the requirement for a novel treatment for deafness there has been slow engagement of clinicians, researchers and pharmaceutical and biotechnology companies in stem cell therapies. There has never been a better time for investment in translational stem cell hearing research and there is now a real opportunity to move this promising research from the laboratory to the clinic: the pharmaceutical and biotechnology industries are vital to this process (64).

Conclusion:

Cell replacement therapy has the potential to have a significant impact on human health during the coming decades. There have been great advances in stem cell therapy research in the laboratory over the past ten years. This study shows that members of the clinical ENT community vary in their knowledge, awareness, attitude towards, and support to, stem cell therapies as a potential treatment for deafness and that there is a clear requirement for further training in this field. It is also clear that this community recognizes the need for such therapies and supports their translation from the laboratory to clinical use and that this will require efforts from Government to encourage biotechnology and pharmaceutical companies to take the initiative in developing and manufacturing such stem cell therapies. An essential step in the translational process is the alignment of the expectations of the clinical community with the direction of the scientific research community; in particular whether stem cells should be pursued as an adjuvant therapy to CI, a combination therapy or as a therapy in their own right. From a scientific perspective a neural sensory cell replacement could be adequate as a co-therapy with implants, whereas hair cell replacement could represent an alternative to implants. The likelihood of the latter will be further influenced by the constraints of the high level of tonotopic organisation of the cochlea which makes hair cell replacement “formidably” challenging (105). Any alignment must take account of the clinical trials require-

ments, regulatory landscape and reimbursement conditions for such therapeutic alternatives -this requires more exploration of the socio-economic case for interventions.

CHAPTER 4:

Financial Aspects of the Future Potential Use of Stem Cell Therapies. (Value-based pricing.)

Aim:

The aim of this chapter is to look at and assess the financial and economic position of stem cell therapy as a potential therapeutics for hearing disorders at their early stages of its development, and the proposal of a management plan for treatment of a certain clinical scenario with sensorineural hearing loss from a clinician's view that may allow efficient intervention and effective resource allocation that will demonstrate value in terms of future required investment in stem cell therapy, and in terms of research and development, manufacturing and decision making and marketing of this therapy and contribute to the debate of value-based planning.

Background:

Escalating healthcare costs continue to be problematic for the overall healthcare industry. This is compounded by continued economic distress, policy changes and the integration of complex innovative technology implementation into the healthcare system. Therefore, stem cell therapy should be integrated within the healthcare system as a cellular therapeutics that will be a cost effective therapy having cost-efficient and robust manufacturing operations which gives advantage to healthcare delivery. Such an approach may assist balancing both short- and long-term challenges to create value for patients as well as stakeholders.

Value-based pricing:

The term "value-based pricing" is used when prices are based on the value of a product as perceived from the customer's perspective. The perceived value determines the customer's willingness to pay and thus the maximum price a company can charge for its product (106).

Value-based pricing or value-optimized pricing, is a pricing strategy. It sets prices primarily, but not exclusively, on the value, perceived or estimated, to the customer rather than on the cost of the product or historical prices (107,108)

Goods that are very intensely traded (e.g. oil and other commodities) or that are sold to highly sophisticated customers in large markets (e.g. automotive industry) usually are sold based on cost-based pricing (i.e cost plus mark-up).

In the long term, by definition, prices based on value are always higher or equal to the prices derived from a cost-based process. If they were lower it would mean that the actual value perceived by the customer is lower than the costs of producing the goods plus a profit margin. This would mean that companies would not in the long term be interested in producing and selling at that price (109)

Value-based pricing is predicated upon an understanding of customer value. In many settings gaining this understanding requires primary research. This may include evaluation of customer operations and interviews with customer personnel. Survey methods are sometimes used to determine the value a customer attributes to a product or a service; the results of such surveys are often interpreted to depict a customer's 'willingness to pay'.

The principal difficulty is that the willingness of the customer to pay a certain price differs between customers, between countries and even for the same customer in different settings (depending on his/her actual and present needs) so that "true" value-based pricing at all times is impossible (110).

Healthcare markets and healthcare delivery systems will undergo tremendous changes in the coming years and this change will be on a global basis (111,112). The demands in the global healthcare market reflect powerful demographic and lifestyle trends which require new preventive, therapeutic and diagnostic systems and technologies. New innovative regenerative medicine technologies will make a shift in disease management and preventive medicine (113). The aim of a positive and sustainable change has prompted investors to concentrate not only on financial performance but also on operational strength and clinical quality in firming up their capital investment agenda (114).

Also, healthcare providers continuously confront changes that directly affect their operational and financial performance. Therefore, due diligence for these new therapeutics should focus on identifying risks and opportunities beyond those for conventional businesses.

Currently the reimbursement pathways in place in the UK healthcare system may act as a barrier to the adoption and diffusion of products into clinical practice. The issues with the current system have been recognised by the authorities responsible for pricing within healthcare, including the Department of Health and the National Institute for Health and Clinical Excellence (NICE), and a new system of medicine and treatment pricing, the ‘Value-Based Pricing’ introduced into the UK January 2014.

The main authority responsible for reimbursement in the UK healthcare system is the National Institute for Health and Clinical Excellence, or NICE. The most important functions of NICE are the appraisal and evaluation of new medical products, the development of quality standards and the development of clinical practice guidelines. NICE also has in place processes to identify new products that may have an impact upon the NHS, enable evidence of clinical and cost effectiveness to be collated to inform judgment on the value of treatment and issue guidance on whether a treatment can be recommended for routine use by the NHS (115).

It has well been reported (116,117,118,119,120) that NICE are considered to have difficulty accepting high up-front costs for new technologies which may be a particularly relevant barrier to the adoption of regenerative medicines into the UK healthcare system.

The current NHS targets appear to be more focused upon improving patient throughput and cost effectiveness than quality of care, and that price is a much more significant driver of decisions than in other healthcare systems (121). The UK healthcare system, including NICE, may prioritise cost effectiveness over clinical utility (117). This characteristic may affect the likelihood of innovative products, such as cell therapies, being used in the clinic and reaching patients.

The analyses of new technologies and treatments which NICE perform, known as Health Technology Appraisals (HTA's), provides the basis for most reimbursement decisions in UK healthcare. These HTA's could be viewed as a method of 'rationing' reimbursement and informing resource allocation decisions (122) and this could be considered to be one of the most important functions of HTA's (123).

Further concerns have recently been raised regarding local healthcare purchasing decisions. In the past, once a product had been recommended for general use by NICE, after the completion of an appraisal, Primary Care Trusts (PCT's) were obliged to make funding available in order to purchase the technologies (124).

The main component of these HTA's, performed by NICE, is cost-effectiveness analysis. In order to calculate how cost effective a new therapy may be NICE must determine the 'incremental cost per QALY' of the new product. Quality-Adjusted Life Years, or QALY, is a measure of "the quantity and quality of life generated by healthcare" (125).

A QALY is a time-adjusted health utility which considers both quantity and quality of life generated by the overall healthcare practice. Quantity is expressed in terms of life expectancy and quality is depicted on the basis of Health-Related Quality of Life (HR-QoL).

The quantity of resulting life is expressed in years and the quality of life generated is expressed in health utilities, with 0 representing death and 1 indicating perfect health. There has been some criticism to the use of the QALY as it does not take into account patient variation, ability to live independently for longer, or return to work after treatment (126). Therefore, as cell therapy products may involve or result in such characteristics, the applicability of this unit is questionable. This was explained (117) that it may be difficult to quantify the reimbursable value of cell-based therapies using QALY as improvements in patient function and utility, and the reduced need for expensive care or equipment as a result of these therapies, is not accounted for in the QALY model.

Once the QALY of the new product has been specified, it is then compared to that of the current gold standard treatment and the difference is calculated (Δ QALY). The difference in cost between the current gold standard and the new therapy is then calculated and this is divided by the change in effectiveness, or Δ QALY. From these calculations, an 'incremental cost effectiveness ratio', or 'incremental cost per QALY', is established. Finally, in order to decide whether this new product is cost effective and whether a recommendation for reimbursement will be considered, the incremental cost per QALY is compared to the Willingness to Pay (WTP) threshold (127).

Willingness to pay for a novel therapeutic:

A novel cell-based therapy as a therapeutic addition or substitution to the current treatment modalities of sensorineural hearing loss is likely to have a place as a potential therapy if there was a reimbursement plan in place for these cellular products. This will help to achieve products' income and adoption by patients and clinicians. Cost effectiveness remains a critical factor along with appropriate medical evidence. For this the Willingness to Pay (WTP) measure will give a fair idea of the patient base and the gatekeepers involved in adoption of a cellular product for treating hearing loss.

Factors effecting 'Willingness to Pay' for a new hearing therapy:

Willingness to Pay (WTP) is necessary to estimate demand for such a cellular product in terms of its market potential and the related cost-benefit analysis. It is the maximum amount of money that may be contributed by an individual and/or a payer to adopt a therapeutic change that should be able to identify the associated benefits (128). This would be established by going through the background information available, clinical trial data and the comparative efficacy of the proposed technologies. Approval by regulators and adoption by gatekeepers will add to the confidence and thereby increase the associated WTP. On the other hand this will encourage patients who have or at risk of developing hearing loss to consider undergoing the procedures for the stem cell therapy.

Due to the socio-economic impact of sensorineural hearing loss on patients and their quality of life, if the stem cell therapy delivers cost-effective quality adjusted life years (QALY's) with a robust reimbursement procedure in place, it would not only be beneficial to patients but also economically efficient.

In the United States alone the individual lifetime costs for severe to profound hearing loss are approximately \$297,000 and in adults aged more than 60 years the corresponding figures were approximated to be on average \$43,000 (129). A major proportion of these losses are due to decreased productivity at work and the requirement of hospitalisation, and additional special education resources, mainly amongst children. Further, lifetime costs for those with pre-lingual onset exceed a million US dollars (130). Disability levels amongst hearing impaired patients vary widely and the patients suitable for a cell therapy will be younger than average and will have a better quality of life post treatment. Therefore, restoration of hearing loss and its removal of resultant disabling conditions through development of improved treatment methods must remain a priority.

In the UK the willingness to pay threshold (WTP), according to NICE, is between £20,000 to £30,000 per QALY. The cost per QALY of the new therapy must be below this threshold to be considered cost effective. In recent years there has been much controversy surrounding this NICE threshold. It has been indicated that the value of QALY is not consistent throughout the NHS and that the value may vary throughout the country (127). There is also debate as to whether, and how, this threshold should change, and there is significant support for both an increase and decrease to the current WTP threshold. Any change to the NICE cost effectiveness threshold could have a substantial impact upon future reimbursement decisions and adoption of the new cell therapies into the NHS. Any increase to the threshold would be beneficial to regenerative medicine products; however, if the threshold were to be decreased, translation of cell therapies from the laboratory to the clinic could be hindered further.

Aims of Value-Based Pricing (VBP):

As mentioned above, a new pricing scheme for medicines will be introduced into the UK healthcare system as of January 2014, this is a 'Value-Based Pricing' (VBP). It aims to improve patient care and outcomes, improve value for money of treatments, facilitate more efficient use of resources, allow better access to medicines, stimulate innovation and account for a broader range of factors, other than cost effectiveness, when pricing medicines (131). VBP also aims to avoid setting a high cost for medicines which will only have moderate benefit (132).

The principles of VBP are to price treatments based upon the price at which the customer values a product relative to other products. It has been suggested that pricing new products based upon the perceived value of customers is an ideal method (126). It has also been suggested that a new definition for VBP would explain setting a "price that reflects value to patients, carers, society and the economy which delivers health benefits that exceed the health predicted to be displaced elsewhere in the NHS and in welfare, due to their additional cost".

VBP should account for the benefits of products that are exhibited throughout the patient journey and set a price for products that ensures the increased health benefits of the new treatment are greater than other health issues that will be affected or lost as a result of directing more funds into the new product and away from other departments within the healthcare system (133).

As VBP pricing will change the way in which medicines are priced and reimbursed, the cost effectiveness threshold used by NICE should be changed according to the need and requirement of the new therapy; however, the introduction of VBP may see a shift from a predominantly NICE threshold method to a Government determined threshold and price setting method based upon clinical need and disease burden. This new price setting method may introduce more definite and system wide prices, reducing uncertainty which was associated with cost per QALY threshold (134); however, NICE will remain

central to reimbursement decisions (121) and will be given powers to account for savings beyond the borders of the healthcare system when assessing cost effectiveness.

The new Value Based Pricing scheme will try to integrate other factors, not only cost effectiveness, into the Health Technology Appraisals HTA's and will consider these factors when making reimbursement decisions. The new method of analysis will again use a basic cost effectiveness threshold, set by the Government; however, this threshold will be flexible and could be altered depending on how the product addresses factors concerned. It needs to be accurate so that the future evidence base for the new therapies cannot be damaged.

The factors that are currently used and to which effective threshold may be altered depending on:

1. A new therapy that demonstrates greater therapeutic innovation and improvements compared to the current gold standard of treatments.
2. Burden of illness: A new therapy that treats diseases where there is a greater burden of illness. The more the therapy targets clinical need it will reflect more on the threshold which then will be increased accordingly.
3. A new therapy that demonstrate wider societal benefits outside of healthcare

The burden of the illness and the clinical need for a new therapy could be particularly relevant to cell-based therapies. If companies begin to target these areas and conditions then the price and reimbursement they receive could be greater than in past reimbursement systems. It is also plausible that the regenerative nature of these therapies could provide more realistic prospects of treating rare conditions for which there is no current cure. Regenerative medicines have the capacity to improve quality of life, which may improve patient function and utility, and therefore reduce burden of illness and need for expensive care and equipment (117).

Also, more weighting would be given to therapies that demonstrate an improvement on the current commonly used treatments. This could increase prices obtained for cell-based therapies and regenerative medicines.

The third factor for which weighting is being considered relates to the wider societal benefits that may occur as a result of a new therapy. It may be obvious to suggest that, due to the usually shorter treatment period when using regenerative medicines compared to other methods of care, their use could shorten the length of hospital stay, the length of nursing time and better directed resources according to need (135) and, thus, reduce healthcare expenditure. Also, the increased absenteeism, reduced worker capacity and worker productivity, as a result of chronic disease, could be much improved using the new cell therapy (136). This will lead to an overall decrease in the loss of the country's economic output due to improved health and reduced disease that significantly affects social and economic welfare.

Impact of Hearing Loss on Quality of Life:

It is estimated that in England and Wales some 8.1 million individuals currently have a hearing impairment. There are 2.8 million who have an impairment of 45 decibels or more in both ears which is the average level that prompts a referral for further care. Hearing disorders requiring therapeutic options are associated with a significant impact on quality of life. Impaired hearing results in social, psychological, cognitive and health effects. Regardless of their aetiology and type, hearing impaired individuals endure anxiety, self-doubt and depression all contributing to social isolation and withdrawal thereby affecting their overall successful ageing. The Hearing Disabilities & Handicap Scale (HDHS) and Hearing Disability Score (DIS) indicate that the most important indicator for life satisfaction is the social support network, followed closely by the handicap score (137). Lack of effective communication and speech intelligibility are the primary reasons for restricted social support amongst hearing impaired individuals. Amongst professionals and those who are still a part of the workforce uncorrected hearing loss can

have a negative impact on their respective job efficacy which might further lead to loss of employment and, therefore, overall functional health status.

The effect of hearing loss on the cognitive function in adult population

In a large prospective observational study (138), it has been shown that hearing loss is independently associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults. Participants were enrolled in the Health ABC (Health, Ageing, and Body Composition) Study (139) a prospective observational investigation started in 1997-1998 that enrolled 3075 well functioning older adults aged 70 to 79 years demonstrate that hearing loss is independently associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults. The magnitude of these associations is clinically significant, with individuals having hearing loss demonstrating a 30% to 40% accelerated rate of cognitive decline and a 24% increased risk for incident cognitive impairment during a 6-year period compared with individuals having normal hearing. On average, individuals with hearing loss would require 7.7 years to decline by 5 points on the 3MS (a commonly accepted level of change indicative of cognitive impairment (140,41) vs 10.9 years in individuals with normal hearing.

Audiometric testing was administered in year 5 (2001- 2002) of the Study. Participants were followed up for 6 years. Of 2206 participants who underwent hearing testing, 1984 older adults (mean age, 77.4 years) had no evidence of cognitive impairment (defined by a Modified Mini-Mental State Examination [3MS] score of 80), and these participants comprised the analytic (baseline) cohort.

Their results are consistent with prior research demonstrating significant associations between greater hearing loss and poorer cognitive function on verbal cognitive tests(142,143,144) and nonverbal cognitive tests (142,143,145) and in cross-sectional and prospective studies (145).

Hearing loss is independently associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults. Further studies are needed to

investigate what the mechanistic basis of this association is and whether hearing rehabilitative interventions could affect cognitive decline.

Proposed Potential Treatment Options of Stem Cell Therapy:

Following on from previous chapters 2 and 3, regarding possible use of stem cell therapy as potential future treatment for deafness, and the suggested chart using the Warren Algorithm (chapter 2) to apply for possible causes of hearing loss in particular sensorineural hearing loss, and also the translational process and outcome of survey study of the clinical community in the UK (chapter 3) in particular, the response is that stem cells would be an adjuvant treatment to a cochlear implant.

From a clinician's aspect specialised in Ear Nose and Throat diseases:

The suggested possible use of stem cell therapies could be applied to addressing the defect in each possible disease that causes the hearing loss and damage. As we have seen previously, the commonest defect that causes hearing loss is the damage of the hair cells; in particularly the outer hair cells and then the inner hair cells, and also their associated neurones, and because there is no regenerating capacity to these cells damages are usually permanent. Therefore, stem cell therapy could be potentially used as future treatment targeting the following defective scenarios:

1. Hair cells (outer and inner cells)
2. Supporting cells
3. Associated neurones
4. Combinations of above (1,2,&3)
5. As Adjuvant to Cochlear implant, plus No. 1
6. As adjuvant to Cochlear implant, plus No. 2
7. As adjuvant to Cochlear implant, plus No. 3
8. As adjuvant to cochlear implant, plus No. 4
9. Replace current treatments (cochlear implant, brainstem implants and hearing aids)

We therefore propose applying the above possibilities to the following diseases as potential targets for stem cells therapy to correct or replace these defective areas:

1. **Presbycusis** (age-related hearing loss): Stem cells could be used to replace and regenerate dead outer and inner hair cells (1), to replace and regenerate supporting cells in the organ of Corti (2), to replace and regenerate their associated neurones (3) and to work as combinations of these together (4). However, stem cells would not be suitable to support the cochlear implant (5-8) as a treatment for presbycusis as in the current financial market it would be extremely difficult to offer a cochlear implant as a treatment for these groups of people. Also, these patients are usually old and have other co morbidities that might make surgery difficult in this age group; however, should stem cell therapies be available as a commercial competitive treatment option in the future it would be an ideal treatment to help millions of people with presbycusis.
2. **Noise-induced hearing loss**: Sensorineural hearing loss due to noise damage could be helped by stem cell therapy to replace and regenerate the outer and inner hair cells in the basal turn of the cochlea (tonotopic organisation) where the main damage starts before involving other parts of the cochlea. This is why the higher frequencies of hearing threshold are affected first, before other frequencies, because of the tonotopic organisation of the cochlea. Stem cell therapy would be able to regenerate or replace these cells or their associated neurones. Stem cells could be used as an adjuvant to cochlear implant in this group of patients. However, these patients may be driven and interested by financial compensation matters rather than hearing restoration.
3. **Childhood deafness**: As mentioned in previous chapters childhood deafness is either due to genetic or environmental causes. Genetic causes are either syndromic or non-syndromic, and there are many genetic syndromes and non-syndromes diseases. These groups of people would need gene therapy if available to treat the defective gene, as well as a possibility of cochlear implants. Stem

cell therapy would be a potential future treatment for these groups of patients as a treatment to replace damaged hair cells or neurones, but more as an adjuvant to cochlear implants to improve hearing across the whole of frequency thresholds of hearing.

Cochlear implants work on the principle of transforming sound into an electrical signal which stimulates the ganglion cells and cochlear nerve. Cochlear implant systems consist of internal and external components. A microphone and sound processor are worn externally behind the ear. The sound processor is connected to a transmitter coil which is worn on the side of the head. Data from the transmitter coil is passed to a receiver-stimulator package which is implanted into a surgically fashioned depression in the mastoid bone. The receiver-stimulator translates the data into electrical pulses that are delivered to an array of electrodes. These are placed surgically within scala tympani of the cochlea (146). The electrodes stimulate spiral ganglion cells that innervate fibres of the auditory nerve. The activation of electrodes provides a sensation of sound but does not restore hearing. So the more available and viable neurones and cells would make cochlear implants more successful and efficient and this is where potential stem cell therapy would be of great help as it provides and regenerates diseased neurones and cells. This would support proposed management options from (1 to 9).

4. **Auditory neuropathies AN (Neuropathic Deafness):** The primary deficit in this type of deafness is due to a defect in the auditory nerve, impairing the transfer of hearing stimuli to the central pathways. It has an incidence of 10-14% of the profoundly deaf population. It has been reported that the incidence of auditory neuropathies could be as high as 40% of this group of the profoundly deaf population. There is currently no drug-based treatment for this type of deafness and the only therapy available is cochlear implantation; which has a very limited role here as it works on the principle of stimulating viable neurones. Therefore, the restoration of even a fraction of a few numbers of spiral ganglion neurones by cell-based therapy will have a significant clinical impact.

Stem cell therapy could be used as a treatment option targeting neurones, or as an adjuvant to cochlear implant, or replace current treatment of implants; therefore management options number (3, 7 and 9).

5. Hearing loss due to ototoxic medications, post infections and meningitis:

These groups of patients suffer with sensorineural hearing loss. In case of damage due to ototoxic medications such as Gentamicin or Streptomycin, these medications have a narrow therapeutic index and can enter the perilymph and then the endolymph of the cochlea causing sensorineural hearing loss due to damage of the outer hair cells of the basal turn of the cochlea and later the inner hair cells. Ototoxicity has now been identified to be genetically associated with mutation of the gene A1555 G mitochondrial on 12S Ribosomal RNA. Stem cell therapy could be used in this group of people to replace or regenerate damaged outer hair cells, as well as the inner hair cells, and their associated neurones. Stem cell therapy could also be used as an adjuvant to cochlear implant in these patients. Therefore, stem cell therapy could be used as management options (1 to 9). This would also be a management option for patients post-meningitis and other infections that cause sensorineural hearing loss.

Value Costs and Factors Affecting Cochlear Implant Effectiveness:

- As we have mentioned in previous chapters the cost of a cochlear implant in the UK healthcare system is estimated to be around £40,000 (NICE) for a unilateral implant and the cost of cochlear implantation in the first three years around £70,000 for bilateral implantation to include assessment, surgery and an extensive rehabilitation program afterwards for the cochlear implant to be successful.
- The cochlear implant industry is worth \$410 million at present with an average single procedure cost, including evaluation, surgery, device and rehabilitation, standing at approximately \$40,000 (147).

- Though the procedure is reimbursable it requires patient adaptation time of between 18-24 months as the implants restore hearing by a non-biological mechanism. This further deters the patients from undergoing the procedure (148)
- The implant is surgically embedded and provides a sense of sound, picked up by a microphone, by stimulating the nerve fibres in the scala tympani. The receiver and stimulator, secured in bone beneath the skin, convert the sound signals received through the speech processor into electric impulses. These impulses are relayed through an internal wire to multiple electrodes which send the impulses to nerve fibres in the scala tympani. The signals are then directed to the brain through the auditory nerve system.
- Rehabilitative therapy post-implantation is vital to ensure success (149).
- Patient variables for instance are hearing history, age of onset, age at implantation, linguistic abilities and availability of oral language development support and impact on the overall benefit provided by these implants (150).
- There are factors that are related to the device itself such as reliability, manufacturing and specification issues.
- Cochlear implants may need a second further procedure to replace the implant or replace the battery of it.

Anticipated future increase in effectiveness:

We anticipate that the cost of potential future stem cell therapy could be anywhere between £10-50,000. We have estimated this figure dependent upon available data and pricing for other regenerative medicine-based products that are currently available. These products range from:

- Regenerative medicine-based products cost per unit of Apligraf (Dermal Skin Equivalent) is around GBP 3,825 (for maximum course treatment): UKMI data.
- Infuse (bone graft consisting of a recombinant protein rhBMP-2 (human bone morphogenetic protein-2) and a sponge of bovine Type 1 collagen is estimated to be around USD 8,900 (Cage, sponge and BMP dose): Medtronic data.

- Carticel (autologous cultured chondrocytes for knee cartilage treatment) is estimated to be around USD 10,360 (culturing, growing, and shipping the cells): Brown University data.

These available figures are in the range of \$ 5000 to 10000 per unit. Given the lack of published economic data on clinical applications in RM, some of the parameters affecting these costs are bound to differ from each other. At present these costs are not seen to be representative of RM development costs due to different underlying technologies and processes for product development, different sample sizes for different applications and disease areas, number of investigational therapeutics and difference in costs on the basis of therapeutic class (151). For instance, estimations regarding the number of RM products in the market would depend on its rate of adoption, cost effectiveness and disease prevalence and, as we have discussed previously, in all disease categories stem cells therapy would have the ability replace or regenerate dead outer and inner hair cells or their associated spiral ganglion neurone. These hair cells and neurones are the most important factors for cochlear implant success and effectiveness; in fact a cochlear implant depends on availability of viable neurone and cells to function.

Therefore three main possibilities are discussed and further analysed by health sectors involved:

1. Stem cell therapy would increase efficiency of cochlear implants by providing large numbers of viable hair cells and neurone; therefore acting as an adjuvant to a cochlear implant.
2. Stem cell therapy may remove the need for subsequent further procedures to a cochlear implant and the cost associated with it.
3. There is clear and abundant evidence from the results of the literature review, discussed in previous chapters, that stem cells therapy could replace the need for a cochlear implant in the near future; once all obstacles are dealt with regarding issues of manufacturing, translations, adoption, and injections.

The table below (Table 1) shows that for each healthcare sector and the main proposed effectiveness of stem cell therapy, most of these proposed possibilities could benefit tremendously from stem cell therapy. We anticipate that stem cell therapy would be of great benefit, especially to society in particular, to a patient and their health Carer, to the NHS and also to commissioners and clinicians.

Health Group	Increase efficiency of C I, hear better across all frequency thresholds	Remove the need for further subsequent surgery	Replace the need for C I
GP, commissioners	No	Yes	Yes
NHS Health care Commissioners Reimbursers	No	Yes	Yes
Patients & Carer	Yes	Yes	Yes
Social care	Yes	Yes	Yes

Clinical Specialism	Yes	Yes	Yes
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Table 1 Anticipated Value-based Usefulness of Cell Therapy Per Healthcare Sector

Potential Savings in Future Costs to Healthcare Systems Using Stem Cell Therapy:

As we have indicated in figures above, in the United States the individual lifetime costs for severe to profound hearing loss is approximately USD 297,000 and in adults aged more than 60 years the corresponding figures were approximated to be on average \$43,000. A major proportion of these losses are due to decreased productivity at work and the requirement for additional special education resources; mainly amongst children. Further, lifetime costs for those with pre-lingual onset exceed a million dollar (129).

In the UK these figures (depending on current exchange rates) would be around £200K for the lifetime costs of profound hearing loss, £30K for the ageing population and £700K for the pre-lingual deafness lifetime costs.

The cost of cochlear implantation in the UK is around £70K for bilateral implantations (NICE).

The estimated cost of a tube of stem cell therapy is around £10K, as we have mentioned above (estimated cost compared to availability of other current cell therapy costs). We

also anticipate that the cost of surgery to inject stem cell therapy would be around £20K (compared to NICE figures about the cost of cochlear implantation).

Therefore we anticipate the estimated cost of stem cell therapy, to include manufacturing and injection, would be £30K.

The current cost of cochlear implantation is £40K for unilateral and £70K for bilateral implantation.

The cost of stem cell therapy treatment as an adjuvant to unilateral cochlear implantation is £30K + £40K= £70K and as an adjuvant to bilateral cochlear implantations would be £30K + £70K + £100K.

Therefore the potential future savings to the UK NHS healthcare system using stem cell therapy would be:

The current cost for each group – cost of stem cell therapy, ± cochlear implant:

◆£ 200K - £ 30K = £ 170K saving for the profoundly deaf population

◆£ 700K - £ 30K = £ 670K savings for the pre-lingual deafened population

◆£ 30K - £ 30K = No anticipated saving for old population

◆£200K - £70K (Stem cell therapy + Unilateral CI) = £ 130K saving for profoundly deaf population

◆£200K- £100K (Stem cell therapy + Bilateral CI) = £100K saving for profoundly deaf population

◆£700K - £70K (Stem cell therapy + Unilateral CI) = £630K saving for pre-lingual deafened population

◆£700K - £100K (Stem cell therapy + Bilateral CI) = £600K saving for pre-lingual deafened population

Table 2 below discusses the potential costs to each treatment modalities and anticipated future savings using stem cell therapy:

Costs	Stem cells including manufacturing £10K & Surgery to inject them £20K	Stem cells plus unilateral cochlear implantations £30K + £40K	Stem cells plus bilateral cochlear implantations £30K + £70K
Total cost	£30K	£70K	£100K
VBP cost for :			
Old population £30K	No saving	No Saving	No saving
Profound Deaf £200K	Yes Saving £170K	Yes Saving £130K	Yes Saving £100K
Pre-lingual Deaf £700K	Yes Saving £670K	Yes Saving £630K	Yes Saving £600K

There are further estimated potential savings for using stem cell therapy mainly related to saving of social care costs and also savings related to getting these people back to work. Disability levels amongst hearing impaired patients vary widely and the patients suitable for a cell therapy will be younger than average and may have a better quality of life post-treatment; therefore, restoration of hearing loss and the removal of resulting disabling conditions through development of improved treatment must remain a priority.

The restoration of normal function by providing adequate hearing could lead to cost benefits over time, due to the lack of, or delayed, requirement to treat and care for those patients. This will no doubt lead to savings by reducing the health and social care burden for the NHS and other systems globally. This would improve patient social care, by helping them to go back quickly to work and function, and certainly cut their social isolation. It will help their psychology and wellbeing.

The average annual salary of a working middle-aged person is around £30K, and the estimated working years in middle-aged people after going back to work and contribution to the society would be around 10 years. However, the working years for a child would be around 40 years. All calculations are done at current constant prices.

Therefore the anticipated benefits to the economy after successful treatment and returning these people back to work would be:

◆£30K X 10 years = £300K benefit in the middle-aged group

◆£30K X 40 years = £1.2M benefit for children

◆No benefit for old/non-working population

Table 3 below shows potential benefits to the economy and contribution to the society for each age group of the deafened population:

Average annual salary of a working middle class person is £30K.	
For middle-aged person	Benefits by working for extra 10 years $£30K \times 10 = £300K$
For child	Benefits by working for 40 years $£30K \times 40 = £1.2 \text{ Million}$
Old/Non-working population	No saving

Table 3 Anticipated benefits after treatment and contribution to society

Cost and Anticipated Changes to Hearing Aid Industry:

In the United Kingdom the Department of Health annual budget is estimated to be more than £200 million for the provision of hearing aids which is usually covered under the National Health Service. In the UK the estimated cost for a hearing aid is about £420 per patient (figures based at cost of providing a hearing aid at the Department of Otolaryngology, Leicester Royal Infirmary). Figures below show pathway and journey for the prescription of hearing aid(s) at the Leicester Royal Infirmary, Leicester for the year 2009-2010. See pathway below and table 2.

The global market for hearing aids is probably worth over £5.5 billion annually. Globally, however, the industry currently turns over \$8 billion, with the unit cost of a device ranging from \$1500 – 8000 with additional fees for professional services, testing, and fitting (147). In spite of the substantial scale of the industry and user base, there is low

compliance amongst users as only one in five patients who needs a hearing aid, actually uses one (152).

Future potential use of stem cell therapy could revolutionise the whole industry for hearing aids by completely replacing the need for them. In the large ageing populations that are increasingly becoming bigger and bigger due to improvement in healthcare life expectancy is longer, therefore a larger and larger population with presbycusis will need help with hearing. As discussed above, stem cell therapy would regenerate and replace dead hair cells in the outer and inner ear in the organ of Corti, and their associated neurons and ganglions so replacing the need for a hearing aid.

PATIENT JOUR- NEY	COST	TIME
INITIAL ASSESSMENT	£55.51	60 MINS
FITTING	£53.62	60 MINS
FOLLOW UP	£10.52	30 MINS
HEARING AIDS	£135.06	150 MINS
REPAIRS (6/12)	£16.7	15 MINS
REPAIRS (12/12)	£16.7	15 MINS
BAHA JOURNEY		
ENT CONS		

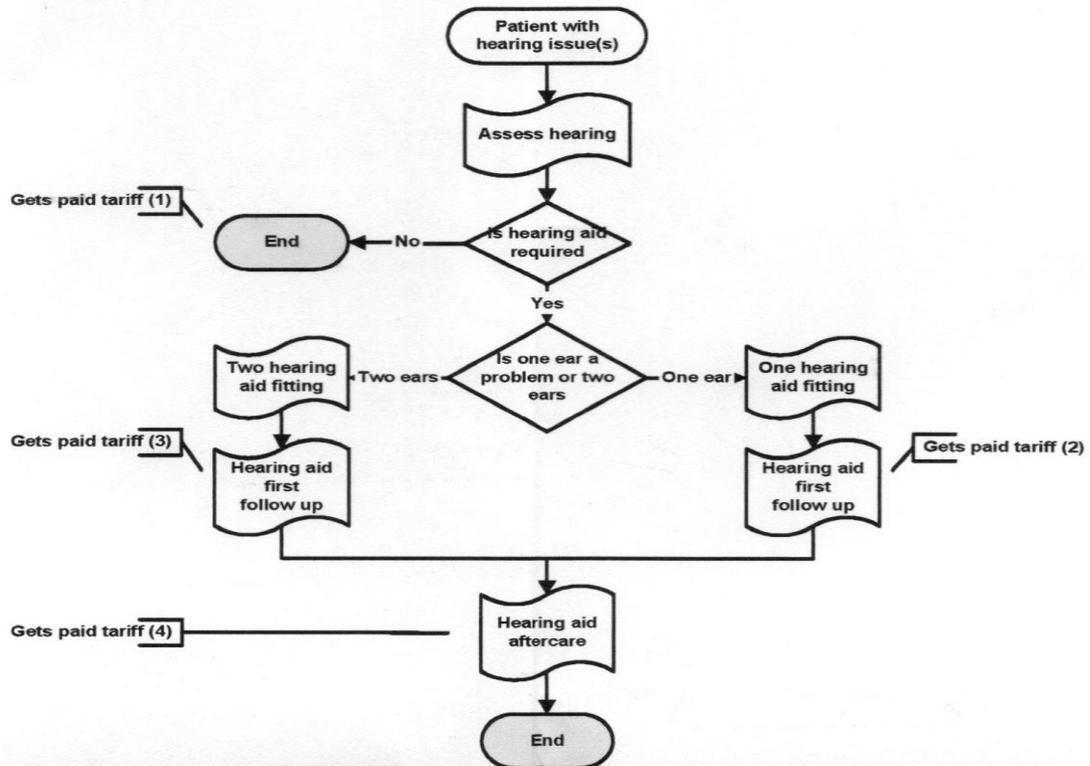
ASSESSMENT	4K	
THEATRE COSTS		
PROCESSOR	3K	7K

Table 2 Estimated cost of a hearing aid journey at LRI Department

Payment by Results

Adult hearing services non mandatory tariff 2009 / 2010

1. Pathway flow diagram



2. The non mandatory tariff are as follows,

Tariff (1)	Audiology hearing aid assessment only	£57
Tariff (2)	Pathway for hearing aid assessment, fitting of <u>one</u> hearing aid device, cost of <u>one</u> device & first follow up.	£ 285
	Breakdown as follows	
	Audiology hearing aid assessment	£ 55
	Audiology hearing aid fitting	£ 69
	Audiology hearing aid device	£112
	Audiology hearing aid follow up	£ 49
Tariff (3)	Pathway for hearing aid assessment, fitting of <u>two</u> hearing aid device, cost of <u>two</u> device & first follow up.	£397
	Breakdown as follows	
	Audiology hearing aid assessment	£ 55
	Audiology hearing aid fitting	£ 69
	Audiology hearing aid device (x2)	£ 112 + £ 112
	Audiology hearing aid follow up	£ 49
Tariff (4)	Hearing aid aftercare (based on ref cost AS3X – Hearing aid repairs)	£26

Note : Tariffs have been adjusted for annual uplifts

Effect of Value-based Pricing on future Potential Stem Cell Therapy:

The above two examples regarding the proposed treatment of stem cell therapy in regards to cochlear implant and hearing aid, and the possible advantages to health groups, indicates strongly that it is plausible to suggest that innovative technologies with regenerative capabilities, such as cell therapies, may diminish, treat or postpone the development of a disease, in particular sensorineural hearing loss, or attenuate the severity of the conditions and their symptoms. Prescott (135,136)) proposes that if regenerative medicines could repair or replace diseased or damaged cells, and potentially 'cure' disease or better manage the cause, this would diminish or delay the onset of associated conditions.

The restoration of normal function by providing adequate hearing could lead to cost benefits over time, due to the lack of, or delayed, requirement to treat and care for those patients. This will no doubt lead to savings by reducing the health and social care burden for the NHS and other systems globally.

This would improve patient social care, by helping them to return to work quickly and function and certainly cut their social isolation. It would help their psychology and wellbeing. Hearing disorders requiring therapeutic options are associated with a significant impact on quality of life. Impaired hearing results in social, psychological, cognitive and health effects. Regardless of their aetiology and type, hearing impaired individuals endure anxiety, self-doubt and depression all contributing to social isolation and withdrawal thereby affecting their overall successful ageing.

CHAPTER 5

Assessment of Hearing loss in children, Screening, Classification and management:

Hearing is essential for normal speech and language development. Early detection of severe hearing loss and appropriate management with hearing aids or cochlear implantation are essential, as the auditory pathway needs early stimulation for proper development. It is for this reasons that it is essential to have a screening programme in place for the early detection of hearing impaired infants.

Assessment of hearing is achieved by a number of objective and subjective tests. Pure tone audiometry is not possible until a child is 4-5 years old. Parental and school concerns regarding hearing are extremely valuable in raising awareness of a hearing problem.

Objective tests

These tests detect reflex response to sound and do not require any cognitive or behavioural response from patient

1. Tympanometry:

This is an important objective test of the middle ear function. The sound transmission from the external canal to the middle ear is optimal when the pressure in the ear canal is the same as the middle ear. It is an examination used to test the condition of the middle ear and mobility of the eardrum (tympanic membrane) and the conduction bones by creating variations of air pressure in the ear canal.

Tympanometry is not a hearing test, but rather a measure of energy transmission through the middle ear. The test should not be used to assess the sensitivity of hearing and the results of this test should always be viewed in conjunction with pure tone audiometry.

Tympanometry is a valuable component of the audiometric evaluation. In evaluating hearing loss, tympanometry permits a distinction between sensorineural and conduc-

tive hearing loss, when evaluation is not apparent via Weber and Rinne testing. Furthermore, in a primary care setting, tympanometry can be helpful in making the diagnosis of otitis media by demonstrating the presence of a middle ear effusion.

A tone of 226 Hz is generated by the tympanometer into the ear canal, where the sound strikes the tympanic membrane, causing vibration of the middle ear, which in turn results in the conscious perception of hearing. Some of this sound is reflected back and picked up by the instrument. Most middle ear problems result in stiffening of the middle ear, which causes more of the sound to be reflected back.

Admittance is how energy is transmitted through the middle ear. The instrument measures the reflected sound and expresses it as an admittance or compliance, plotting the results on a chart known as a tympanogram.

Normally, the air pressure in the ear canal is the same as ambient pressure. Also, under normal conditions, the air pressure in the middle ear is approximately the same as ambient pressure since the eustachian tube opens periodically to ventilate the middle ear and to equalise pressure. In a healthy individual, the maximum sound is transmitted through the middle ear when the ambient air pressure in the ear canal is equal to the pressure in the middle ear

A tympanogram is a graphic representation of the relationship of external auditory canal air pressure to impedance; the latter is usually reported in terms of tone of its derivatives, compliance in arbitrary units. Pressure in the external auditory canal is varied from -200 daPa through +200daPa while monitoring impedance. Impedance is lowest (maximal compliance) when pressure in the canal equals pressure in the middle ear. Ears can be classified into three basic groups on the basis of the configuration of the tympanogram.

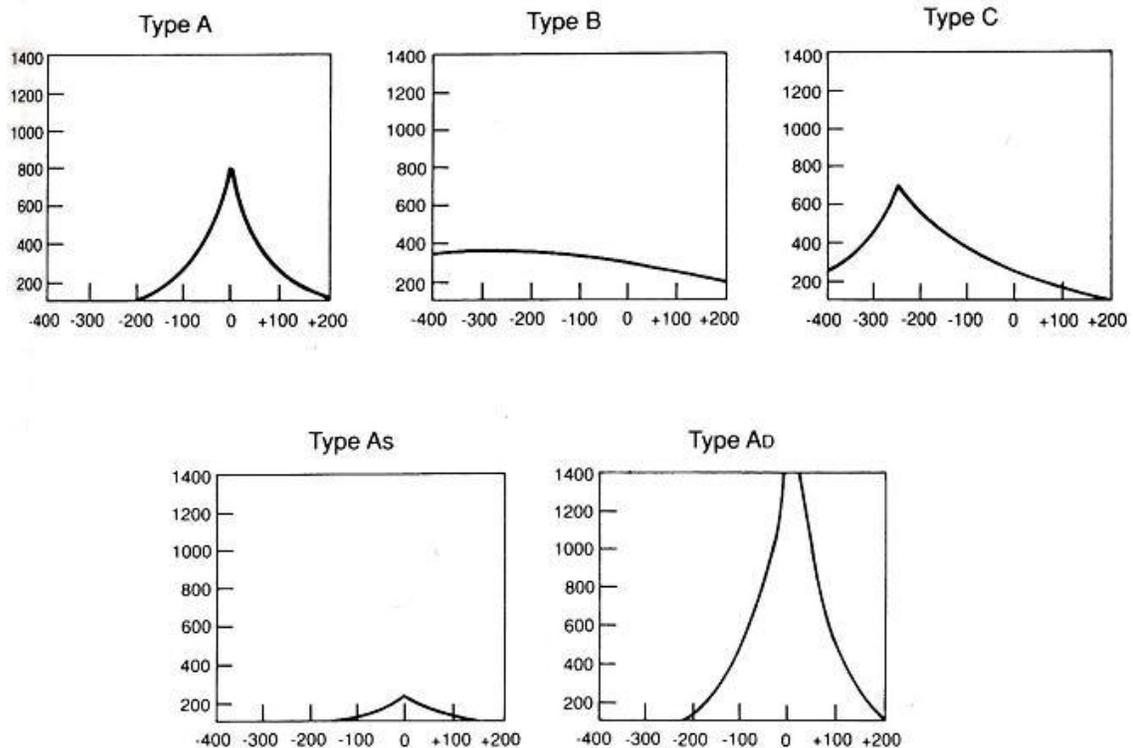
2. **Type A.** The peak compliance occurs at or near atmospheric pressure indicating normal pressure in the middle ear. There are three subgroups.

A - normal shape reflects a normal mechanism

AD - A deep curve with a tall peak indicates an abnormally compliant middle ear, as seen in ossicular dislocation or erosion, or loss of elastic fibers in the tympanic membrane.

AS - A shallow curve indicates a stiff system, as in otosclerosis.

3. **Type B** - No sharp peak, with little or no variation in impedance over a wide range, usually secondary to non-compressible fluid in the middle ear (otitis media), tympanic membrane perforation or obstructing cerumen.
4. **Type C** - Peak compliance is significantly below zero, indicating negative pressure (sub-atmospheric) in the middle ear space. This finding is often indicative eustachian tube dysfunction.

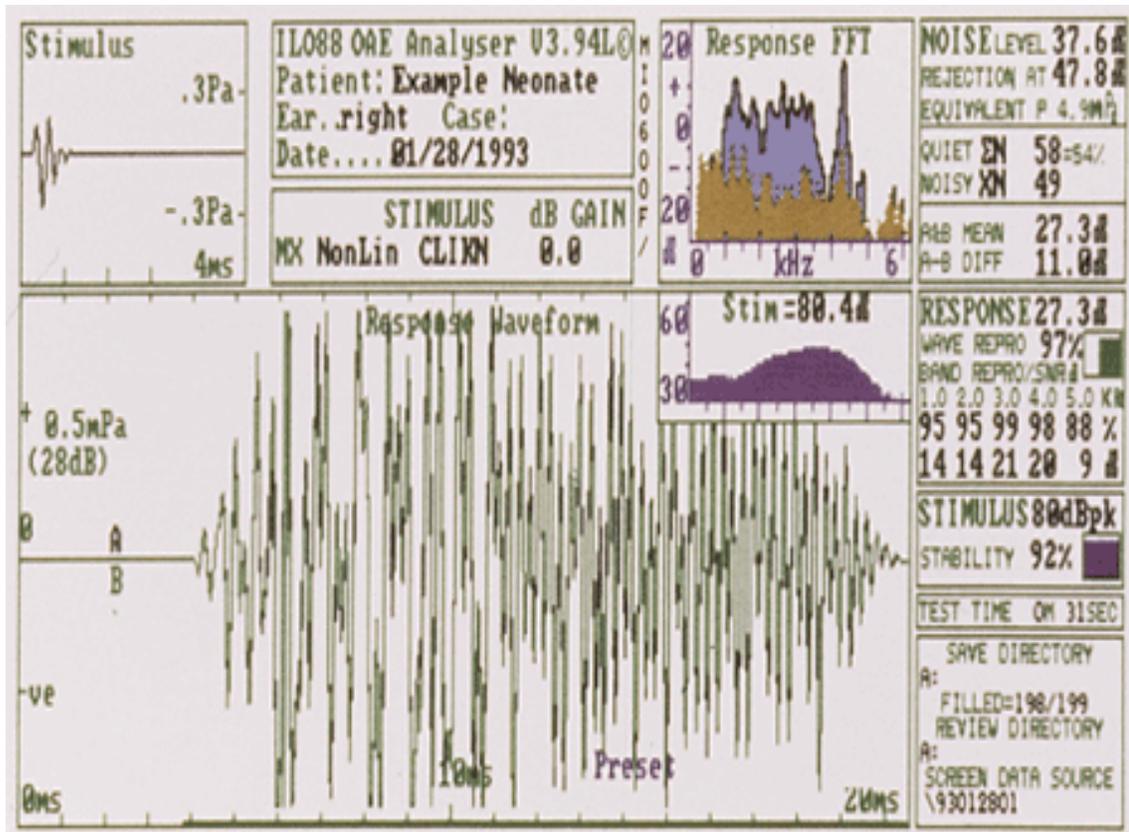


2- Oto-acoustic emissions

The primary purpose of otoacoustic emission (OAE) tests is to determine cochlear status, specifically hair cell function. This information can be used to (1) screen hearing (particularly in neonates, infants, or individuals with developmental disabilities), (2) partially estimate hearing sensitivity within a limited range, (3) differentiate between the sensory and neural components of sensorineural hearing loss, and (4) test for functional (feigned) hearing loss. The information can be obtained from patients who are sleeping or even comatose because no behavioural response is required.

Otoacoustic emissions (OAEs) are sounds of cochlear origin, which can be recorded by a microphone fitted into the ear canal. They are caused by the motion of the cochlea's sensory hair cells as they energetically respond to auditory stimulation. OAEs provide a simple, efficient and non-invasive objective indicator of healthy cochlear function and OAE screening is widely used in universal new-born hearing screening programmes. As part of the audiological diagnostic test battery, OAEs can contribute to differential audiological diagnosis, they can be used to monitor the effects of treatment and they can be helpful in the selection of hearing aids and of surgical options. As a research tool, OAEs provide a non-invasive window on intracochlear processes and this has led to new insights into the mechanisms and function of the cochlea and also to a new understanding of the nature of sensory hearing impairment.

Otoacoustic emissions (OAEs) are sounds which arise in the ear canal when (paradoxically) the tympanum receives vibrations transmitted backwards through the middle ear from the cochlea. These vibrations occur as a by-product of a unique and vulnerable cochlear mechanism which has become known as the 'cochlear amplifier' and which contributes greatly to the sensitivity and discrimination of hearing.



Oto-acoustic emissions

OAE recordings are made *via* an ear canal probe which is deeply inserted into the ear canal. Click stimuli of around 84 dB SPL peak equivalent (p.e) level normally evoke a robust TEOAE response only if hearing threshold is 20 dB HL or better (153,154,155). Unlike other audiometric tests, it is not necessary for the stimulus to be near to threshold levels to detect departures from normal function using OAEs. Middle ear status affects OAEs and can prevent their detection (156).

The oscillatory sound pressure waveform seen in TEOAE responses actually corresponds to the motion of the eardrum being pushed backwards and forwards by fluid pressure fluctuations generated inside the cochlea. The sealing of the ear canal by the probe increases the recorded OAEs' sound pressure below 3 kHz, as otherwise drum vibrations would simply move air in and out of the ear canal. The response is long and

complex because responses from different parts of the cochlea arrive at the ear canal at different times and at different frequencies. Although clicks are ‘wide-band’ stimuli, exciting the whole of the cochlea, TEOAE responses can give a frequency specific indication of cochlear status (157), by splitting the response into frequency bands after recording. Separate responses from different parts of the cochlea are obtained. TEOAE responses are strongest and easiest to detect in the primary speech frequency band, 1–4 kHz. In young ears, TEOAEs extend up to 6–7 kHz(152), but many clinically normal adult ears give weak TEOAEs (less than 3 dB SPL), with no substantial response above 4 kHz.

The normal cochlea does not just receive sound; it also produces low-intensity sounds called OAEs. These sounds are produced specifically by the cochlea and, most probably, by the cochlear outer hair cells as they expand and contract. OAEs could not be measured until the late 1970s, when technology created the extremely sensitive low-noise microphones needed to record these responses.

The 4 types of otoacoustic emissions are as follows:

- Spontaneous otoacoustic emissions (SOAEs) - Sounds emitted without an acoustic stimulus (ie, spontaneously)
- Transient otoacoustic emissions (TOAEs) or transient evoked otoacoustic emissions (TEOAEs) - Sounds emitted in response to an acoustic stimuli of very short duration; usually clicks but can be tone-bursts
- Distortion product otoacoustic emissions (DPOAEs) - Sounds emitted in response to 2 simultaneous tones of different frequencies
- Sustained-frequency otoacoustic emissions (SFOAEs) - Sounds emitted in response to a continuous tone

3- Evoked response audiometry (ERA)

Evoked (Electrical) response audiometry records the bioelectrical potentials that arise in the auditory pathway in response to sound stimulation. These bioelectrical potentials have very small amplitude, and they are difficult to separate from other neural activity. To achieve this, the summation of different responses to multiple stimuli is used to enhance the auditory response and cancel other electrical background activity.

ERA does not require patient's active cooperation, and the complex tracing obtained must be interpreted by the tester. There are three types of ERA:

- Electrocochleography
- Auditory brainstem response
- Cortical electrical audiometry

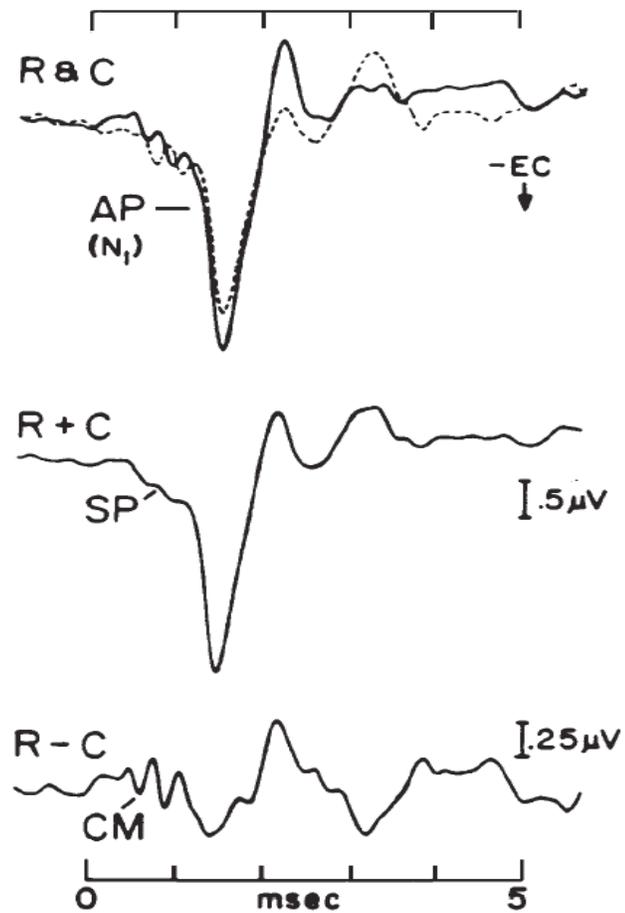
Electrocochleography: (ECOG) is a technique of recording electrical potentials generated in the inner ear and auditory nerve in response to sound stimulation, using an electrode placed in the ear canal or tympanic membrane. The test is performed by an otologist or audiologist with specialised training, and is used for detection of elevated inner ear pressure (endolymphatic hydrops) or for the testing and monitoring of inner ear and auditory nerve function during surgery.

The most common clinical applications of electro-cochleography include:

- Objective identification and monitoring of Ménière's disease and endolymphatic hydrops (EH)
- Intraoperative monitoring of auditory system function during surgery on the brainstem or cerebellum
- Enhancement of Wave I of the auditory brainstem response, particularly in patients who are hard of hearing
- Diagnosis of auditory neuropathy

A resting endolymphatic potential of a normal cochlea is + 80 mV. There are at least 3 other potentials generated upon cochlear stimulation:

- Cochlear microphonic (CM)
- Summating potential (SP)
- Action potential (AP)



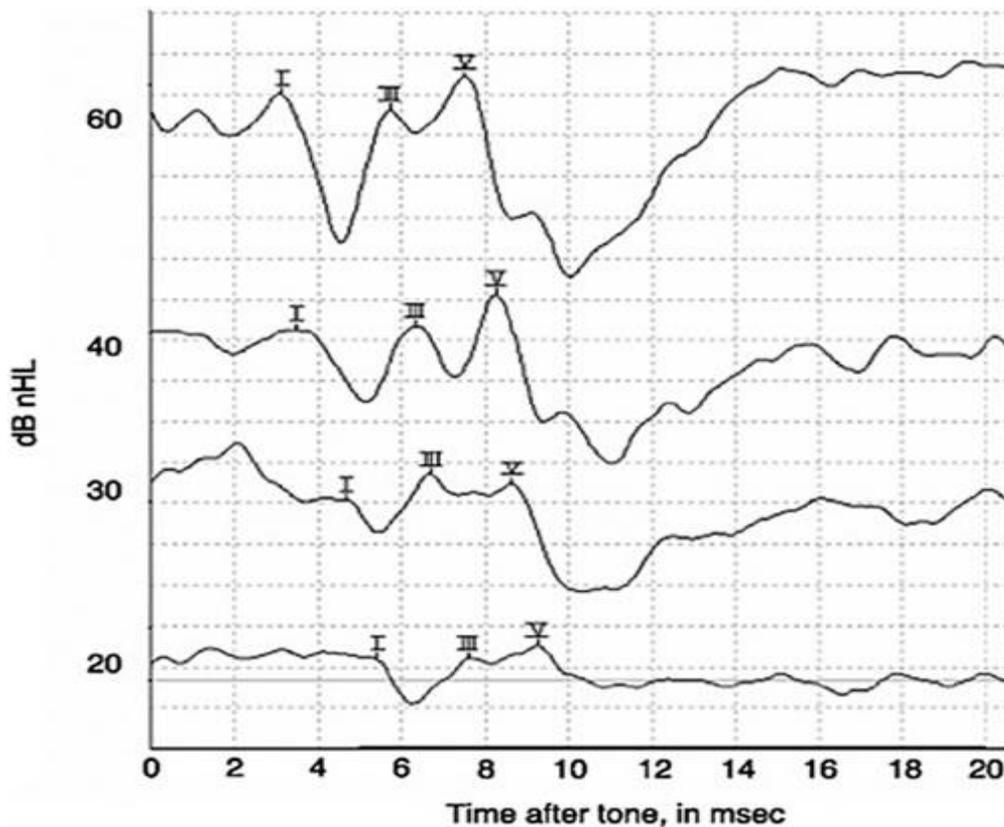
Electrocochleography

Auditory brainstem response (ABR):

ABR is a neurologic test of auditory brainstem function in response to auditory (click) stimuli. ABR audiometry is the most common application of auditory evoked responses. Test administration and interpretation is typically performed by an audiologist.

The most common applications:

- Threshold determination, especially in children in neonatal screening, can detect threshold but not frequency specific.
- Acoustic neuroma diagnosis. Latency wave I-V > 4.2 ms
- Intra-operative testing



Auditory brainstem response

Cortical electrical audiometry (CERA):

Measures the electrical response to a sound stimulus in the cortex and subsequently the entire auditory mechanism.

Clinical applications:

- Threshold determination CERA is the best of these three tests to determine thresholds across all frequencies.
- Assessing central problems

Subjective tests:

These tests require cooperation from the child, therefore; they are age, cognitive and motor function dependent. All subjective testing require at least two testers. The best results are achieved at paediatric hearing assessment centres, where appropriate time and expertise are available for each individual child's need.

Newborn/neonatal hearing screening:

Since 2005, all UK babies are screened for congenital hearing loss. This occur in the first few days after birth. It is performed by specially trained screener usually a paediatric nurse. It involves two objective tests:

- Oto-acoustic emission
- Auditory brain response test at 30db.

If they fail either test in either ear then they are referred to a paediatric audiologist for a more detailed evaluation including brain stem evoked responses.

Hearing Tests in children:

Children age 6-24 months: Distraction tests:

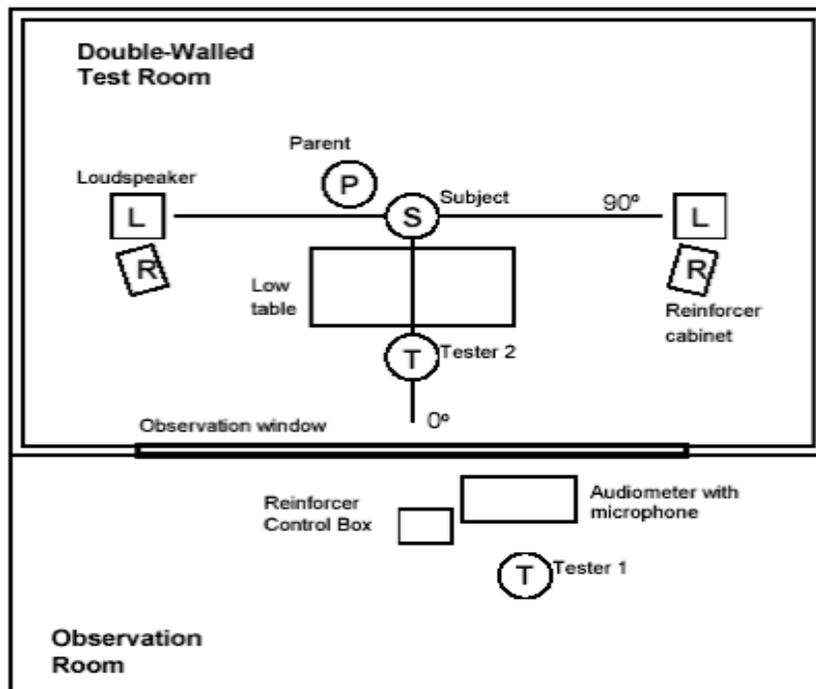
Performed in an appropriate paediatric audiological setting with experienced paediatric testers. This test can be used to screen for hearing loss and gives an estimate of thresholds in the better hearing ear.

The child sits at a table on his or her parent's lap. Tester one also sits at a table playing with the child. Tester two introduces sounds of varying intensity to one side and behind

the child. A positive response is denoted by the child turning to the sound. More frequency specific information can be obtained using a sound-generating box producing warble tones.

Children age 6-24 months: Visual response audiometry:

This is performed in the same setting position as for distraction testing. Tester one distracts the child whilst tester two presents pure tones at calibrated loudness levels, free field via a loud speaker in front of the child, or with two speakers either side. A positive response with correct turning towards the noise is rewarded by a light flashing or a toy moving on top of the speaker.



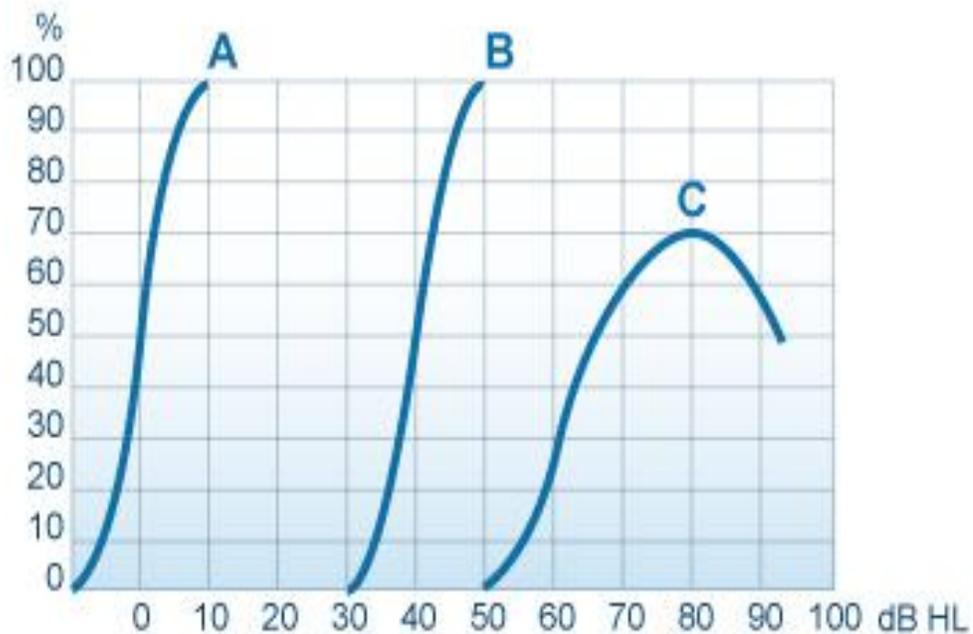
Visual response audiometry

> 24 Months : performance / play audiometry:

This technique is essentially like pure tone audiogram but instead of a child pressing a button when hear the sound, they are conditioned to perform a task such as put the marble in the cup. It can be performed free field or with head phones.

2 – 5 years : Speech audiometry:

This technique involves children pointing to or picking up the relevant toy when asked to show me the ... the toys are tested so that they cover a range of speech patterns. The words can be presented at varying volume intensities free field or with head phones. One example is the McCormick toy test.



Speech audiometry

A- represent normal hearing

B- Conductive hearing loss

C- Sensorineural (reto-cochlear) hearing loss

Speech audiometry has become a fundamental tool in hearing-loss assessment. In conjunction with pure-tone audiometry, it can aid in determining the degree and type of hearing loss. Speech audiometry also provides information regarding discomfort or tolerance to speech stimuli and information on word recognition abilities.

In addition, information gained by speech audiometry can help determine proper gain and maximum output of hearing aids and other amplifying devices for patients with significant hearing losses and help assess how well they hear in noise. Speech audiometry also facilitates audiological rehabilitation management.

> 5 years: Pure tone audiometry:

Pure tone audiometry (PTA) is the key hearing test used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss. It provides the basis for diagnosis and management. PTA is a subjective, behavioural measurement of hearing threshold, as it relies on patient response to pure tone stimuli. Therefore, PTA is used on adults and children old enough to cooperate with the test procedure. As with most clinical tests, calibration of the test environment, the equipment and the stimuli to ISO standards is needed before testing proceeds. PTA only measures thresholds, rather than other aspects of hearing such as sound localization. However, there are benefits of using PTA over other forms of hearing test, such as click auditory brainstem response. PTA provides ear specific thresholds, and uses frequency specific pure tones to give place specific responses, so that the configuration of a hearing loss can be identified. As PTA uses both air and bone conduction audiometry, the type of loss can also be identified via the air-bone gap. Although PTA has many clinical benefits, it is not perfect at identifying all losses, such as 'dead region. This raises the question of whether or not audiograms accurately predict someone's perceived degree of disability.

This test assesses sensitivity when the signal is transmitted through the outer, middle, and inner ear and then through the brain to the cortex. Testing may be performed using headphones, insert earphones, or sound fields.

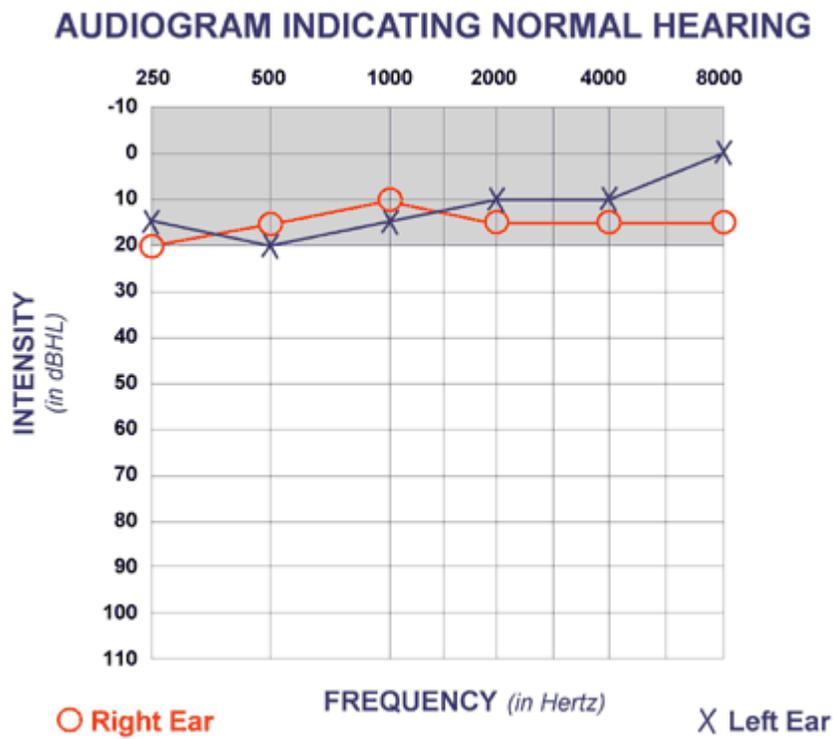
Headphones are placed over the outer ear. Circum-aural headphones have a large cushion and fit around the ear, contacting the head. These generally are used to reduce ambient noise. Supra-aural headphones are more common and rest on the ear or pinna, but they typically provide no ambient noise reduction and may collapse the ear canals.

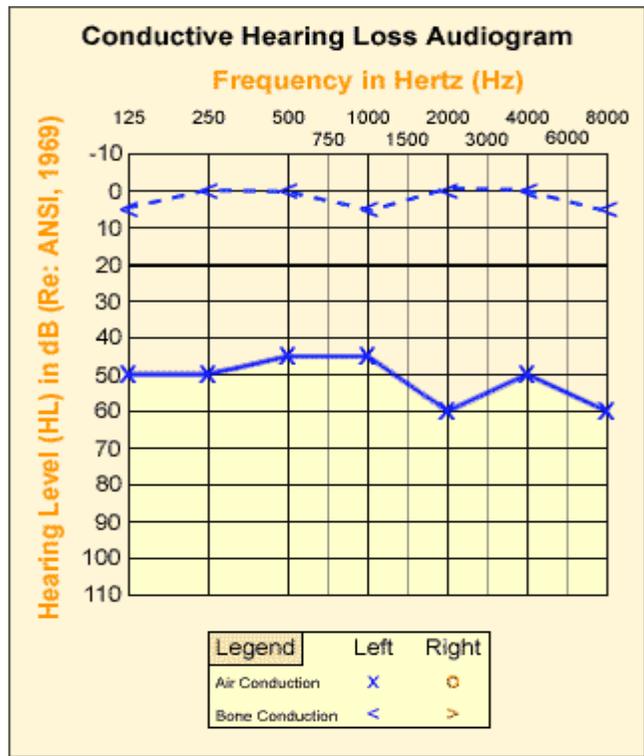
Insert earphones are transducers housed in a small box approximately 2" by 3" by 0.5". The signal is transmitted down a tube to foam tips, which fit in the ear canal. Insert earphones help reduce collapsing ear canals, and they reduce ambient noise and crossover of auditory stimuli to the non test ear via skull transmission.

Sound-field (free-field) testing signals are presented via speakers, usually at a 45° azimuth to the patient's face. This form of testing is used with infants, toddlers, and other individuals with special needs for whom earphone use may be problematic. During sound-field testing, an individual sits in the centre of the room, facing forward, halfway between each speaker. Typically, visual-reinforcement audiometry (toys light and animate when the child responds to sound); conditioned-orientation response audiometry (toys on both sides test localisation); or play audiometry (various games, eg, dropping a block in response to sound) are used. These conditioned responses to auditory stimulus provide reinforcement that allows for measurable responses and longer interest in the test situation.

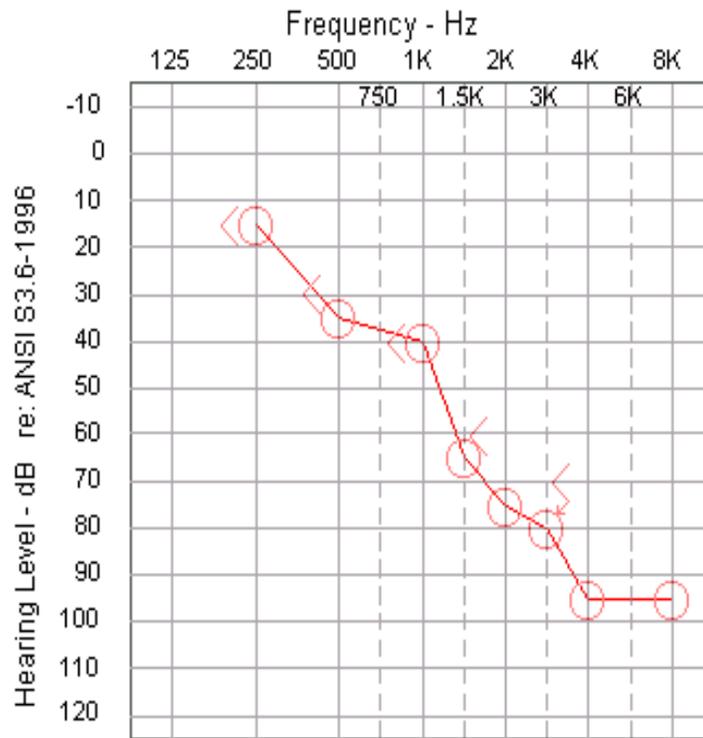


Pure tone audiometry





Sensorineural Deafness



Hearing depends on the function of specialised sensory cells in the cochlea of the inner ear, the hair cells. These cells are mechano-electrical transducers that generate action potential in the auditory nerve that leads to hearing. Damage or loss of these cochlear hair cells leads to many types of congenital and acquired hearing loss.

As reported previously in chapter 1, the incidence of congenital deafness is about 1 in 1000 born children and is usually detected by universal neonatal screening a further 1 in 1000 children become deaf before adulthood, and parental or school concern may raise awareness of these children. 4 in 10000 children are born profoundly deaf (1-3).

Management of congenital hearing loss

The management of congenital hearing loss requires a multidisciplinary approach including:

- Paediatric audiologist
- Otolaryngologist
- Paediatrician
- Teacher of the deaf
- Speech therapist
- Parents
- Deaf community
- School involvement

Investigation

50% of congenital deafness are caused by environmental factors, and 50% are caused by genetic factors.

The investigations vary depending on whether the hearing loss is present at birth or late onset.

Failed neonatal screening

- If a child fails neonatal screening, they referred to a paediatric audiologist for further testing
- If a severe hearing impairment is confirmed then the following management is recommended

Congenital hearing loss is due to either:

- a) Environmental causes; or
- b) genetic causes

A. Environmental Causes are:

Factors suggesting environmental causes of hearing loss include:

1. Poor maternal health or difficult pregnancy
2. Birth complication
3. History of perinatal infection, especially viruses like cytomegalovirus, or toxoplasmosis
4. Early children's diseases necessitate admission to Special Care Baby Unit (SCBU), or need assisted ventilation
5. Hyperbilirubinaemia or ototoxic medication

B. Genetic Causes are:

Sensorineural hearing loss (SNHL) is one of the most common birth defects. Genetic causes of SNHL can be found in half of pre lingual cases and the remaining half are ascribed to environmental or unidentified genetic factors

Factors suggesting genetic causes of deafness include:

- Hearing loss in First and second degree relatives
- Hearing loss in a relative occurring before the age of 30
- Consanguinity or parents from same ethnically isolated area

Examination

Examination of a child includes ear and general examination. The external, middle and inner ear should be examined looking for any abnormalities.

A complete physical examination should be performed by a paediatrician looking for features suggestive of syndromic hearing loss. A child with hearing loss should also have a development assessment. During examination it is important to look for abnormalities:

- Eye: colour, position, cataract, retinal findings
- Ear: skin tag, pre-auricular sinus, shape and size of ear, ear canal abnormalities
- Abnormal facial features
- Hair colour
- Shape of skull
- Neck abnormalities, large thyroid gland
- Skull shape
- Skin pigmentation

Infection screen

Screen for infection is very important, especially for **Cytomegalovirus (CMV)**. Cytomegalovirus (CMV) is the most common intrauterine infection causing hearing loss in the UK. It can cause wide range of general and intracranial problems and is found in up to 0.5% of all births. The most common environmental cause of SNHL is congenital cytomegalovirus (CMV) infection, with an estimated overall birth prevalence of approximately 0.3–2.4% (158). The vast majority (approximately 90%) of these infants exhibit no signs of congenital infection, which is asymptomatic at birth. Approximately 10% of infected infants are born with clinical symptoms of congenital CMV in-

fection. SNHL reportedly occurs in 22–65% of children with symptomatic congenital CMV infections and 6–23% of children with asymptomatic infections (159).

Late-onset and progressive natures are characteristic of SNHL with congenital CMV infection. The frequency of SNHL in children with asymptomatic congenital CMV infection is also uncertain. The gold standard for diagnosis of congenital CMV infection is the isolation of the virus from urine or saliva in the first 2 weeks of life. However, asymptomatic congenital CMV infection in children who develop late onset SNHL after 2 weeks of age cannot be diagnosed on the basis of viral isolation from urine or saliva. Detection of CMV DNA in infant blood or umbilical cord using polymerase chain reaction (PCR) assays is a more feasible method to identify children with late-onset of SNHL.

Other Investigations:

- Newborn heel prick: for thyroid Function test
 - Full blood count to exclude acute leukaemia
 - Lipid profile for hyperlipidaemia
 - Glucose for Diabetes
 - ESR for vasculitis
 - Toxicology for ototoxic drugs and chemicals
 - Screen for autoimmune disorder
 - Dipstick for haematuria
 - Metabolic screen
 - CT Scan of the temporal bone gives information regarding malformation of the external, middle and inner ear.
 - MRI scan to look for suspected neurological lesions such as congenital nerve abnormalities, and to determine the patency of cochlea following meningitis
 - ECG for abnormalities of Q-T interval as in autosomal recessive disorder Jervell Lange syndrome

Syndromic Causes of Hearing Loss:

1. Pendred's Syndrome:

Due to mutation of the pendrin gene on chromosome 7q31. This is an autosomal recessive type of inheritance that causes severe progressive sensorineural hearing loss and thyroid gland abnormalities such as goitre, hypothyroid or euthyroid status of the gland.

2. Usher's Syndrome:

Due to defective genes MYO7A, US1C and CDH23. An autosomal recessive disorder that causes profound hearing loss and progressive loss of vision due to retinitis pigmentosa. There are three clinical types.

3. Waardenburg Syndrome:

Autosomal dominant mode of transmission. Six genes identified for this syndrome that cause sensorineural hearing loss and pigmentation problems such as heterochromia iridis (different coloured eye irises) and hair colour abnormalities. There are four types of Waardenburg syndrome. It may also present with limb abnormalities and Hirshsprung's disease (intestinal abnormalities).

4. Alport syndrome:

This is inherited as an autosomal dominant, recessive or X-linked. Defective collagen type 4 causes abnormalities in the basement membrane of inner ear, kidney and retina. Presentation with SNHL, microscopic haematuria and ocular abnormalities. Three genes have been identified: COL4A3, COL4A4, COL4A5.

5. Branchio-oto-renal syndrome:

An autosomal dominant disorder characterised by variable hearing loss which may be sensorineural, conductive or mixed. Different malformation of the ears and kidneys may also occur. Two genes are identified for this syndrome: EYA1 and SIX1 responsible for the regulation of embryonic development of these organs.

6. Neurofibromatosis NF2:

This is an autosomal dominant disorder due to a defective gene responsible for tumour suppression function on chromosome 22. This leads to the formation of different types of tumours, typically bilateral vestibular Schwannoma's (benign tumours of the 8th cranial nerve responsible for hearing), meningioma's of the brain and spinal cord and eye lens abnormalities.

7. Down's syndrome:

Commonest syndrome, it has an incidence of one in 1000 births. Caused by trisomy 21. Characterised by varieties of facial feature abnormalities such as eyes up-slanting, palpebral fissures, ears typically small low set pinnae and narrow ear canals. Hearing loss can be sensorineural, conductive or mixed.

Non-syndromic Hearing Loss:

1. Connexin 26:

Due to Gene defect GJB2 (Gap Junction B2 protein) on chromosome 13. Most common and first identified non-syndromic hearing loss.

2. A1555G mitochondrial mutation:

This causes predisposition to amino glycoside toxicity due to mutation of the A1555G gene. It accounts for 15% of all amino glycoside-induced deafness.

In children the most common cause of conductive hearing loss is due to otitis media with effusion (glue ears):

This is inflammation of the middle ear and collection of thick mucinous secretions in the middle ear cavity. Risk factors for the development of this may be due to recurrent upper respiratory tract infections, anatomical abnormalities such as cleft palate, parental smoking, bottle-feeding and atopy. Males are more affected than females. There is bi-

modal peak age of presentation with the first peak at 2 years of age in up to 40% of children being affected by otitis media with effusion, and a second peak at 5 years of age with an incidence of 20% (36).

Chronic suppurative otitis media (CSOM), with or without cholesteatoma, is another cause of conductive hearing loss. CSOM without cholesteatoma is characterised by chronic ear discharge with a tympanic membrane perforation and hearing loss which is usually conductive in nature but a sensorineural component may co-exist. It has a prevalence of 0.6% in the adult population. Common causative pathogens are bacterial infection secondary to *Pseudomonas aeruginosa*, *Staph.aureus*, and *Proteus* species.

Cholesteatoma with chronic suppurative otitis media is a serious condition.

Cholesteatoma can be defined as a skin (or keratin) in the wrong place, i.e. in the middle ear. It has an incidence of 6 cases per 100000 of population; with a slightly higher figure for children. It can be congenital or acquired. Congenital cholesteatoma results from an abnormal focus of embryonic squamous epithelium in the middle ear space.

Sudden onset of sensorineural hearing loss (SSNHL):

The average age of patients presenting with SSNHL is 11 years 2 months (22 months-18 years).

Aetiology of SSNHL is unknown in 30% of cases presented, viral (30%), due to an anatomic abnormality (20%), endolymphatic hydrops (10%), autoimmune (5%), perilymphatic fistula (5%), and suppurative labyrinthitis (5%). Eight patients had initial treatment with oral steroids of which 50% had improvement on audiograms. The true incidence of SSNHL is unknown. Younger children may be unable to express hearing loss. Unique aspects of paediatric SSNHL are delayed presentation and higher percent of anatomic findings. In our study, 70% presented more than 2 weeks after experiencing symptoms. Anatomic abnormalities are in 20% of patients. Hearing improvement occurred in 50% of children treated with oral steroids. Intratympanic steroid treatment is another option but may have practical limitation in the paediatric population (160)

SNHL develops due to loss of cochlea hair cells or their associated neurons. Lost hair cells are neither replaced by cell division nor regeneration from endogenous cells present in the inner ear epithelium rendering SNHL an irreversible condition. There is little mortality risk factor associated with SNHL, a non-fatal disease, but there is a very high disability factor (37,38), which makes this disorder a good potential candidate for a novel RM based therapeutic modality. Sensorineural hearing loss may be congenital or acquired.

Current modalities of treatment:

1. Ventilation Tubes (Grommets) insertion:

The current treatment in children with otitis media with effusion (glue ears) is insertion of a ventilation tube. The procedure is usually carried out after a period of watchful wait of about three months.

2. Hearing aid:

The hearing aid is an electro-acoustic device. A microphone converts the external acoustic signals into electrical energy which is received by an amplifier to increase its amplitude and then transmits to the receiver. The receiver converts the modified electrical signal back into acoustic signal that is directed towards the inner ear.

In the United Kingdom the Department of Health annual budget is estimated to be more than £200 million for the provision of hearing aids, which is usually covered under the National Health Service. In the UK the estimated cost for hearing aids is about £420 per patient (figures based at cost of providing hearing aids at the Department of Otolaryngology, Leicester Royal Infirmary). The global market for hearing aids is probably worth over £5.5 billion annually.

Globally, however, the industry currently turns over \$8 billion, with the unit cost of a device ranging from \$1500 – 8000 with additional fees for professional services, testing, and fitting (147). Globally, most of these devices are not covered by private and

Government health insurance and only certain hearing tests and services are covered under Medicare, a U.S. Federal Government programme of health assistance for people aged 65 and older in the United States. Some reimbursement is available in Europe in the public medical service sector, though accompanied by long waiting lists. Likewise, in Japan, hearing impaired people may receive public support for the purchase of hearing aids through the local welfare office on a special handicap identity card. In spite of the substantial scale of the industry and user base, there is low compliance amongst users as only one in five patients who needs a hearing aid, actually uses one(152).

Longer HA use related to older age, poorer hearing, and higher maternal education. Parental consistency ratings revealed similar findings—younger children and children with milder HL wore HAs less consistently than older children and children with more severe HL. Parents' estimates and data logging were significantly correlated; however, results suggested that parents overestimate the amount of time their children wear their Hearing aids (161)

3. Cochlear Implant:

In the UK the National Institute of Clinical Excellence (NICE) 2009 recommends that a cochlear implant in one ear is recommended as a possible option for everyone with severe to profound deafness if they do not get enough benefit from hearing aids after trying them for three months. Cochlear implants in both ears are recommended for the following groups with severe to profound deafness only if they do not get enough benefit from hearing aids after trying them for three months and the implants are placed during the same operation:

- children
- adults who are blind or have other disabilities which mean that they depend upon hearing sounds for spatial awareness.

The cochlear implant team should carry out an assessment to find out if an implant would help before they consider a cochlear implant. They should take into account any disabilities or difficulties in communicating which might mean that the usual hearing

tests are not suitable. In such cases they should consider other methods for testing hearing. A later operation to place a cochlear implant in the second ear is only recommended for the following groups if they already had a cochlear implant in the other ear when the guidance was issued:

- children
- adults who are blind or have other disabilities which mean that they depend upon hearing sounds for spatial awareness.

In all cases, if more than one type of cochlear implant is suitable, the least expensive should be used. Costs should include the cost of the implant and the support package and how reliable the system is. When an implant is placed in a second ear during the same operation the cost for the second implant should include currently available discounts on list prices of 40% or more.

The estimated cost of cochlear implantation in the first three years is around £70000 to include assessment, surgery and follow up. The cochlear implant industry is worth \$410 million at present with average single procedure cost, including evaluation, surgery, device and rehabilitation, standing at approximately \$40,000 (147). Though the procedure is reimbursable it requires patient adaptation time of between 18-24 months as the implants restore hearing by a non-biological mechanism. This further deters the patients from undergoing the procedure (148). The implant is surgically embedded and provides a sense of sound, picked up by a microphone, by stimulating the nerve fibres in the scala tympani(162). The receiver and stimulator secured in bone beneath the skin convert the sound signals received through the speech processor into electric impulses. These impulses are relayed through an internal wire to multiple electrodes which send the impulses to nerve fibres in the scala tympani (163). The signals are then directed to the brain through the auditory nerve system. Rehabilitative therapy post-implantation is vital to ensure success (149). Further, patient variables for instance hearing history, age of onset, age at implantation, linguistic abilities, and availability of oral language development support impact the overall benefit provided by these implants (150).

4. Bone-Anchored Hearing Aids (BAHA) Surgery:

The Bone-Anchored Hearing Aid system (BAHA) is a hearing aid which uses the principle of bone conduction. In normal hearing sound may be transmitted to the inner ear both by air (through the external ear canal) or through the bones of the skull. In individuals who are unable to hear using air conduction, whether due to a congenital malformation of the ear canal or due to chronic ear infection, a hearing aid which utilises bone conduction is the most appropriate. The BAHA comprises a vibration transducer which is coupled to a titanium implant anchored to the temporal bone of the skull. Surgery is required for the placement of the titanium fixture. The BAHA system offers advantages over conventional bone conduction hearing aids. Conventional bone conduction aids require a transducer, placed on the opposite side of the head, to be held in place by a tight steel band and may cause problems with pressure effects (especially in children), an unnatural circumstance and loss of sound quality (164,165). The use of BAHA provides benefits both in terms of audiological tests and quality of life (166,167), and they may improve speech perception in noise and improved patient reported outcomes for unilateral sensorineural hearing loss, but no evidence of improved sound localisation (168,169,170,171).

The incidence of congenital atresia of the external auditory canal with associated middle ear abnormalities is estimated at 1 in 10,000 live births, with between 15 and 30% of these being bilateral (172).

No data was found on the prevalence of bilateral chronic suppurative otitis media which is severely exacerbated by air conduction hearing aids.

The average cost to insert BAHA's, including obligatory ENT and audiology follow up has been estimated to be £5,654 for adults and £8,453 for children.

The low compliance associated with electronic devices does not discourage their huge market, which suggests a novel cell based therapy as a therapeutic addition or substitution is likely to have a place as a therapy. To secure a place as part of routine healthcare therapeutics, an unencumbered reimbursement plan for cellular products may help and

guarantee product income and adoption by patients and clinicians. Cost effectiveness remains a critical factor along with appropriate medical evidence.

CHAPTER 6:

CONCLUSION:

Adoption of stem cell therapies, are we ready?

This chapter summarises the key research findings and contributions of this thesis, discusses the current available resources and limitations of the research outcomes in regard to stem cell therapy, and suggests areas for further work.

Because this research is exploratory in nature, its main contributions are new insights with explanatory power, rather than a statistically tested hypothesis.

Over the last two decades translational process has come to be recognised as a core issue for regenerative medicine. This is primarily due to the technically challenging, high-risk and capital-intensive processes required to get regenerative therapies into the clinic.

The social and economic demand for therapeutic treatment for hearing loss is enormous. Over the past recent years there has been remarkable progress in the research of stem cell therapy and the time has now come to move this research into the clinical part where millions of people could be benefited.

There is a clear therapeutic opportunity from a clinician's point of view to move the cell-based therapy from the laboratory to the clinical side. We are persuaded by the scientific evidence and discovery that has been made and the mileage in stem cell therapy that this is the right time for the pharmaceutical and biotechnology companies to take the initiative in this field.

As clinicians in Otolaryngology there is a clear clinical requirement to have a novel treatment for deafness based on the clinical evidence and reimbursement evidence to use a stem cell therapy; and it is extremely viable to try and marry clinical need with emerging putative technology and identify potential gaps that need bridging into each step of the process that apply to the use of stem cell therapies.

As the underlying science expands, translation issues need to be resolved and firms within the sector will have to actively extend their scope to focus on such issues to build a successful venture.

The research reported in this thesis was designed to address the necessary important steps needed in the translation and potential adoption process of this therapy from a scientific background, clinical community perspectives and the socio-economic analysis of this therapy compared to current conventional treatments. The understanding of these necessary mechanisms facilitate translation of scientific knowledge of stem cell therapy to be potentially adopted as future treatment of hearing loss particularly sensorineural hearing loss which could benefit millions of people all over the world.

Chapter 2:

This chapter discussed the developmental steps necessary to secure adoption of stem cell therapy in the context of the literature. This work examined the development steps necessary to secure adoption using the recently published Warren algorithm as an analogue of the clinical commissioners' approach in order to identify bottlenecks in the process.

The Warren et al Algorithm has been developed to allow commissioners to make yes/no decisions on funding from a clinical perspective; we have used it for the first time in our research here to structure a review of technology maturity and to identify some of the key issues from a developer's perspective. This algorithm would allow maturity and applicability of regenerative medicine to be judged by health preferential. This will assist health professionals in judging the maturity and applicability of regenerative medicine. In addition, this algorithm also helps evaluate new tests and treatments rapidly in order to decide whether they should be funded by an independent healthcare provider. It is intended that the algorithm is populated using information which is easily and quickly available in the public domain such that any new approach can be compared to

the current best care. This process is rapid and robust relying on a focus on clinical outcomes relevant to patients' care.

We have divided the algorithm into three main sub-divisions distinguishing maturity of evidence, disease and patients and accumulation of evidence.

The first sub-division that is related to the maturity of the evidence for stem cell therapies as a potential treatment for deafness shows that there is no licence available for stem cell therapies for deafness. This subdivision also show that there is no mature evidence that a treatment has been used and as yet there has been no a phase III trial. Sub-division 2 relates to different causes of deafness and current options of treatment available.

The third subdivision of the algorithm relates to the accumulation of the evidence showing that there is an increasing body of evidence to show biological plausibility; in particular the maturity of outcomes in animal models as a precursor to clinical trials. This is taking of the order of 20 years to secure and then the necessary effort to move from animal evidence to first in man paediatric trials. It has also shown the additional steps necessary to satisfy, accumulate and to secure routine clinical use.

Chapter 3:

This chapter addresses key steps in the translational process to potentially move stem cell therapy from the laboratory to the clinical side as a novel treatment for deafness taking the perspective of the expert clinical user rather than the clinical commissioner, a generalist.

The author carried out a study to explore the UK Ear, Nose and Throat community's perspective on such therapies using a 22 item questionnaire that was specifically created by authors for the first time.

The study shows that members of the clinical ENT community vary in their knowledge, awareness, attitude towards and support to stem cell therapies as a potential treatment

for deafness and that there is a clear requirement for further training in this field. There is clear indication that the knowledge of stem cell therapies within the clinical community needs to be increased as the majority of the clinicians completing the questionnaire (87%) indicated they had no or very little knowledge regarding the potential use of stem cell therapies to treat deafness. The study also shows that there is common agreement among respondents (>90%) that there is a requirement for a new treatment for deafness replacing current conventional treatment with hearing aids.

An essential step in the translational process is the alignment of the expectations of the clinical community with the direction of the scientific research community, and in particular whether stem cells should be pursued as an adjuvant therapy to CI, a combination therapy or as a therapy in their own right. Any alignment must take account of the clinical trials requirements, regulatory landscape and reimbursement conditions for such therapeutic alternatives – this requires more exploration of the socio-economic case for interventions.

Chapter 4:

This chapter discussed the financial aspects relating to future potential stem cell therapy to treat deafness. Hearing disorders requiring therapeutic treatment are associated with a significant impact on quality of life resulting in social, psychological, cognitive and health effects. Hearing impaired individuals endure anxiety, self-doubt and depression all contributing to social isolation and withdrawal; thereby affecting their overall well-being and productivity that leads to bigger financial burden on society and healthcare system.

The restoration of normal function, by providing adequate hearing, could lead to cost benefits over time, due to the lack of, or delayed, requirement to treat and care for those patients. This will no doubt lead to savings by reducing the health and social care burden for the NHS and other systems globally. This would improve patient social care, by

helping them to return to work quickly and to function and certainly cut their social isolation. This will help their psychology and wellbeing.

Financial analysis showed there are significant cost savings when using potential stem cell therapy for different health sectors, including NHS system commissioners, reimbursers, and General Practitioners, as well as to the social carer and clinicians. These identified newer approaches using a value-based pricing approach would favour therapies for early onset hearing loss because of the high consequential social care costs.

Chapter 5:

This chapter discuss hearing loss in children, classification of congenital hearing loss.

It also discusses causes and management of deafness in children in a multidisciplinary team approach.

Investigation of deafness and treatment modality available including hearing aids, cochlear implants and bone anchored hearing aids.

Screening for hearing loss and test available for this including objective and subjective tests are discussed in details, and rehabilitation for these children.

Summary Conclusion:

The evidence presented in this thesis and the evidence of the systematic review strongly supports the following:

1. Stem cell therapy would increase efficiency of cochlear implants by providing large numbers of viable hair cells and neurons; therefore acting as an adjuvant to cochlear implants; and
2. Stem cell therapy may remove the need for subsequent further procedures to a cochlear implant and the cost associated with it; and
3. There is clear abundant evidence from the results of the literature review that stem cells therapy could replace the need for a cochlear implant and hearing aids in the near future for some indications; and
4. Value-based pricing estimations to the potential stem cell therapy suggest that there are significant cost saving to the NHS health system and other systems globally adopting the new technology; and
5. Further work is needed, in particular corroborate and to build upon the initial clinical and economic assessments presented here; necessitating both further research to persuade potential adopters of biological plausibility and to be followed by clinical trials carried out in order to obtain better estimates of the clinical benefits and potential side effects; since the rate of adoption is dependent on these. Further investigations into the clinical effectiveness of the putative hearing therapy, when compared to alternative approaches in routine clinical practice and patient-related outcomes (such as health-related quality of life gains and reduction of social care costs), are needed to complement the findings on cost effectiveness and help reimbursement agencies make well-informed coverage decisions to patient benefit; and
6. Researchers, developers and suppliers must identify unmet clinical needs and channel resources towards investigating, exploring and developing corresponding therapeutics while keeping in mind the later translational and commercial challenges inherent in manufacturing and supplying such therapeutics. Innova-

tors must work in partnership with care delivery organisations and clinicians to develop products that improve therapeutic prognosis or offer an equivalent effect at reduced costs.

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