The PATH study: Preparing for the Adoption of innovative hearing THerapies

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DECLARATION

I, Dr Rishi Mandavia, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Background:

Innovative drug, gene and cell therapies are being developed to address the unmet clinical need of people with hearing loss. With approval for clinical use on the horizon in the next 5 years, it is essential to start preparing for the implementation of these therapies in hearing healthcare services.

Aim:

To provide stakeholders who develop, will use and pay for innovative hearing therapies, with a detailed understanding of the elements that influence their adoption and implementation and with practical strategies to facilitate their uptake in the UK healthcare system.

Method:

1) To inform product development and decisions on value for money, I constructed an early health economic model with input data from literature searches and 26 interviews.
2) To characterise and understand the elements that influence the adoption and implementation of innovative hearing therapies in the UK healthcare system, I conducted 37 semi-structured interviews drawing upon insights from the early health economic model.
3) To add to this understanding, I performed a hermeneutic review of elements that influence the adoption and implementation of innovative therapies in general.
4) To integrate the findings from my thesis, I constructed a framework that maps the elements that influence innovative hearing therapy adoption and implementation, and that summarises practical strategies to facilitate uptake.

Results

I found that alliances between clinicians, scientists, patients, biotechnology and hearing technology companies can facilitate adoption of innovative hearing therapies, benefitting

from pooled resources, diffusion networks and established market access. Timely clinician education can break down engrained clinical practices and gain clinician buy-in. Early engagement with patients can help ensure these therapies meet patient needs and generate patient and public interest, which can influence clinician uptake and policy decisions. Precision diagnostics are critical to the development and uptake of innovative hearing therapies; co-development strategies and novel regulatory pathways can accelerate their development. Accelerator organisations can help navigate healthcare systems, assist with manufacturing and distribution strategies, support clinical trialing, help develop business cases, and lobby decision makers. Additional insights revealed that novel payment strategies and robust business cases can help make procurement affordable and avoid delays in adoption. Real world data can increase confidence to take-up innovative hearing therapies, support payment strategies, early access programs and help fulfil regulatory requirements.

Conclusion

My research has resulted in a framework that can accelerate the uptake of innovative hearing therapies across healthcare systems. Stakeholders can use my framework to gain detailed information on the processes that need to take place for adoption and implementation of these therapies as well as strategies to facilitate these processes.

IMPACT STATEMENT

This is the first research project that has investigated adoption and implementation processes in the field of innovative hearing therapies (IHTs). Uniquely drawing upon health economics and implementation science, my thesis has resulted in the development of a framework that can be used to provide those who develop, will use, and pay for IHTs, with a detailed understanding of the elements that influence their adoption and implementation and with practical strategies to facilitate their uptake.

More specifically, my framework can be used to provide an understanding of how healthcare system environments can influence adoption and implementation and on how to navigate environments to facilitate uptake. It also provides an understanding of stakeholder perspectives and motivations on IHTs and how these can be influenced. It can be used to explore activities that can help prepare for IHT adoption and implementation before the therapy is ready to be released onto the market, as well as activities that can accelerate IHT uptake once the therapy is ready for assessment by decision makers. Stakeholders can use my framework to gain information on decision making processes that need to take place for IHT adoption as well as strategies to facilitate these processes. They can also use my framework to explore potential impacts and activities that can influence implementation processes once an IHT is introduced into the healthcare system. Importantly, my framework provides information on how real world data collection can be used to promote uptake as well as strategies to facilitate real world data collection.

Overall, my framework can be used to help accelerate patient access to IHTs and help reduce waste and disruption commonly associated with the implementation of innovative medical therapies. My framework can also be used to provide empirically based information that can inform and support initiatives that have been developed to accelerate the introduction of innovative therapies outside of the hearing domain, including for example the NHS Accelerated Access Collaborative (AAC) and the NHS Innovation Accelerator (NIA). With this in mind, my planned future research includes developing an electronic toolkit, based on the findings of my framework, and validated for use outside the hearing domain,

that will enable users across healthcare specialties to flexibility gain an understanding of the elements that influence innovative medical therapy adoption and implementation.

The framework presented in this thesis has been selected to feature in the Lancet Commission on Hearing loss to provide information on barriers and facilitators of novel hearing interventions, and will therefore benefit from wide readership, boosting potential impact. On a personal level, as a training ENT surgeon, I hope that my framework can help my hearing healthcare colleagues prepare for IHTs that are set to change our future roles as clinicians.

ACKNOWLEDGEMENTS

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Professor Carl May has been instrumental in my PhD fellowship, expertly helping me navigate through and learn about implementation science, qualitative research methods and theory development. His patience, positivity and enthusiasm for his subject area are a real inspiration to me, which I hope to emulate and pass on to my students in the future.

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WORD COUNT

The word count is 53233 words excluding Appendices and references.

ABBREVIATIONS

AAC	NHS Accelerated Access Collaborative
ABM	Agent-based modelling
ACF	Academic Clinical Fellowship
AdVisHE	Assessment of the Validation Status of Health-Economic decision models
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
ARC	Applied Research Collaboration
ATTC	Advanced Therapy Treatment Centres
ATMPs	Advanced therapy medicinal products
BCHD	Bone Conduction Hearing Device
BNF	British National Formulary
BRC	Biomedical Research Centre
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CRN	Clinical Research Network
CRO	Contract Research Organisation
CROS aid	Contralateral Routing of Signals aid
CtE	Commissioning through evaluation
DALYs	Disability adjusted life years
dB	Decibel
EAP	Early Access Programme
EI	Ear Institute
ENT	Ear, Nose and Throat
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EUnetHTA	European Network for Health Technology Assessment
FBC	Full blood count
FDA	US Food and Drug Administration

GBP	Great British Pound
GDP	Gross Domestic Product
GP	General practitioner
HL	Hearing loss
HRQoL	Health related quality of life
HTA	Health Technology Assessment
HUI-3	Health Utilities Index Mark 3
ICER	Institute for Clinical and Economic Review
IHT	Innovative hearing therapies
iNMB	incremental net monetary benefit
ISCT	In silico clinical trials
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research, Society for Medical Decision Making
IT	Intratympanic
i4i	NIHR Invention for Innovation (i4i)
KOL	Key opinion leader
MCDA	Multi criteria decision analysis
MDT	Multidisciplinary team
MEA	Managed Entry Agreement
MP	Member of Parliament
MTEP	Medical Technologies Evaluation Programme
MRI	Magnetic Resonance Imaging
NDA	Non-disclosure agreement
NHS	National Health Service
NIA	NHS Innovation Accelerator
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NPT	Normalisation Process Theory
PRIME	PRIority MEdicines
PROMs	Patient reported outcome measures
PSA	Probabilistic sensitivity analyses

RCT	Randomised controlled trial
QALY	Quality Adjusted Life Year
SAWP	Scientific Advice Working Party
SNHL	Sensorineural hearing loss
SRA	Sponsored Research Agreement
SSNHL	Sudden onset sensorineural hearing loss
TA	Technology appraisal
TAR	Technology Assessment Reviews
UCL	University College London
UCLH	University College London Hospitals NHS Trust
UMC	University Medical Center (UMC)
U&E	Urea and electrolytes
VDRL	Venereal disease research laboratory

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CHAPTER 1: INTRODUCTION TO THESIS

How this PhD fellowship came about

I am an Ear Nose and Throat (ENT) surgical trainee in London and since qualifying from medical school have received parallel clinical and research training via the Academic Foundation Programme, a National Institute for Health Research (NIHR) Academic Clinical Fellowship (ACF) as well as during this PhD Clinical Research fellowship. During my time as an ACF and positioned as an ENT clinical researcher within the University College London (UCL) Ear Institute (EI), I met and learnt from world-leading academics and clinicians aiming to further our understanding on hearing and develop treatments for deafness. I gained a particular interest into the emerging field of innovative hearing therapies (IHTs). This is a term used to describe novel drug, gene, cell, tissue-engineered or Advanced Therapy Medicinal Products (ATMPs)[*] that aim to address areas of unmet need by protecting, restoring or regenerating the hearing system. I recognised that this field has the potential to drastically change hearing healthcare services, as well as my future role as an ENT surgeon. To gain further insights I took the opportunity to become a Trial Delegate Principal Investigator for the REGAIN trial,[1] the first clinical trial of an IHT, as well as Associate Principal Investigator for the Audible-S trial,[2] investigating a first-in-class drug for sudden hearing loss. During these experiences I gained valuable insights into IHT development, testing as well as their potential practical use in healthcare systems. Reflecting on my experiences and discussions with industry, scientists, clinicians, and patients, within and outside the hearing field, I considered that whilst these innovative therapies may bring unique opportunities, their implementation into healthcare systems will present diverse and distinct challenges. I was enthusiastic to contribute to this area and started planning a PhD project that could help prepare the UK healthcare system for the successful uptake of IHTs. Building upon established collaborations with health economists at Radboud University

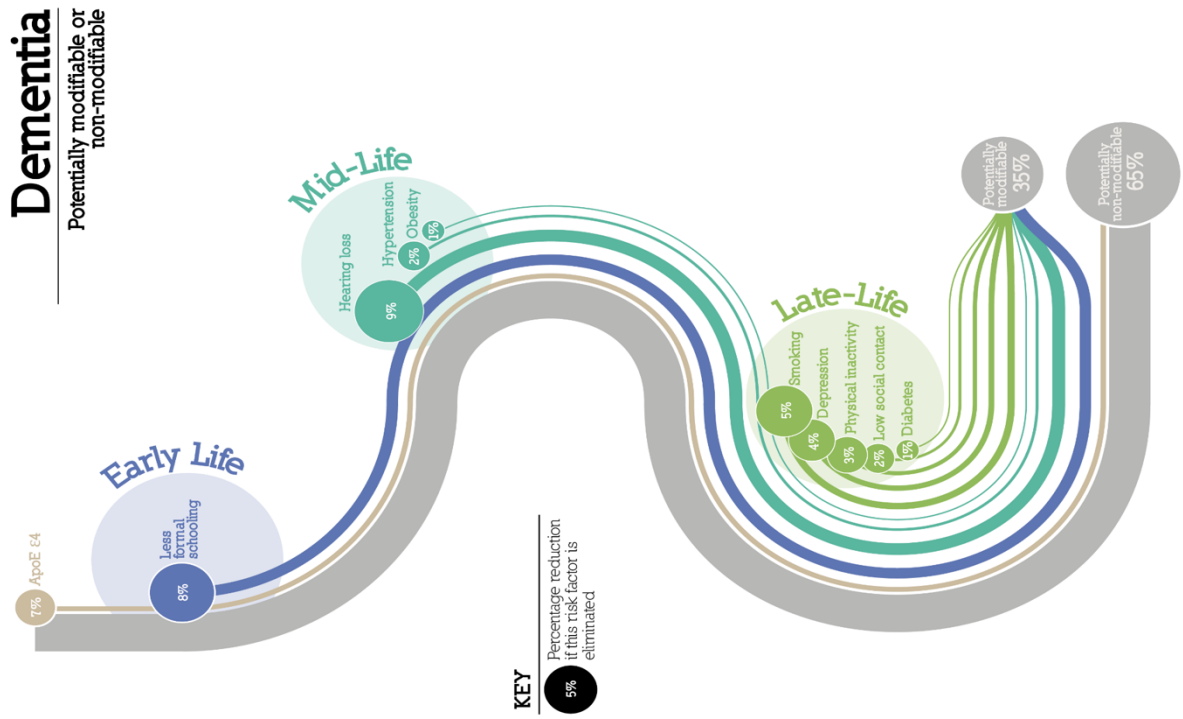
[*]Advanced Therapy Medicinal Products, are a heterogeneous class of medicinal products that includes products based on genes (gene therapy medical products), cells (somatic cell therapy medical products) or tissues (tissue engineering medical products)

Medical Center (UMC), I initially set out to develop an early health economic model that could be used by decision makers to decide which IHTs may represent value for money; and by industry to help inform product development and market access, thereby accelerating the adoption of valuable IHTs in the UK healthcare system. At the early stages of planning this research, it became apparent that successful uptake would be dependent upon numerous elements other than effectiveness and cost-effectiveness. I therefore sought expertise in the field of implementation science, utilising our department's position within the NIHR Applied Research Collaboration (ARC) North Thames. With expert supervision in the fields of IHTs, early health economic modelling and implementation science, I successfully secured funding for a PhD project that uniquely draws upon early health economic modelling and implementation science to provide a robust investigation of adoption and implementation processes in the field of IHTs. In this introduction I present an overview of the field of IHTs and provide context to the aims and objectives of my thesis.

Hearing loss

Hearing loss is a major international health problem with considerable personal, social and economic impacts affecting over 1.5 billion people worldwide.[3] The deaf-blind American author Helen Keller said in 1910, "blindness separates people from things, but deafness separates people from people."[4] Since then it has been established that the health and quality of life of people with hearing loss is poorer than that of the general population[5] and that hearing loss contributes to social withdrawal and isolation.[6] From an economic standpoint, the annual cost of hearing loss is significant, estimated to be over US $980 billion globally, primarily due to unemployment.[7] Recently, hearing loss acquired in mid-life has been identified as the most important modifiable risk factor for dementia (see Figure 1), with mild hearing loss doubling the risk and severe hearing loss increasing the risk of dementia five-fold.[8]

Figure 1: Potentially modifiable risk factors for dementia. Hearing loss acquired in mid-life carries the greatest potential for dementia risk reduction.[8]



The most common form of hearing loss is sensorineural hearing loss (SNHL), which describes damage or dysfunction of the inner ear, or the auditory pathways that connect the inner ear to the brain, and accounts for 90% of cases.[9] The main causes of SNHL are degenerative processes associated with aging, noise exposure, exposure to medications that can damage the hearing system, genetic mutations presenting at birth or in later life, as well as chronic conditions such as cardiovascular disease and autoimmune diseases.[9] Management of SNHL is currently limited to hearing aids and cochlear implants.[10,11] These devices benefit many affected people with hearing loss, but do not restore natural hearing and provide limited benefit for the understanding of speech in noisy environments, which remains the greatest unresolved problem in the hearing field.[11,12] Owing to this unmet need, and enabled by major discoveries in the genetic pathways and molecular mechanisms that underlie SNHL,[13,14] the last decade has seen the birth and development of the field of IHTs.[12,14,15]

Innovative hearing therapies (IHTs)

The field of IHTs is complex and rapidly evolving, driven by a growing number of biotechnology companies.[14–16] The latest 2021 estimates suggest 28 IHTs in clinical trials and at least 61 in the preclinical pipeline with development taking place globally across 50 institutions in the US, Europe, UK, Japan and Israel.[14–16] These therapies target different indications within SNHL, the mainstay of which include monogenic disorders, drug and noise induced, idiopathic sudden onset and age related SNHL. Monogenic causes of SNHL represent the majority of cases of genetic deafness and account for approximately 60% of deafness in newborns and can also result in delayed onset hearing loss.[16] There are currently 20 gene therapies in development, the most advanced of which are gene replacement therapies aiming to restore hearing in people with specific gene mutations.[15,16] Drug induced SNHL is most commonly caused by aminoglycoside antibiotics and platinum based chemotherapeutics that are toxic to inner and outer hair cells, resulting in permanent hearing loss.[17,18] There are currently 11 compounds in development intending to protect the hearing system from drug induced hearing loss, with 7 undergoing clinical testing in humans.[14] Noise induced SNHL contributes to one-third of hearing loss cases and appears to be increasing in prevalence particularly at younger ages owing to increasing noise exposure from common recreational activities.[19] Age related SNHL, also known as presbycusis, is a complex disorder that results from the cumulative effects of aging on the auditory system.[10] It is the most prevalent sensory deficit in the elderly with approximately half of adults in their seventh decade displaying hearing loss that is severe enough to impede communication.[20] Sudden onset SNHL (SSNHL) affects approximately 20 people per 100,000 each year and describes a rapid loss of hearing, usually in one ear and in the majority of cases, the cause is unknown (idiopathic SSNHL).[9] There are reported to be 10 therapies currently in development for noise induced SNHL, 11 for age related SNHL and 9 for idiopathic SSNHL.[14] The underlying pathologies of these indications may overlap, so experimental treatments that successfully demonstrate efficacy for one of these indications may provide a springboard to extended clinical studies for the other indications.[16,21,22]

Table 1 provides an overview of current IHTs in development, including companies developing IHTs, therapy approaches, lead indications, products, therapy modalities and phases of development. This table has been developed drawing upon information from Isherwood et al[16] and Schilder et al.[15]

Table 1. Overview of current IHTs in development.[15,16]

Company	Therapy Approach	Lead indication	Product	Therapy modality	Phase of development
13Therapeutics	Otoprotection	SNHL (Age related)	P13	Drug	Preclinical
13Therapeutics	Otoprotection	SNHL (Noise Induced)	P13	Drug	Preclinical
Acousia Therapeutics	Otoprotection	SNHL (Drug Induced) (Cisplatin)	ACOU085	Drug	Preclinical
Acousia Therapeutics	Regeneration	SNHL (Age related)	Otopotin	Drug	Preclinical
Affichem	Otoprotection	SNHL	AF243 (naturally occurring dendrogenin)	Drug	Preclinical
Affichem	Regeneration	SNHL	AF243 (naturally occurring dendrogenin)	Drug	Preclinical
AGTC	Gene Correction Therapy	SNHL (Genetic)	GJB2 gene	Gene Therapy	Preclinical
Akouos	Gene Correction Therapy	SNHL (Genetic)	AK-OTOF	Gene Therapy	Preclinical
Akouos	Gene Correction Therapy	SNHL (Genetic)	AK-CLRN1	Gene Therapy	Preclinical
Akouos	Gene Correction Therapy	SNHL (Genetic)	AK-antiVEGF	Gene Therapy	Preclinical
Akouos	Gene Correction Therapy	SNHL (Genetic)	GJB2	Gene Therapy	Preclinical
Akouos	Gene Correction Therapy	SNHL (Genetic)	Undisclosed	Gene Therapy	Discovery
Akouos	Gene Correction Therapy	SNHL (Genetic)	Undisclosed	Gene Therapy	Discovery
Anida Pharma	Otoprotection	Drug induced hearing loss	AP-001 (NPD1)	Drug	Preclinical
Anida Pharma	Otoprotection	SNHL (Age / noise induced)	AP-001 (NPD1)	Drug	Discovery

Frequency Therapeutics	Regeneration	SNHL (Noise Induced, idiopathic sudden sensorineural hearing loss)	FX-322 (PCA-Progenitor Cell Activator)	Drug	Phase IIa
AudioCure Pharma GmbH	Otoprotection	SNHL (Sudden onset)	AC102	Drug	Phase I
AudioCure Pharma GmbH	Regeneration	SNHL (Sudden onset)	AC102	Drug	Phase I
Audion Therapeutics	Regeneration	SNHL (Age related)	LY3056480	Drug	Phase II
Auration Biotech	Otoprotection	SNHL	AU-934 (KB-R7785)	Undisclosed	Undisclosed
Auris Medical	Otoprotection	SNHL (Sudden onset)	AM-111	Drug	Phase III
Auris Medical	Reduction of Tinnitus percept	Tinnitus	Keyzilen (AM-101)	Drug	Phase II/III
Auris Medical	Reduction of Tinnitus percept	Tinnitus	AM-102	Drug	Preclinical
Auris Medical	Acute vertigo	Tinnitus	AM-125 (Betahistine)	Drug	Phase II
Autifony Therapeutics Ltd	Otoprotection	SNHL (Age related)	AUT00206	Drug	Phase II
Boehringer Ingelheim	Regeneration	SNHL (Age related)	Undisclosed	Gene Therapy	Preclinical
BridgeBio	Gene Correction Therapy	SNHL (Genetic)	BBP-815	Gene Therapy	Preclinical
Cognosetta	Otoprotection	Tinnitus and age related	CS0022	Drug	Preclinical
Decibel Therapeutics	Otoprotection	SNHL (Drug Induced) (Cisplatin)	DB-020 (sodium thiosulfate)	Drug	Phase I
Decibel Therapeutics	Gene Correction Therapy	SNHL (Genetic)	DB-OTO	Gene Therapy	Preclinical
Decibel Therapeutics	Gene Correction Therapy	SNHL (Genetic)	AAV.103	Gene Therapy	Discovery

Decibel Therapeutics	Gene Correction Therapy	SNHL (Genetic)	AAV.104	Gene Therapy	Discovery
Decibel Therapeutics	Gene Correction Therapy	Bilateral Vestibulopathy	DB-ATO	Gene Therapy	Preclinical
Decibel Therapeutics	Gene Correction Therapy	SNHL (Genetic)	AAV.201	Gene Therapy	Discovery
Decibel Therapeutics	Gene Correction Therapy	SNHL (Genetic)	Undisclosed	Gene Therapy	Discovery
Dendrogenix	Regeneration	SNHL (Sudden onset)	DX243	Drug	Preclinical
Fennec Pharmaceuticals	Otoprotection	SNHL (Drug Induced) (Cisplatin)	Pedmark (STS: sodium thiosulphate)	Drug	Phase III
Frequency Therapeutics	Regeneration	SNHL (Noise Induced)	FX-322 (PCA-Progenitor Cell Activator)	Drug	Phase IIa
Gateway Biotechnology	Otoprotection	SNHL (Noise Induced)	GW-101	Drug	Phase IIb
Gateway Biotechnology	Otoprotection / regeneration	SNHL (Noise Induced)	GW-102	Drug	Preclinical
Gateway Biotechnology	Regeneration	SNHL (Noise Induced)	GW-103	Drug	Preclinical
Gateway Biotechnology	Otoprotection	SNHL (Drug induced, Cisplatin)	GW-301	Drug	Preclinical
Gateway Biotechnology	Tinnitus	Tinnitus	GW-201	Drug	Preclinical
Hoba Therapeutics	Otoprotection	SNHL	HB-097	Drug	Preclinical
Hoba Therapeutics	Regeneration	SNHL	HB-097	Drug	Preclinical
IntraBio	Meniere's Disease	Meniere's Disease	IB2000	Undisclosed	Preclinical
Khondrion	Mitochondrial disease	SNHL (Genetic)	KH-176	Drug	Phase IIb

Knopp Biosciences	Reduction of Tinnitus percept	Tinnitus	Selective modulators of KCNQ2	Drug	Preclinical
Kyorin	SNHL	SNHL	Undisclosed	Drug	Preclinical
Nordmark Arzneimittel GmbH & Co KG	Otoprotection	SNHL (Sudden onset)	Ancrod	Drug	Phase II
Novartis/GenVec	Regeneration	SNHL	CGF166	Gene Therapy	Suspended
O-ray Pharma	Otoprotection	Prevention of SNHL post cochlear implantation	OR-102C	drug	Preclinical
O-ray Pharma	Otoprotection	Otitis	OR-404IT	drug	Preclinical
O-ray Pharma	Otoprotection	Autoimmune Inner Ear Disease	OR-102A	drug	Preclinical
O-ray pharma	Otoprotection	SNHL (Age related)	OR-112	drug	Preclinical
Orbis Biosciences	Balance	Ménière's disease	ORB-202 (Betamethasone)	Drug	Preclinical
Oricula Therapeutics	Otoprotection	SNHL (Drug induced, Aminoglycoside)	ORC-13661/DB-041	Drug	Phase I completed
Otologic Pharmaceutics (Acele BioPharma)	Otoprotection	SNHL (Noise Induced, acute noise and blast injury)	NHPN-1010	Drug	Phase I (Phase II is in preparation)
Otologic Pharmaceutics (Acele BioPharma)	Regeneration	SNHL (Acute and Chronic)	OPI-001	Drug + RNAi	Preclinical
Otomagnetics	Drug delivery system	SNHL	Magnetic injector with bio-degradable magnetic particles	Drug delivery system	Preclinical
Otonomy	Balance	Ménière's disease	OTIVIDEX (OTO-104) (dexamethasone)	Drug	Phase III
Otonomy	Otoprotection	SNHL (Drug induced, Cisplatin)	OTO-510	Drug	Preclinical

Otonomy	Reduction of Tinnitus percept	Tinnitus	OTO-313 (gacyclidine)	Drug	Phase I/II completed
Otonomy	Regeneration	SNHL (Severe)	OTO-6XX	Drug	Preclinical
Otonomy	Regeneration	Hidden hearing Loss	OTO-413 (BDNF)	Drug	Phase I/II
Otonomy	Gene Correction Therapy	SNHL (Genetic)	GJB2 gene	Gene Therapy	Preclinical
Pipeline Therapeutics	Regeneration	SNHL associated with speech in noise difficulty	PIPE-505	Drug	Preclinical
Pragma Therapeutics	Otoprotection	SNHL (Age related)	mGlu7 blockers	Drug	Preclinical
Pragma Therapeutics	Otoprotection	SNHL (Noise induced)	mGlu7 blockers	Drug	Preclinical
Quark Pharma	Balance	Ménière's disease	QPI-1017	siRNA	Discovery
Quark Pharma	HL (undisclosed)	SNHL	QPI-3000R	siRNA	Discovery
Rescue Hearing Inc	Gene Correction Therapy	SNHL (Genetic)	RHI100 Gene therapy (AAV-vectors)	Gene Therapy	Preclinical
Rophibio	Stem cell therapy	Autoimmune Inner Ear Disease	RF-GS03	Cell Therapy	Preclinical
Rinri Therapeutics	Regeneration	Auditory neuropathy SNHL	Undisclosed	Cell Therapy	Preclinical
Sensorion	Otoprotection	SNHL (Drug induced, Cisplatin)	SENS-401	Drug	Phase I
Sensorion	Otoprotection	SNHL (Sudden onset)	SENS-401	Drug	Phase II
Sensorion	Otoprotection	SNHL (Genetic)	Usher-GT	Gene Therapy	Preclinical
Sensorion	Gene Therapy	SNHL (Genetic)	OTOF-GT	Gene Therapy	Preclinical
Sensorion	Otoprotection	SNHL (Drug induced, Aminoglycoside)	SENS -401	Drug	Discovery
Sensorion	Reduction of Tinnitus percept	Tinnitus	SENS -401	Drug	Preclinical

Sensorion & Cochlear Ltd	Otoprotection	Cochlear Implant users	SENS-401	Drug	Preclinical
Sound Pharmaceuticals	Otoprotection	SNHL (Noise Induced)	SPI-1005 (Ebselen)	Drug	Phase II
Sound Pharmaceuticals	Otoprotection	Ménière's disease	SPI-1005 (Ebselen)	Drug	Phase III
Sound Pharmaceuticals	Otoprotection	Chemotherapy-induced ototoxicity	SPI-3005	Drug	Phase II
Sound Pharmaceuticals	Otoprotection	SNHL (Drug induced, Aminoglycoside)	SPI-3005	Drug	Phase II
Sound Pharmaceuticals	Regeneration	SNHL (Severe to Profound)	SPI-5557	Undisclosed	Preclinical
Spiral Therapeutics	Otoprotection	SNHL (Drug induced, Cisplatin)	LPT99	Drug	Phase I
Strekin AG	Otoprotection	SNHL (Sudden onset)	STR001	Drug	Phase III
Surrozen	Undisclosed	Hearing loss	Undisclosed	Undisclosed	Discovery
Synphora	Balance	Ménière's disease	Latanoprost (Xalatan®)	Drug	Phase II
Ting Therapeutics	Undisclosed	SNHL	TT001	Undisclosed	Preclinical

Activity in the field of IHTs currently focuses on therapy discovery, product development, building networks, clinical trial delivery and raising investment to support these activities.[23] The field has been successful in attracting sizeable public funds from for example, the National Institutes of Health (NIH),[23] the European Horizon programme,[1] as well as from patient charities.[24] Considerable private funds have also been raised from biotechnology and pharmaceutical companies as well as from venture capitalists.[25,26] Some companies have generated further investment by 'going public', floating their companies on the stock market, where shares can be purchased by the general investing public.[27] Recent events have demonstrated the fragility of this field; for example Frequency Therapeutics, a leading company in IHT development, experienced a 72% fall in stock prices following publication of their phase 2a study showing that their small molecule drug FX-322 had no discernible

hearing benefit over placebo for patients with SNHL.[28] Years earlier, Otonomy, experienced the same following their Phase III trial of a novel therapy to treat Meniere's disease (a disorder of the inner ear), which failed to reach its primary endpoint.[29] To date no IHTs have been approved for use in patients.

Key challenges to translation that face the field include the complexity and diversity of causes of SNHL which are only partially known.[21] Moreover, our ability to phenotype SNHL is limited, with current hearing measures primarily focused on hearing levels and not being able to identify the underlying cause, which is crucial for patient selection and in the detection of efficacy signals.[12] Integration of auditory science discoveries into clinical trials of IHTs can help address these challenges as has occurred in the hearing technology industry with cochlear implants.[30] Whilst advances have been made in identifying genetic causes of SNHL, there have been no concerted efforts to include genetic testing in the diagnostic work up of presentations of SNHL, limiting our understanding of implicated genes and our ability to target them.[12,15] Biotechnology companies developing gene therapies are addressing this by offering routine genetic testing to patients with hearing loss,[31,32] and by setting up registries collecting data on patients with suspected genetic SNHL.[33] Another key challenge is therapy delivery. The inner ear is located within the temporal bone of the skull, and further protected by a blood labyrinthine barrier, requiring either intratympanic injections (injection through the ear drum) for most small molecule drugs or intracochlear delivery for cells and genes. These delivery routes are accompanied by considerable resource and access implications; companies are looking to address this via strategic collaborations between biotechnology and hearing technology companies, for example utilising cochlear implants for targeted delivery of IHTs.[34]

Some companies have successfully completed trials for IHTs, demonstrating both efficacy and safety. For example Fennec Pharmaceuticals has shown in a multicentre phase III trial that intravenous (IV) administration of their formulation of sodium thiosulphate (PEDMARK) protects against cisplatin chemotherapy-induced SNHL in children with hepatoblastoma[35] and is awaiting FDA approval for clinical application.[36] Sound Pharmaceuticals, a privately held biopharmaceutical company, has developed a novel anti-inflammatory drug (SPI-1005) and are opening a phase III trial to treat patients with Meniere's disease, following positive

results of a phase IIb trial.[37] Considering the rapid progress in this field, experts expect that the first IHTs will be approved for clinical use over the next five years.

Preparing for IHTs

The challenges associated with the uptake of innovations into healthcare systems is well documented, with an average 15 to 17 year delay from innovation discovery to routine use.[38] The novelty and complexity of innovative medical therapies appears to present additional and distinct challenges to uptake.[39–43] This has been apparent for example in Ophthalmology, where the introduction of novel anti-VEGF injections into clinical services led to reports of delayed implementation, subclinical outcomes and economic inefficiencies.[44,45] Given these challenges and the expectation that IHTs will look to enter healthcare systems within the next five years, it appears essential for healthcare systems to start preparing for IHTs to accelerate patient access, optimise healthcare system efficiencies and minimise disruption.

Valuable insights on preparing for innovative medical therapies can be gained from established processes including constructive technology assessment, anticipatory governance and responsible innovation.[46,47,49] These processes all highlight the importance of gaining the perspectives of diverse stakeholder groups on medical innovations and their potential impacts as early as possible to anticipate events, social issues or behaviours that will influence implementation.[47-50] This exploration of different stakeholder perspectives can be integral in developing strategies to increase the likelihood of implementing innovations that are of value to society.[47-53] The field of implementation science has produced a growing body of research to provide a better understanding and explanation of the broader determinants of medical innovation implementation; and a number of implementation theories have since emerged.[54-57] It is clear from this work that successful adoption and implementation of medical innovations into healthcare systems is dependent upon numerous complex elements, including existing healthcare infrastructures and practices, the perspectives of stakeholders, education and training, evidence of efficacy and safety, cost-effectiveness, affordability, resource availability, regulatory processes, payment strategies

and others.[58] The term 'Adoption' describes the decisions made by people or organisations to use a therapy, whilst the term 'implementation' refers to the processes that follow to execute the decision.

The focus of my thesis

To help pave the way and prepare for IHTs, my thesis draws upon health economics and implementation science and aims to:

> Provide stakeholders who develop, will use and pay for IHTs, with a detailed understanding of the elements that influence their adoption and implementation and with practical strategies to facilitate their uptake in the UK healthcare system.

To meet this aim, my thesis has four objectives.

1) To inform IHT product development and decisions on value for money.

Early health economic modelling, a derivative of health economic modelling, offers insights into the commercial viability of new medical technologies and can provide important information at the early stages of development that can increase the chances of developing technologies that represent value for money.[59] They are constructed using mathematical modelling, the best available evidence, and stakeholder input.[59] I will develop the first health economic model in the field of IHTs that will provide information on the potential cost-effectiveness of IHTs, as well as inform product development, market access, and pricing, thereby informing adoption and implementation. Importantly, developing an early health economic model in this field and disseminating its findings will also provide insights into the perspectives of stakeholders trying to steer the adoption of IHTs as well as an insight into their views on health economic modelling. I discuss the outcome of this work in Chapter 2 of this thesis.

2) To characterise and understand the elements that influence the adoption and implementation of IHTs in the UK healthcare system.

To achieve this, I will carry out semi-structured interviews with stakeholders to perform a detailed investigation of the elements that influence the adoption and implementation of IHTs in the UK healthcare system. The initial interview schedule and baseline coding framework for this study will be developed drawing upon insights from the development of the early health economic model, as well as Normalisation Process Theory (NPT),[55,60–62] a well-established implementation theory which provides an empirically tested theoretical framework that explains the processes by which interventions become routinely used in healthcare practice. I discuss the outcome of this work in Chapter 3 of this thesis.

3) To provide an understanding of the elements that influence the adoption and implementation of innovative therapies across healthcare specialties and systems.

I will perform a hermeneutic review to place the results of Chapter 3 in context with the literature on innovative medical therapy adoption and implementation across healthcare specialities and systems. By doing this I will be able to see how the literature compares, and importantly, gain a deeper insight and understanding into elements discussed in Chapter 3 as well as explore elements not identified. I report the findings of this hermeneutic review in Chapter 4.

4) To integrate the findings from my thesis into a framework of adoption and implementation for IHTs.

I will construct a framework that integrates the findings from my thesis so that they can be used by stakeholders across the IHT translational pathway to gain an understanding of the elements that influence IHT adoption and implementation and to identify strategies to facilitate their uptake. I present this framework in Chapter 5 of this thesis.

My research will represent an original contribution to the literature, being the first study to assess the potential cost-effectiveness of IHTs. It will also be the first study to investigate

implementation processes within this field and provide practical strategies to facilitate uptake. The planned research methods are novel and can be of value to fields outside of IHTs. The qualitative interview study will uniquely be informed by findings from the health economic model to inform its topic guide and analysis, contributing to a broad and in-depth exploration of elements that influence implementation processes and meaning that health economics will form an important component within my framework. The hermeneutic review will unconventionally be conducted after and be informed by the results of the interview study. This ordering will help me carry out a more focussed literature review that contextualises the findings from the interview study, adding to my understanding and contributing to a robust framework of adoption and implementation. Throughout this research process I aim to draw upon my background and experience as a clinician on the 'front-line' of the NHS so to develop a framework that can be easily understood and practically used by stakeholders across the translational pathway to facilitate uptake of IHTs. I anticipate that the framework I construct will be distinct to other implementation frameworks given that it will draw on both health economics and implementation science; and it being developed by a clinician. I also envisage that my framework will be unique in its ability to provide practical, 'how-to' support for carrying out implementation endeavours, particularly in the field of IHTs.

CHAPTER 2: EARLY HEALTH ECONOMIC MODEL FOR INNOVATIVE HEARING THERAPIES

Introduction

Healthcare systems are experiencing rising costs owing to an aging population and the ongoing development of new healthcare interventions across specialities. Indeed, healthcare expenditure in developed nations has been increasing faster than gross domestic product (GDP) over the past 40 years and in the UK, the percentage of GDP spent on healthcare has doubled in the past 40 years.[63,64] Maintaining this trend will become increasingly unsustainable, and with finite healthcare budgets, decision makers need to make decisions on which interventions represent value for money and are worth funding. Over the last 2 decades, there has been increasing interest in using early health economic modelling to make value decisions by providing an understanding on the likely cost-effectiveness of an intervention in development.[59] This information can also be used by industry to inform decisions on product development, market access and pricing. Investors look to these models to help inform their investment decisions; and scientists and clinicians can use them to direct their focus on disease areas with growth potential.

Early health economic modelling draws on mathematics, the best available evidence as well the assumptions and inputs of stakeholders within the investigated healthcare area. Developing an early health economic model in the field of IHTs will help inform product development and decision making. Importantly it will also provide insights into the perspectives of stakeholders trying to steer the adoption of IHTs, and into their views on health economic modelling.

At the time of writing, no early health economic models have been published in the field of hearing loss. A recent systematic review by Borre et al[65] on economic analyses within hearing healthcare found 117 studies. The majority of economic analyses have been set in high income countries with relatively few in low and middle income countries.[65] Sixty-one studies evaluated hearing loss strategies exclusively in paediatric populations, 32 in adults

and 24 in both. The interventions assessed included hearing screening (n = 35), cochlear implantation (n = 34), hearing aid use (n = 28), vaccination (n = 22), and other aspects of hearing healthcare (n = 29). Quality-adjusted life-years (QALYs) were the most commonly reported health outcome measure with a small proportion of studies reporting DALYs (Disability adjusted life years). No health economic models were found in the field of IHTs.

This chapter presents the first early health economic model for IHTs. Idiopathic SSNHL is used as a case example, because it is a lead indication for several emerging hearing therapies.[15]

Objective: To inform IHT product development and decisions on value for money.

Methods

Ethics approval and consent to participate

As per UCL guidelines, owing to interviews conducted with participants by the virtue of their professional role (e.g., NHS clinicians), UCL ethical approval was required.[66] Ethical approval was granted by UCL Research Ethics Committee 12241/001. Informed consent was sought from all participants.

Target population

The target population simulated through my model consisted of patients with unilateral idiopathic SSNHL in the NHS in England. Idiopathic SSNHL is sub-type of sensorineural hearing loss that develops suddenly, within the course of 3 days, usually in one ear, and with no known cause (idiopathic).[10] It affects approximately 20 people per 100,000 annually, with about 66,000 new cases per year in the US.[67] The most widely used treatments for idiopathic SSNHL are systemic and intratympanic steroids, with considerable limitations in their effectiveness and evidence base.[67] It is estimated that 35 to 68% of cases of idiopathic SSNHL fail to recover; and clinical experience suggests that this is an underestimation.[67] In case of non-recovery of hearing, patients are offered a hearing device.

Decision analytic model

I constructed a decision analytic model following ISPOR-SMDM Best Practice Guidelines[68] (the ISPOR-SMDM Best Practice Guidelines provide expert consensus recommendations that set international standards for health economics outcomes research) to assess the potential costs and effects of using IHTs in adult patients with idiopathic SSNHL. Please see Appendix 1 for the completed ISPOR Consolidated Health Economic Evaluation Reporting Standards (CHEERS), checklist.[68] This was compared to the current standard of care. My model consists of a decision tree to map the early management of idiopathic SSNHL and a state-transition model to simulate long-term follow-up. The structure of the decision tree and state transition model was based on best available evidence[10,67,69–71] and validated by expert opinion. Model assumptions are summarised in Table 2 and were reviewed by expert participants (n=26).

Table 2: Model assumptions

The decision tree starts with a cohort of 50-year-old individuals with mild, moderate, severe and profound idiopathic SSNHL
All patients entering the decision tree have idiopathic SSNHL meaning that no other causes could be revealed by MRI or laboratory tests
All patients have unilateral idiopathic SSNHL
All patients had SSNHL confirmed by a hearing test and ENT follow-up appointment
Recovery to baseline was defined as hearing level within 10 dB of the contralateral/unaffected ear
The effectiveness of steroid therapy was independent of the specific steroid used
Oral and intratympanic steroids did not have side effects
Patients had a baseline of symmetrical hearing
Following entering the state-transition model, patients remained in the same hearing level up to death. Other causes of hearing loss were not taken into account
The 'recovery to baseline' health state and the health states without amplification were not accompanied by costs
Patients with mild idiopathic SSNHL could only receive a hearing aid. Patients with moderate, severe or profound SSNHL could receive a hearing aid, CROS aid or BCHD
Patients with moderate or severe idiopathic SSNHL receiving a CROS aid tried a hearing aid first
Patients with profound idiopathic SSNHL did not try a hearing aid before receiving a CROS aid
Patients with moderate or severe idiopathic SSNHL receiving a BCHD tried a hearing aid and CROS aid first
Patients with profound idiopathic SSNHL only tried a CROS aid before receiving a BCHD.
The time between provision of a hearing aid or a CROS aid and it needing to be replaced was set at 3 years. The cost of a new aid was averaged over 3 years to obtain annual costs.
Hearing aids were fitted in one ear only.
The cost of a BCHD was calculated based on the mean price of three common types of BCHD (Cochlear BAHA 5, MEDEL Bonebridge, Oticon Ponto).
Hearing aids and CROS aids did not carry complications. BCHDs carried complications of skin problems and implant failure.
Utility gain due to amplification was assumed to be the same for a hearing aid and CROS aid.

MRI, Magnetic Resonance Imaging; CROS aid, Contralateral Routing of Signals aid; BCHD, Bone Conduction Hearing Device; SSNHL Sudden onset Sensorineural Hearing Loss.

Participant involvement

Participants were interviewed via semi-structured interviews, using purposive and snowball sampling to select participants within the categories: ENT clinicians, audiologists, health economic modelling experts, discovery scientists, hearing loss representatives from companies developing hearing devices or IHTs, patients with idiopathic SSNHL. As per ISPOR-SMDM best practice guidelines, Table 3 provides an overview of included participants.

Table 3: Information on expert participants

Frequency	Expert group	Country
11	ENT Clinicians	UK
4	Audiologists	UK
4	Health economic modelling experts	UK (n=1), Canada (n=1), Netherlands (n=2)
2	Discovery scientists	UK (n=1), France (n=1)
2	Industry representatives	UK (n=1), Switzerland (n=1)
3	Patients with idiopathic SSNHL	UK

Participants were contacted via email, including a study information sheet (see Appendix 2 for professional information sheet and Appendix 3 for patient information sheet). A snowball sampling technique was also utilised where, at the end of each interview, interviewees were asked to propose other participants relevant to this study. Participants identified via this snowball sampling technique were approached via email invitation which included a study information sheet.

A total of 26 participants were interviewed. Participation was voluntary and informed consent was obtained. I interviewed participants in person or via telephone between April 2019 and June 2019. During the evolving interviews, participants were shown the most recent version of the decision tree and state transition model, and an explanation of the decision tree and state transition model was provided. Participants were then asked a schedule of questions concerning their views on: 1) the structure of the decision tree and state transition model 2) specific parameters and values used and 3) the assumptions used in the model. The specific questions asked within the topic guide and the extent to which probes were explored depended upon the area of expertise of each participant. The schedule of questions evolved as I developed the model. An example initial topic guide can be seen in Appendix 4. Individual interviews lasted between 30 and 60 minutes and were digitally recorded and transcribed. The responses obtained from participants were used to develop and refine the decision tree and state transition model. They were also used to review and provide input on transition probabilities, utility scores and costs.

I took hand-written, anonymised, field-notes during and after these interviews to record my reflections on: stakeholder perceptions on health economic modelling and the strategic intentions of stakeholders trying to steer the adoption of IHTs into healthcare systems. I also recorded my reflections following question and answer sessions during presentation of my early health economic model at 8 international conferences. I used these insights to inform the topic guide and coding framework for the interview study (Chapter 3).

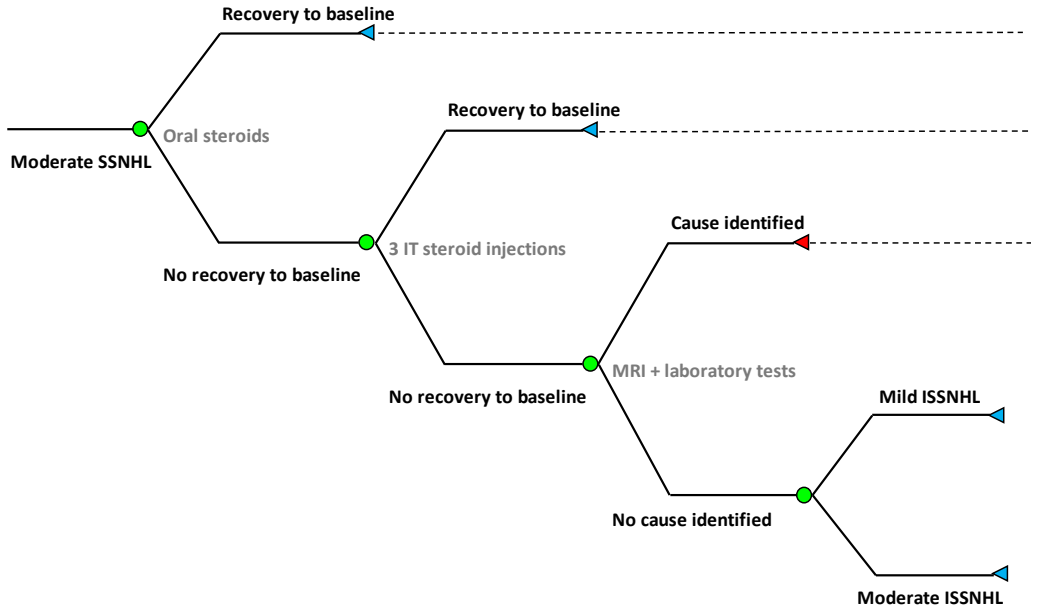
Decision tree

I constructed a decision tree to map the costs and outcomes of the acute treatment pathway for patients presenting with SSNHL, at four different severities, mild (25-40 decibel [dB] loss), moderate (41-70 dB loss), severe (71-95 dB loss) and profound (>95 dB loss), for both the current NHS standard of care and for IHTs (see Figure 2). The decision tree only includes parameters that differ in effect, incidence and costs between strategies, and that therefore contribute to a difference in the cost-effectiveness. Non-differentiating variables were not included in the model following consultation with experts. For example, an initial hearing test for either the existing or the novel strategy will occur at the same incidence, with the same effect, at the same costs and will therefore not differ between strategies.

For the current NHS standard of care, patients with SSNHL are mapped to receive oral steroids, followed by three intratympanic steroid injections, 1 to 2 weeks apart in the event that hearing does not recover to baseline (baseline defined as hearing level within 10dB of the unaffected ear). Patients whose hearing does not recover to baseline following intratympanic injections undergo Magnetic Resonance Imaging (MRI) and laboratory testing to exclude identifiable causes of SSNHL. Patients that do not recover to baseline either stay at their initial level of hearing loss or improve to a less severe level of hearing loss.

For the new strategy, steroids have been replaced by an IHT that can return hearing back to baseline. The final outcomes of the decision tree include: recovery to baseline, or, mild, moderate, severe or profound idiopathic SSNHL.

Figure 2: A section of the decision tree showing the current standard of care for patients with moderate idiopathic SSNHL (The full decision tree is available in Appendix 5)

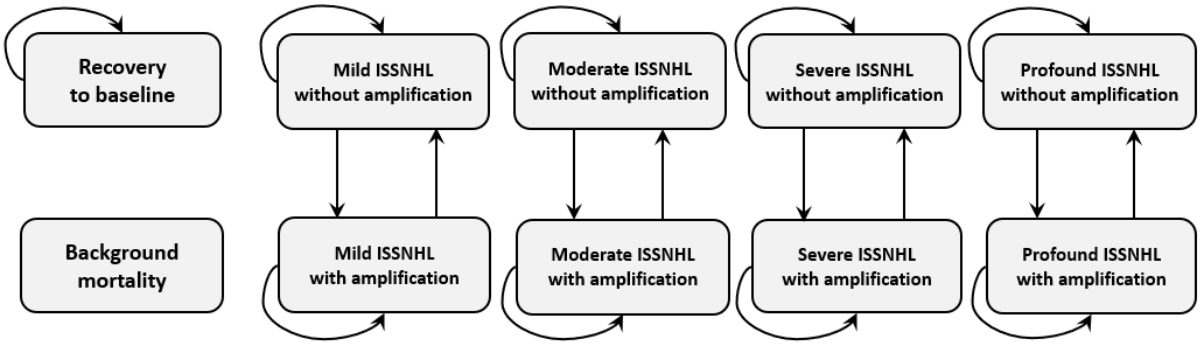


State-transition model

The decision tree is followed by a state-transition model, to simulate the long-term costs and impacts on quality of life due to idiopathic SSNHL (see Figure 3). In the state-transition model, patients enter the hearing health state that corresponds to their hearing level at the end of the decision tree. Following the first cycle, patients are able to move to a 'hearing loss with amplification health state'. This includes a hearing aid for patients with mild hearing loss; patients with moderate, severe or profound hearing loss are able to receive a hearing aid, a contralateral routing of signal (CROS) aid or a bone conduction hearing device (BCHD).

Patients with amplification were able to move back to their unamplified hearing loss state, recognising compliance issues with hearing devices. Patients from all health states were able to move to "death" (all-cause mortality). The state-transition model adopted a cycle length of one year and spanned the patient's lifetime until death, owing to the life-long costs and effects of hearing loss.

Figure 3: State-transition model



ISSNHL, idiopathic sudden sensorineural hearing loss

Probabilities

Data on transition probabilities were derived following scientific and grey literature searches and reviewed by expert participants (n=26). Table 4 shows the probabilities used in the decision tree and the state-transition model, together with their standard errors and sources.[69–74] All-cause mortality rates were obtained from the Office for National Statistics and were age dependent (Table 5).[72]

Table 4: Transition probabilities

Parameter	Value	Standard error	Reference
DECISION TREE			
Initial severity of hearing loss			
Mild	0.17**	0.013	[69]
Moderate	0.37**	0.017	[69]
Severe	0.22**	0.014	[69]
Profound	0.24**	0.015	[69]
Recovery after oral steroids			
Mild	0.45*	0.109	[70]
Moderate	0.44*	0.059	[70]
Severe	0.26*	0.060	[70]
Profound	0.07*	0.031	[70]
Recovery after intratympanic steroids			
Mild	0.29*	0.117	[71]
Moderate	0.38*	0.097	[71]
Severe	0.17*	0.141	[71]
Profound	0.06*	0.059	[71]
Final hearing loss when mild at onset and not recovered to baseline			
Mild	1.00	0.000	[71]
Final hearing loss when moderate at onset and not recovered to baseline			
Mild	0.73*	0.111	[71]
Moderate	0.27*	0.111	[71]
Final hearing loss when severe at onset and not recovered to baseline			
Mild	0.20**	0.163	[71]
Moderate	0.40**	0.200	[71]
Severe	0.40**	0.200	[71]
Final hearing loss when profound at onset and not recovered to baseline			
Mild	0.13**	0.085	[71]
Moderate	0.27**	0.111	[71]
Severe	0.40**	0.123	[71]
Profound	0.20**	0.100	[71]
STATE-TRANSITION MODEL			
Proportion receiving amplification			
Mild	0.30*	0.023	[73]
Moderate	0.52*	0.020	[73]
Severe	0.75*	0.029	[73]
Profound	0.67*	0.064	[73]
Non-compliance rate			
Mild	0.13*	0.035	[74]
Moderate	0.30*	0.088	[74]
Severe	0.30*	0.088	[74]
Profound	0.30*	0.088	[74]
Mortality rate	Age-dependent	-	[72]

Beta* and Dirichlet** distributions were assigned to the parameters for use in the probabilistic sensitivity analysis. Beta distributions were used for bivariate probability distributions and Dirichlet distributions were used for multivariate probability distributions. Standard errors needed for these distributions are also displayed.

Table 5. All cause mortality rates[72]

Age	Mortality probability per person per year
under 1	0.00399
1-4	0.00010
5-9	0.00010
10-14	0.00010
15-19	0.00025
20–24	0.00035
25–29	0.00045
30–34	0.00060
35–39	0.00090
40–44	0.00140
45–49	0.00210
50–54	0.00310
55–59	0.00469
60–64	0.00757
65–69	0.01188
70–74	0.01872
75–79	0.03319
80–84	0.05824
85-89	0.10488
90 and over	0.20192

Outcome measures

Effectiveness was measured in QALYs based on lifetime follow-up. A QALY is a generic measure of health that factors both length and quality of life into a single measure. It is calculated by the number of years spent in a health state, multiplied by its utility score. A utility score represents the health-related quality of life (HRQoL) and ranges from 0 to 1, where 0 represents total loss of health-related quality of life, i.e., death, and 1 represents perfect health.[75]

Utility scores for HRQoL and their standard errors were obtained from systematic literature searches and reviewed by expert participants. Health Utilities Index Mark 3 (HUI-3) was used since it has been found to be a more valid and responsive instrument to change in hearing loss HRQoL than EQ-5D.[76] To account for declining quality of life with age, an annual disutility score was applied to utility scores.[77] Table 6 summarises the utilities used and their sources.[75,77–79] Effects were discounted at a 3.5% per annum rate as per NICE guidelines.[78]

Table 6: Utilities

Health state	Value	Standard error	Details	Reference
Recovery to baseline	0.95*	0.081		[77]
Death	0.00	-		[75]
Mild HL	0.81*	0.046		[77]
Moderate HL	0.77*	0.031	Calculated by taking the mean of the utility scores for mild (0.81) and 'moderate/severe' HL as per Linssen et al.(40) (0.73)	[77]
Severe HL	0.67*	0.031	Calculated by taking the mean of the utility scores for moderate (0.77) and profound HL as per Arndt et al.(25) (0.56)	[77,79]
Profound HL	0.56*	0.066		[79]
Utility gain				
HA/CROS	0.09	np		[77]
BCHD	0.11	np		[79]
Age correction	0.0024*	0.001		[77]

HL, hearing loss; HA, hearing aid; CROS, contralateral routing of signal hearing aid, BCHD, bone conducting hearing device,

*Beta distributions

Cost information

Cost analysis was performed from an NHS healthcare provider perspective (only healthcare costs were included). Unit costs were calculated in British Pounds (GBP) and were primarily obtained from NHS reference costs.[80] Other sources included NICE guidelines,[10] the British National Formulary (BNF),[81–83] University College London Hospitals (UCLH) NHS Foundation Trust,[84] Cambridge University Hospital NHS Foundation Trust,[85] University Hospitals Birmingham NHS Foundation Trust[86] the literature[87] and NHS England.[88] Tables 7 and 8a and 8b provide a detailed breakdown of costs used for the decision tree and state-transition model respectively. All unit costs were reviewed and agreed upon by experts.

Table 7: Unit costs used in decision tree

Unit	Unit costs	Details	Reference
Oral steroids			
Prednisolone	£6.11	60 mg for 7 days, tapering over 5-7 days	[10]
Omeprazole	£0.39	20 mg once a day for 2 weeks	[83]
Intratympanic steroid injections			
Steroids for 3 injections	£4.17	Average of dexamethasone (0.3-0.4 ml of 5 mg/ml once a day x 3 days) and methylprednisolone (25 mg x 3 doses)	[10]
Syringe + needle	£6.36	Conventional loss of resistance syringe and epidural needle	[89]
EMLA cream	£0.41		[82]
Paracetamol	£0.03	2 x 500 mg	[83]
Procedural ENT appointment	£91.00		[80]
MR imaging			
Scan	£114.00	Without contrast, including cost of reporting	[90]
Laboratory testing			
Phlebotomy	£3.00	Includes staff time and equipment	[90]
ESR	£3.13		[87]
FBC	£3.10		[87]
ANA	£4.94		[87]
ANCA	£5.60		[84]
VDRL	£3.61	Using rapid plasma reagin	[84]
U&E	£3.10		[91]
Glucose	£3.10		[91]
Audiometry			
Hearing test	£62.00		[80]
Follow-up			
Non-procedural ENT appointment	£96.00		[90]

ESR, erythrocyte sedimentation rate; FBC, full blood count; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; VDRL, venereal disease research laboratory; U&E, urea and electrolytes

Table 8a: Costs for transition states in state-transition model

Transition to amplification state		
Mild	£267.78	[84,88,90]
Moderate	£2,141.21	[80,81,84–86,88,90,92]
Severe	£3,840.32	[80,81,84–86,88,90,92]
Profound	£4,844.69	[80,81,84–86,88,90,92]
Amplification state		
Mild	£143.11	[84,88,90]
Moderate	£279.37	[80,81,84–86,88,90,92]
Severe	£402.58	[80,81,84–86,88,90,92]
Profound	£494.95	[80,81,84–86,88,90,92]

Table 8b: Detailed unit costs used in state-transition model

Device	**Unit**	**Transition**	**Cycle**	**Every (years)**			**Reference**
Hearing aid							
Device	£88.00	£88.00	£29.33	3			[90]
Assessment	£54.78	£54.78	£18.26	3			[88]
Fitting	£72.00	£72.00	£24.00	3			[90]
Follow-up	£53.00	£53.00	£17.67	3			[90]
Aftercare (repairs)	£155.04	-	£51.68	3			[88]
Batteries	£6.50	-	£2.17	3			[84]
Total		**£267.78**	**£143.11**				
CROS aid							
Device (including assessment, fitting and follow-up)	£330.00	£330.00	£110.00	3			[84]
Repairs (bad ear)	£47.64	-	£15.88	3			[84]
Repairs (good ear)	£8.04	-	£2.68	3			[84]
Batteries	£26.02	-	£8.67	3			[84]
Total		**£330.00**	**£137.23**				
BCHD					**Skin problems**	**Implant failure**	
Device*	£4,598.33	£4,598.33	-				[84–86]
Implant + abutment (without processor)*	£975.50	-	-			£975.50	[84–86]
Operation	£3,455.00	£3,455.00	-			£3,455.00	[80]
Pre-assessment operation	£155.00	£155.00	-				[90]
Audiology assessment (soft band trial)	54.78	2x £109.56	-				[88]
MDT meeting	£76.00	£76.00	-				[90]
Fitting	£297.00	£297.00	£59.40	5		£297.00	[80]
First visit audiologist	£105.00	£105.00	-				[90]
First visit ENT surgeon	£118.00	£118.00	-				[90]
Follow-up audiologist	80.00	2x £160.00	2x £32.00	5		2x £160.00	[90]
Follow-up ENT surgeon	96.00	3x £288.00	-		2x £192.00	3x £288.00	[90]
Abutment nursing and repairs*	300.00	-	£300.00	1			[84–86]
Processor upgrade*	2,500.00	-	£500.00	5			[84–86]
Batteries	6.76	-	£6.76				[92]
Total		**£9,361.89**	**£898.16**		**£194.08**	**£5,175.50**	

BCHD, Bone Conduction Hearing Device; MDT, multidisciplinary team, CROS, contralateral routing of signal.
For * the mean costs of three NHS trusts were taken.

-Cost of transition to amplification state 'Mild' was calculated by adding the costs of receiving a hearing aid.
-Cost of transition to amplification state 'Moderate' and 'Severe' were calculated by the following: (costs of transition to amplification state 'Mild') + (proportion of patients receiving a CROS aid x cost of receiving a CROS aid) + (proportion of patients receiving a BCHD x cost of receiving a CROS aid) + (proportion of patients receiving a BCHD x cost of receiving a BCHD) + ((proportion of patients receiving a BCHD x proportion of patients with skin complications) x (cost of skin complications)) + ((proportion of patients receiving a BCHD x proportion of patients with implant failures) x cost of implant failures)).
-Cost of transition to amplification state 'Profound' was calculated by the following: (proportion of patients receiving a hearing aid x cost of receiving a hearing aid) + (proportion of patients receiving a CROS aid x cost of receiving a CROS aid) + (proportion of patients receiving a BCHD x cost of receiving a CROS aid) + (proportion of patients receiving a BCHD x cost of receiving a BCHD) + ((proportion of patients receiving a BCHD x proportion of patients with skin complications) x cost of skin complications)) + ((proportion of patients receiving a BCHD x proportion of patients with implant failures) x cost of implant failures)).
-Cost of amplification state 'Mild' was calculated by adding the cycle costs of a hearing aid
-Cost of amplification state 'Moderate', 'Severe' and 'Profound' were calculated by the following: (proportion of patients receiving a hearing aid x cycle costs of a hearing aid) + (proportion of patients receiving a CROS aid x cycle costs of a CROS aid) + (proportion of patients receiving a BCHD x cycle costs of a BCHD)
-Table 8b provides the specific costs together with references. Table 9 provides the proportion of patients of each severity, receiving each type of device; and complication rates following BCHD

In the state-transition model, costs were incurred for transitioning into an amplification state and for staying in an amplification state. These costs depended on the type of amplification used, which included: a hearing aid, and/or a CROS aid, and/or a BCHD. The proportion of patients of each severity, receiving each type of device was determined following expert input and is summarised in Table 9.

Table 9: Proportion of patients of each severity, receiving each type of device; and complication rates following BCHD

	Proportion of patients	Standard error	Reference
Mild			
Hearing aid	1.00	0.000	Expert opinion
CROS aid	0.00	0.000	Expert opinion
BCHD	0.00	0.000	Expert opinion
Moderate			
Hearing aid	0.62	0.077	Expert opinion
CROS aid	0.20	0.039	Expert opinion
BCHD	0.18	0.040	Expert opinion
Severe			
Hearing aid	0.27	0.062	Expert opinion
CROS aid	0.39	0.039	Expert opinion
BCHD	0.35	0.032	Expert opinion
Profound			
Hearing aid	0.01	0.009	Expert opinion
CROS aid	0.52	0.018	Expert opinion
BCHD	0.47	0.027	Expert opinion
Complications BCHD			
Skin problems*	0.20	0.025	[93,94]
Implant failure	0.04	0.005	[94]

For * a mean value was taken across 2 publications

The cost for a BCHD also included costs for common complications, including skin complications and implant failures. Complication rates were obtained from the literature[93,94] and from experts and were taken as 20% and 4% for skin complications and implant failures, respectively (Table 8). The minimum possible cost incurred for patients for the IHT included a hearing test (£62) and an ENT follow-up appointment (£96) with a total cost of £158 (please see Tables 7 and 8). Costs were discounted at a rate of 3.5% as per NICE guidelines[78] and all unit costs were adjusted to 2018 according to NHS Healthcare Inflation rates (Table 10).

Table 10: NHS Healthcare Inflation rates

Year	NHS Inflation rates
2011	1.2[95]
2015	0.050[96]
2016	0.642[96]
2017	2.700[96]
2018	2.300[96]
2011→2018	1.110
2015→2018	1.025
2016→2018	1.022

Validation

I verified the model's validity using the AdViSHE checklist.[97] This checklist covers five aspects of validation: conceptual model, input data, computerised model and operational validation and other validation techniques. The conceptual model, input data and model outcomes were tested on its face and operational validity by consulting with 26 participants, including ENT surgeons (n=11), audiologists (n=4), health economic modelling experts (n=4), discovery scientists (n=2), industry representatives (n=2) and patients with idiopathic SSNHL (n=3). Participants were approached via email invitation. No other health economic models on idiopathic SSNHL were found for cross-validation. The computerised model was validated by sub-unit, extreme value testing and testing of traces to detect possible coding errors. The model was checked for inaccuracies by an expert in economic modelling.

Analysis

The model was developed and built using Microsoft Excel. Adults with idiopathic SSNHL were sent through the model to determine mean expected costs and effects (QALYs) per patient, from onset of idiopathic SSNHL until death, for the current standard of care and the IHT. I conducted four different but related analyses: Headroom analysis, scenario analysis, threshold analysis and sensitivity analysis, taking into account NICE's cost-effectiveness threshold of £20,000/QALY.[78]

The headroom analysis explored the room for improvement in the current treatment of idiopathic SSNHL; specifically, the maximum added value of an IHT. The headroom analysis

assumed patients entering the model at 50 years of age,[69] receiving a 100% effective and a zero cost IHT. Effectiveness is defined as percentage of patients whose hearing recovered to baseline. Therefore 100% effectiveness indicates that 100% of patients returned to their baseline hearing. The scenario analyses explored the effects on cost-effectiveness of: different starting ages of patients, different severity of idiopathic SSNHL at onset, combined use of steroids with the IHT. The threshold analysis was used to determine the maximum cost of the IHT in order to be cost-effective, at different levels of effectiveness. In the sensitivity analysis, the effect of varying uncertain parameters on the outcome was assessed including: utility of hearing loss states (without amplification); utility gain following amplification; adoption rates of a hearing aid, CROS aid or BCHD.

Results were expressed using the incremental net monetary benefit (iNMB) of the IHT. The iNMB represents the added value of an intervention, compared to the current standard of care, in monetary terms. The iNMB was calculated using the formula: iNMB = ($QALY_n$ x threshold value – $Costs_n$) – ($QALY_c$ x threshold value – $Costs_c$)
[n = IHT, threshold value = 20,000/QALY, c = current treatment]. A positive iNMB indicates that the IHT is cost-effective compared to the current standard of care. The higher the iNMB, the greater the added value of the IHT in monetary terms.

The results for all analyses were obtained using probabilistic sensitivity analyses (PSA), taking the mean across 5000 simulations to account for uncertainty around parameters. 95% confidence intervals were calculated using the percentile method, using the 2.5 and 97.5 percentiles.

Results

Headroom analysis

The results for the headroom analysis are shown in Table 11, scenario '1'. The total costs and QALYs per patient from 50 years of age to death for the current standard of care are £6,963 [£5,032-£8,894] and 14.78 [12.09-17.47] respectively. The total costs and QALYs for the IHT are £158 [£158-£158] and 16.39 [13.53-19.25], respectively. This results in savings of

£6,805 [£4,875-8,736] and an increment in QALYs of 1.61 [0.79-2.43] per patient. For the headroom scenario, the iNMB of an IHT is £39,032 [£21,103-£56,962].

Table 11: Scenario analysis

Scenario	Steroids	Age	Severity	Cost current	Cost new	QALY current	QALY new	iNMB
1	None	50	All	£6.963 [5,032, 8,894]	£158 [158, 158]	14.78 [12.09, 17.47]	16.39 [13.53, 19.25]	£39,032 [21,103, 56,962]
				Incremental costs		**Incremental QALYs**		
1	None	50	All	-£6,805 [-8,736, -4,875]		1.61 [0.79, 2.43]		£39,032 [21,103, 56,962]
2	Oral + IT	50	All	-£6,793 [-8,688, 4,898]		1.61 [0.80, 2.42]		£38,933 [22,076, 55,790]
3	IT	30	All	-£8,263 [-10,633, -5,892]		1.99 [0.97, 3.01]		£48,125 [25,848, 70,403]
4	IT	70	All	-£4,543 [-5,784, -3,303]		1.01 [0.50, 1.52]		£24,666 [13,716, 35,615]
5	IT	50	M/S/P	-£7,864 [-10,163, -5,566]		1.81 [0.95, 2.67]		£43,994 [25,782, 62,205]
6	IT	50	S/P	-£12,644 [-16,538, -8,750]		2.73 [1.50, 3.96]		£67,329 [40,290, 94,369]
7	IT	50	P	-£16,017 [-20,988, -11,047]		3.46 [1.89, 5.03]		£85,291 [51,668, 118,913]

IT, intratympanic; M, moderate; S, severe; P, profound
All scenarios assumed the IHT to be 100% effective and cost £0
95% confidence intervals are shown between box brackets

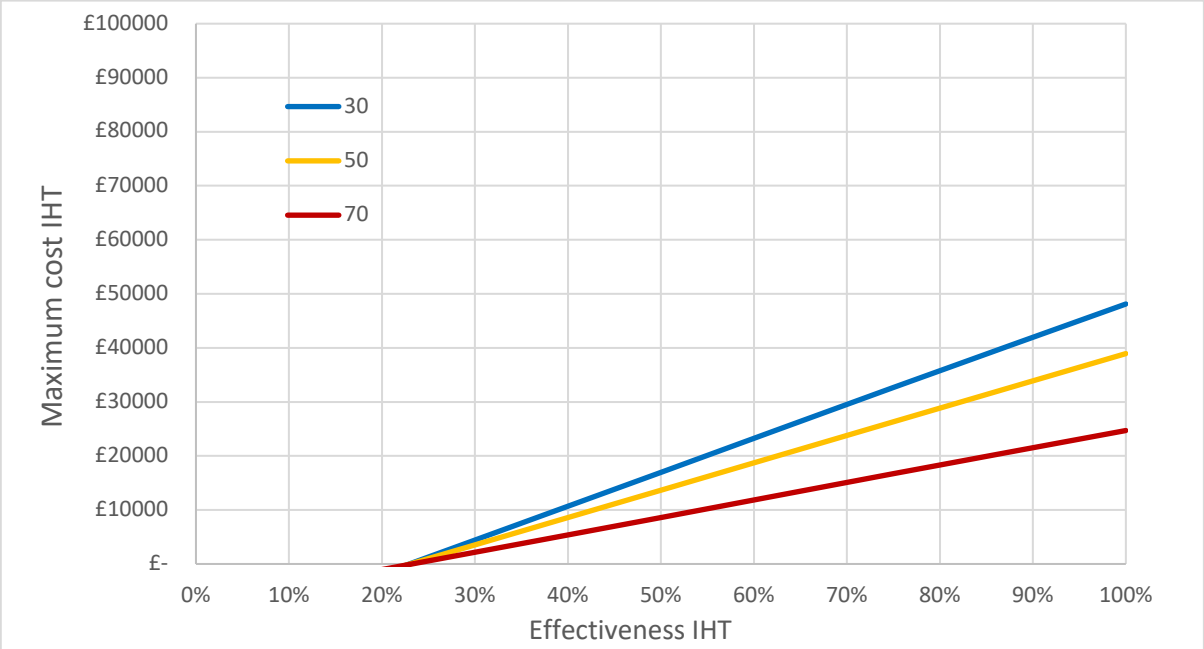
Scenario analysis

Table 11 shows the results of the scenario analysis. When compared to the headroom scenario (scenario 1), adding oral and intratympanic steroids to the IHT (scenario 2) has a minimal effect on the iNMB. Only treating 30 year old patients increases the iNMB to £48,125 [£25,848-70,403], whereas only treating 70 year old patients, decreases the iNMB to £24,666 [£13,716-35,615]. Increasing the severity of the hearing loss at onset increases the iNMB (scenarios 5, 6 and 7), owing to increasing costs of the current standard of care. All iNMBs carried wide confidence intervals (CI) that were greater than zero.

Threshold analysis:

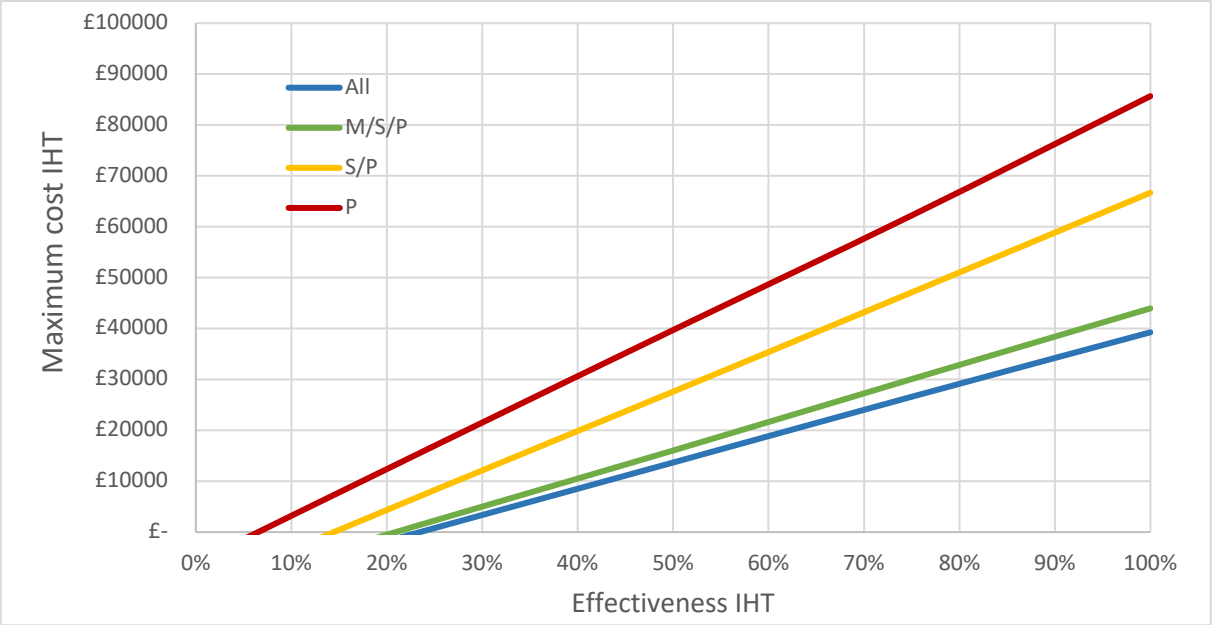
The threshold analysis is illustrated in Figures 4 and 5. The lines in the graphs represent an iNMB of £0, identifying 1) the maximal cost for each level of effectiveness, and 2) the minimum effectiveness required at each cost point, for the IHT to be cost-effective, compared to the current standard of care. For example, if age of onset of idiopathic SSNHL is 70 years, and the IHT is 75% effective, the maximum cost of the IHT in order to be cost-effective is £16,714, taking into account NICE's cost-effectiveness threshold of £20,000/QALY. Appendices 2 and 3 illustrate these results with confidence intervals.

Figure 4. Threshold analysis – starting age.



Appendix 6 illustrates the confidence intervals for these data

Figure 5. Threshold analysis - severity of hearing loss

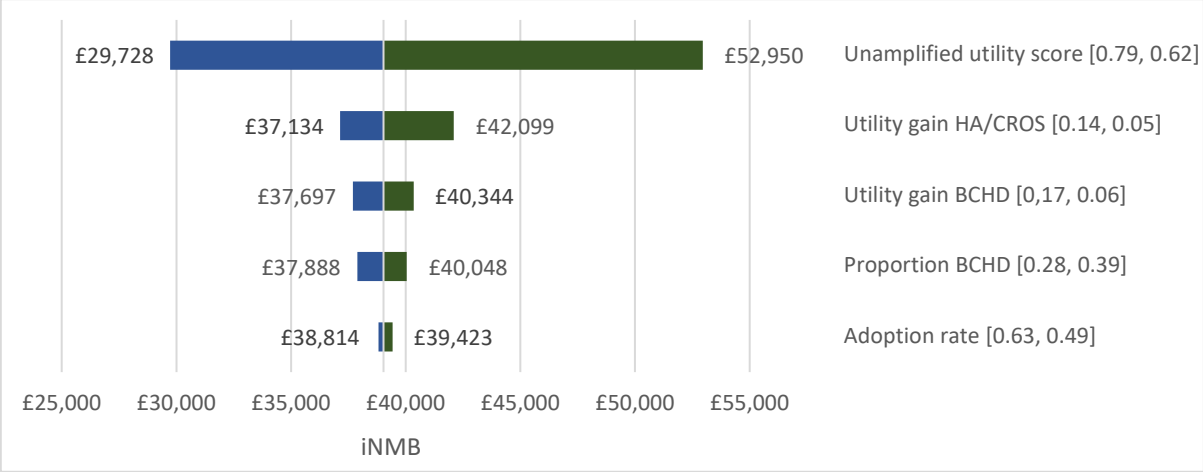


M, moderate; S, severe; P, profound. Appendix 7 illustrates the confidence intervals for these data

Sensitivity analysis

The results of the sensitivity analysis are shown in the tornado plot in Figure 6. Varying the parameter 'unamplified utility score' produced the largest impact on iNMB of the IHT. This was followed by utility gain following a hearing aid/CROS aid.

Figure 6. Incremental NMB variation in sensitivity analysis



The vertical line in the middle represents the iNMB of the headroom scenario (£39,032). 'Unamplified utility score,' 'Proportion BCHD' and 'Adoption rate' are taken as the mean 'Unamplified utility score,' 'Proportion BCHD' and 'Adoption rate' for mild, moderate, severe, and profound idiopathic SSNHL.

Discussion

Summary of findings:

The headroom analysis revealed an iNMB of £39,032 compared to the current standard of care. This means that in a perfect scenario, where an IHT were 100% effective and cost £0, the added monetary value of the IHT to a 50-year-old across their lifetime would be £39,032 compared to the existing standard of care. Along with cost and degree of effectiveness, the starting age of treatment and severity of idiopathic SSNHL at onset are major determinants of the iNMB for an IHT. The scenario and threshold analyses illustrate the uncertainty of my findings with wide confidence intervals.

Implications

There is clear room for improvement in the current standard of care for patients with idiopathic SSNHL in the UK healthcare system, and IHTs for idiopathic SSNHL can be cost-effective, making this an attractive area for discovery scientists, clinicians, investors, and decision makers. This model can be used by industry and decision makers to assess: 1) the maximum price-point of an IHT at different levels of effectiveness, and 2) the minimum effectiveness required at each price point, for the IHT to be cost-effective. The model allows for these assessments to be tailored to age of onset of idiopathic SSNHL and severity of idiopathic SSNHL, the two major determinants of cost-effectiveness as identified from my analysis.

By providing this information *before* a therapy has entered the market, my model will assist industry to develop IHTs that are cost-effective in the UK healthcare system. With a growing number of IHTs on the horizon, my findings will help investors, policy makers, regulators and guideline developers decide which therapies represent value for money and are worth commissioning. Overall, my research will increase the likelihood of developing IHTs that can be adopted into the UK healthcare system and therefore used by patients.

Future research

The wide confidence intervals presented demonstrate that more reliable data on transition probabilities and utility scores for the current standard of care are warranted to make more reliable estimates. Varying 'unamplified utility score' and 'utility gain following a hearing aid or CROS aid' produced the largest impact on iNMB for the IHT. Research to more accurately delineate these parameters would help improve the accuracy of this model. The SeaSHeL study, led by myself, is an ENT trainee and audiologist collaborative UK prospective cohort study of adult patients presenting with SSNHL across 97 NHS Trusts, with 653 patients recruited to date (www.seashel.co.uk).[98] The study is mapping the patient pathway and collecting data on the characteristics and outcomes of adult patients presenting with idiopathic SSNHL in the NHS. Utility data pre and post treatment are also being collected. I will utilise data from the SeaSHeL study to refine and validate this economic model.

Limitations

The precise treatment pathway for patients with idiopathic SSNHL varies between regions within the UK and between countries, despite published guidelines. As a result, my model cannot be fully representative of all treatment pathways. However, I expect similar trends in cost-effectiveness and my detailed account of the model allows for assessment of transferability to other situations. Owing to the hypothetical nature of the IHT, a drug safety profile of the IHT was not included, which would have an impact on the price of the IHT. The existing literature on idiopathic SSNHL is limited, mainly consisting of retrospective, heterogenous studies with different treatment regimens, including differences in time between hearing loss onset and start of treatment, as well as differing definitions of hearing loss severity and outcome. Data were also limited for calculating utility gain following hearing amplification strategies. Moreover, no data were available on the proportion of patients with idiopathic SSNHL receiving differing hearing devices, and hearing device non-compliance rates. For these data, I sought input from expert participants who also fine-tuned my model and validated my assumptions. Recognising the limitations of using data from expert participants, multiple (n=26) expert participants were recruited to validate my model; and a sensitivity analysis was performed to assess uncertainty. I acknowledge the wide confidence intervals in the scenario and threshold analyses but highlight that these

confidence intervals were all greater than zero, indicating that an IHT would be cost-effective compared to the current standard of care.

Costs were based on NHS England healthcare prices and may therefore differ from other countries. The same applies to expert opinions, which were mainly of a UK perspective. Finally, as with any health economic model, assumptions were made during its development. To mitigate bias, these assumptions were reviewed and agreed upon by multiple expert participants (n=26).

I acknowledge that an assessment of budget impact would have been complementary to this early health economic model and useful to stakeholders. However, no IHTs have been released on the market and there are no available estimates on potential price or associated monitoring costs. Assumptions for IHT price point for administration and monitoring would have been considerable and difficult to justify. Future research on the budgetary impact would be beneficial once estimates on IHT price point and monitoring become available.

Conclusions

This chapter describes the first health economic model for IHTs and shows that IHTs can be cost-effective under NICE's cost-effectiveness threshold, with considerable room for improvement in the current standard of care. My model can be used to inform the development of cost-effective IHTs; and help decision makers decide which therapies represent value for money and are worth commissioning. Insights gained during the development of this economic model were used to inform the topic guide and coding framework for Chapter 3.

CHAPTER 3: INTERVIEW STUDY

Introduction

Understanding the elements that determine the adoption and implementation of IHTs is important for stakeholders in the field.[99] This understanding can help industry and scientists develop IHTs that have a higher chance of uptake by healthcare systems. It can also be used by clinicians, patient groups and decision makers to prepare for promising upcoming IHTs and help increase access to people with hearing loss. For IHTs already developed, this information can be used to assess the potential for adoption and develop effective strategies to increase chances of uptake.

Implementation science offers the tools to provide this understanding by offering a foundation for exploring implementation processes, conceptualising the practical workability of new healthcare interventions and identifying strategies that can facilitate uptake of interventions into routine use.[55,100,101] It is described as the scientific study of methods to promote the uptake of research findings and interventions into routine practice, thereby improving the quality and effectiveness of health services.[54,102] Health economics, a branch of economics, can also be used to contribute to this understanding. Using empirical data and expert opinions, health economic models provide information on whether interventions represent value for money; and importantly their construction can also give information on the underlying motivations of stakeholders trying to influence uptake as well as their views on health economic modelling.

This chapter draws upon insights from a well-established implementation theory, Normalisation Process Theory (NPT) as well as the early health economic model on IHTs (Chapter 2), to perform a detailed investigation of the interacting elements that influence the adoption and implementation of IHTs in the UK healthcare system. NPT is a widely used implementation theory that explains the conditions in which interventions can become embedded within clinical work.[55] It has been empirically tested in a variety of areas, including mental health governance processes; telehealth and telemedicine systems;

decision support technologies; managing chronic illness; diagnostic tools for cancer; and others.[55,60,62,99] NPT has 4 key constructs: 1) Coherence, which describes making sense of the intervention. 2) Participation, the collective work people do to engage to bring the intervention into practice. 3) Action, mobilising skills and resources to make the intervention workable. 4) Monitoring, the appraisal work that people do to assess the novel intervention.

A number of other implementation theories were considered to inform this chapter, including the COM-B model,[103] the model of institutional readiness,[58] and the organizational readiness model.[57] The COM-B model proposes that there are three components to any behaviour (B): Capability (C), Opportunity (O) and Motivation (M). Capability comprises the knowledge and skills required to engage in a particular behaviour. Opportunity involves the external factors which make the execution of a particular behaviour possible (e.g., resource requirements); and Motivation describes the internal processes that drive the desire to carry out the behaviour.[103] The COM-B model highlights that interventions need to target one or more of these components to deliver and maintain effective behaviour change.[103] The model of institutional readiness,[58] is focussed on regenerative therapies and conceptualises how these therapies are adopted into organisational settings. It sets out the integral factors for healthcare systems to be ready for a new technology including demand for the new technology; strategic focus; relative need and benefit of the new technology; evaluation processes in place; enablers within and outside of the organisation; receptivity; adoptive capacity and sustainability.[58] The organisational readiness model[57] is focussed on the preparedness of organisational members to implement change. There are two key components: change commitment (the extent to which organisational members have the determination to implement the change); and change efficacy (the extent to which organisational members share a sense of confidence in their capabilities to implement change).[57]

Whilst any of these theories would have been useful in informing this chapter, NPT was considered particularly relevant because it has been specifically constructed to explain the processes by which interventions become routinely used in clinical practice and has been widely used in a number of clinical settings.[55,60,62,99] Moreover NPT has been developed for

use by clinicians and designed so that it can be used flexibly to shape the coding and analysis of qualitative research and construct other implementation theories.[55,60,62,99]

Objective:
To characterise and understand the elements that influence the adoption and implementation of IHTs in the UK healthcare system.

Methods

Ethical considerations

Ethical approval was granted by UCL Research Ethics Committee 11965/001.

Study design

The study adopted a qualitative design using semi-structured interviews, informal discussions, and non-participant observation. The methodological orientation underpinning the study was abductive analysis and the extended case method,[104] drawing on insights from the early health economic model described in Chapter 2 and NPT.[55] Abductive analysis is a qualitative data analysis approach that aims to extract meaning from observations to build a theory. The fundamental principle of abductive analysis is that it enables the researcher to start from existing theories, look for empirical surprises within observations that do not 'fit' within existing theories, and create a new theory that accounts for exceptions.[104] This form of analysis enables the researcher to benefit from existing theories whilst taking advantages of surprises during the research process. The extended case method describes the detailed study of empirical cases with a view to extract general principles from specific observations.[104] The method benefits from flexibility, giving researchers the licence to analyse and relate observations made at different time points and in different situations to construct meaning.[104]

Semi-structured interviews with participants

Participant selection

I wanted to interview and gain the perspectives of a broad range of stakeholder groups, so to gain a detailed understanding of the elements that influence the adoption and implementation of IHTs; and so that my findings will be useful to a wide range of stakeholders. Utilising my supervisors' extensive network within the field of IHTs I used a purposive sampling approach to select a core group of expert participants across the translational pathway. I categorised expert participants into the following groups: Market makers; Regulators and policy makers; End users. Market makers describe the participants that develop IHTs or work to drive the uptake of IHTs. Regulatory and policy makers include participants involved in IHT regulation and policy making as well those involved in health economics and generating clinical evidence. End users include those that will use, pay for and provide IHTs. Table 12 provides an overview of included participants. Participants were contacted via email, including a study information sheet (Appendix 8). I also utilised a snowball sampling technique in order to sample a variety of perspectives. At the end of each interview, I asked interviewees to propose other participants relevant to this study and specifically participants that may have different perspectives to their own. Following discussion with my supervisors, these participants were purposively sampled. Participants identified via this snowball sampling technique were also approached via email invitation which included a study information sheet. My methods of participant recruitment resulted in a heterogenous sample of key participants from many different contexts. Thirty-seven participants were interviewed.

Table 12: Overview of participants

Market Makers	Number of participants	Perspective
Representatives from organisations facilitating/driving implementation of medical therapies	3	UK
Representatives from Contract Research Organisations (CRO's)	2	Europe, US
Representatives from biotechnology, pharmaceutical and hearing technology companies developing IHTs	6	UK, Europe, US, Australia
Representatives from hearing technology companies developing existing hearing devices	3	UK, Europe, US, Australia
Discovery and Clinical scientists in the field of IHTs	11	UK, Europe, Australia, Asia
Representatives from other specialities with experience in implementing innovative therapies	2	UK, US, Canada, Asia
Regulators and policy makers		
Representatives from healthcare regulators	3	UK, US
Representatives from policy organisations	4	UK, Europe, US, Asia
Health economists	2	UK, Europe
Experts in health policy	3	UK, US, Canada, Asia
Experts in clinical trials	4	UK, US, Europe
Representatives from research funding bodies	1	UK
Experts in medical ethics	1	UK, Australia
End Users		
Ear Nose and Throat Surgeons with a specialist interest in otology and knowledgeable in the field of IHTs	5	UK, US, Europe
Audiologists knowledgeable in the field of IHTs	3	UK, US
Senior representatives from ENT and Audiology bodies	4	UK, US, Europe
Representatives from the Royal College of Surgeons with an interest in innovations in surgery	2	UK
Representatives from hearing loss charities	1	UK
General Practitioners	1	UK
Representatives from private providers of hearing services	4	UK, US

Semi-structured Interviews

Participation was voluntary, informed consent was obtained and all transcripts were anonymised. Interview transcripts formed the formal data for analysis. I interviewed participants in person or via telephone between June 2019 and February 2020. The initial topic guide was theoretically informed by NPT. More specifically, NPT offers a translational framework to support qualitative investigation.[105] This translational framework focusses on four domains including 1) Social structural resources, 2) Social cognitive resources 3) Capability, 4) Contribution; and contains suggestions of questions that can be used flexibly to inform interview schedules. I used this framework to inform my baseline interview questions. My baseline interview questions were also informed by insights gained during the construction of the early health economic model (Chapter 2). These insights were developed via hand-written, anonymised, field-notes taken during and after 26 interviews I carried out with experts and patients (Table 3) to validate my early health economic model, and recorded reflections on: the underlying meaning and effects of health economic models; perceptions of health economic modelling; the strategic intentions of stakeholders trying to steer the adoption of IHTs into healthcare systems. I also recorded insights following question and answer sessions of my presentation of the early health economic model at 8 international conferences, as well as following discussions with my PhD supervisors.

The topic guide (Appendix 9) followed an interview schedule comprising 14 questions, each of which contained specific probes. The specific questions asked within the topic guide and the extent to which probes were explored depended upon the area of expertise of each participant. Individual interviews lasted between 30 and 70 minutes and were digitally recorded and transcribed. I made contemporaneous notes alongside the recordings. Data analysis commenced after completion of the first interview, and subsequent interview schedules evolved iteratively. Changes made to interview schedules were audited together with reasons for changes.

Field notes, informal discussions, and non-participant observation.

I took hand-written, anonymised, field-notes throughout the study to capture informal discussions amongst participants and non-participants (those not interviewed during this

study) pertinent to the research question. Such notes were taken during question-and-answer sessions at conferences, meetings and presentations as well as in my role as: Study lead for the SeaSHeL Study (the largest prospective cohort study of adult patients presenting with sudden hearing loss, with over 700 patients recruited), Delegate Principal Investigator for the REGAIN trial (the first clinical trial of an IHT), Associate Principal Investigator for the Audible-S trial (investigating a first-in-class drug for sudden hearing loss) and as an ENT NHS clinician. Field notes taken during and after the 26 interviews I carried out with experts and patients to validate my early health economic model (Chapter 2) were also included. These notes were intended to help generate meaning and develop an understanding of the elements that shape the adoption and implementation of IHTs. This process also enabled engagement with a wider range of stakeholders than would have been possible with formal interviews alone.

Analysis

Data analysis was performed using the principles of abductive analysis and the extended case method.[104] NPT's translational framework[105] contains suggestions of categories within the domains Social structural resources, Social cognitive resources, Capability, Contribution that can be used flexibly to develop a coding framework. I used these suggestions together with insights gained during the construction of the early health economic model (Chapter 2) to develop my initial coding framework. Table 13 displays my initial coding framework that further evolved as interviews were analysed. This method of analysis benefitted from permitting the use of the empirical and well-established NPT to guide analysis, whilst capturing empirical surprises.

Table 13: Baseline coding framework

Social Structural Resources	
	Change in roles
	Changes in practices and norms
	Knowledge needed
	Resources needed
Social Cognitive Resources	
	Attitudes
	Motivation
Capability	
	Integration
	Interactions and coalitions
	Role of cost-effectiveness
Contribution	
	Becoming skilled
	Collection action
	Making sense and coherence
	Reflective monitoring

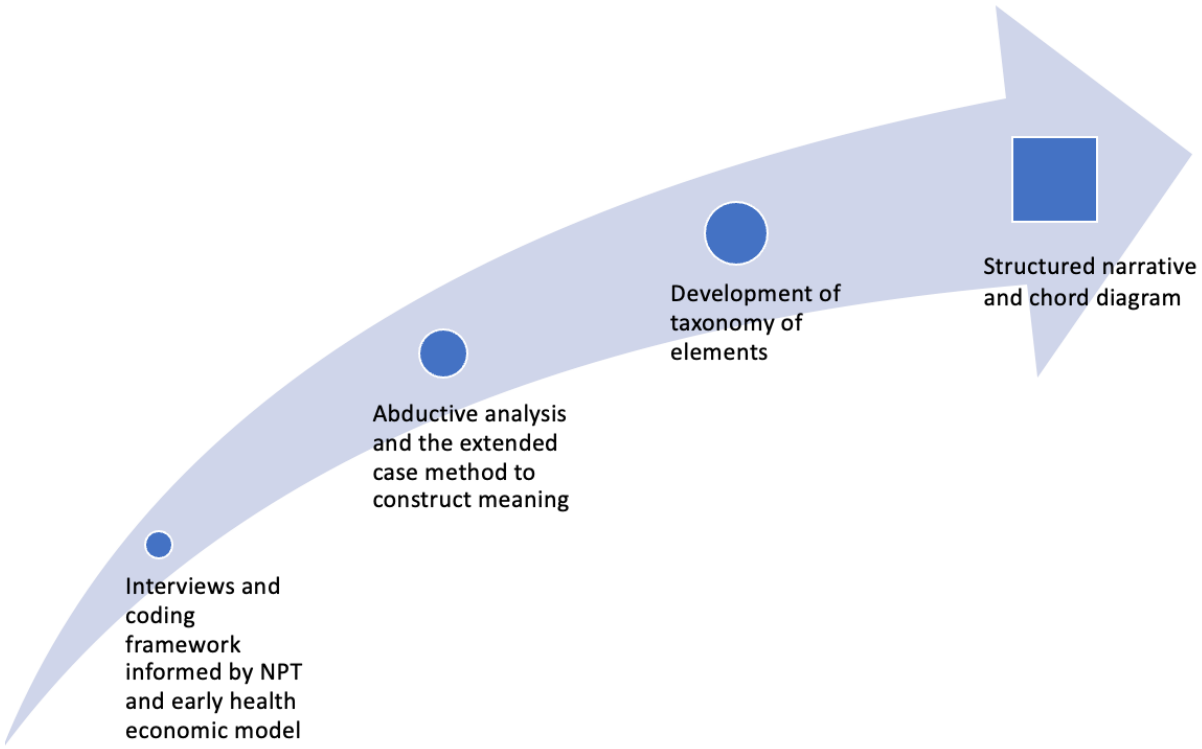
Data analysis was continuous. I coded empirical materials and extracted data using the evolving coding framework, scrutinising for surprises, whilst focusing on the research objective. Data was stored, organised, and analysed using NVivo 12. One PhD supervisor (CM) read a sample of transcripts and cross-checked the data extraction process. The constant comparative method of qualitative analysis, which describes the analytic process of comparing different pieces of data against each other for similarities and differences,[106] was used to regularly and systematically compare and assess codes across the coding framework (across dataset, time, and inter-situation). Abductive analysis was used to extract and construct meaning from the data, taking into account empirical surprises which added to the meaning making process. Detailed memos were developed to describe emerging conceptualisations and record the development of a taxonomy that summarises and describes the interacting elements that influence the adoption and implementation of IHTs in the UK healthcare system. Separate memos were maintained to identify how different elements interact to influence adoption and implementation.

Memos were then synthesised to produce:

1) A structured narrative that characterises each element, explaining how each element influences adoption and/or implementation and explaining how elements interact with one-another to influence adoption and implementation of IHTs in the UK healthcare system.
2) A chord diagram that identifies how different elements interact to influence implementation and adoption processes in the field of IHTs in the UK healthcare system.

I discussed my coding and analyses at regular intervals during meetings with my supervisors to reduce bias. Figure 7 illustrates the process of my analysis.

Figure 7. Overview of analytic process



Results

Qualitative analysis revealed 27 elements that influence the adoption and implementation of IHTs in the UK healthcare system. During the process of qualitative analysis, a taxonomy of categories was developed to help organise and present elements. These categories include:

1) Contexts (The setting or environment in which an IHT will be adopted and implemented)
2) Preconditions (Factors that need to be considered prior to IHT release onto the healthcare market)
3) Activities (Activities that can be carried out to facilitate IHT adoption and implementation)
4) Decision making mechanisms (Processes of reasoning that need to take place for IHT adoption and implementation)
5) Consequences (Consequences following the adoption of an IHT that influence implementation)

Table 14 presents the 27 elements, allocated to each category. The ordering of elements within each column reflects the order in which each element is explained in the narrative summary below.

Table 14: The elements that influence the adoption and implementation of IHTs in the UK healthcare system.

Contexts (The setting or environment in which an IHT will be adopted and implemented	**Preconditions** (Factors that need to be considered prior to IHT release onto the healthcare market)	**Activities** (Activities that can be carried out to facilitate IHT adoption and implementation)	**Decision making mechanisms** (Processes of reasoning that need to take place for IHT adoption)	**Consequences** (Consequences following the adoption of an IHT that influence implementation)
Complexity of the UK healthcare system	Developing alliances between clinicians, scientists and industry	Collecting real world data	Sense making	Resource requirements
Current practices	Developing alliances amongst healthcare professionals and scientists	Providing patient and public information	Regulatory and decision making processes	Raising investment for research, development and procurement
Clinician perspectives	Early evaluation and evidence of effectiveness and safety	Working with accelerator organisations	Cost-effectiveness analyses	Payment strategies
Patient perspectives	Education and training	Developing coalitions between companies	Ethical considerations	Change in clinician roles
Motivations for adoption and implementation	Route of administration	Developing a business case		Impact on hearing healthcare services
	Indication	Developing precision diagnostics		Minimising impedance

An interactive chord diagram has been developed that illustrates which elements interact to influence the adoption and implementation of IHTs in the UK healthcare system. This interactive chord diagram can be most easily and clearly viewed using the following link: https://public.flourish.studio/visualisation/2042271/

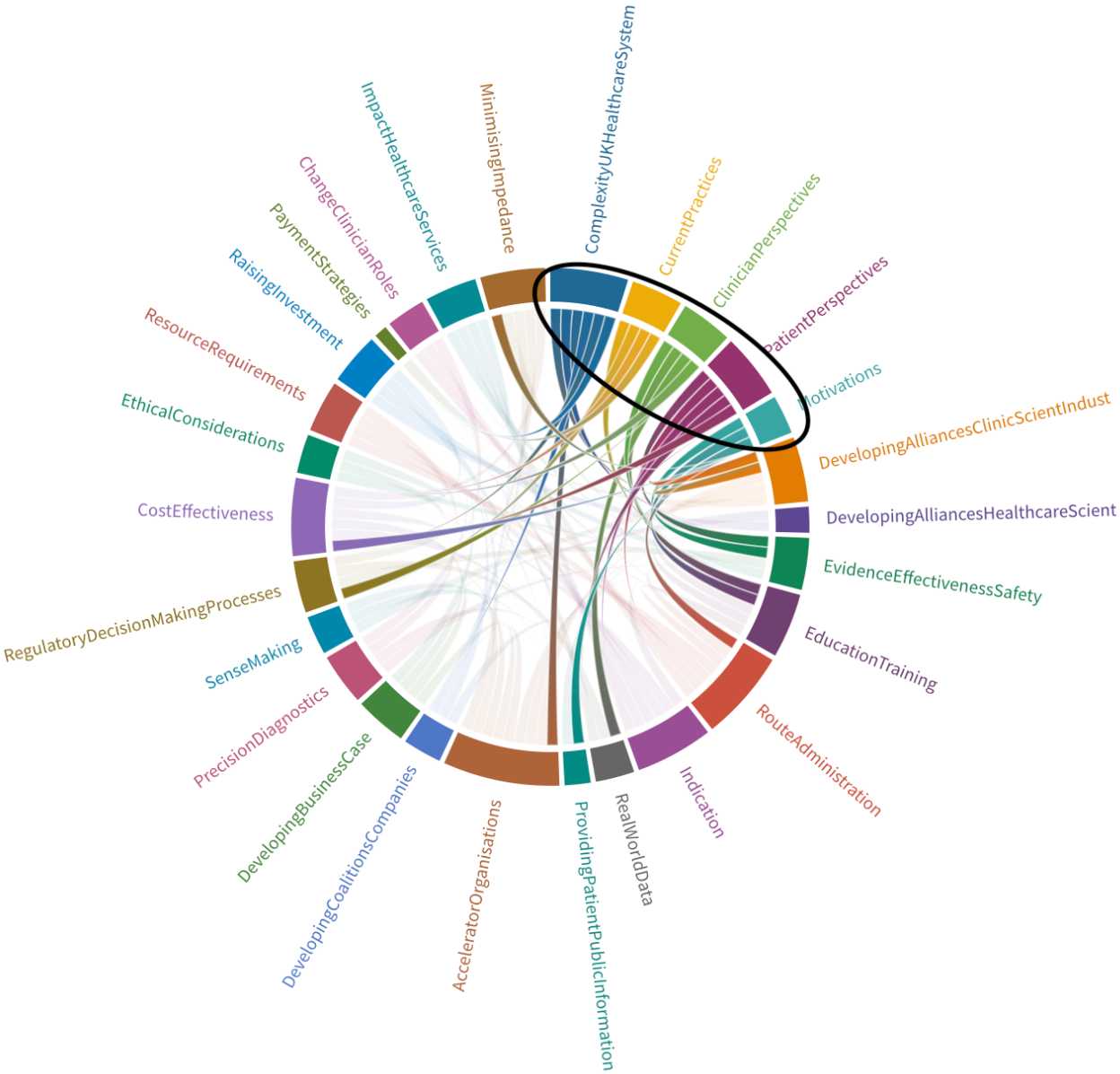
Clicking on a specific element in the chord diagram will show the elements it interacts with. This helps illustrate the complexity of the adoption and implementation of IHTs, how elements are interconnected and the importance of having an awareness of different elements, rather than focusing on individual elements in isolation.

For ease of reference, I have inserted 'snapshots' of the chord diagram within this results section, which relate to each of the columns in Table 14.

The narrative below explains each element in Table 14 and also explains how elements interact to influence the adoption and implementation of IHTs in the UK healthcare system.

Contexts *(The setting or environment in which an IHT will be adopted and implemented)*

Figure 8. Snapshot of chord diagram for elements within column 'Contexts'



Complexity of the UK healthcare system ***(The UK healthcare system is seen to be complex for the purposes of adoption and implementation)***

- The complexity of the UK healthcare system and its regulatory processes may act as a deterrent to companies looking to introduce or invest in IHTs and makes adoption and implementation challenging and slow.
- Working with accelerator organisations and developing strategic alliances with stakeholder groups can help navigate the UK healthcare system.
- UK regulatory bodies are working to simplify and assist in the navigation of the UK healthcare system.

The UK healthcare system including its NHS, was considered by participants to be inflexible and complex; and that as a result, adoption and implementation of IHTs may be challenging and slow. Participants expressed that the underlying complex decision making and regulatory mechanisms of the NHS make it difficult to plan for the adoption of IHTs, and that more of a reactionary approach is taken by decision makers, introducing uncertainty and risk. This leads to apprehension amongst biotechnology companies, hearing technology companies, discovery scientists, investors and key opinion leaders (KOLs) to introduce innovative therapies into the NHS.

> DiscScien1: *"Getting something taken up by the NHS is just so complex and challenging. It's easier to change the therapy itself, to the detriment of the therapy, rather than negotiate or work towards changing the system."*

The complexity of the NHS and it's decision making processes was seen as a key deterrent to companies, particularly those with more limited resources, such as start-ups, who may be unable to endure the lengthy and expensive process of adoption into the NHS. Smaller companies therefore may decide to avoid the NHS and focus their efforts on other healthcare systems, and once better-established may then seek entry into the NHS. As a result, the NHS may be at risk of losing out on potentially innovative therapies developed by start-ups. Participants expressed that NHS decision makers, owing to resource limitations, are risk-averse and tend to adopt therapies that are 'low risk' of being financially wasteful.

Truly innovative therapies that carry inherent risks and challenges are generally met with more resistance by NHS decision makers, making adoption challenging.

> RepHearDevComp1: *"I mean part of our strategy is actually to avoid the NHS like the plague….. If you are developing something from scratch, that is truly novel and there's inherent risk around it, then you'd be quite foolish, I think, to see the NHS as your primary customer."*

To help navigate the complexity of the NHS, participants discussed that companies developing IHTs would benefit from working with organisations with a detailed understanding of the NHS that can help accelerate adoption (see element 'Working with accelerator organisations'). Similarly, companies would benefit from establishing alliances with groups within the NHS, including existing hearing technology companies and clinicians with a detailed understanding of the inner workings of the NHS, its research infrastructure as well as potential levers for decision making and uptake (see elements 'Developing alliances amongst healthcare professionals and scientists', 'Developing coalitions between companies' and 'Developing alliances between clinicians, scientists and industry').

UK decision making and regulatory bodies recognise that their processes are complex and are working to simplify and assist in the navigation of the UK healthcare system to break down barriers and facilitate uptake of innovative therapies (see element 'Regulatory and decision making processes').

Current practices *(Current clinical practices will influence uptake of IHTs)*

- The uptake of IHTs will be influenced by the safety, effectiveness and cost of existing treatments as well as areas of unmet need.
- Companies developing IHTs and their KOLs should clearly articulate areas of unmet need to boost demand for IHTs.

Participants expressed that successful integration and acceptability of an IHT is highly dependent on how effective existing treatments are, their costs, risks and how they are perceived by patients, clinicians and decision makers. IHTs will need to address areas of unmet need within the current standard of care; and will need to compete with existing

hearing interventions, particularly in terms of effectiveness and cost to warrant adoption, or could be combined with existing interventions. Existing interventions for SNHL have limitations, which are well acknowledged by hearing healthcare professionals, however potentially less so by members of the public and decision makers.

> ClinScien1 "*Right now, hearing aids augment existing function but they don't replace absent function. Cochlear implants replace function, but only to a certain degree because of the limitations of how electrical stimulation directly to the auditory nerve can impact hearing. But if you can completely restore hearing that would just profoundly change things - imagine telling a seventy-year old they can have hearing like they did when they were twenty; that would be pretty terrific."*

Participants discussed that cochlear implants, whilst being potentially transformational have disadvantages including: being difficult to access with strict indications; involving an invasive operation under general anaesthetic that inherently damages the inner ear; and requiring long-term maintenance. Moreover, cochlear implants are limited in terms of not replacing normal hearing, rather serving more as a topographic amplifier. Participants also noted that hearing aids have relatively poor uptake and compliance, with many patients disappointed with their performance, particularly in background noise, and frustrated with maintenance issues. There were also views that current hearing aids and cochlear implants are unjustifiably expensive. These limitations of existing interventions represent areas of unmet need and opportunities for IHTs, and this is well recognised by hearing technology companies, biotechnology companies as well as investors.

> DiscScien1: "*Strictly speaking, hearing aids and cochlear implants are not actually treatments. They are devices, they don't actually change the underlying phenomenon, so there is huge scope for novel therapeutics."*

Participants discussed the importance of clearly articulating the limitations of existing treatments as well as unmet need, so that patients, the public, decision makers and investors can make sense of the need for IHTs, driving motivations to support their adoption (see elements 'Sense making' and 'Raising investment for research, development and procurement'). However, at the same time, it is important to keep expectations realistic, considering the relative infancy of the field.

Clinician perspectives *(Clinician perspectives will influence the uptake of IHTs)*

- Clinicians can be sceptical over the evidence base for the clinical and cost-effectiveness of innovative therapies in general. Use of real world data appears more convincing to clinicians.
- ENT surgeons and audiologists appear to be well-invested in current strategies; early clinician training will help increase clinician engagement and uptake of IHTs.

Clinician participants discussed that the entry of IHTs could increase awareness and publicity of hearing loss, potentially leading to increased patient demand for both IHTs and current hearing interventions. This increase in demand could destabilise existing UK hearing services, which are already under pressure and experiencing funding cuts. The introduction of IHTs would therefore need careful planning with the development of efficient treatment pathways (see element 'Impact on hearing healthcare services').

> GP1: "*I have some reservations with anything that's new and that's not because I am a luddite, it's scepticism based on experience. The problem is that the demand could potentially be massive, and it could cause some destabilising influence into an already quite unstable system.*"

Clinicians also expressed scepticism over the evidence base for the clinical and cost-effectiveness of innovative medical therapies in general; including over evidence traditionally considered to be of high quality, such as randomised controlled trials (RCTs). Owing to their controlled nature, there were concerns that evidence from RCTs may not be representative of the real world, and due to publication bias, have a tendency to report positive findings. Concerns were also raised that cost-effectiveness analyses can be overly reliant on assumptions and used by decision makers to stifle clinical decision making as well as reduce healthcare costs. Clinicians therefore may be unconvinced by such research, impacting their decision to use innovative therapies for their patients. Real world data (data collected systematically from routine clinical practice) was considered more influential in informing clinical decisions (see elements 'Collecting real world data' and 'Cost-effectiveness analyses').

> ENT1 "*with the best will in the world, any evidence, including cost-effectiveness evidence of these new shiny things that's produced by manufacturers will be biased, and then they get approved and integrated into the system and by then, the genie's out the bottle and it's too late when post-marketing surveillance proves that it's not very effective. This is the pattern we see again and again."*

Clinician participants recognised the considerable investment required for the uptake of innovative therapies and conveyed a sense of responsibility towards the sustainability of the NHS. Drawing upon previous experiences of using costly, and disruptive therapies that were later found to be ineffective, clinicians expressed that using 'real world data' would reduce the risk of adopting ineffective, and ultimately wasteful therapies.

Participants discussed that ENT surgeons and audiologists appear generally well-invested in current strategies and devices, owing to their training, current skill-set, embedded practices and long-term relationships with existing hearing technology companies that have participated in their education. Further that there seems to be a relative paucity of awareness amongst ENT surgeons and audiologists about IHTs, which are often considered to be a distant ambition. As a result, many clinicians are not engaged with the field, which may represent a barrier to future adoption. Senior hearing healthcare professionals with considerable experience and competence in current treatments may resist taking up IHTs owing to apprehension around whether their existing skill set will become less useful; and the potential undesired requirement to carry out training in a novel field. These perspectives highlight the importance of early clinician education and training on IHTs which can help break-down: engrained clinical practices, insecurities and challenges of using IHTs, as well as vested interests or allegiances with existing hearing technology companies (see element 'Education and training').

Patient perspectives *(Patient perspectives on IHTs will influence their adoption and implementation)*

- Patients appear enthusiastic for IHTs owing to current unmet need.
- Patients may be willing to undergo invasive treatment if their hearing is sufficiently poor and if the therapy is effective.

- Patients appear most convinced by research carried out in real world settings, and by research outcomes that are understandable.

Patients were considered a crucial stakeholder group, exerting considerable influence on decisions made by policy makers, payers and clinicians on innovative therapy adoption and implementation. Therefore, gaining patient input and buy-in appears to be an important lever for IHT adoption. This has been recognised by biotechnology companies developing IHTs who are investing in building relationships with patient groups (e.g., through sponsoring events) (see elements 'Providing patient and public information' and 'Developing alliances amongst healthcare professionals and scientists').

It was discussed that patients are enthusiastic for IHTs to be brought into the UK healthcare system, owing to limitations with existing devices and perceived lack of advancements in the field. Patients expressed preference for less invasive, medical (as opposed to surgical) strategies, with a low risk profile, performed in an out-patient setting. However, patients appear willing to undergo invasive surgery with the risk of potential complications provided that their baseline hearing is sufficiently impacting their quality of life and the therapy is effective. Patients may also be more willing to undergo invasive, higher risk procedures for regenerative, rather than protective therapies (see elements 'Route of Administration and 'Indication')

> Patient1:*"Obviously I would prefer a minimally invasive treatment, like a tablet, but if I had a considerable hearing loss and was offered an invasive operation that would regenerate my hearing mechanism, I'd certainly take it – it all depends on how desperate you are. I'm not sure if I'd take the risk of an invasive operation to protect my existing hearing."*

Concerns were raised that the evidence base for existing hearing devices and for IHTs are poorly accessible to patients, who are often unable to understand research findings and access the research owing to permission restrictions. It was considered that patient input should be sought in the writing and dissemination of research findings to improve accessibility, helping to stimulate patient demand for IHTs, exerting pressure and influencing decisions made by decision makers (see element 'Raising investment for

research, development and procurement'). This can be facilitated through involving patient representatives from the beginning of the research process. It was also discussed that patients are sceptical over research generated by industry and are most convinced by research that is conducted on the everyday patient in their usual environment. Patients also appear to be influenced by patient testimonials and by outcome measures that are understandable to patients, such as improvements in quality of life rather than commonly used audiological outcomes such as the Pure Tone Audiogram, which was considered to not accurately reflect hearing ability.

There was a degree of mistrust amongst patients towards private hearing aid providers, who were considered to be financially driven; and it was suggested that there may be more appetite for IHTs uptake if provided by government rather than private providers.

Motivations for adoption and implementation *(The underlying motivations of stakeholders will influence IHT uptake)*

- Delivering patient benefit, curiosity, and raising the profile of ENT surgery appear to be strong motivators for clinicians to adopt IHTs.
- Gaining recognition by delivering IHTs can be a motivating factor for clinicians and hospitals.
- Good evidence of effectiveness and safety appears a powerful motivator for hearing loss clinicians to provide IHTs, and for patients to seek them.
- Financial reward appears the primary motivator for companies and investors.
- Researchers also appear to have financial motivations.
- Patient demand for IHTs may be a powerful motivator for healthcare systems and clinicians to provide them.

Clinician participants expressed that patient benefit would be their main motivator for taking-up IHTs. Current treatments for SNHL do not fully meet the needs of patients and addressing this unmet need, improving patients' ability to communicate and function is a strong motivator. Some senior hearing loss clinicians have stepped away from busy hospital practices to join biotechnology companies, believing that this collaboration will promote the

development of IHTs that can transform lives. Curiosity in generating new knowledge and in developing novel, potentially minimally invasive transformative therapies and mastering their use appears to be another strong motivator amongst hearing loss professionals.

> DiscScien3:"*I think there's quite a lot of people who are motivated by curiosity. Hearing loss is a very understudied area, and there is an inherent interestingness of the sorts of questions that need to be answered and there is a real a joy of doing that sort of exploration discovery.*"

ENT surgeon participants discussed that their speciality is relatively poorly evidence based and less 'cutting-edge' when compared to other surgical specialities, receiving less attention from decision makers, funders and the media. They would be motivated to lead the delivery of IHTs to raise the profile and demand of ENT surgery, helping to compete with other surgical specialties and realising that if they fail to do so, other allied specialties may take the opportunity.

> ENT4: *"I've just been preparing a talk for a public meeting and some of our treatments in the past have been so poorly evidence based that it's almost embarrassing and we need to move with the times to protect our work and our speciality. At the end of the day if we are refusing to accept new practices and move with exciting innovations, we'll be left behind and somebody else will come in and take that role and that could be the audiologist or AVM [audio vestibular medicine physician]."*

Another motivation for IHT adoption by hearing healthcare professionals is gaining recognition from their peers and patients as being at the forefront of their field. This can provide opportunities for developing links with industry, whilst increasing demand from patients, leading to potential financial benefits, via private practice, sponsored travel, paid lecturing and research funding. Conversely, some professionals may be motivated by fear of being viewed as a laggard, forcing themselves to adopt IHTs. Hospitals may be motivated to use IHTs to generate publicity, and to establish themselves as a centre of excellence, which could attract more patients to the hospital generating revenue and making hospitals more attractive to leading clinicians.

Good evidence of effectiveness and safety is a powerful motivator for hearing loss clinicians to provide IHTs, and for patients to access them. Such evidence would also be encouraging to discovery scientists, potentially validating their research, and demonstrating to funders that hearing loss is a growth area, worthy of further investment (see element 'Raising investment').

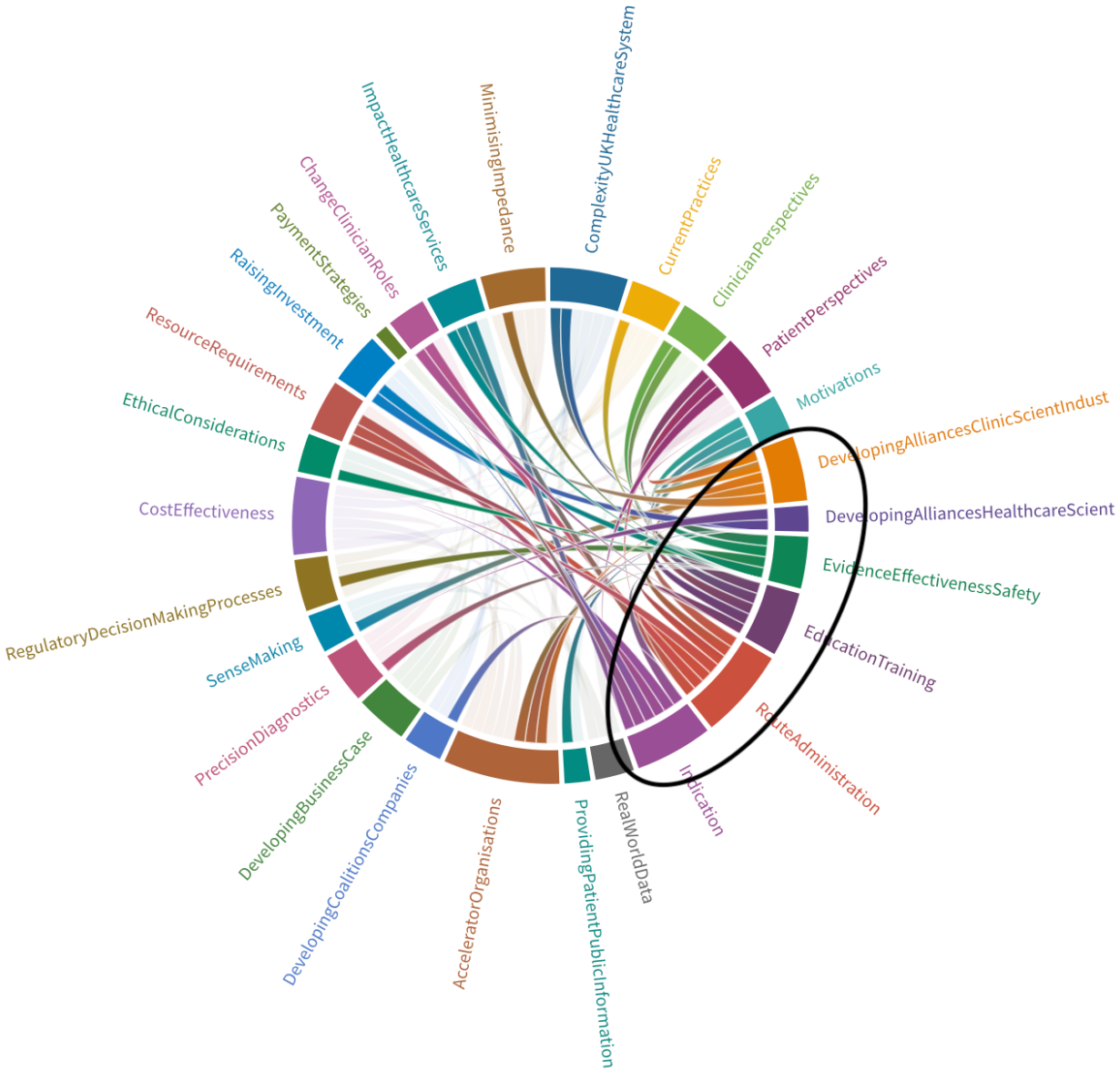
Financial reward appears the primary motivator for companies and investors. SNHL is the most common sensory deficit in the world, and an effective IHT has the potential to make sizable returns. This is well understood by clinicians, scientists and healthcare providers, leading to scepticism over studies sponsored by companies. Companies also appear motivated by patient benefit, and therefore may engage to make the therapy as widely accessible as possible, however financial interests would be prioritised. Researchers also seem to have financial motivations, to explore research avenues more likely to result in research funding, enabling them to maintain and grow their research units.

> RepNovTherComp2: *"I mean, the bottom line is that sensorineural hearing loss is the most common sensory deficit in the world, and if anyone can come up with a treatment for this is going to make billions of dollars. So money is the main driver in all of this for companies."*

Participants conveyed that patients would be enthusiastic to receive IHTs, as demonstrated by high patient recruitment rates in clinical studies; and patient demand for IHTs will be a powerful motivator for healthcare systems and clinicians to provide them (see elements 'Education and training' and 'Raising investment for research, development and procurement'). Healthcare systems that refuse access to effective novel interventions often experience considerable push-back from patients, patient support groups and the media, with potential political pressure.

Preconditions *(Factors that need to be considered prior to IHT release onto the healthcare market)*

Figure 9. Snapshot of chord diagram for elements within column ‘Preconditions’



Developing alliances between clinicians, scientists and industry *(Developing alliances between clinicians, scientists and industry can facilitate adoption and implementation)*

- Working with biotechnology companies can provide the resources needed to take discoveries to market as soon as possible.
- Biotechnology companies developing IHTs are looking to form alliances with clinicians to establish ‘diffusion networks.’
- Alliances between clinicians, scientists and biotechnology companies can bring challenges; potential solutions are discussed.

Participants discussed that clinicians and scientists in the field of IHTs are gradually changing their strategies on translation, whereby they work within a traditional university and government grant structure to develop the science; and then form 'spin-out' companies that raise investment, or that are acquired by established biotechnology companies, to support translation of a therapy. University and government funding and infrastructure provide the 'seed funding' for discovery science but are insufficient to translate the basic science into viable and deliverable therapies. This translation requires long-term investment and diverse skill-sets that are available through biotechnology companies with sizeable resources to develop and commercialise innovative therapies (see element 'Raising investment for research, development and procurement').

> ClinScien4: "*Government grants are mostly staffed by basic scientists whose focus is maintaining discovery research funding and they fundamentally feel that the practical research outcomes of a new therapeutic is not interesting and really should fall to industry. So you get hardly anywhere with the Government funding agencies. Also the amount of money that's involved is just not enough. When I was working in the university setting, our typical grant would be about $250,000 a year, and to get the work done that we're doing to advance these programmes we're burning through about $40 million a year and it's just the level of science is much more rigorous."*
>
> ClinScien5: *"The coordination of our basic science with industry expertise in bringing this to application and commercialisation is really very important, because many of the ideas that are generated through the basic science research lack the business acumen and the ability to bridge what we call the 'Valley of Death'. A great idea may not make it over the 'Valley of Death' if it doesn't have the right application on the business side."*

Some senior, esteemed clinicians and scientists with rewarding positions in universities and hospitals have moved to establish or work within biotechnology companies, foregoing career stability and capitalising on intellectual property early, to work within a stimulating and resource-rich environment and to take their discoveries to market as soon as possible, in the hope of providing IHTs to patients and transforming the field (see element 'Motivations for adoption and implementation').

ClinScien2: "*I think this [moving to work for a biotechnology company] has more potential to transform the lives of humans and to transform the field [as compared to] anything that I have ever worked on before, and from a practical standpoint, you cannot accomplish this in a university setting."… "I used to think, when I was naïve, that if I had a great idea, I would convince the world that it was a great idea and that everything would take care of itself, but it doesn't work that way. These therapies require a large upfront investment, and it's not the kind of investment that the NIH [National Institutes of Health] makes, it's the kind of investment that venture capitalists make, and if it wasn't for that, this stuff wouldn't happen. I mean, it would be impossible to me do this research if I didn't make the move from university to industry."*

Universities appear to be encouraging academics to work with industry to maximise and monetise the benefits of academic innovation, whilst sharing the financial benefits, rather than seeing them all pass to industry. Similarly, some government organisations encourage leveraging of their funding to generate investment from industry, realising that this is crucial for translation. Their 'seed funding' can work to de-risk early-stage projects and attract larger scale funding from industry. For instance, the NIHR Invention for Innovation (i4i) programme provides funding for early-stage projects that have strong potential for commercialisation and are attractive to investors.

RepOrgImp2: "*There's a growing desire for universities to be seen as entrepreneurial hotbeds. So there is a bit of top-down pressure on academics to spin out companies fairly quickly, because it's a great IP revenue generator for universities."*

Participants considered that biotechnology companies are able to take a longer-term view on innovative therapies than government funders, recognising that a positive signal for a therapy, albeit with limited indications, may lead to further opportunities, resulting in sizeable future returns (see in element 'Raising investment for research, development and procurement'). Many IHTs under development focus on orphan diseases with limited patient numbers; and such disease-targets would struggle for government funding support, typically reserved for diseases affecting larger patient populations. It was also conveyed that companies developing IHTs are looking to work with clinicians to establish 'diffusion

networks', recognising that decision makers, patients and the public are sceptical over information provided by industry, whilst clinicians are considered trustworthy and have access to well-established credible networks to promote IHTs (see elements 'Patient perspectives' and 'Education and training'). Involving clinicians in designing and delivering trials can also act a potent premarketing tool and gain clinician buy-in at an early stage.

> RepCRO1: *"Pharmaceutical companies often do most of their premarketing at the time of the clinical trial, especially phase II and III, where you can convince the doctors involved in the trial, and these are the very people that become the champions, who are going to use your drug, spread the information, get attention from other doctors and the community and give confidence to others and create the buzz around your drug …. We also use our clinical trials as a kind of training tool, the doctors that are involved in the trial become confident in the drug and feel involved in its development and want it to be successfully rolled out."*

Companies developing IHTs discussed that they plan to sponsor clinician training and conferences to establish strong relationships with clinicians and develop KOLs with influence over their clinical group (see element 'Education and training'). Clinicians and in particular KOLs can provide access to patients as well as important feedback into the ongoing development and testing of IHTs. Trainees were considered an excellent conduit for dissemination, frequently moving between centres. Biotechnology companies are therefore keen to work with clinicians across the translational pathway from therapy development to training and implementation, and finally to long-term monitoring of safety and effectiveness, recognising that this increases credibility and the chances of long-term uptake. The relationship between clinicians and industry appears 'looser' in developing countries where industry can provide direct concessions to clinicians to help drive uptake.

These alliances between clinicians, scientists and biotechnology companies can also bring challenges. Working across government and industry can lead to difficulties in prioritising interests, such as where intellectual property lies. Non-disclosure agreements (NDA's) typically taken between academic groups and industry can preclude collaboration between academic institutions, potentially limiting the utilisation of broader skillsets and patient recruitment. Establishing collaborations, often favoured by government grants, can be

viewed as laborious by industry, delaying the route to market. Publication strategies can also differ; industry often time publications to 'fit' their business strategy and publications funded or part-carried out by industry may be perceived as biased.

> ClinScien4: *"X [company] is currently holding up publication of some of my papers because of various business strategies and stuff and that's the price you pay – I accept it."*

Solutions have been considered to address these challenges. Intellectual property can be protected (both for the academic institution and industry), whilst the mechanisms of therapies can still be discussed, benefitting from the input and scrutiny of the wider scientific community. Sponsored Research Agreements (SRAs) between companies and universities could be established, wherein companies fund university research, authors maintain full control to publish their work, and in return the company has access to data. Once sufficient data is available, companies can increase their investment, run trials and proceed through the regulatory processes. This alliance between clinicians, scientists and industry appears crucial in successfully developing IHTs and driving their uptake.

> ClinScien4: *"It [alliances between clinicians, scientists and industry] is vital, I don't think you can do it without industry. Clinician scientists have to get out their ivory tower. They can't frown at working with industry, because for a molecular therapeutic, a trial for 20/30 patients can run into a million dollars which is the size of an average NIH award. So just for your drug stock for a trial you can blow your whole research budget and not get anything done. So I think government agencies are just not capable of doing that."*

Developing alliances amongst healthcare professionals and scientists (alliances amongst healthcare professionals and scientists can facilitate adoption and implementation)

- Developing alliances amongst healthcare professionals and scientists can help develop precision diagnostics[+], promote awareness of IHTs and secure research funding.

[+]Precision diagnostics refers to investigative tests that can determine the specific underlying cause of hearing loss and measure response to treatment, thereby facilitating optimal patient selection for trials as well as detection of efficacy signals.

Participants highlighted the importance for audiologists, auditory physiologists, ENT surgeons and scientists to collaborate to develop precision diagnostics and site of lesion testing, thereby improving patient selection for IHTs and helping to establish effectiveness (see element 'Developing precision diagnostics'). It will also be important to establish relationships with other professionals that see patients with hearing loss, including GPs, neurologists, old age psychiatrists, emergency doctors, care of the elderly doctors, paediatricians and oncologists, to promote awareness of IHTs and referral pathways. Developing networks and collaborations amongst these healthcare professionals and scientists can also help secure research funding and deliver IHT research studies. Proposed strategies to develop these alliances include highlighting common goals and objectives, writing research grants to promote multidisciplinary applications, establishing collaborations amongst professional bodies, and holding joint conferences.

Clinical participants expressed that healthcare professionals including audiologists, ENT surgeons, speech therapists, radiologists, general practitioners and psychologists will need to work together to prepare their respective specialties for IHTs, as well as work in multidisciplinary teams (MDT) to determine patient selection and monitor patient outcomes, similar to cochlear implants. These groups are eager to establish alliances with patient groups and charities, recognising that patients and members of the public are a persuasive lobbying group that can help influence decision makers and research funders, and help motivate clinicians to take-up IHTs (see element 'Raising investment for research, development and procurement').

> Aud2: *"Working with patient organisations and charities will be vital. They are critical in making the societal and economic case, gaining broader acceptance of the new therapeutic and getting decision makers to procure them and getting clinicians to use them."*

Early evaluation and evidence of effectiveness and safety *(Early evaluation as well as generating evidence of effectiveness and safety is important for IHT adoption and implementation)*

- Early health economic modelling can provide useful information on potential cost-effectiveness and inform product development.
- Evidence of effectiveness and safety was considered amongst the most important elements for IHT uptake.
- From a patient perspective, the effectiveness and safety of an IHT can overcome concerns over administration route and side-effect profile.
- Having outcome measure(s) that are easily understood by patients will increase the influence of the evidence.
- Demonstrating evidence of efficacy is crucial for companies developing IHTs to attract ongoing financial investment.

Early evaluation via early health economic modelling was considered by participants to be a useful tool to provide information on the potential for IHTs to be cost-effective in their intended context. These models can be used by decision makers to identify at an early stage IHTs that are likely to add value. Companies can use early health economic models to inform strategies on IHT development and pricing so to increase the likelihood of IHTs being cost-effective whilst maximising their price-point. Such models can also be used to generate investment in the development of IHTs (see element 'Raising investment for research, development and procurement'). Participants discussed that the construction of early health economic models usually involves the mapping of patient pathways which can also serve to provide an understanding of how an IHT can fit into the patient pathway (see element 'Sense Making').

Evidence of effectiveness and safety was thought to be crucial for the adoption of an IHT, having major influence on regulatory and decision making processes. Further that clear evidence of superiority of an IHT (as a stand alone or in combination with existing devices) compared to current practices would eventually translate to changes in clinical practice; however, the process of adoption and implementation could still take considerable time, dependant on numerous other elements.

> RepOthSpec2: "*So, if you've got a new drug that's been thoroughly tested and it really is superior to standard treatment, it will eventually get adopted despite clinical*

freedoms. Now clinicians can ignore it but over time, if you take the example of proton pump inhibitors in the 1980s and 1990s, these eventually replaced vagotomy surgery. It does take time, but clear evidence of superiority makes it easy for health policy-makers or for NICE to stand up to clinicians and say, get your act together, follow the evidence, you need to use what's effective."

Participants expressed that innovative therapies that have not been through a rigorous evaluation pathway should not be embedded into routine practice, citing a number of surgical interventions (e.g. sleeve gastrectomy) that have entered clinical practice supported by case reports and KOLs rather than robust evidence. Many of these interventions were later found to be ineffective or to have safety concerns. This must be avoided in the field of IHTs to gain the support of clinicians, decision makers and patients. It was also discussed that the type of evidence plays a critical role in adoption and implementation; data collected systematically from routine clinical practice can be more influential to clinicians, patients and decision makers than data from RCTs (see elements 'Clinician perspectives', 'Patient perspectives' and 'Collecting real world data').

From a patient perspective, the effectiveness and safety of an innovative therapy can overcome concerns over administration route and side-effect profile (see element 'Patient perspectives' and 'Motivations for adoption and implementation'). In Ophthalmology, anti-VEGF injections have become widespread owing to their effectiveness and safety, despite a relatively unpopular administration route. In the field of IHTs, intratympanic injections may therefore have potential for widespread uptake. The outcome measure used is also important; measured outcomes that are easily understood and relatable to patients have more influence than statistical outcomes.

Evidence of efficacy appears crucial for companies developing IHTs to attract more financial investment, which is essential for their survival in a competitive, costly and high-risk market (see element 'Raising investment for research, development and procurement'). Companies developing IHTs therefore often design their trials with strict inclusion criteria, close to the preclinical model, to increase the chance of demonstrating a positive signal. They recognise that a narrow inclusion criteria will limit their patient market, increase the therapy price-

point and reduce cost-effectiveness; however that these are worthwhile trade-offs to establish a positive signal. Once an innovative therapy enters the market, companies hope that clinicians will gradually start using the therapy for other conditions, expanding the market. In the field of IHTs, whilst companies compete to develop the first effective therapy, there is general support and encouragement amongst them for any to succeed, to support investment into the field.

> DiscScien2: *"So, the strategy of a company is to design a trial so that the drug has the highest chance of being effective, and once effectiveness is shown to say OK, let's get some further investments and broaden it."*

Education and training *(Effective clinician education and training will facilitate adoption and implementation)*

- Tailored clinician education and training, integrated into current training programmes appears crucial for clinician uptake of IHTs.
- Training delivered by KOLs can be valuable in promoting clinician trust and information uptake.
- Patient demand for innovative therapies appears a powerful driver to stimulate clinician training.
- Trainees, rotating from specialist hospitals could help raise awareness and promote of IHTs, increasing referrals to specialist centres.

Evidence of innovative therapy effectiveness and safety does not mandate uptake by clinicians. Participants discussed that few clinicians within the field would act as early adopters, keeping abreast with the literature and driving uptake. Clinicians would require education and training on IHTs to be aware of their utility and evidence base; and effective clinician training will help break-down: engrained clinical practices, insecurities and challenges of using IHT, as well as vested interests or allegiances with existing hearing technology companies (see elements 'Clinician perspectives' and 'Developing alliances between clinicians, scientists and industry').

Representatives from biotechnology companies developing IHTs highlighted the importance of clinician education and training to raise awareness, uptake and improve patient outcomes, whilst minimising complications, and therefore investment in clinician training forms a core part of their implementation strategy (see element 'Developing alliances between clinicians, scientists and industry').

> RepNovTherComp2: *"What we really acknowledge is how important training is once a therapeutic comes out because if training isn't sufficient and people don't do it well, outcomes will be poorer, effectiveness is less and as a result there'll be more barriers to get it implemented."*

Effective clinician education and training appears heavily dependent on clinician trust in the information source. Training delivered by a KOL within the speciality can be valuable in promoting clinician trust and information uptake. Companies recognise this and work to gain support from KOLs to train clinicians effectively (see element 'Developing alliances between clinicians, scientists and industry'). Other education routes include conferences and specialty training events. An effective strategy employed by companies is to focus training on a disease and circuitously provide information on a novel therapy (soft selling), where KOLs are compensated to deliver education rather than selling a therapy, removing conflicts of interest.

> RepOrgImp1: *"We've seen how powerful the right KOL can be. We've used some good KOLs that went out to train clinicians, but with a focus on training on the disease, not on the new drug or trying to sell the new drug - the focus was more on upskilling the clinician, and removing insecurities about using new treatments, there is a subtlety around that, that kind of soft selling which is particularly successful. The beauty of this approach is that KOLs have no conflict of interest because they're being paid to deliver education not to deliver a sales pitch on the drug and this process reinforces that they are a KOL and gives them a position of authority meaning that the message is received without wariness."*

Patient demand for innovative therapies appears to be a powerful driver to stimulate tailored clinician training and self-directed learning. For example, strong patient demand for IHTs could motivate ENT surgeons to learn about IHT delivery and motivate GPs to be aware

of IHTs and identify referral routes (see element 'Motivations for adoption and implementation'). Companies recognise this and invest in building relationships with patient charities and patient groups to raise awareness of their IHT and stimulate patient demand (see elements 'Providing patient and public information' and 'Developing alliances amongst healthcare professionals and scientists').

> GP1: *"Implementation science, as you know, is a dark art and how clinicians learn about novel treatments is never straightforward. Patient demand however will be a strong force - if patients demand the new therapy, it will soon get into the medical knowledge of general practitioners and ENT surgeons without any problems."*

To prepare for IHTs, it may be necessary to integrate education and training on IHTs into existing training programmes before their release on the market, with tailored training for different clinical groups. Participants conveyed that ENT surgeons would benefit from training on: pathophysiology, including genetic and molecular mechanisms underlying SNHL; mechanisms of action of IHTs; and therapy administration. Audiologists may benefit from training on precision diagnostic testing and the IHTs available, whilst GPs would need to receive training to gain a general awareness of IHTs, their indication, and referral routes. As 'the gatekeepers' to the NHS, GP's could strongly influence the uptake of IHTs and their training was considered vital. Training for other clinician groups including oncologists (ototoxicity related hearing loss), care of the elderly physicians (age-related hearing loss), and geneticists (genetic hearing loss) also appears important to support uptake.

In-depth training for all ENT surgeons would be expensive and may not be necessary with IHTs likely only being offered in select centres, by a small number of ENT surgeons and audiologists.

> ENT5: *"I mean I think the general ENT surgeon needs to have an awareness that it exists but not necessarily to know the nitty gritty about how it all works, unless they were delivering it, day in, day out."*

An efficient strategy could be to provide advanced training to a sub-group of expert ENT surgeons and audiologists with a specialist interest in IHTs. This expert subgroup could also carry-out placements within allied specialties such as clinical geneticists (for gene

therapies), and enrol in new, part-time courses being set-up to train clinicians in the fields of gene and cell therapies. Companies developing IHTs appear to support the development of subspecialty expert groups and centres, recognising that that this may lead to better patient outcomes and fewer complications, promoting uptake.

Participants discussed that the method of administration and complexity of the therapy will likely influence training requirements (see element 'Route of administration'). Oral tablets and intratympanic injections may fit in well with existing skill sets, however, an invasive approach to the inner ear may necessitate further specialty training, representing a potential barrier to adoption, particularly if the therapy were indicated for a large patient population.

Route of administration *(How the IHT is administered will influence adoption and implementation)*

- Non-invasive administration would facilitate IHT uptake. Therapies requiring invasive administration can be successfully implemented as long as they are clearly superior to existing treatments.
- ENT surgeons may prefer to use therapies requiring a procedure; however, these preferences can be overcome by evidence of superior effectiveness and by clinician training.
- An IHT that is a pharmaceutical product, may benefit from NICE's funding mandate.

Participants conveyed that an IHT delivered via a non-invasive route would facilitate adoption and implementation, owing to requiring less financial (consumables, space) and human resources (training and workload) than invasive administration methods, minimising disruption to existing infrastructure and improving cost-effectiveness (see elements 'Cost-effectiveness analyses', 'Impact on hearing healthcare services', and 'Resource requirements'). An easy to administer, non-invasive IHT, may also permit administration by non-ENT specialists, improving access and saving costs. However, at the outset, it is unlikely for IHTs to be administered by non-ENT specialists, owing to their novel nature, (likely) high cost, and the need for specialist testing and diagnostics to confirm eligibility and measure treatment effect. In the longer term there may be scope for audiologists or nurse

practitioners to administer well established, non-invasive therapies, that are easy to administer, under the supervision of a doctor.

Method of administration may also impact the size of the market. It was considered by participants that patients would be more willing to try IHTs whose method of administration were minimally invasive and requiring less recovery time. Orally administered approaches would fulfil these criteria and provide access to a larger patient market than surgical approaches, which may be contraindicated for patients with underlying health problems, particularly the elderly with the highest burden of hearing loss. Whilst a minimally invasive approach would be preferred by patients, case-examples from other specialities including cataract surgery demonstrate that patients are willing to undergo invasive routes of administration as long as the therapy is effective, safe and superior to existing treatments.

> RepOthSpec1 *"Even though cataract surgery is invasive, people don't really fear it. People are thrilled to be told that they have their cataract surgery coming up."*

Participants discussed that ENT surgeons may prefer therapy administration via an invasive, procedural route, utilising their unique surgical skill set, and helping to ensure that IHTs stay within ENT surgery. Further that from a private practice perspective, ENT surgeons generate more income from procedures than prescribing drugs, adding financial incentive to a procedural route (see element 'Motivations for adoption and implementation'). However, participants expressed that clear evidence of comparative effectiveness as well as effective clinician training can overcome inherent clinician preferences on treatment route (see elements 'Evidence of effectiveness and safety' and 'Education and training'.

> Aud1: *"The ENT surgeon is not going to profit off providing prescriptions. They'll get an office visit out of it but ... surgeons make their money not when they're in offices, but when they're at the operating table. A tablet would mean that they're going to have a lot more visits where people are coming in to have a chat and write a prescription which is a lower margin event for them, so I think ENT surgeons won't be so keen on tablet therapies."*

If the IHT is a drug (or pharmaceutical), rather than a device, this may assist adoption from a UK regulatory perspective, since the drug would likely enter NICE's Technology Appraisal

(TA) process, undergo a cost-effectiveness analysis and if recommended, would receive a funding mandate, meaning that it would have to be provided by NHS England within 90 days of NICE's guidance. Devices on the other hand are usually assessed via NICE's Medical Technologies Evaluation Programme (MTEP) and undergo a cost-minimisation analysis. For a device to be recommended by MTEP, it would need to be found to be cost saving or cost neutral as compared to the current standard of care, which is difficult to achieve. Even in the event of a favourable result, MTEP's do not offer a funding mandate, making this route more challenging from an innovative therapy perspective.

> RepReg1: *"Well, if it's a drug, they've got a much better chance of getting it embedded because it's only the technology appraisal process where there is a funding mandate. In other words, when NICE says yes to a drug, funds have to be made available…. For the Medical Technologies Evaluation Programme we don't use cost-effectiveness, we use cost minimisation, and so it has to be cost saving or cost neutral. So, if it is cost incurring in any way then we can't evaluate it and we can't produce a positive recommendation."*
>
> RepReg2: "*For NICE, unlike drugs, which generally all go through technology appraisal to receive a funding mandate, there is no funding mandate for medical devices at the moment, unless they are therapeutics and then they go through technology appraisal."*

Indication *(The indication of the IHT will influence adoption and implementation)*

- IHTs targeting younger patients and patients with more severe levels of hearing loss may be easier to implement.
- High cost IHTs targeting small populations do not necessarily represent a barrier to adoption.
- Companies developing IHTs appear to design trials with strict inclusion criteria to increase the likelihood of demonstrating efficacy, hoping to generate further financial investment.

IHTs targeting more severe levels of hearing loss may be easier to embed into healthcare systems since patients may be more willing to take-on the potential side-effect profile, costs and time requirements.

RepNovTherComp2: *"Someone with profound hearing loss is going to tolerate a higher risk profile than somebody with a mild to moderate hearing loss, who has much more to lose and potentially less to gain."*

Moreover, some healthcare systems, including in the US, do not generally reimburse treatments (such as hearing aids) indicated for mild or moderate levels of hearing loss; and this may be extended to IHTs, requiring patients to pay out-of-pocket, limiting uptake. The indication of the IHT also influences potential cost-effectiveness (see element 'Cost-effectiveness analyses') and should be considered by IHT developers and decision makers. IHTs indicated for younger patients or for patients with more severe forms of hearing loss will have a higher chance of being cost-effective, increasing value for money and chances of adoption (see results from early health economic model, Chapter 2).

Participants expressed that a large proportion of IHTs currently in development focus on very specific disease targets, and if found to be effective, would be indicated for small numbers of patients, making the price point high (to recoup costs of development), potentially reducing patient access and uptake in healthcare systems. However, a small population of eligible patients would not represent a significant overall cost burden to a healthcare system. In the UK, NICE's threshold of £20,000-30,000 per QALY is flexible and may be shifted to higher levels if the patient population is small, if the therapy is innovative, or if the therapy is more effective than current practice.

ClinScient2 *"So, I think in these rare diseases where you're talking about maybe 30 patients in the country who might end up being candidates to have this done, even if the cost of treatment was a million dollars for treatment, that's not going to break the bank."*

Participants from some companies developing IHTs acknowledged that their therapy price point will likely be high, potentially limiting widespread uptake. However, their strategy is to focus on demonstrating efficacy regardless of profitability, generate further financial investment, secure their survival in a competitive market, whilst enabling further development of their therapy pipeline in the hope that this will realise future profits (see element 'Raising investment for research, development and procurement'). Once a positive

signal is found, companies can also look to scale-up and broaden the indications of their therapy.

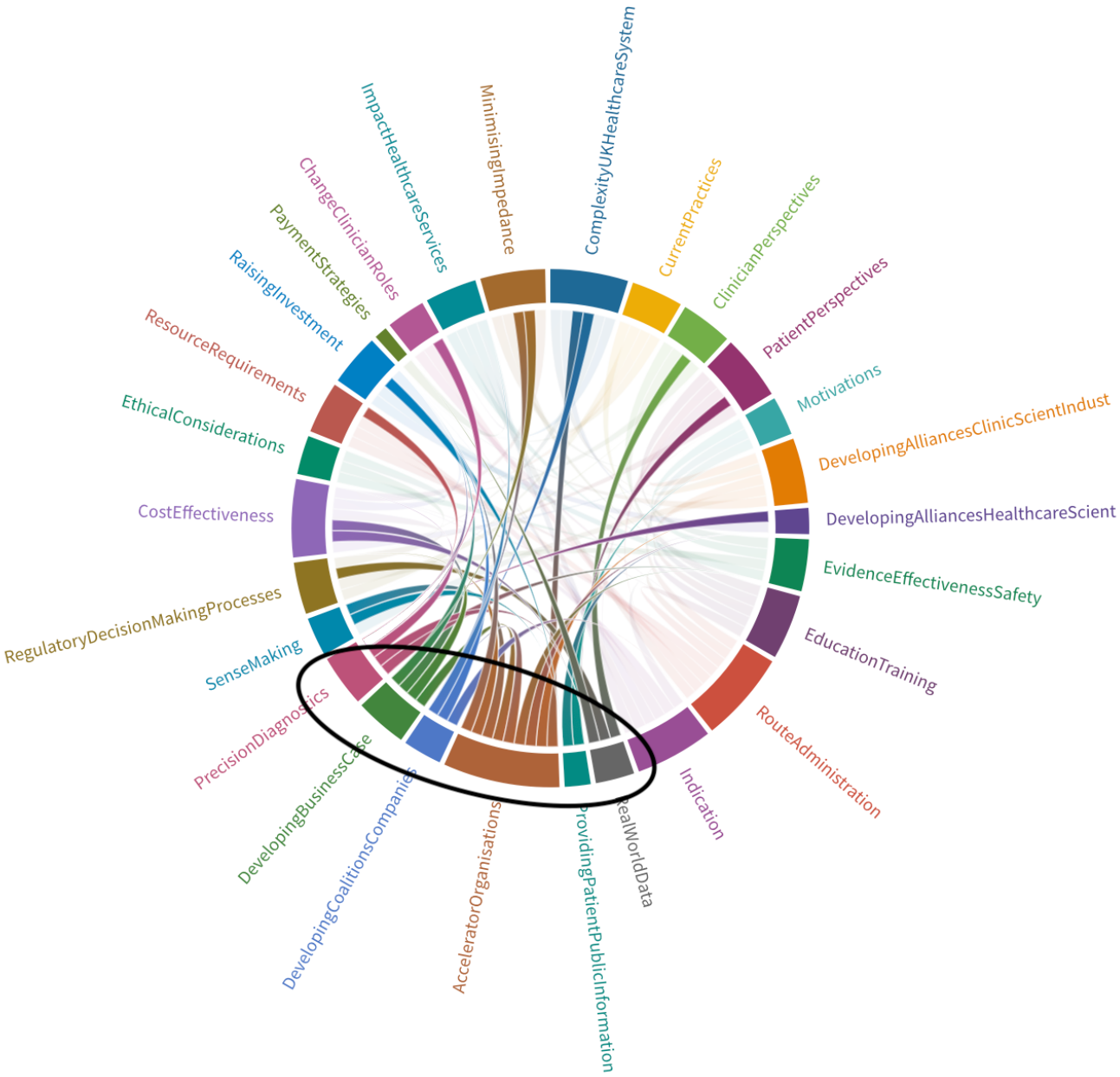
> RepNovTherComp3: *"And even if it's found to work for a very specific patient population, there would be hope that it would also work for other target conditions with broader patient populations….a positive result would also help keep the field going by attracting further investment so it would be tremendously exciting and important for the field."*

Companies developing IHTs therefore tend to design trials with strict inclusion criteria, closest to their pre-clinical models, so to increase the likelihood of demonstrating efficacy. Clinicians are beginning to recognise this strategy, which feeds into their perspectives on RCT evidence (see element 'Clinician perspectives').

Regenerative and gene hearing therapies appear to attract more investment and attention from biotechnology companies, who consider that there is more scope to show efficacy for these types of therapies than protective ones. Patient selection for trials for protective therapies may also be more challenging due to potentially slower onset of hearing loss (e.g. noise induced hearing loss), confounding factors in inclusion criteria, relatively less severe levels of hearing loss, and smaller patient populations. It was also suggested that as the field evolves, regenerative and gene therapies will be developed and indicated for larger patient populations, which could have a significant impact on healthcare markets, requiring novel payment strategies (see elements 'Impact on hearing healthcare services', 'Resource requirements' and 'Payment strategies').

Activities *(The activities that can be carried out to facilitate IHT adoption and implementation)*

Figure 10. Snapshot of chord diagram for elements within column ‘Activities’



Collecting real world data *(Data collected from routine clinical practice can influence adoption and implementation)*

- Clinicians appear more convinced to take-up IHTs that are supported by real world data.
- From a regulatory perspective, evidence of effectiveness and safety for IHTs does not only need to be from RCTs.
- Establishing registries may be central to generating real world data for IHTs.

Participants expressed that clinicians can be wary of evidence generated from RCTs particularly if sponsored by industry, owing to concerns over external validity and publication bias, citing examples of drugs (e.g. Donepezil for Alzheimer's) that were found to be effective in trials, rolled out into clinical practice at considerable expense, but following 'real world' assessment were found to have limited impact (see element 'Clinician perspectives'). These experiences can demotivate clinicians who appear to be more convinced and more willing to use innovative therapies that are supported by high quality, real world, externally valid data of effectiveness and safety.

> RepOthSpec2: *"I think the most important factor to get something implemented and used in the NHS is having a strong and convincing evidence base, and that the evidence is accepted by clinicians. That means getting data from real world settings, not in a highly controlled RCT, so you can show that this drug actually works in your environment for your patients, and the data hasn't been influenced by industry or other vested interests. That is hugely convincing."*

Representatives from healthcare regulators discussed that from a regulatory perspective, evidence of effectiveness and safety for innovative therapies does not only have to be from RCTs, which have limitations including: sizable resource requirements, extensive time to set up and report, limited external validity and challenges to collect long-term data. Rather, safety data could be generated via an RCT, whilst effectiveness and cost-effectiveness data be generated alongside its use in a healthcare system (e.g. via a cohort study) (see element 'Regulatory and decision making processes').

> RepReg3: *"Randomised control trials tend to have a lot of inclusion and exclusion criteria that often makes it difficult to generalise the findings of that trial into the general population. They are also extremely expensive and take a long time to plan and run. So to a great extent at [X regulatory agency), we have begun looking at using real world evidence for both devices and drugs and utilising the data that occurs from routine clinical use of that therapy. This will make evidence generation so much more efficient, but the data has to be captured in a way that creates 'valid scientific evidence' – i.e. is captured in a robust and systematic way."*

Establishing registries to facilitate prospective data collection on IHTs was considered central to generating convincing real world data on safety and effectiveness. Such data would also provide information on duration of treatment results as well as need for adjunctive treatments, such as hearing aids or implants.

> RepOthSpec1: *"I think everything that's novel needs some sort of electronic tag so we know where it is being used, how effective it is and if there are any adverse events."…."It would be excellent to have long-term data so we could confidently say to patients - this treatment is going to work and last for 10 years and after that you may need to go back to a cochlear implant or hearing aid."*

Registries would need to be well funded and managed to ensure data accuracy, completeness and longevity; and would need to capture relevant outcome data including hearing outcomes and patient reported quality of life. Healthcare systems such as the NHS need to evolve to better support the accurate collection of routine data. Industry will establish their own databases of outcomes for their therapies, however a central independent registry would benefit from receiving higher volumes of data and ability to make comparisons between therapies. Centrally collected, accurate registry data could also contain phenotypical and genotypical patient data, helping to develop precision diagnostics that will be critical for IHT implementation (see element 'Developing precision diagnostics'). Registry data could also support graduated payments structures (see element 'Payment strategies') facilitating IHT procurement.

Providing patient and public information *(Providing information to patients and the public on IHTs may facilitate adoption and implementation)*

- Patient information and education may boost patient motivation and demand for IHTs, exerting pressure on clinicians and decision makers to take them up.
- Companies recognise this and invest in building relationships with patient groups.
- Patient organisations are working to develop strong networks with clinicians, researchers, industry and policy makers to increase their knowledge and influence.

Patient information and education on IHTs, including the unmet need they hope to address, was considered vital to boost patient motivation for IHTs, a central factor to drive adoption

and implementation (see element 'Motivations for adoption and implementation'). Once well-informed, patients can become a strong advocate group, forming alliances with clinicians and industry to exert pressure and influence decisions made by decision makers and regulators (see elements 'Developing alliances amongst healthcare professionals and scientists' and 'Raising investment for research, development and procurement'). Companies recognise this and invest in building relationships with patient charities and patient groups (e.g. through sponsoring events) to raise awareness of their product and stimulate patient demand.

> RepOrgImp2: *"There's nothing more powerful than having citizens drive or create demand for a type of drug or treatment."…."I think patients really need to be well informed about the novel treatment so that they can really force uptake and influence their own care."*

Patient education can also help increase patient engagement in research, including recruitment to trials, advancing research in the field and ultimately, willingness to take-up the IHT. Informed patients may also be motivated to seek IHTs from their doctors and health services, increasing therapy demand and driving clinician training (see element 'Education and training').

Participants discussed the importance of patient information being evidence-based and disseminated via trusted portals, including the patient's clinical team, patient charities, approved websites and media channels.

> RepHearLossChar1: *"So I think that amongst people and patients there's this sort of sense that new is better but we know that that is not really the case, so we need to be careful to accurately show the evidence to patients in a patient-friendly way."*

Participants also discussed how patient organisations within the hearing field are strategically working to develop strong networks and collaborative links with clinicians, researchers, industry and policy makers in order to increase their knowledge, expertise and influence within the field of IHTs. This knowledge can empower them to become an important stakeholder group, enabling them to contribute to IHT research and

development. This knowledge can also increase their influence in terms of shaping regulatory and policy decisions.

Working with accelerator organisations *(Organisations with an understanding of the healthcare market and with networks of key stakeholder groups can help facilitate adoption and implementation)*

- Accelerator organisations can help navigate complex healthcare systems, establish dialogues between key stakeholder groups, and help develop strategies to optimise integration of an IHT.

Participants expressed that whilst companies producing innovative therapies usually have market access specialists, healthcare systems including the NHS can be very complex to navigate (see element 'Complexity of the UK healthcare system'). Accelerator organisations, independent from industry, with a detailed understanding of the patient pathway, the healthcare market (public and private), its key stakeholders, existing clinical research infrastructure as well as regulatory and decision making frameworks can provide expertise in navigating healthcare systems**.** This will help identify where the IHT can 'fit' in the pathway (see element 'Sense making') as well as develop tailored, healthcare system-specific strategies to optimise integration.

Representatives from companies developing IHTs discussed that they are eager to engage with decision making groups, including commissioners at an early stage to develop an understanding of the needs of the healthcare system (including target areas for efficiency savings), the procurement process and how well the IHT is suited. This information would help companies tailor their therapy to increase chances of uptake, whilst helping decision makers plan for innovative therapies.

> RepOrgImp1: *"Having commissioners involved from the very start is probably the best approach to remove many of the barriers of implementation and with the payers on board, the clinicians tend to follow suit, particularly if they're incentivised or they're given the resources needed to deliver whatever the novel therapy is."*

However, decision makers need to maintain impartiality, and direct communication with companies can be considered uncompetitive. Independent accelerator organisations can help address this by facilitating indirect communication between companies, decision makers and regulators. This could include making clinical commissioning groups aware of upcoming therapies and assisting in the development of a tailored business case, so that budgets are organised to facilitate procurement (see element 'Developing a business case').

Companies introducing innovative therapies recognise the importance of effective clinician training and KOL recruitment for therapy implementation (see element 'Education and training'), and accelerator organisations could help develop links between these companies and clinical groups (see element 'Developing alliances between clinicians, scientists and industry'). Accelerator organisations could also help develop relationships between companies developing IHTs and patient groups and charities, gaining their input and galvanising support for an IHT, which appears an important factor for adoption (see elements 'Developing alliances amongst healthcare professionals and scientists', 'Raising investment for research, development and procurement', and 'Motivations for adoption and implementation'.) Another potential role for accelerator organisations is to help broker collaborations between existing hearing technology and biotechnology companies, identifying potential synergies and opportunities for mutual benefit (see element 'Developing coalitions between companies).

> RepHearDevComp3: *"A central group could coordinate early, meaningful discussion with all the players on how to successfully introduce a new therapy in the market and what does it mean in the healthcare system, and how can we successfully roll it out and leverage synergies?.... What I've heard from a lot of people in the field is it depends who that central group is, if they're seen as independent it makes a big difference."*

In the UK an accelerator organisation could help provide access to the UK's clinical research infrastructure, including facilities, investigators, characterised groups of patients, as well as valuable clinical networks such as the NIHR Clinical Research Network (CRN), the NIHR Audiology Champion network, and Trainee research collaboratives with a track record of delivering hearing research and disseminating information. Companies developing IHTs

appear enthusiastic to access these networks to: 1) help design and deliver research studies to generate clinical evidence; 2) access and influence clinicians and patients 3) build credibility.

Developing coalitions between companies *(Coalitions between hearing technology companies and biotechnology companies can facilitate adoption and implementation)*

- Coalitions between hearing technology companies and biotechnology companies could lead to pooling of resources, helping market entry.

Whilst IHTs represent a potential commercial threat to existing hearing technology companies, there appears to be an appetite to form mutually beneficial coalitions, recognising that IHTs will likely add to the market, rather than replace sections of the market (see element 'Impact on hearing healthcare services'). Informants discussed that it would be highly unlikely for there to be a wonder, 'silver bullet,' curative IHT for the foreseeable future, leaving a large market for existing hearing technology companies; and rather than driving existing companies out of business, IHTs could reveal new combination opportunities.

> Aud1: "*I really don't expect these therapeutics to be curative or act as blanket treatments for all types of hearing loss. I expect them to improve hearing and they may be synergistic with other things. The idea that taking someone with profound deafness, pop a pill in, all of a sudden, they have normal hearing, I think is pipe dream. I don't think that we will completely get rid of the cochlear implant in the next 50 years. I think that cochlear implants will continue to evolve and become more integrated."*

Participants appreciated that since the last decade there have not been substantial advances in hearing devices; and that the introduction of IHTs can help drive competition and innovation. This can incentivise coalitions, helping existing companies stay relevant and keep control of the market.

> ENT3: *"At the [X] meeting, they were debating whether or not cochlear implantation has progressed and developed in the last 30 years. And they came to the conclusion that actually it hadn't. And devices that were first implanted in 1978, were really,*

very, very similar to what we do now. So there is a real appetite amongst clinicians for something novel, that's without a doubt."

Existing hearing technology companies are looking to, and in some cases have already, acquired or invested in biotechnology companies developing IHTs to maintain their position in the market. Coalitions between hearing technology and biotechnology companies could lead to pooling of resources (knowledge, skill-set, financial, licencing), and increase the use of existing devices, which can be used as adjunctive treatments or delivery vehicles. Participants from biotechnology companies acknowledged the challenges of delivering innovative therapies into the inner ear and considered existing devices as potential 'Trojan hoses', granting access to the cochlea. Early coalitions are already forming, capitalising on the expertise of existing hearing technology companies on specialist inner ear mechanics and engineering. Working with existing companies can also improve market access, including to well-established networks within the clinical community and patient groups. Hearing aids form the mainstay of market, and biotechnology companies are particularly keen to work with hearing aid companies to gain access to clinicians and patient populations.

RepHearDevComp2: *"In our organisation we see around X hearing impaired people every single day in our shops worldwide, and companies developing new therapeutics realise this and have already approached me …. we pretty much know most of the novel therapeutic companies, because many of them have actually come to us for advice or input or guidance."*

RepCRO2: *"If your drug is actually going to clear the shelves of hearing aids or CIs, then I'd actually try to collaborate with hearing aid or CI companies, to prevent enemies, and to gain access to what is actually their market - this will boost success of the new drug…..I would actually include them in my marketing strategy, to reduce barriers and tap into their market, finding a way to the clinical community."*

Concerns were raised over the practicality of combining cochlear implants with IHTs. The number of patients receiving cochlear implants annually is relatively few, with cochlear implants being priced towards the limit of cost-effectiveness. Combining a cochlear implant and an IHT, may leave little room in terms of additional price and may represent a barrier,

considering the likely significant cost of an IHT. However, if the indication of the IHT were very broad, this would increase the number of patients using combination treatments, driving down the price-point. The manufacture of a new brand of cochlear implant in China may also help drive down prices, making combination treatments more affordable.

To help continue to foster coalitions between hearing technology companies and biotechnology companies, the communication and language used around IHTs may need to become more realistic. At the moment, many publications around IHTs discuss their potential to cure hearing loss and transform the market, which is unrealistic for the foreseeable future and unhelpful for collaboration.

> RepHearDevComp2: "*Hearing aid manufacturers often see these new pharmaceuticals or therapeutics as a threat instead of a complementary solution, and I think this is because when you read the publications and the materials from novel companies it's always replace and we cure hearing loss. This needs to change to become more realistic and to discuss the potential synergies."*

Developing a business case *(The development of business cases for IHTs can facilitate adoption and implementation)*

- Effective business cases help decision makers plan budgets and redirect funds.
- Accelerator organisations could help develop trusted business cases.

Participants discussed that a clear business case, prepared early, will help decision makers plan for IHTs in their future budgets and redirect funds as necessary to avoid delays in adoption and implementation. It was considered that an effective business case would need to cover 3 core areas: 1) improvement in quality of patient care 2) budget impact, including where the therapy is 'cash-releasing' 3) operational efficiency, including impact on clinical pathway.

> RepOrgImp1: "*For anything to be embedded in service provision and to accommodate a new intervention, you need to put together a strong case for investment which also identifies the return on investment. So health systems or commissioning groups are starting to require a coherent business case that covers: quality improvement in patient care, budget impact and efficiencies."*

This approach may be particularly useful in the NHS, where, even if an innovative therapy were assessed to be cost-effective and subsequently receive a funding mandate from NICE, insufficient resources prevent commissioners from procuring a therapy until their budgets have been re-organised, resulting in delays in adoption (see elements 'Cost-effectiveness analyses' and 'Regulatory and decision making processes'). Moreover, decision makers are generally risk-averse owing to budgetary constraints, and business cases can help mitigate against potential blame of adopting a therapy that is later considered wasteful.

> RepOrgImp2: "*The risk of failure for new interventions is relatively high, and adopting a failed therapy may impact individual career prospects, so if there's enough doubt on the new intervention, it's just going to be avoided. However, a good business case can be used by decision makers to say - well there was clear justification for me to make this decision – my decision was based on the evidence."*

Companies often produce business cases 'in-house', which can be considered by decision makers to be overly technical, insufficiently tailored to the healthcare system, and inflated in favour of the therapy, leading to scepticism. Companies therefore look towards trusted independent organisations with good knowledge and networks within the healthcare market to develop or independently verify their business cases, increasing trust and accessibility (see element 'Working with accelerator organisations').

Developing precision diagnostics *(developing precision diagnostics will facilitate adoption and implementation of IHTs)*

- Precision diagnostics will play a key role in the development and uptake of IHTs.

IHTs will target specific molecular and genetic causes underlying hearing loss, the majority of which are not identified by current clinical diagnostics. Novel tests (precision diagnostics) will therefore be needed to diagnose the underlying mechanism, gene or site of the hearing loss to support the development and use of IHTs.

Precision diagnostics was considered by participants as amongst the most important elements for the adoption and implementation of IHTs, playing a key role in recruiting

patients with the appropriate genotype and phenotype, identifying positive signals, establishing dose response relationships and optimal timing of therapy delivery, thereby helping to establish IHT clinical and cost-effectiveness. Biotechnology companies developing IHTs recognise this and are in the process of developing networks and databases to help collect phenotypical and genotypical patient data that will be critical in patient selection for trials and in the development of precision diagnostics (see element 'Read world data').

> ClinScien1: *"When a new hearing therapeutic is developed, it will trigger a more exacting evaluation of patients, and this field of precision diagnostics will let us characterise our patients and find the patients that will improve most from the new therapeutic. This will generate higher levels of efficacy, which will increase the drive of clinicians and patients to use novel hearing therapeutics, increasing their likelihood of being taken up by the healthcare system."*

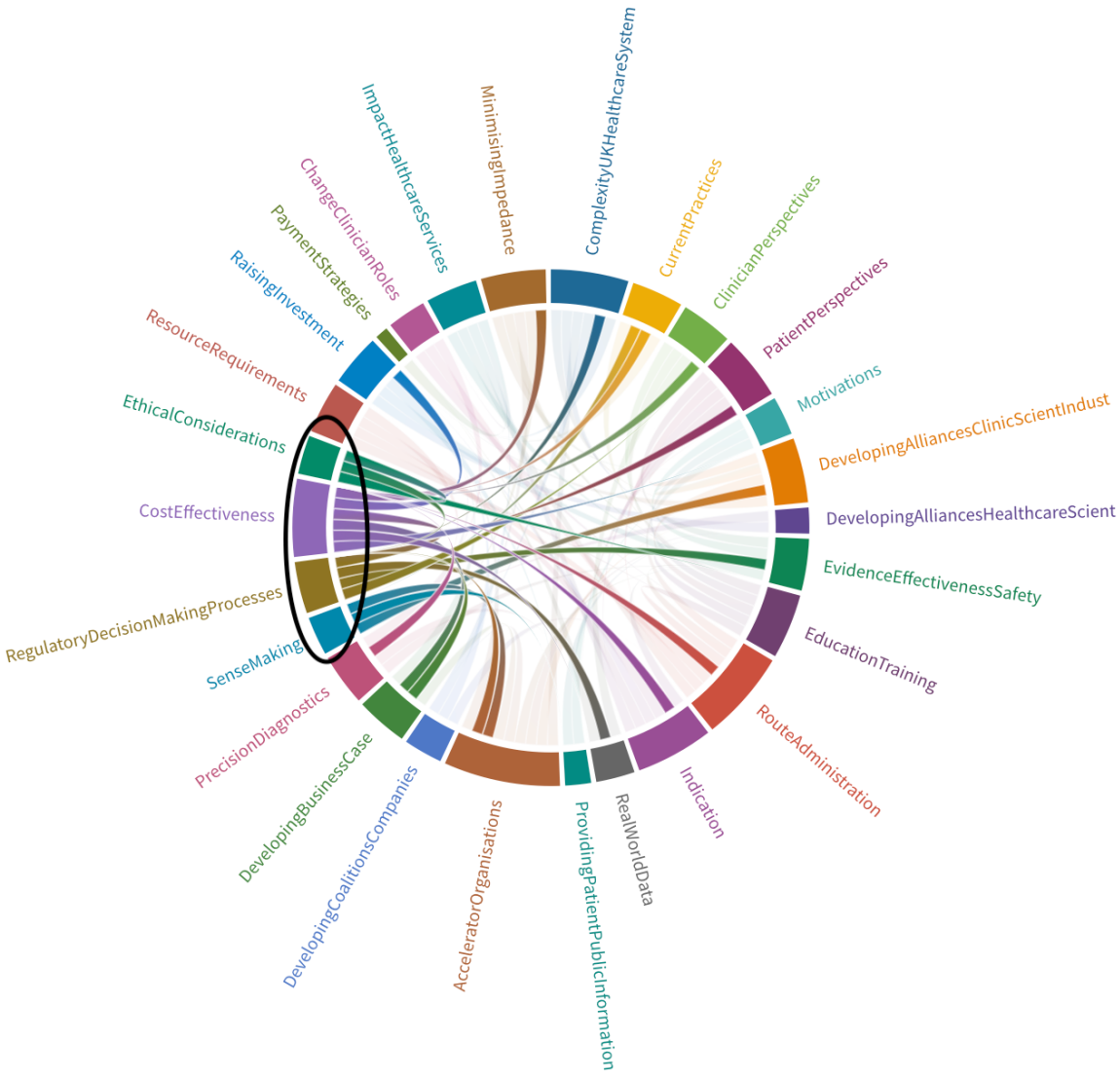
Progress in precision diagnostics was considered by participants to be slow, with relatively little investment to-date. However, there are recent indications that precision diagnostics are receiving greater attention and investment and participants forecasted that once an effective IHT has been developed, there will be a surge in investment in precision diagnostics for hearing loss. A 'catch-22' situation therefore exists, where precision diagnostics are ideally first needed to demonstrate an effective IHT, however, precision diagnostics require an effective IHT to trigger investment in their development. An effective IHT will most likely come first relying on existing tests, to broadly assess suitability and effectiveness. Until precision diagnostics are developed, clinicians and scientists in the field should ideally make better use of existing tests (e.g. speech in noise tests and otoacoustic emissions) to obtain as detailed a diagnosis as possible.

> ClinScien4: *"One of the reasons we don't have precision diagnostics at the moment is that we really have nothing else to offer the patient in terms of treatment, so having a precision diagnostic now wouldn't change the clinical course and would be unnecessarily expensive. Once we have the first hearing therapeutic that shows a signal, all bets are off; the field will truly explode with much higher investment into R&D for precision diagnostics."*

It was also discussed that the existing hearing technology industry are increasingly gaining an interest in developing precision diagnostics recognising the potential impact of IHTs and the opportunities available. Their involvement may accelerate the development of precision diagnostics whilst providing access to large patient populations who are already using their hearing devices.

Decision making mechanisms *(Processes of reasoning that need to take place for IHT adoption and implementation)*

Figure 11. Snapshot of chord diagram for elements within column 'Decision making mechanisms'



Sense making *(Understanding how the IHT will fit into the healthcare system will facilitate uptake)*

- Understanding how the IHT differs to existing interventions and how it could be incorporated into the healthcare pathway will facilitate uptake.
- Collaborations between companies developing IHTs, clinicians and accelerator organisations can help provide this understanding.

Participants discussed that understanding how an IHT will 'fit' into a given healthcare system is crucial for its adoption and implementation, including understanding how it differs to existing interventions and how it could be best incorporated into the healthcare pathway. This will include assessing: whether existing hearing testing and treatment facilities will be adequate, if current patient pathways will need to be changed, whether hearing healthcare professional skill-sets are sufficient; and where in the existing patient pathway patients should receive the IHT. To explore this, companies developing IHTs can collaborate with clinicians, as well as accelerator organisations with a detailed understanding of specific healthcare systems (see elements 'Developing alliances between clinicians, scientists and industry' and 'Accelerator organisations'). This process of sense making will also be facilitated by effective clinician training (see element 'Education and training') as well as tailored information sharing to patients and decision makers (see element 'Providing patient and public information'). The more complex an IHT is, the harder it may be for participants in the healthcare system to make sense of it, which may impede adoption.

> ClinScien1: "*Companies realise that it is important for them to have a good understanding of the target health care system and its pathway of care so that they can develop a therapeutic that can be usable. It's also important that they work with clinicians so that clinicians understand the novel therapeutic and provide input on how best to fit the therapeutic into the current pathway of care or how the pathway of care may need to be tweaked to help make the new therapeutic fit.*"

Regulatory and decision making processes *(Regulatory and decision making processes influence adoption and implementation)*

- Current methods of evidence generation for regulatory processes appear to delay patient access to innovative therapies.
- Regulatory bodies are implementing strategies to streamline regulatory processes.
- Concerns were raised that NICE's funding mandate may be counter-productive and that NICE's decision making processes may be influenced by political and societal pressures.
- Cost-effective therapies favoured by regulators are not necessarily affordable, potentially disrupting healthcare services.

Participants discussed that the core components for regulatory decision making processes were safety, effectiveness, patient preference, and cost-effectiveness. Further that evidence generation via RCTs for regulatory purposes appear to delay innovative therapy adoption, potentially resulting in therapies becoming outdated by the time they complete the regulatory process. A popular solution proposed was for safety data of an IHT to be generated via an RCT, whilst effectiveness and cost-effectiveness data is generated alongside its use in a healthcare system (via a cohort study) (see element 'Collecting real world data').

> RepFund1: *"From our perspective, the main barrier and lag is how long it takes for the health technology assessment programme to generate the clinical and cost-effectiveness evidence, following which NICE makes their appraisal decision. This takes 10 years, by which time the therapy can be old news. One of the solutions we think is to establish therapy safety in the same way we do now, but then implement the therapy and generate evidence of effectiveness and cost-effectiveness alongside its implementation."*

Participants explained that in the UK, NICE acts as the financial gatekeeper to the NHS, reviewing evidence of effectiveness and cost-effectiveness within its Technology Appraisal programme and then deciding whether to recommend the therapy. A NICE recommendation (under the Technology Appraisal programme) carries a funding mandate, making it mandatory for NHS commissioners to provide the novel therapy. However, despite this mandate, there can be considerable delays to adoption and implementation owing to commissioners having insufficient resources to provide the therapy. Moreover, clinicians are

not duty bound to follow NICE guidance, and clinician training appears to play an important role in convincing clinicians to use the therapy (see element 'Education and training'). An effective lever that decision makers and regulatory bodies have to persuade clinicians to use a novel intervention is to decommission existing treatments.

There appears to be a general drive to evolve regulatory processes internationally, to facilitate more rapid assessment and uptake of innovative therapies. NICE for example have developed an Implementation and Adoption Team, who work with health and social care organisations to facilitate the adoption and implementation of cost-effective interventions through: providing a tool-kit that offers guidance on regulatory processes; providing case-studies describing how other therapies have been embedded successfully; assisting in developing a business case to encourage commissioners to provide novel interventions; bringing together partners, including NHS England, NHS improvement, Healthcare Education England and NHS Clinical Commissioners to support uptake. Attitudes towards regulatory bodies appear to be gradually changing, where companies developing innovative therapies see regulatory bodies favourably as a partner, recognising that effectiveness and safety standards also serve to protect their interests.

Concerns were raised by participants that NICE's decision making processes may, over-time, have been influenced by political and societal pressures. For example, NICE'S threshold of £20,000 - £32,000 per QALY was considered by some participants to be too high, not accurately reflecting opportunity costs within the healthcare system. Further that placing greater weight on health gain in rare diseases unfairly increases the likelihood of cost-effectiveness. Whilst these decisions reward innovation, the costs to society may be unsustainable and this is reflected by commissioners being unable to provide a number of therapies recommended by NICE.

> HealthEcon1: *"NICE knows that their threshold does not represent health opportunity costs. What they say is, well we know that, but we're going to continue with this because that's what society wants or they're a bit vague about it and say it's important to reward innovation. At the moment, we have a situation where NICE is approving things that are unaffordable at a local level in the NHS but are forced onto the NHS*

with the funding mandate. As a consequence, the NHS does its best to wriggle out of that requirement so there's very slow and low uptake of new stuff."

Clinicians appear to be mindful of limited NHS resources and are keen to make efficiency savings for patient benefit (see element 'Clinician perspectives'). Most clinicians are not versed in health economics and look to NICE to interpret the evidence and guide decisions on which therapies are worth providing. However there appears to be growing apprehension that cost-effective therapies (as determined by NICE) are not necessarily affordable, and that their adoption may disrupt the health service and reduce clinician morale.

GP1: *"I know from NICE's methods that although they can say something is cost-effective, they don't say whether it is affordable. For example, looking at IVF, IVF is cost-effective as an intervention but it's not affordable. We can't really meet NICE's recommendations on IVF because it's just not affordable, which is quite disheartening – it makes us look bad for not being able to provide something that has been recommended."*

Cost-effectiveness analyses *(Evidence of IHT cost-effectiveness can influence decisions on adoption)*

- Cost-effectiveness analyses will be influential in determining national uptake of IHTs.
- Stakeholders appear eager to contribute to the construction of economic models to potentially steer outcomes.
- There are concerns over uncertainty and potential bias of economic models. Construction of economic models by independent organisations and validation of economic models using real world data can increase confidence.
- An IHT found to be cost-ineffective can still enter the NHS and private markets.

Participants discussed that once an effective IHT is developed, decision makers, particularly in government funded healthcare systems, will need to decide whether the therapy represents value for money. Cost-effectiveness analyses may be the fairest tool available to make such value decisions and can allow decision makers to separate themselves from

stakeholders within the healthcare market. Participants also raised that health economic modelling can serve to minimise the accountability of decision makers procuring an IHT that may later be considered wasteful.

> HealthEcon1: *"We can probably agree that a) we should try to improve people's health b) everybody counts, that inevitably leads you down the path of health economics - which is let's look at the benefits, let's look at the health opportunity costs. What health could be delivered elsewhere with those resources? A sociologist wouldn't do it like this. A sociologist would just say there's this constituency over here called health economists who've got their own interests. They have a particular ideological position and health economic modelling is their weapon or means of expression that they use to exert their particular power and their interests. I strongly reject that. The geeky bit of health economics lets you do a decent job of making value judgements in a scientific, explicit and accountable way - accountable to the evidence."*
>
> RepOrgImp1: "*An economic model showing cost-effectiveness means you've de-risked the payer. Because if something goes wrong, they just have to point at that report and say - well, the science and data said it was going to be fine. I've not made any error here."*

In the NHS, cost-effectiveness analyses are influential, forming a critical part of NICE's decision making structure. In the US, cost-effectiveness analyses are not part of the formal decision making framework of organisations including the FDA and the Centers for Medicare and Medicaid Services (CMS). Rather, decisions are made based on evidence of effectiveness and safety with price determined by the healthcare market. Participants explained that in practice, the FDA, CMS as well as US private insurers, consider cost and evidence of cost-effectiveness in their decision making process, particularly for novel therapies with a high potential cost burden; albeit not in as structured a way as NICE.

> RepReg3: *"If you look at CMS, the largest payer in the US, their determination of coverage does not include cost or cost-effectiveness. But having said that, I can assure you that if a drug or a device costs a lot of money or if it costs more than other products and it's going to be used in a huge population, they are going to look at cost and cost-effectiveness much more closely."*

Participants discussed that health economic models are often based on incomplete data and assumptions by experts, and that stakeholders, aware of the potential for health economic models to influence policy decisions, are eager to contribute to their construction, steering decisions on model assumptions so that they can try to align the outcome of the model to suit their intentions. In relation to this, participants commented that the process of developing health economic models can help expose underlying biases, motivations and views of stakeholders within the market, assisting in making 'sense' of and navigating a complex market (see elements 'Motivations for adoption and implementation' and 'Sense making').

> HealthEcon2: *"There is a clear political pressure to influence decisions on which interventions to adopt, and I don't just mean political pressure from minsters, I mean political pressure with a small p, so not just from the pharmaceutical industry but around the whole web of interests, from clinicians, patient groups, the incumbents and so on. But the great thing about decision analytic modelling is that it can expose these interests and expose underlying reasons for making decisions."*

Clinician participants expressed apprehension that economic models can be used by decision makers to enforce cost-control, stifling clinical judgment and limiting the use of innovative therapies. Similarly, some hearing discovery scientists urged caution over the extent to which such analyses are used to influence decision making, given limitations of the evidence base, outcome measures available, and therefore uncertainly in model output. Inputting 'real world' data into cost-effectiveness models can help convince stakeholders and decision makers that the model was reflective of actual practices.

> RepOrgImp1: "*Yes, there are biases, and when building your model you have to consider how are people trying to influence the model for their own interests."… "To build an economic model you need to estimate the health effect, the costs, the health opportunity costs, all of which require value judgements which will be influenced by people's impress, their interests."*

Concerns were raised over economic models built by industry or based on data from industry supported studies, which can be biased towards demonstrating cost-effectiveness. A large proportion of economic models appraised by NICE are constructed by industry,

although are reviewed by teams of academics contracted to NICE, called Technology Assessment Reviews (TAR) teams, who are able to refine the economic model. Measures can be taken to increase the confidence in cost-effectiveness analyses, including, transparent publication of results with details of stakeholder groups involved, access to the raw data used to populate the model, details of assumptions made, publishing a lay summary of the model including limitations, and validating economic models with real world data (data collected from routine clinical practice). To increase confidence in their models, industry appears to be moving towards commissioning independent academic organisations to conduct cost-effectiveness analyses.

There has been criticism by health economists that NICE's cost-effectiveness decision making structure has been politicised, with overly generous cost-effectiveness thresholds, meaning that too many interventions are considered cost-effective, avoiding unpopular decisions, whilst making healthcare provision unsustainable. Moreover, that NICE's funding mandate may be counter-productive, forcing commissioners to provide services that they often cannot afford, resulting in commissioners 'applying the brakes', delaying adoption until they can re-structure their budgets.

> HealthEcon1: *"I think the process has been weakened bit by bit, the scientific value judgements have been bent in order to make politically expedient decisions, and I think the social value judgements that they now make are not really evidence-based. For example there's no evidence to support that we place greater weight on health gain in rare diseases compared to common diseases."*

Another concern raised was that whilst economic models provide information on cost-effectiveness, they do not always provide information on affordability, potentially driving the implementation of unaffordable, but cost-effective interventions, to the detriment of the healthcare system. This distinction between cost-effectiveness and affordability may also explain why establishing cost-effectiveness often does not translate to successful adoption and implementation; even if an IHT is found to be cost-effective, providers cannot adopt it if they cannot afford to pay for it. It is important to note however that economic models are able to provide information on affordability, via budget impact analyses. These analyses are used to estimate the likely change in expenditure to a specific budget holder

resulting from a decision to reimburse a new healthcare intervention. The budget impact is usually calculated using a budget impact model. Elements 'Developing a business case' and 'Payment strategies' discuss how clear business cases and effective payment strategies can help decision makers plan budgets and make payments so that IHT procurement is affordable.

An innovative therapy found to be cost-ineffective, may struggle to access the NHS market. However, the therapy could still gain access to the private and self-pay market, which, whilst smaller, is still profitable and easier to navigate. Numerous companies developing interventions in healthcare have purposely only accessed the private market, with profitable returns and a large patient pool. An example is Aesthetic medicine, a field that is not reimbursed by the government healthcare system, but that represents a particularly profitable sector.

> RepCRO1: *"Look at the aesthetic market, nothing is reimbursed - and the sector is booming, because people can and do choose to pay from their own pocket if they value the treatment – there is a real trend of people paying for their own treatments."*

An IHT found to be cost-ineffective, but with evidence of clear superiority to existing treatments, could generate considerable backing from the public, clinicians, industry and politicians to gain entry to the NHS market. Patients and patient charities can be particularly influential, lobbying Members of Parliament and attracting media attention.

> ENT3: "*There could be a concerted group that will fight for it, go out and lobby, head to parliament and demonstrate, grab the media attention and really put pressure to overturn the decision – think about what happened to medicinal cannabis."…."Even if it's not found to be cost-effective, if its effective and there are clinicians who believe in it, and there are patient advocates who believe in it, they'll probably make a good enough argument to eventually get it through."*

NICE's cost-effectiveness decision making framework allows for flexibility on a case-by-case basis, taking into account the novelty of the intervention, its effectiveness, the unmet need of the target patient population, and the comparison to the current standard of care. In the UK, reserve funds have been set aside for expensive, cost-ineffective therapies that address

areas of unmet need. The NIH in the US has similar funding mechanisms for expensive orphan diseases.

Ethical considerations *(Ethical considerations will influence adoption and implementation)*

- Regulatory bodies can inadvertently take ethical decisions away from stakeholders within a healthcare market following approving a therapy.
- Sufficient public opinion against an IHT on ethical grounds may trigger political input.
- IHTs that generate financial reward for clinicians or inequality in access may raise ethical concerns.

Ethical considerations appear to be influenced by evidence of effectiveness, safety and cost-effectiveness. Clear evidence that an IHT is more effective, safe or more cost-effective than existing interventions could inadvertently influence ethical considerations of an IHT therapy and help 'trump' other potential ethical concerns and promote its routine use. Regulatory bodies (such as NICE, the FDA) can also inadvertently take ethical decisions away from stakeholders within a healthcare market following approving a therapy. Once approved, stakeholders may deliberate less on ethical issues, assuming that these have already been considered by regulatory bodies; even though these bodies tend to focus on effectiveness, safety or cost-effectiveness, rather than ethical assessment. Similarly, if regulatory bodies decide not to approve a therapy, this may trigger unwarranted ethical concerns.

> ExpMedEth1: *"If a regulatory or decision making body like NICE says this is approved, go ahead with it, it will help clinicians say yes it's ethically sound - it almost takes ethical conundrums out of the doctors' head and they start acting, which is strange because the decision making body wouldn't have necessarily considered the ethics of the intervention."*

Certain types of therapy may stimulate ethical controversy and subsequent challenges, particularly those interfering with natural mechanisms, such as genetic manipulation, or stem cell therapies. Sufficient public opinion against an innovative therapy on ethical grounds may trigger political input. Ethical considerations appear to also be linked to public fear, where thresholds of ethical concern are raised for diseases that are feared. For example, experimental treatments for conditions including Parkinson's disease or cancer are

more likely to be considered ethically acceptable by the public than experimental treatments for conditions such as hearing loss. Lobbying the public effectively, so that they are aware of the dangerous impacts of hearing loss may be helpful in this context.

Should the IHT generate financial reward for clinicians, via private practice or through industry incentives, concerns were raised that clinicians may over-use the therapy for financial gain. This has been noted to occur for intratympanic steroid injections, where clinicians can carry out the procedure unnecessarily to generate profits.

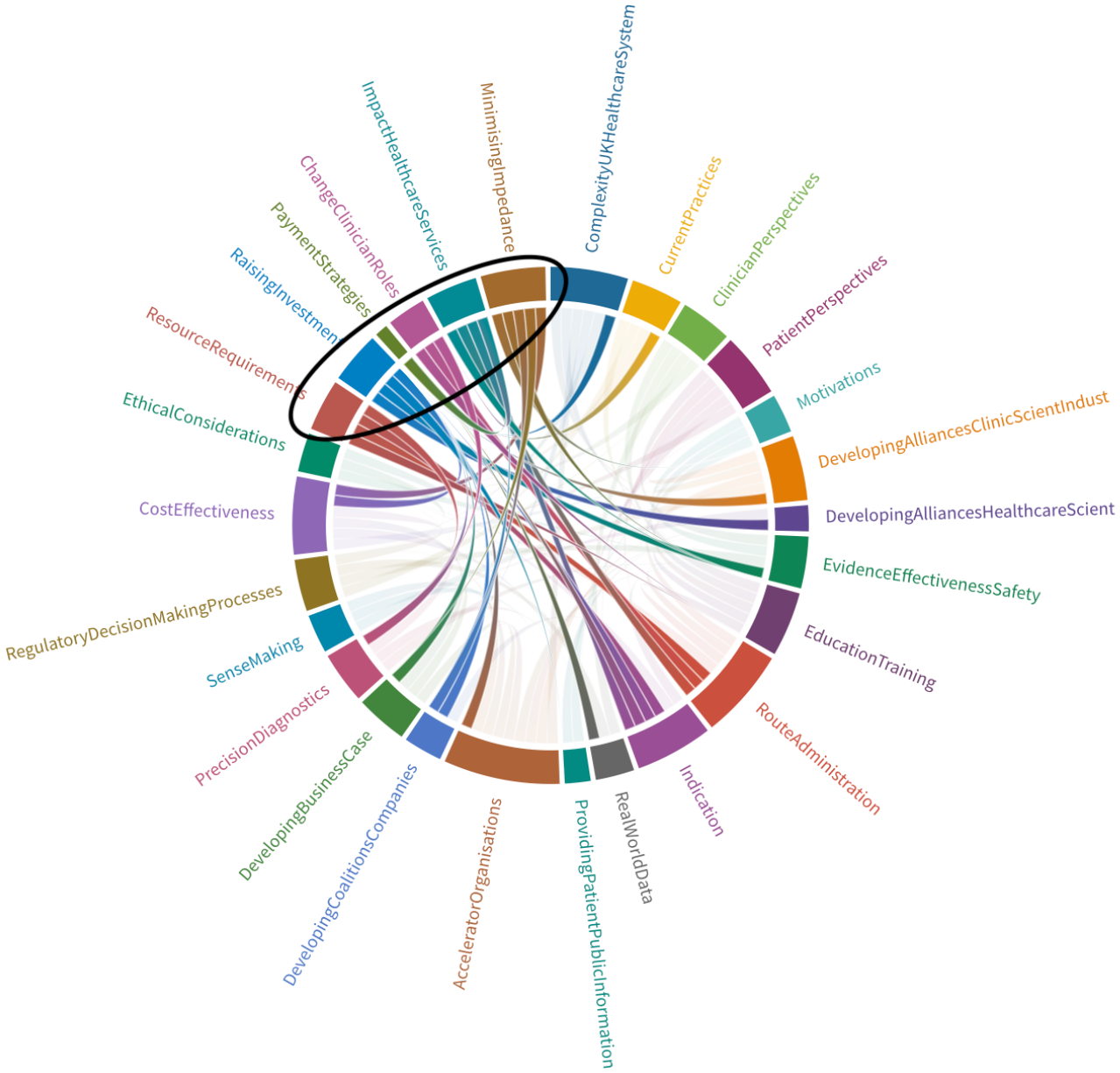
> ClinScien4: *"There are private practitioners out there that no matter what your ear complaint is you get a steroid injection, because it bills out about two hundred dollars. There are people out there that see medicine as their private business and the truth is that there is a lot of unnecessary surgery, which is a major ethical misstep."*

Inequality of access is another ethical concern, where, owing to limited resources and therapy pricing, IHTs may not be available under government healthcare schemes, only available to more wealthy individuals, via the private market, leading to inequalities. The carbon footprint of an IHT was not considered by participants as an important factor for adoption at this present time. This area will likely become more important in the near future owing to rising public and political awareness and pressure. Some hearing technology companies have recognised this, performing environmental assessments of their products with social responsibility programmes in place. Should the device have an unfavourable assessment, this will trigger an internal review.

> RepHearDevComp2: "*It [carbon footprint] is not really considered at the moment and doesn't form part of the business model. But I think that it will become more and more prominent over the next year or so and if you factor in the carbon footprint into your therapeutic development plan, I think you're a step ahead of the curve there."*

Consequences *(Consequences following the adoption of an IHT that influence implementation)*

Figure 12. Snapshot of chord diagram for elements within column ‘Consequences’



Resource requirements *(The resources required by the IHT will influence implementation)*

- Whilst it is likely that early IHTs will be costly, they will probably be indicated for a small proportion of patients, limiting the overall cost burden.
- Associated resource requirements will also need to be considered.

The research, development, regulatory and manufacturing costs of IHTs will be substantial, and this will be reflected in their price-point for procurement. Representatives from IHT

companies discussed that they are working to streamline costs and increase efficiencies to minimise the price of the end product, increasing accessibility. Concerns were raised that IHTs could be unaffordable, particularly for resource poor healthcare systems, unless such therapies consist of repurposed drugs from other applications. However, it was considered that the first IHTs developed will likely be indicated for a small proportion of patients, limiting the overall cost burden to a healthcare system. Difficulties will arise when large numbers of patients are eligible for expensive and effective therapies.

> ClinScien5: *"Looking at the cost of various therapeutics like gene therapies for other conditions, such as blindness, the price tag is astronomical. I would think that that could be a significant problem for healthcare systems. How does a country or a healthcare system manage to shoulder that, or would it go along the current trend where most new innovative treatments are just paid for by the patient directly?"*

Associated costs will also need to be considered, including purchasing necessary diagnostic tests and delivery equipment (see element 'Precision diagnostics'), as well as space, time, hardware and software resources. Meeting these resource requirements without additional funds will require diverting resources from other healthcare services, reducing patient access to other treatments.

> ClinScien3: *"I've spoken to a number of people who say you can't forget the significant resources needed to diagnose people for novel hearing therapeutics and deliver the therapy. This includes purchasing new precision diagnostics, software upgrades, the space and time to run the tests and deliver the therapy, the impact on patient flow, and the reduced revenue by maybe not offering other services due to time or space limitations. You know if you slow down patient flow for other treatments, waiting lists get bigger and hospitals get paid less."*

Resources will also be needed to train clinicians to use the therapy. IHT companies will likely contribute to these costs, recognising that it is in their interest to do so (see elements 'Education and training' and 'Developing alliances between clinicians, scientists and industry'). Delivering IHTs may increase the workload of clinicians across the hearing healthcare pathway (GPs, audiologists, ENT surgeons), with the degree of added workload dependant on indication of the therapy and method of administration (see elements 'Route

of administration' and 'Indication'). A therapy administered surgically, with broad indications may considerably add to the work-load of ENT surgeons, whilst a tablet therapy may add to the volume of patients seen by GPs. Audiologists may be required to perform a large battery of tests per patient, considerably adding to their workload. Participants highlighted the importance for decision makers to be made aware of direct and indirect resource requirements for IHTs as early as possible to help plan for uptake (see element 'Developing a business case').

Raising investment ***(Raising investment for IHT research, development and procurement will facilitate adoption and implementation)***

- Key stakeholder groups can work together to raise investment for IHTs.
- Effectively communicating the case for IHTs appears important for investment; anxiety or fear can be a powerful lever.

Compared to other global diseases, hearing loss attracts relatively little investment into research, therapy development and therapy procurement. Participants expressed that key stakeholders in the hearing loss market, including professional bodies, patient charities and industry need to work together to make the case for investing in IHTs, competing with other diseases and treatments (see element ''Developing alliances amongst healthcare professionals and scientists'.

> RepOrgImp2: *"There are many areas making an impact. We constantly hear about antimicrobial resistance, epidemics in obesity and diabetes and have to consider where sensorineural hearing loss will fit in all this. A very strong argument is going to be needed to be made by all those groups in the landscape, not just the companies to generate further investment."*

Patients and the public, represented by charities and patient groups can play an important role in raising awareness and resources from decision makers. UK hearing loss charities have a track record of successfully lobbying to gain investment to improve patient access to hearing services by writing to Members of Parliament and the Department of Health as well as engaging with healthcare regulators and commissioners. Companies developing IHTs acknowledge the influence of hearing loss charities and patients and are strategically

establishing relationships with these groups through sponsoring charity events and funding research activity (see element 'Providing patient and public information)'. Charities appear to welcome these relationships, to achieve a common goal of increasing investment and patient access to effective treatments. Charities are careful to avoid conflicts of interest that could be discrediting, including direct funding by industry.

> RepNovTherComp2: *"The best way to do it is to get the patients who have the disease, to band together and write to the congressmen or MP, and get a champion in Congress or in the House of Commons, or whatever political system you're in, and then from there try to find a way to direct money to this particular problem."*

Effectively communicating the case for IHTs was considered important for investment, striking a balance between being easily understood, whilst incorporating the science to make a convincing argument. Anxiety or fear can be a powerful tool to motivate public and political opinion, and generate investment, and arguments for IHTs could be framed to highlight the consequences of untreated hearing loss, such as dementia, mental health problems or unemployment.

> ExpMedEth1: *"In the context of adoption of new therapies, people are motivated by fear. An article on what foods will prevent cancer or dementia will get thousands of more clicks than an article on preventing age-related hearing loss and that's because everybody's scared they might die of cancer or get dementia, with few worried about age related hearing loss. So if we tap into people's fear, peoples' motivation for taking active measures increases. So framing the argument around people's fear will help drive adoption."*

Participants also discussed that investment into innovative therapies is linked to positive results, where investors and funding bodies are re-assured that there is potential for a return on their investment. IHTs as a field has yet to see considerable progress in demonstrating efficacy in humans; and this apparent lack of progress makes it challenging to raise funding or investment. As evidence of efficacy is established, investment and funding opportunities will likely increase, accelerating progress. Demonstrating potential cost-effectiveness of IHTs via early health economic modelling (see element 'Early evaluation and evidence of effectiveness and safety') can also help raise investment.

Successful adoption and implementation of a hearing therapy will lead to further investments, since barriers to uptake would have been exposed, navigated and overcome. The development of the first effective IHT will also help trigger media and public attention around hearing loss, generating further investment for the field.

> DiscScien4: *"One of the difficulties in our field [IHTs] is that other fields are ahead of us and funders' expectations are - well, why can't you be like the other fields? So when we submit a grant we're actually marginalised because we are behind other disease areas which have demonstrated success in humans and that puts us at a disadvantage. It's not convincing to say - well, you know, it's working in mice and we believe that it's going to work in humans. So the lack of progress in the field is making things harder. Once we break that ceiling and show a positive result in humans that will be huge for the field and the money will follow."*

Payment strategies *(Effective payment strategies can facilitate adoption)*

- Effective payment strategies can help healthcare systems make IHTs accessible to their populations.
- Strategies discussed included: negotiating based on market-size, advanced purchasing guarantees, government loans with purchasing promises, graduated payments, and co-payments.

Effective payment strategies were considered by participants to form an important component of the adoption process, enabling healthcare systems to afford to procure and make available high-cost innovative therapies to their populations, whilst helping avoid multiple tiers of healthcare (with limited access to those with greatest need).

> ExpPol1: *"Everybody is concerned about what the cost of these hearing therapies are going to be, and how can you bring the cost down so that these therapies will be available to everybody, not just to those in higher socioeconomic parts of society."*

Participants discussed that healthcare systems can try to drive down prices based on the size of their market and buying power. Healthcare systems can also make advance purchasing guarantees, purchasing large volumes over a prolonged time-course to lower unit costs. For example, promising to purchase large volumes over ten years. This would

help companies secure investment to produce large volumes of therapies, driving down costs and therefore prices. Governments can also offer large loans with purchasing promises, which companies can bid on, facilitating entry to market and stimulating competition, whilst driving down costs and providing safeguards against over-reliance on single providers. Other strategies include graduated payments, linked to effectiveness, whereby a proportion is paid upfront, and further proportions paid every year that the treatment proves effective. This provides security for decision makers against therapies whose results are time-limited; however, requires long term monitoring.

> RepNovTherComp4: "*Some of the gene therapy companies have proposed to insurers and to governments that the payment for these things should be graduated. So in other words, let's say the total cost is a million dollars, they pay $200,000 upfront for the treatment and then they pay $200,000 a year for every year that the treatment proves to be durable until you get to a million dollars. You wouldn't want to pay a million dollars for something that worked for a year and a half and it didn't work anymore."*

Co-paying practices were also discussed, where healthcare systems set a base reimbursement for a treatment, which is the maximum amount a government or insurance company can pay, and the patient pays the remaining amount.

Change in clinician roles *(Changes in clinician roles can facilitate implementation)*

- GPs may play a key role in identifying and referring patients for IHTs.
- Audiologists will likely be required to provide novel precision diagnostic tests and may be also required to administer IHTs.
- ENT surgeons will likely be responsible for making management plans, administering IHTs and monitoring patients.
- There may be a role for specialist nurse practitioners to perform minimally invasive, high volume procedures.

<u>GPs</u>

Participants expressed that as gatekeepers to secondary care, GPs will be responsible for referring patients to services providing IHTs and will therefore play a central role in their

successful implementation. Training GPs so that they are aware of IHTs, their indications and referral pathways will therefore be crucial (see element 'Education and training'), and GPs would likely embrace this role, owing to limitations in current treatment options for patients with hearing loss.

> GP1: "*Yes, it would probably improve a GP's role; it would provide GPs with more options and referral routes to treat their patients. At the moment treatments for sensorineural hearing loss are so limited, which is frustrating for GPs and their patients."*

It was considered unlikely that GPs would personally administer IHTs owing to their novelty, potential side effects, cost-burden, need for specialist diagnostics and detailed understanding of underlying disease pathophysiology. In the longer term, once the therapy is well embedded and depending on route of administration, with clear protocols and guidance, it may be possible for GPs to administer IHTs, increasing efficiency of the treatment pathway (see element 'Route of administration').

<u>Audiologists</u>

The provision of IHTs would likely require audiologists to perform a battery of hearing tests for each patient, which could extend to novel precision tests (see element 'Developing precision diagnostics'). As more therapies enter the market, with broader indications, the number of hearing aids provided by audiologists may reduce; however, there will still be a role for hearing aids, given that it is unlikely for IHTs to completely regenerate the hearing system. There was general consensus that at the outset, audiologists would have more of a diagnostic rather than delivery role, however in the longer term there may be scope for audiologists to administer well established, non-invasive IHTs, that are easy to administer, under the supervision of a doctor. IHTs may also increase research opportunities for audiologists to develop precision diagnostics, and recruit patients into clinical trials.

> Aud3: *"Usually, most people think of an audiologist as a hearing aid provider, they don't think of all the other stuff that happens as well. With novel hearing therapeutics, people will see audiologists as having more of a diagnostic role."*

Increasingly, portable hearing screening tests are coming to market, and being used in clinical trials for IHTs. If sufficiently precise, such portable tests may help reduce the workload of audiologists, providing more time for precision testing.

ENT surgeons

ENT surgeons were considered best placed to make diagnoses, formulate management plans, administer IHTs and monitor patents, owing to their baseline anatomical and pathophysiological knowledge as well as medical and surgical training. IHTs would also increase the treatment options available to ENT surgeons, who may, depending on therapy method of delivery, indication and effectiveness, develop more of a medical than surgical role. ENT surgery is already a mixed medical and surgical specialty, and its clinicians were thought to be well placed to meet the requirements of both surgical and medical therapies.

> SenRepENT1: *"In ENT the national average patient conversion from outpatients to surgery is less than 15%. So we are already fairly outpatient based specialists and yes, we are called surgeons but there's a lot of our work which is done in the outpatient setting, and therefore I don't think there'll be any resistance from ENT's to provide medical treatments, because they are already used to it."*

Minimally invasive, effective therapies with broad inclusion criteria could lead to ENT surgeons seeing more patients, conducting more consultations and outpatient procedures and performing fewer surgeries. Similar to audiologists, ENT surgeons will likely have more research opportunities as IHTs are developed, helping to design and recruit to clinical studies.

Nurse practitioner

Once an IHT is well embedded, there may be opportunities for provision by specialist nurse practitioners as occurs in Ophthalmology. This is more likely for minimally invasive, high volume procedures, such as intratympanic injections, under the supervision of ENT surgeons. Some centres in the UK and US have already successfully set up specialist nurse clinics to provide intratympanic steroid injections. However, for the foreseeable future IHTs would probably be provided by ENT surgeons owing to their expertise in hearing healthcare, and the cost of the therapy. ENT surgeons may also prefer to keep all ENT procedures,

including intratympanic injections within their speciality, to guard their specialty, preferring to train ENT trainees rather than specialist nurses.

> ENT3: *"I personally think intratympanic injections are a really nice skill for a registrar to learn. It's nice to keep that skill within our specialty. So, for our new IT [intratympanic] injection clinic, I'm hoping that one of the registrars interested in otology will be motivated to do the clinic. Could a specialist nurse do it? I suspect they could. I've met a practitioner who has a background in audiology that does intratympanic injections at [X] hospital and actually he's very good. But let's keep it within ENT."*

Impact on hearing healthcare services *(The impact of the IHT on hearing healthcare services will influence implementation)*

- The introduction of IHTs may necessitate the development of new treatment pathways.
- The degree of healthcare service impact will be influenced by the therapy's delivery mechanism, indication and degree of effectiveness.

Participants conveyed that a large proportion of patients with hearing loss do not present to hearing services and that the introduction of IHTs may increase awareness and publicity around hearing loss, potentially leading to a surge in patient demand for both IHTs and current hearing interventions. This may necessitate the development of new efficient treatment pathways for IHTs, such as dedicated 'day units' where patients can see an ENT surgeon, undergo investigations and receive an IHT on the same day. This already happens for intratympanic steroid injections in certain centres in the UK and US.

> *ENT3: "If the novel therapeutic has a high demand and needs delivery via an IT injection [intratympanic injection], services could re-organise themselves to improve efficiencies. For example at our unit we have set up a dedicated intratympanic injection clinic, where people come for a hearing test and have their intratympanic steroid injection. It's far more time efficient than doing sporadic IT injections within a standard clinic where you have to the find the equipment, wait for a microscope and so on, which takes ages."*

It was considered that the degree of healthcare service impact will be influenced by the therapies' delivery mechanism (see element 'Route of administration'). An IHT administered by tablet could be provided by a GP, reducing demand for hospital services and easing implementation. Administration via a procedure such as intratympanic injection, may, owing to limited numbers of ENT surgeons, limit patient access, and potentially require new healthcare roles to be created, such as hearing specialist nurses with their own dedicated clinics. The introduction of such roles may delay implementation owing to training requirements and may be contentious and attract opposition from ENT surgeons and patients (see element 'Change in clinician roles'). Should the IHT require surgery that is distinct from existing practices, this would require further advanced training, with associated time and financial resources (see elements 'Education and training')

The indication and degree of effectiveness of the IHT may also impact hearing healthcare services (see element 'Indication'). An IHT that were to successfully regenerate the hearing system and be indicated for a large patient population served by existing hearing technology companies, could be disruptive, resulting in considerable changes to patient demand for existing hearing services. Participants highlighted however that the development of a 'silver bullet' therapy is extremely unlikely, rather, that the first IHT be indicated for a very specific patient population with a limited service impact; and that this could trigger further investment in the field, accelerating the development of other IHTs, leading to greater service impacts.

> RepHearDevCom3: "*I mean, imagine the dream scenario - you could buy a single tablet, swallow it and your hearing is fully restored. I mean, this would be a fundamental change to our system - you won't need the devices anymore. So this would be super-disruptive. But I don't expect such a therapeutic to exist in the next decade or even longer. Instead you will have therapies with specific indications, with limited efficacy that will gradually grow the field.*"

Should the IHT be widely indicated and require surgery, there would likely be insufficient ENT surgeons, resulting in delayed implementation and the need to re-structure existing services. An effective IHT could also reduce the number of follow-ups and long-term hearing investigations needed, reducing healthcare costs, but potentially reducing system activity

and revenues. The introduction of IHTs may also result in changes in the balance between private and government providers. If government decision makers decide not to offer IHTs, this could increase the size of private and self-pay services.

Minimising impedance *(Minimising impedance to IHT uptake)*

- The degree of impedance appears to be linked to degree of perceived threat.
- Forming coalitions between hearing technology and biotechnology companies can help minimise impedance.
- The formulation of robust business cases can help avoid resistance from decision makers.
- Demonstrating clear evidence of superior effectiveness may mitigate resistance from clinicians with vested interests.

Individual groups or companies may work to slow or impede implementation of IHTs and the degree of impedance appears linked to degree of perceived threat. Participants discussed that developing networks that can influence the market is one of the key reasons why companies sponsor clinical and patient events as well as nurture KOLs (see elements 'Education and training' and 'Providing patient and public information'). Existing hearing technology companies may direct some of their well-established networks and KOLs to deter clinicians, patients and decision makers from IHTs. This could include generating critical publications and doubt over the safety and effectiveness of IHTs. The forming of coalitions between hearing technology and biotechnology companies, realising mutual benefits and opportunities can help prevent this (see element 'Developing coalitions between companies').

> RepOrgImp2: "*Well established companies like hearing device companies aim to build such strong allegiances with their clinicians, so that any new therapy is rejected by the clinician before the health system has a chance to even have a say. All the training provided is really a way of retaining control. And it's just about making sure that Dr X is going to continue to buy from us even if another company comes along with a cheaper and better solution, or at least give us enough time to come up with our version of it, so that they end up buying our version".*

Payers, regulators and guideline developers can also slow adoption. Demonstrating effectiveness and cost-effectiveness appears to be an important factor to convince these groups, particularly in the NHS setting (see element 'Cost-effectiveness analyses'). However, even if a therapy is effective, cost-effective and accompanied by a funding mandate, NHS commissioners often do not have the resources to provide it, delaying adoption (see elements 'Cost-effectiveness analyses' and 'Regulatory and decision making processes'). Potential solutions include the formulation of robust and easy to understand business cases, demonstrating how the innovative therapy can be affordable (see element 'Developing a business case'), as well as utilising effective payment strategies (see element 'Payment strategies').

Resistance may also arise from other groups, including discovery scientists who can argue that the underlying pathophysiology of hearing loss, and therefore the mechanism of action of IHTs is insufficiently understood, with subsequent safety concerns. There may also be underlying motivations to resist translation that shifts the focus away from areas of research interest, with subsequent reductions in funding opportunities (see element 'Motivations for adoption and implementation'). It was suggested that realigning incentives for scientists with a focus on translation rather than publications and grants can help mitigate this.

IHTs could also challenge conventional surgical approaches such as cochlear implantation, and some ENT surgeons may resist IHTs that reduce their case-load of operations, owing to fears of losing volumes of procedures which utilise their extensive training, and that are remunerated favourably in the private sector. Demonstrating clear evidence of superior effectiveness and safety will likely mitigate this and help drive uptake amongst ENT surgeons (see element 'Evidence of effectiveness and safety'.

> Repothspec1: "*I would say that unfortunately, there is a profit-making motive amongst doctors, which of course varies. In my experience I would say this is far more in resource poor countries. In the UK and Canada it's definitely not so strong, but there is still a profit motive. So a novel therapeutic that may adversely hit surgical private practice may be resisted to a degree by ENT surgeons who would look to promote*

existing surgical practices that are more lucrative. But of course if there is clear and well known evidence that shows that the novel therapeutic is more effective than surgery, the surgeons will have no choice but to use it."

Discussion

Summary of findings

In this study, through qualitative investigation with a diverse range of expert participants I have provided a detailed explanation of the elements that influence the uptake of IHTs into the UK healthcare system. These elements offer insights into the environment in which IHTs will be adopted and on how to navigate this environment to facilitate uptake. Insights are also provided on the factors that need to be planned for before an IHT is released onto the market as well as on the activities that can be performed to drive uptake. The elements provide information on the decision making processes that influence IHT adoption and on strategies to facilitate these processes. The elements also discuss the consequences and activities following the adoption of IHTs that may influence implementation.

Important discoveries include IHT adoption and implementation being strongly reliant on alliances formed between clinicians, scientists and biotechnology companies. I found that clinicians as well as discovery and clinical scientists look towards partnering with or establishing biotechnology companies with sufficient resources to accelerate therapy translation, whilst biotechnology companies seek to establish trustworthy diffusion networks with clinicians to promote uptake. I also found that important coalitions are developing between biotechnology companies and existing hearing technology companies, recognising the opportunity of combination approaches, pooling of resources as well as utilisation of established market access.

I found that timely clinician education is crucial for IHT implementation, helping to break-down engrained clinical practices and allegiances with existing hearing technology companies. It can also provide an awareness of how IHTs can fit into the patient pathway and promote information dissemination. Education of clinicians can extend to clinical groups

outside the hearing field, including GPs and care of the elderly doctors to promote awareness of IHTs and referral pathways, supporting recruitment to IHT clinical trials and improved patient access. Patient and public demand for IHTs appears a powerful stimulus for clinician education and uptake of IHTs, whilst also exerting significant influence on policy decisions. My findings suggest that biotechnology and hearing technology companies recognise these factors, and as a result, sponsored clinician training, KOL development, as well as indirect marketing and information dissemination to patient groups (e.g., via sponsoring of charity events or research activity) form key components in their implementation strategies. I found that clearly and convincingly articulating the limitations of existing hearing devices, the consequences of untreated hearing loss and the benefits of IHTs also forms part of the strategy amongst biotechnology companies to help influence the motivations of patients, the public, decision makers and investors to support IHT uptake and compete with other diseases vying for investment. Similarly, involving patients in the dissemination of research findings can help improve impact of research findings, driving patient demand and influencing decisions made by decision makers.

My results suggest that clinicians, patients and decision makers may be unconvinced by IHT safety and efficacy data generated from RCTs owing to apprehensions over trial design and external validity. Scepticism also appears to exist on outputs of health economic models constructed by industry and reliant on expert assumptions, due to concerns over potential bias. Real world data (data collected from routine delivery of care) on IHT safety and effectiveness can be more influential, increasing confidence amongst clinicians, patients and decision makers to take-up IHTs; and can also validate and increase the confidence in outputs from health economic models. Real world data may also support IHT payment strategies, support early access programs and fulfil regulatory monitoring requirements.

I found that the availability of precision diagnostics will play a key role in the development of IHTs, so that patients with the appropriate genotype and phenotype are recruited into trials, increasing the chances of success. Whilst investment into the development of precision diagnostics to-date has been relatively modest, there are signs that precision diagnostics are starting to receive greater attention and investment from auditory science, clinicians and biotechnology companies. My results suggest that there appears to be

apprehension that cost-effectiveness models generally do not provide information on affordability, and can promote the implementation of cost-effective, but unaffordable interventions, potentially explaining the limited uptake of cost-effectiveness analyses in decision making. Establishing affordability may be better addressed via the construction of robust and easy-to-understand business cases, which can also help decision makers plan for future budgets and redirect funds as necessary to avoid delays in adoption.

I also found that healthcare system regulatory and decision making processes are generally seen by industry and clinicians as complex, slowing adoption and implementation processes. My results suggest that working with independent accelerator organisations with a detailed understanding of a healthcare system, its key stakeholder groups, the patient pathway as well as regulatory and decision making frameworks may help navigate the healthcare system and accelerate uptake. Some IHTs may be accompanied by considerable procurement costs, and I found that several novel payments strategies are being developed to help address these costs and facilitate patient access.

Implications

This is the first study to investigate adoption and implementation processes in the field of IHTs. By providing a detailed explanation of elements that influence IHT adoption and implementation as well as practical strategies to facilitate uptake, my findings can be used to accelerate the uptake of IHTs into the UK healthcare system. More specifically, they can be used to gain an understanding of stakeholder perspectives on IHTs, as well as potential strategies to influence these. Importantly, my results can help inform the formation of strategic alliances and coalitions that appear crucial for IHT development and uptake. They can also help guide the collection of safety and effectiveness data as well as the construction of health economic models that will be influential to clinicians, patients and decision makers. My results can help inform tailored clinician education on IHTs as well as stimulate clinician engagement and information uptake. Industry and decision makers can use my findings to understand how the IHT indication and route of administration can influence uptake and impact on healthcare systems. They can also use my findings to inform the development of effective business cases that can help decision makers plan budgets and redirect funds. Industry and clinicians can use my findings to navigate healthcare system

regulatory and decision making processes as well as be aware of novel payment strategies that can promote adoption. My results can also help industry identify potential ethical concerns around IHTs and develop strategies to help overcome these and shift public opinion. Strategies are discussed to help raise investment for IHT research, development and procurement, including how to effectively lobby decision makers and compete with other disease areas and treatments.

Strengths and limitations

A key strength of this research is its rigorous approach, with empirical data extracted from 37 in-depth interviews and field notes. Moreover, data collection and analysis were informed by my early health economic model that involved 26 detailed interviews with stakeholders as well as a well-established implementation theory (NPT). During the development of my health economic model (Chapter 2), my interviews with stakeholders revealed underlying perspectives on IHTs, on health economic models and on how health economic models can be used to influence IHT uptake into healthcare systems. These insights informed the topic guide and coding framework of this qualitative study, contributing to a broad exploration of elements that influence adoption and implementation, and resulting in health economics forming an important component of the study. NPT is an empirically tested implementation theory that has been validated by over 250 studies and that explains the processes by which healthcare interventions become routinely used in practice.[62] It has been designed to be used flexibly to shape the coding, analysis and interpretation of qualitative research.[62] The use of NPT to inform this study helped develop an interview schedule and coding framework that facilitated in-depth investigation of a wide range of topics that have been found to influence adoption and implementation, whilst offering the flexibility to investigate and analyse topics not included within NPT.

A potential critique is that since my interview schedule and coding framework were informed by NPT, the subsequent analysis and results could be considered to validate NPT, rather than contribute towards novel findings. However, I highlight that the interview schedule and coding framework were also informed by insights gained during the construction of the health economic model (Chapter 2); and that the use of abductive

analyses meant that the interview schedule and coding framework evolved as interviews progressed to investigate findings that did not fit within the coding framework.

The use of purposive sampling to identify informants may limit the generalisability of my findings and be prone to researcher bias. To mitigate this, I used snowball sampling, where interviewees were asked to propose other participants relevant to my study. I performed the data extraction, coding and analysis and this process may also have been liable to researcher bias. However, a sample of transcripts and their data extraction were cross-checked by my supervisors to minimise potential bias. Patients were not interviewed during this study. However, patients were interviewed during the early health economic model (Chapter 2) and relevant data obtained were analysed for the purpose of this study. I also gained valuable patient insights in my role as: Study lead for the SeaSHeL Study[98], Delegate Principal Investigator for the REGAIN trial[1], Associate Principal Investigator for the Audible-S trial[2] and as an ENT NHS clinician. In these roles, I took hand-written, anonymised, field-notes to capture insights gained that were pertinent to the research question. These notes contributed to the data analysis in this chapter.

Conclusions

This is the first study to investigate adoption and implementation processes in the field of IHTs. By providing a detailed explanation of elements that influence IHT adoption and implementation as well as practical strategies to facilitate uptake, my findings can be used by stakeholders across the IHT translational pathway to accelerate the uptake of IHTs into the UK healthcare system.

CHAPTER 4: HERMENEUTIC REVIEW

Introduction

The term 'innovative therapies ' can be used to describe a category of novel therapies, including gene, cell, tissue-engineered, combined advanced therapies or advanced therapy medicinal products.[107,108] The number of these innovative therapies has grown considerably owing to better understanding of underlying disease mechanisms, and with growing investment by private investors, companies and venture capitalists attracted by their huge promise, representing a potential shift from treatment to cure and with the prospect of addressing areas of high unmet need.[38,39,58] There has also been sizeable investment by governments due the potential economic impact of innovative therapies, where targeted public investment can convert a strong science base into a wealth-generating industry, underpinning a high-wealth, knowledge-based economy.[39,109,110] A recent estimate suggests that there are over 1220 ongoing clinical trials for cell, gene and tissue-based therapies with 1085 developers and close to $20 billion raised in investment in 2020 alone.[111]

The challenges associated with the uptake of innovations into healthcare systems has figured for many years in the policy domain, where healthcare systems can be highly generative of new technologies but poor in ensuring they are implemented at scale.[58] The novelty and complexity of innovative therapies presents a diverse range of specific adoption and implementation challenges making them particularly susceptible to the frequently quoted 'valley of death' for healthcare innovations.[39–43] To help address these challenges and accelerate successful uptake, there has been increasing focus on identifying and understanding the determinants that influence the successful uptake of innovative therapies into healthcare systems.[41] Learning from this body of work can advance our understanding of the elements that influence the adoption and implementation of IHTs.

This chapter presents a hermeneutic review that will place the findings from Chapter 3 in context with the literature on innovative therapy adoption and implementation across healthcare specialties and systems. A hermeneutic review is a type of narrative review that

allows the researcher to search and extract information from the literature flexibly with the aim of advancing understanding of a subject.[112] This review will help me appreciate how the literature compares, and importantly, will provide me with deeper insights into the elements discussed in Chapter 3 as well as explore elements not identified. The scope of this review means it will incorporate a range of therapies across healthcare specialities and systems and it is important to acknowledge that there is likely to be variation according to setting, therapies and stakeholders involved.

Objective: To provide an understanding of the elements that influence the adoption and implementation of innovative therapies across healthcare specialties and systems.

Methods

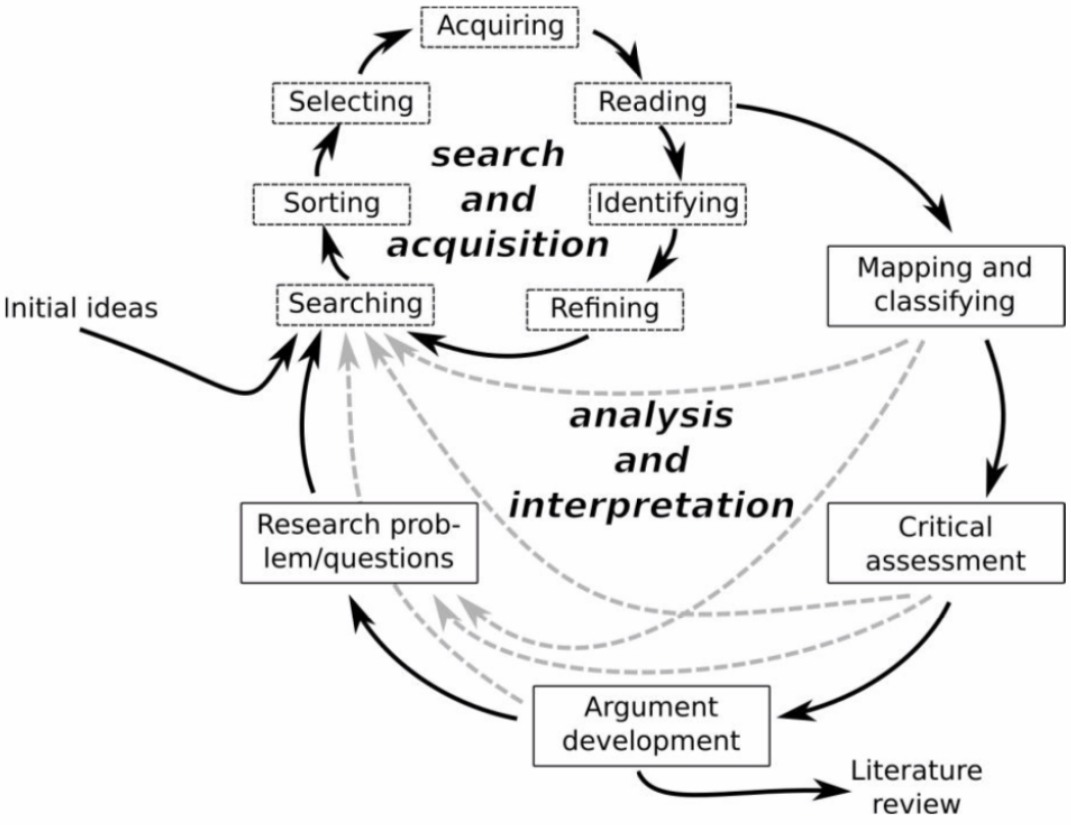
Careful consideration was given to the most suitable type of review to address the aim of this chapter. The conventional systematic review typically involves narrowly focused questions, an exhaustive search methodology with the extraction of all possibly relevant primary studies, followed by limiting the dataset using explicit inclusion and exclusion criteria.[113] The key contribution of systematic reviews is to summarise the findings of relevant individual studies, and if appropriate, combine results from several studies to provide more reliable results and generalisable 'facts'.[113,114]

Given the broad objective of this chapter, the large and heterogenous body of literature on innovative therapies, and most importantly, the focus on providing understanding rather than summarising findings, I considered that a systematic review was not the appropriate review design. A narrative review, enabling scholarly summary along with interpretation, appeared more appropriate.[115] Specifically, I decided to conduct a hermeneutic review, a type of narrative review. This type of review allows the researcher to search, access and extract information from the literature flexibly in order to develop or advance understanding of a subject. The search may or may not be systematic, detailed search strategies may or may not be provided, and inclusion/exclusion criteria may or may not be adopted.[112,113] As articles are included and analysed, the focus is on regularly assessing where remaining gaps in understanding lie, with the researcher free to alter search terms

and identify additional articles and data as necessary to further understanding.[113] The end product consists of a narrative summary of information that provides a detailed understanding of the problem of interest.[112,113] Given that the search strategy and data extraction may change during the course of the review to further understanding, hermeneutic reviews are often not replicable.[113,116]

The process of carrying out a hermeneutic review has been discussed by Boell and Cecek-Kecmanovic[112] and Greenhalgh et al[113,117] and is illustrated in Figure 13, along with a key that summarises terms used in the diagram.

Figure 13. The process of conducting a hermeneutic review. Reproduced from Boell and Cecez-Kemanovic[112]



Key:

- Searching: Identifying relevant publications
- Sorting: Sorting results e.g., by publication date or relevance
- Selecting: Selecting articles for acquisition and reading
- Acquiring: Acquiring of full texts
- Reading: Reading and understanding of acquired articles
- Identifying: Identifying further search terms and additional articles
- Refining: Refining search strategies to improve the precision of literature searches
- Mapping and classifying: Analysis and classification of ideas from included articles
- Critical assessment: How useful included articles are in understanding the problem of interest, and where gaps in understanding are
- Argument development: Synthesising information from included articles that provides an understanding of the problem of interest; and developing future directions of research and rationale for future research
- Research problem/questions: Development of future research questions

This diagram illustrates that a hermeneutic review consists of two interlinked cycles: 1) Searching the literature and acquiring relevant articles and 2) Performing analysis and interpretation. As information accumulates from the first cycle, it becomes necessary to map and classify ideas, consider how understanding has evolved, where ongoing gaps in understanding lie and identify further relevant sources of information. Through this progressive focusing an understanding of the problem of interest can be developed.[112]

I conducted a PubMed search using the search string: (Adoption OR implementation OR uptake) AND (drug* OR gene* OR cell* OR advanced therapy medical product* OR ATMP* OR tissue*) AND (healthcare OR healthcare system* OR health care) AND (treatment* OR therap* OR intervention*) on the 5th October 2020. To help extract information relevant to current healthcare system contexts and access as much of the literature as possible, the search was limited to review articles published after the economic crises of 2008.

Criteria for articles to be included were: Articles that discussed elements that influence the adoption and/or implementation of innovative therapies. An element was defined as: any component, factor, actor, resource, activity, process, or viewpoint that influences the adoption and/or implementation of innovative therapies. Innovative therapies were defined as novel gene, cell, tissue-engineered, combined advanced therapies or advanced therapy medicinal products. Inclusion was not limited by healthcare field, system, or country.

Exclusion criteria were: non-English language, publication before 2008.

I used reference lists of included articles to identify other articles (in both the grey and scientific literature) that would add to my understanding of the elements that influence the adoption and implementation of innovative therapies. I identified additional articles by searching the Google search engine for reports or meetings referred to but not referenced in the included articles.

NVivo was used to extract data from each included article that added to my understanding of the elements that influence the adoption and implementation of innovative therapies. Extracted data were allocated into the table of elements that was developed in Chapter 3. For data that did not 'fit' into these elements, I developed new elements to describe the data.

As data were extracted from included articles, I developed an evolving narrative, which explained how each element influences adoption and/or implementation of innovative therapies.

Results

The PubMed search revealed 5618 articles, all of which underwent title and abstract screening. 54 articles were selected for full-text analysis. A further 30 articles were identified by: screening of reference lists and by searching the Google search engine for reports or meetings referred to by included articles.

Appendix 10 provides an overview of included articles, providing information on: healthcare field; country of focus; relevance of article to review; type of therapy; elements that influence adoption and implementation.

The elements identified in this review that influence the adoption and implementation of innovative therapies across healthcare specialities and systems are summarised in Table 15 and are explained in the narrative summary below. To help present these elements, they have been allocated into the same column headings as used in Chapter 3: Contexts, Preconditions, Activities, Decision making mechanisms, Consequences. The ordering of elements within each column reflects the order in which each element is explained in the narrative summary below. Twenty-two elements were identified in this review, four of which were not identified in Chapter 3. These included: 1) Current infrastructure 2) Characteristics of clinicians and patients 3) Manufacture and distribution 4) Patient pathway.

Table 15: The elements that influence the adoption and implementation of innovative therapies across healthcare specialities and systems.

Contexts (The setting or environment in which an innovative therapy will be adopted and implemented)	**Preconditions** (Factors that need to be considered prior to innovative therapy release onto the healthcare market)	**Activities** (Activities that can be carried out to facilitate innovative therapy adoption and implementation)	**Decision making mechanisms** (Processes of reasoning that need to take place for innovative therapy adoption and implementation)	**Consequences** (Consequences following the adoption of an innovative therapy)
Current infrastructure	Developing collaborations between stakeholders	Collecting real world data	Sense making	Resource requirements
Clinician perspectives	Evidence of effectiveness and safety	Providing patient and public information	Regulatory and decision making processes	Raising investment for research, development and procurement
Motivations for adoption and implementation	Education and training	Working with accelerator organisations	Cost-effectiveness analyses	Payment strategies
	Patient pathway	Developing precision diagnostics	Ethical and legal considerations	Change in clinician roles
	Route of administration			
	Characteristics of clinicians and patients			
	Manufacture and distribution			

Context *(The setting or environment in which an innovative therapy will be adopted and implemented)*

Current infrastructure *(The existing healthcare infrastructure will influence therapy adoption and implementation)*

- Healthcare systems with decentralised decision making infrastructures, established collaborations between industry, university and healthcare providers as well as experienced clinical trial units appear well placed to adopt innovative therapies.

Healthcare systems with decentralised decision making processes appear well placed to adopt innovative therapies.[41,118] These systems tend to have less bureaucracy, simple and coordinated governance processes and more flexibility to reallocate resources and plan budgets.[42,118] The Canadian health system provides an example with 10 autonomous provinces setting their own priorities and exerting their own control over the management and allocation of healthcare resources.[42]

Healthcare systems with established collaborations between industry, universities and healthcare providers; and with centralised and accessible datasets can provide an excellent environment for innovative therapy evidence generation and long-term monitoring.[64] Similarly healthcare systems with experienced clinical trial units and with clinicians with sufficient time and expertise to meet regulatory requirements will promote adoption of innovative therapies.[119] The UK with its national health system, advanced research infrastructure including the NIHR CRN, single healthcare provider status, comprehensive longitudinal health records, and strong links across academia, industry and healthcare, has many of the essential building blocks in place for the adoption of innovative therapies.[64,120] However, despite these attributes, there is some sentiment that the current environment in the UK is not conducive to innovative therapy translation,[119] with further progress required in areas including: evidence generation, clinician training, patient and public engagement, forming collaborations between stakeholder groups, developing of precision diagnostics, regulatory and decision making processes and payment strategies to realise the benefits of this infrastructure.[41,64] These areas are discussed as separate elements within this narrative summary (see elements 'Evidence of effectiveness and safety', 'Collecting real world data, 'Cost-effectiveness analyses', 'Education and training', 'Providing patient and public information', 'Developing collaborations between stakeholders', 'Developing precision diagnostics', 'Regulatory and decision making processes', 'Payment strategies').

Healthcare systems with early alert systems may be better placed to prepare for innovative therapy adoption.[121,122] The NIHR Horizon Scanning Centre as part of Euroscan, provides an example of such a system, prioritising technologies most likely to have an impact on health services and disseminating information to support forward planning by reimbursement authorities, healthcare providers and research funders.[122] The Cell and Gene Therapy

Catapult has utilised the NIHR Horizon Scanning resource to identify new and emerging technologies in different fields, for instance in inherited retinal disease and such analyses have been used to inform innovative therapy commissioning and planning decisions.[121,122]

Clinician perspectives *(Clinician perspectives on innovative therapies will influence their uptake)*

- Safety, effectiveness, unmet need and cost appear to be important factors for clinicians to take-up innovative therapies
- Regulatory processes are often considered by clinicians to be unclear, deterring their engagement in innovative therapy implementation. Greater clarity is required.
- Clinicians appear to consider education from companies an effective and useful route of information transfer.

Clinicians typically consider safety and effectiveness as the most important factors to guide their decisions to use an innovative therapy,[111] and are enthusiastic to adopt innovative therapies, particularly if no alternative exists.[107,108] The cost of the therapy also plays an important role in clinician adoption, particularly in government health systems, where clinicians often carefully consider resource implications; especially when safety and effectiveness are similar to existing treatments.[107]

From an international perspective, NICE has been recognised by clinicians as a leader in therapy assessment, with their economic evaluations providing an effective means for assessing value for money.[42] UK clinicians recognise the key role of NICE in the adoption of innovative therapies; however there are concerns that NICE's economic evaluations are not suited for innovative therapies, resulting in unfavourable assessments (see element 'Cost-effectiveness analyses').[42] Assessments for innovative therapies, particularly those indicated for rare diseases, may be better carried out by specialised services commissioning, allowing early adoption, whilst facilitating real world data collection and ongoing therapy assessment prior to system-wide adoption (see element 'Collecting real world data').[42] In countries with less established regulatory processes, clinician viewpoints can subvert organisational procedures, leading to the potential adoption of therapies with insufficient evidence of effectiveness and safety.[123]

Clinicians commonly do not feel well versed in regulatory processes for innovative therapies and often consider these processes to be arduous, inconsistent and bureaucratic, deterring their engagement.[42] To help address this, it is important for regulatory processes to be transparent and streamlined with harmonisation across regulatory processes, reducing uncertainty and helping to increase clinician engagement (see element 'Regulatory and decision making processes').[42,122,124–126]

Whilst mindful of potentially biased information, education and training from companies developing innovative therapies are generally seen by clinicians as an effective and useful route of information transfer.[118,127] The scientific literature is generally considered by clinicians to be the most trustworthy and accurate information source, however can be time-consuming to search and absorb.[118] Element 'Education and training' discusses how companies strategically invest in clinician training to stimulate information dissemination amongst clinicians, accelerating therapy uptake.

Motivations for adoption and implementation *(The underlying motivations of stakeholders will influence uptake)*

- Clinicians and healthcare institutions can be strongly motivated by being seen to be innovative, whilst scientists tend to be motivated by acquiring grants and publications.
- Governments appear motivated to improve the health of their population and to realise economic benefits for their citizens.

Clinicians and healthcare institutions can be strongly motivated by novelty and by being perceived as innovative or 'cutting-edge,'[41] particularly when no established treatments exist for a given disease; and industry can target these motivations to help stimulate uptake.[118,123] From a decision maker perspective, it is important for this motivation to be restrained until there is good evidence of effectiveness, safety and cost-effectiveness.[123] The motivations of scientists tend to be centred around publications and acquiring grants, rather than on translation from discovery to clinical practice.[128] It has been suggested that incentives for scientists should be realigned, with a focus on translation, helping to drive implementation and patient access to innovative therapies.[128]

Governments are motivated to accelerate the adoption of innovative therapies, not only to improve the health of their population, but also to help develop an industry that will result in economic benefits for their citizens.[39] To achieve these objectives, governments have developed non-profit initiatives such as the Californian Stem Cell Research and Cures Initiative, or the Cell and Gene Therapy Catapult in the UK that work to connect businesses with the country's research and academic communities (see element 'Working with accelerator organisations').[39] These initiatives need to contend with the government's potentially conflicting motivations of improving health and wealth;[39] for instance the decision on whether to support the adoption of an innovative therapy which is effective but that will not generate wealth.

Preconditions *(Factors that need to be considered prior to innovative therapy release onto the healthcare market)*

Developing collaborations between stakeholders *(Developing collaborations between stakeholders across the translational pathway will facilitate adoption and implementation)*

- Gaining patient perspectives on how the innovative therapy can best 'fit' into the patient pathway can help facilitate uptake.
- Collaborating across clinical specialities will encourage learning from case studies of implementation.
- Partnerships between companies developing innovative therapies and those developing precision diagnostics can help realise the benefits of precision diagnostics at the time of therapy market entry.

Early discussions between stakeholders across the translational pathway including researchers, patients, health care professionals, research funders, industry, regulators and policymakers helps avoid the development of innovative therapies that do not resonate with users and decision makers.[41,122,129,130] Collaboration between these groups also helps identify potential barriers to adoption and explore solutions.[131,132] Engagement with

patients appears to be particularly important, providing information on whether the innovative therapy addresses patient unmet needs and whether it will be 'in-demand'.[41,133–135]

There has been criticism from the World Health Organization that patients are insufficiently involved in innovative therapy development and decision making, which may be linked to manufacturers' and authorities' lack of experience on how to integrate patients in their decisions making structures.[136] To help gain patient perspectives, it is important for manufacturers, clinician organisations and decision makers to establish relationships and engage with patient organisations.[137] This can be fostered by developing patient information channels between professional organisations and patient groups, which provide useful information to patients about their healthcare condition, potential treatments and on decision making processes.[138,139] Decision making bodies and industry can engage with patients and gain patient perspectives by actively involving patients or patient representatives in their committee structures.[140] Some companies developing innovative therapies establish relationships with patient charities by sponsoring patient charity events or contributing to charity research grants, gaining access to patients with the objective of gaining patient perspectives.[118,141] Collaborating across clinical specialities can encourage learning from case studies of implementation, helping to combine know-how on payment strategies, regulatory processes, trial delivery, decision making frameworks, training infrastructures, market access strategies, registry development and service restructuring, thereby facilitating innovative therapy uptake.[125,136,137]

Industry are enthusiastic to work with leading clinicians and scientists, who can use their expertise to appraise the developing therapy;[128,140] and gaining input from external experts can represent a cost-efficient way (particularly for small companies) to obtain selective expertise, rather than having all expertise 'in-house'.[128,142] Companies of all sizes, developing innovative therapies can also benefit by forming strategic partnerships with each other, combining expertise as well as capital.[128] Partnerships between companies developing innovative therapies and those developing precision diagnostics can be particularly beneficial, helping to provide a combined package at launch, realising the benefits of precision diagnostics (see element 'Developing precision diagnostics').[138]

Evidence of effectiveness and safety *(Evidence of effectiveness and safety is critical for adoption and implementation)*

- It is important for clinicians and decision makers to reach agreement on what constitutes sufficient evidence of effectiveness to warrant regulatory approval.
- The use of patient reported outcome measures (PROMs) in clinical studies on innovative therapies can help ensure that data is meaningful to patients and decision makers, increasing support from these influential groups.
- There can be uncertainty about the strength of the relationship between surrogate data and its relevant real clinical endpoint, potentially limiting the influence of this data.
- Clinical trials networks, patient registries, collaborative clinical research networks and engagement with patient groups can help deliver innovative therapy trials, helping to generate evidence of effectiveness and safety.
- Novel trial designs have been suggested to complement evidence generation for innovative therapies.

Evidence of effectiveness and safety appears essential for innovative therapy uptake,[41,122,123,127,143–145] however there does not appear to be consensus in the literature on what constitutes sufficient evidence to warrant regulatory approval,[41,143] and it is important for clinicians within the field and decision makers to reach agreement on this.[58] RCTs provide the highest quality of evidence,[38,125,146] however a trial's applicability to real world settings will be questioned by some clinicians, who may be more influenced by the testimony of their colleagues and by data generated from real world settings (see element 'Collecting real world data').[41,146,147]

The choice of outcome measures for clinical studies on innovative therapies is critical in ensuring that data is meaningful to stakeholders.[12,41,124,138,143,146] PROMs have been found to be the most understandable by patients and decision makers, increasing the chances of gaining support from these influential groups. However, validated PROMs are lacking in a number of disease areas[124,137,145,146] and it has been suggested that the development of validated PROMs may help facilitate innovative therapy adoption.[148]

Surrogate endpoints are often used in studies assessing the effectiveness of innovative therapies and whilst surrogate endpoint data are quicker and easier to acquire than real clinical endpoint data, there is often uncertainty about the strength of the relationship between a given surrogate and its relevant real clinical endpoint, potentially limiting the influence of study findings.[120,129] It has therefore been recommended that before a surrogate outcome is used for studies on innovative therapies, a systematic review be conducted examining the evidence for the validation of the surrogate-outcome relationship.[129]

Clinical trials networks can help provide academic teams, biotechnology companies, and Clinical Research Organisations (CROs) access to expert trial teams and centres to deliver innovative therapy trials, thereby helping to generate evidence of effectiveness and safety for innovative therapies.[12,125] In the UK, the NIHR CRN provides infrastructure and resources to support the rapid set-up of trials by streamlining approval processes, funding local research support staff and linking NHS clinical research expertise across hospital sites.[12,120] However procedural difficulties for trials for innovative therapies have been noted.[120] For example, some of the governance documentation relating to clinical trials in the NHS are not well suited for the trialing of cell and gene-based therapies; contracts and costing templates do not necessarily accommodate the added complexity of clinical trials (such as the stipulation of traceability); and expertise on cell and gene therapy clinical trials tends to be dispersed.[119] It has been suggested that the speed and ease of clinical studies for innovative therapies could be improved if there was a degree of centralisation of this expertise and if therapy-specific costing and contract documentation were created.[120]

Novel trial designs have been suggested to complement evidence generation for innovative therapies. For example In silico clinical trials (ISCT) have been recommended for testing the safety and efficacy of new drugs, facilitating evidence generation whilst reducing the size, duration and costs of traditional clinical trials.[149] ISCTs involve the development of patient models, based on available data, that predict individual patient responses to an intervention and can be used to generate large populations of virtual patients, including patients with extreme characteristics that only a large clinical trial could capture.[149] ISCTs can also be used

to extrapolate the results of a clinical trial to later end points, avoiding the costs of prolonging the clinical trial.[149] Responsive-adaptive randomisation has also been suggested for regenerative medicines which maximises allocation to the most effective treatment and minimises the required sample size. This design has the potential to reduce the number of patients allocated to the less effective treatment, therefore reducing the ethical concerns associated with randomisation. However, for new study designs such as these, the magnitude of the risks of bias are not yet well understood and therefore they would be unlikely to be submitted for licensing purposes.[129]

Education and training ***(Effective clinician education and training will facilitate adoption and implementation)***

- Training primary care clinicians on innovative therapies will help drive uptake.
- Genomic medicine and cell biology should be further embedded into training programmes.
- Companies developing innovative therapies can invest in clinician education and training to increase uptake.

Primary care practitioners form a critical 'link' in the successful implementation of innovative therapies and training primary care practitioners on innovative therapy indications and patient pathways enables them to direct eligible patients to centres providing innovative therapies.[126,137,139,150] Providing clinicians across both primary and secondary care with information on pivotal clinical trials, degrees of effectiveness and safety, information on mechanism of action, as well as training on potential ethical issues appears to increase clinician confidence in using innovative therapies for their patients (see element 'Ethical considerations' and 'Regulatory and decision making processes').[118,126,127,132,137,139,147,150]

Research suggests that a large proportion of clinicians are insufficiently trained in genetics and cell biology to facilitate wide scale implementation of cell and gene innovative therapies.[142,147,151] To help address this, genomic medicine and cell biology should be further embedded into clinician education and training programmes.[142,147,151]

It has also been suggested that clinicians, during their training should be given the opportunity to work with professionals from other disciplines, such as engineering, computing, policy development as well as with industry, to develop skills outside the traditional clinical domain to facilitate the development and implementation of innovative therapies.[38,133,142,150]

Companies developing innovative therapies invest in clinician education and training to stimulate communication between clinicians which is a powerful and effective means of information dissemination, increasing acceptance and uptake of innovative therapies.[118,123,127,141] This includes strategically appointing influential KOLs to act as a catalyst for innovative therapy adoption, owing to their credibility amongst peers and extensive networks.[118,123,141] Clinicians involved in trials for innovative therapies are also used as an effective conduit to provide training and disseminate information.[118,137,141]

Clinician education and training in low and middle income countries is heterogeneous with often more focus on infectious diseases than non-communicable and chronic diseases, owing to historic burden of disease.[131] This coupled with less dedicated clinical or basic science research training, represents a barrier to the uptake of innovative therapies in these settings.[131]

Patient pathway *(How well the innovative therapy can fit within the existing patient pathway will influence adoption and implementation)*

- Early dialogue between stakeholders will help identify how the innovative therapy can be best incorporated into the healthcare system and patient pathway.
- Developing patient journey maps can facilitate efficient integration.
- The establishment of specialist delivery centres for innovative therapies can provide a 'seed-bed' for therapy delivery.

A innovative therapy that can fit easily into the existing patient pathway will facilitate adoption and implementation.[110] Early dialogue between manufacturers, regulators, payers, patients, clinicians and researchers will help identify how the innovative therapy can be best incorporated into the healthcare system and whether new patient pathways are

needed.[39,120,138] Developing patient journey maps can assist in this process, providing a detailed schematic of the current patient pathway and identifying areas of unmet need and opportunities for innovative therapies.[41,135]

Innovative therapies involving complex diagnostics and delivery will likely be restricted to central clinical centres with greater resources. Centralising innovative therapies can help streamline costs, help ensure sufficient staffing expertise and promote best practices.[134,152] However, indirect costs to the patient and inequalities in access must be balanced against this model of service provision.[108,133,138] The establishment of specialist delivery centres for innovative therapies can provide a 'seed-bed' for innovative therapy delivery, helping to generate long-term real world data collection, develop specialised knowledge and skills as well as trial and improve logistical arrangements and systems such as the development of links to manufacturing sites (see element 'Manufacture and distribution').[39,41,153,154] For example, in the UK, advanced therapy treatment centres are being developed sharing knowledge and experiences across specialties and providing stakeholders and investors with a clearer pathway to clinical and commercial success.[41,109,137] These centres also aim to foster partnerships between healthcare organisations and industry bringing together clinical, manufacturing and logistical expertise.[41,58]

Route of administration *(How the innovative therapy is administered will influence adoption and implementation)*

- Administration requirements and subsequent resource implications should be carefully considered by decision makers.

Innovative therapies requiring administration in specialist conditions (e.g. operating theatre) with specialist equipment or requiring longer treatment regimens and specialist training will add to resource requirements impacting implementation (see element 'Resource requirements').[118,155] It is important for decision makers to consider these resource implications early, through discussions with the company developing the innovative therapy, with clinician KOLs familiar with the innovative therapy, as well as with researchers carrying out early assessments (see element 'Cost-effectiveness analyses').[118,155]

Characteristics of clinicians and patients ***(the characteristics of clinicians and patients can influence innovative therapy uptake)***

- Younger clinicians, specialist clinicians, research-oriented clinicians and clinicians with established relationships with the manufacturing company appear more likely to use an innovative therapy.
- Patients of a young age, with higher socioeconomic status and unsatisfactory response to existing therapies appear more likely to receive an innovative therapy.

Younger clinicians appear to have a higher propensity to use innovative therapies than older, more experienced clinicians, likely owing to older clinicians having more established prescribing practices.[141] Specialist clinicians, with expertise in the therapeutic area typically have higher rates of uptake, as do more research-oriented clinicians who keep abreast with the scientific literature. This appears to be due to having a better understanding of the field and of the therapy, translating to increased confidence to use the therapy for their patients.[141] Clinicians involved in clinical trials of innovative therapies seem more likely to use the therapy for their patients, and this appears to be due to already being trained and versed in innovative therapy delivery.[141] Importantly these clinicians can form an important catalyst for innovative therapy uptake amongst their clinical colleagues (see element 'Education and training').[118,141] Clinicians also appear more likely to provide innovative therapies if already providing other treatments from the sponsoring company, due to confidence in, and established relationships with that company.[141]

At the patient level, predictors of higher innovative therapy delivery include young age, higher socioeconomic status and unsatisfactory response to existing therapies.[141] Doctors seem less likely to prescribe innovative therapies for elderly patients since they are often considered to be at higher risk of adverse effects than younger patients.[141] High income patients from higher socioeconomic groups and with higher levels of formal education are more likely to receive innovative therapies earlier, owing to their ability to pay for out-of-pocket treatments as well as their greater ability to navigate healthcare systems.[141] Patients with unsatisfactory response to existing therapies appear to prompt clinicians to consider their individual cases more seriously and these patients themselves are more willing to receive potentially higher risk innovative therapies.[141]

Manufacture and distribution *(Manufacturing and distribution strategies influence the implementation of innovative therapies)*

- The manufacture of innovative therapies may be best addressed by decentralised manufacturing.
- The distribution of novel gene and cell therapies can be facilitated by leveraging existing tissue and blood bank infrastructures.
- Hospitals may need to act as cell or tissue procurement services and work closely with manufacturers to help produce innovative therapies.

The manufacture of innovative therapies is complex, balancing efforts to produce precise, safe, high quality and effective products, whilst achieving efficiency.[38,39,41,58,64,154,156] Companies should consider the manufacturing strategy of their innovative therapy and establish a dialogue with regulators early to assess feasibility and plan for regulatory requirements.[43,157] Accelerator agencies such as the UK's Cell and Gene Therapy catapult, can provide support on developing manufacturing strategies as per regulatory quality standards (see element 'Accelerator agencies').[39]

The manufacture of innovative therapies may be best addressed by decentralised manufacturing, with small factories, located close to end users and providing responsiveness, personalisation and traceability, whilst minimising storage and transportation requirements.[38,43,154,158,159] Challenges of decentralised manufacturing should be considered, including higher costs, reduction in oversight by central management and vulnerability to staff turnover.[41,43,158] To help overcome these challenges, decentralised manufacturing will need to exploit the benefits of automation of unit operations as well as intelligent systems that can responsively coordinate supply chains.[38,41,42,129,158]

Innovative therapies often have complex storage and transportation requirements;[133,153,154,158] and it has been suggested that the distribution of novel gene and cell therapies can be facilitated by leveraging existing tissue and blood bank infrastructures and learning from the successes of efficient blood transport networks.[119,154,158] For example the NHS Blood and Transplant service has been identified by the Cell and Gene Therapy

Catapult as a key model to facilitate delivery of cell and gene therapies with extensive experience in handling live tissue, logistics, and managing the associated regulatory hurdles.[39]

Manufacturers of innovative therapies may require hospitals to act as cell or tissue procurement services and specialist centres are being developed with this in mind, establishing close links to manufacturing sites (see element 'Patient pathway').[41,58,109,153,154]

Activities *(Activities that can be carried out to facilitate innovative therapy adoption and implementation)*

Collecting real world data *(Data collected from routine clinical practice can influence adoption and implementation)*

- Real world data can be used to assess the safety, effectiveness and cost-effectiveness of innovative therapies, as well as provide an overview of the patient pathway, informing policy decisions.
- Real world data can be used to support novel payment strategies and fulfil regulatory monitoring requirements.

Whilst RCTs represent the highest level of evidence, conducting RCTs for innovative therapies carry important limitations including limited capture of long-term outcomes and concerns over external validity which can influence uptake.[38,122,129,130,133,143,145,147,160] It may also be challenging to conduct RCTs for innovative therapies, when for example it is unethical to assign participants to an invasive control arm (e.g. involving tissue engineered products) or in rare conditions where it may be unfeasible to enrol adequate numbers of patients.[120,122,129,138,147,154] RCTs for innovative therapies such as gene therapies, are also particularly expensive and complex, involving monitoring with precision diagnostics, use of costly therapies, and targeting rare diseases where patients are geographically dispersed.[120,143,145,160]

Owing to these limitations, it has been suggested that once early phase trials have demonstrated safety, innovative therapies can be assessed via the systematic collection of data as the innovative therapy is used in routine conditions.[132,133,137] This real world data collection can be used to assess the safety, effectiveness and cost-effectiveness of innovative therapies, as well as provide an overview of the patient pathway, informing policy decisions.[130,132,139,148,161,162]

Long-term real world data collection can also help inform innovative therapy payment strategies (see element 'Payment strategies'), support early access programs and fulfil regulatory monitoring requirements (see element 'Regulatory and decision making processes').[132,152,157,163]

The value and utility of real world data will depend on data accuracy, standardisation and completeness.[64,134,143,149,163] Patient registries and national trainee collaboratives have been found to be effective in collecting real world data.[12]

Providing patient and public information *(Providing information to patients and the public on innovative therapies can facilitate uptake)*

- Providing patient information can help drive patient demand for innovative therapies, as well as help patients make decisions and maintain adherence.

Patient information can help drive patient demand for innovative therapies, an important lever to influence clinician and regulator decision making.[118,137,141] Dissemination of information can be via traditional and social media and can utilise networks of professional bodies and patient charities. Companies can disseminate information to patients via direct or indirect (e.g. sponsoring patient charity events) marketing, depending on country regulations.[118,141]

Commencing an innovative therapy can be confusing and providing patients with easily accessible and understandable information on therapy effectiveness, risks, mechanism of action and delivery regimen is crucial to help patients make decisions and maintain adherence.[64,124,138,139,163]

Working with accelerator organisations *(Organisations with an understanding of the healthcare market and with networks of key stakeholder groups can help facilitate adoption and implementation)*

- Accelerator organisations have been formed to promote faster adoption of innovative therapies into healthcare systems.
- These organisations can help link key stakeholder groups, assist in product development, testing, and in gaining market access, including lobbying decision makers.

In several countries, publicly funded accelerator organisations have been formed to promote faster adoption and implementation of innovative therapies.[39] These include for example, the New York State Stem Cell Science, the Canadian Centre for Commercialization of Regenerative Medicine, the California Institute for Regenerative Medicine and the UK Cell and Gene Therapy Catapult.[39]

These organisations work to develop links between academic researchers, government funding bodies, clinicians and industry to identify investment and collaboration opportunities for innovative therapy development and testing.[39,129] They also help support clinical trials, advise on regulatory processes and provide support on innovative therapy manufacturing and logistics (see element 'Manufacturing and distribution').[39] Another role is providing expertise in health economics and business model development.[39] Importantly, these organisations can play a lobbying role, pushing for regulatory and policy adjustments to accelerate innovative therapy adoption.[39]

More broadly, accelerator organisations can provide developers with an early understanding of their target healthcare market, including disease burden, patient preferences, existing treatments available, budgeting and finance mechanisms as well as reimbursement profiles of alternative treatments.[41,108,133,164] This will provide an understanding on how well the innovative therapy will 'fit' within the target healthcare market (see element 'Sense making').[108,128,134,142] Accelerator organisations can also provide companies with an understanding of clinical training pathways within a healthcare system

so to develop educational strategies that can promote uptake and effective delivery (see element 'Education and training').[118,134]

Developing precision diagnostics *(precision diagnostics will facilitate adoption and implementation of innovative therapies)*

- Precision diagnostics can help establish innovative therapy effectiveness whilst reducing research and development costs.
- Companies developing innovative therapies are exploring opportunities for co-development, however co-development strategies face challenges.
- Effective clinician training, establishing multidisciplinary teams and utilising machine learning approaches can facilitate precision diagnostics interpretation.

In trials for innovative therapies, precision diagnostics can facilitate recruitment of patients with the appropriate genotype and phenotype, helping to establish clinical effectiveness, without having to include large patient numbers, thereby reducing research and development costs.[12,38,63,125,132,134,137,141,144,165–168]

From a clinical perspective, precision diagnostics can optimise patient selection, improve outcomes and help reduce adverse events.[63,126,132,137,138,141,144,168–170] There is also an appreciation that precision diagnostics can increase the market share of innovative therapies by establishing enhanced safety and effectiveness, whilst serving as a gatekeeper to patients, through which subsequent therapies must pass.[64,166]

Owing to these advantages, companies developing innovative therapies are showing increasing interest in exploring opportunities for co-development of precision diagnostics.[63,138,165,166,171] However co-development strategies face challenges. In the US, Canada and Europe, the regulatory frameworks responsible for approving innovative therapies and precision diagnostics are different, and as a consequence, innovative therapy and precision diagnostic development often take place independently.[38,63,138,170,171] The development times of precision diagnostics are typically shorter than for innovative therapies and business models also differ; companies developing therapies typically adopt high margin, high risk strategies, whilst diagnostic companies have low margins and

strategies based on high volume.[166,171] Decisions on profit sharing can be complex considering diagnostic products are typically undervalued compared to their therapy counterparts with precision diagnostics having weaker intellectual property protection and payers tending to reimburse for diagnostic services on a cost-based, rather than a value based system.[64,166] Co-development also represents a potential risk for diagnostic companies given that the fate of the diagnostic can be tied to that of the therapy, with many drugs failing in Phase I or II of clinical trials.[166] To help address some of these challenges, regulators are implementing streamlined regulatory systems that can be applied to both precision diagnostics and innovative therapies .[138,166,171]

Importantly, as precision diagnostics evolve, there may be challenges faced in terms of their interpretation and uptake into clinical decision making.[172] Training clinicians on precision diagnostics (see element 'Education and training') as well as setting-up multidisciplinary teams with appropriate expertise to interpret precision diagnostics and guide therapy delivery appears to offer a solution.[150] Bioinformatic and machine learning approaches as well as mathematical models, similar to those used in Ophthalmology, can also be used to integrate complex multidimensional data from precision diagnostics and inform clinical decision making.[12,138,172]

Decision making mechanisms *(Processes of reasoning that need to take place for therapy adoption and implementation)*

Sense making *(Understanding how the innovative therapy will fit into the healthcare system will facilitate adoption and implementation)*

- Sense making will help clinicians and decision makers make decisions on innovative therapy adoption.
- Clinician training, engagement between stakeholder groups and working with accelerator groups can facilitate sense making.

Clinicians appear more likely to use an innovative therapy if they clearly understand the differences to currently available interventions and how the therapy can form a part of their

management plan.[118,139] Clinician training seems crucial in establishing this understanding (see element 'Education and training'). To make decisions on innovative therapy adoption, payers and policy makers will need to have an awareness of: what the therapy is looking to address; how the innovative therapy will address this unmet need; the likely size of treatable populations; the differences between the innovative therapy and existing therapies as well as how the innovative therapy may fit within the patient pathway including potential impacts to system infrastructure (see element 'Patient pathway').[58,109,139,147,154,163,173,174] This process of sense making will require engagement between stakeholder groups across the translational pathway, including clinicians, patients, industry and decision makers.[163] Accelerator organisations can help bring these groups together and assist in providing this understanding (see element 'Accelerator organisations').[39,58]

Regulatory and decision making processes *(Regulatory and decision making processes influence adoption and implementation)*

- Regulatory processes are frequently considered slow, expensive and complex.
- To help address these challenges a number of strategies have been developed by regulators to streamline regulatory processes.

Challenges

Regulatory processes are frequently considered to be slow and impede innovative therapy adoption owing to their high costs, inexperience in assessing innovative therapies, comprehensive evidence requirements, complexity, and the considerable differences in regulatory processes between countries.[38,39,41,42,107,119,120,122,131,134,156,160,166,175]

Regulatory processes in developing countries have been found to be particularly bureaucratic and unclear resulting in significant delays in regulatory decisions as well as insufficient long-term monitoring.[130,131] Europe faces specific regulatory complexity since, although market approval for pharmaceuticals are centralised through the European Medicines Agency (EMA),[107] regulatory decisions are made at a national level with considerable variability in regulatory processes and decisions between countries.[175,176]

These challenges appear to unfavourably impact smaller companies, with observations that small company size appears to be an independent predictor of a negative regulatory outcome.[129]

Strategies to facilitate adoption

Adaptive licensing approaches, acknowledging that information on innovative therapies continues to evolve over time have increasingly been adopted by regulators.[120,162] Here, the single moment between non-approval and approval is replaced by progressive reduction of uncertainty, where access to innovative therapies is based on a combination of data from RCTs and ongoing observational studies, permitting more timely market entry.[162]

Regulators have also developed a range of Early Access Programs (EAPs) and fast track appraisal systems to accelerate patient access to innovative therapies.[110,122,133,160] For example, in the EU, EAPs enable regulators to grant conditional approval for an innovative therapy in the absence of comprehensive clinical data if: (1) there is a positive benefit to risk assessment, (2) it is likely that comprehensive clinical data will be provided, (3) that an unmet clinical need will be met, and (4) that the benefit to public health of immediate availability outweighs the risks of proceeding in the absence of additional data.[122,133] The EU's European Medicines Agency (EMA) has implemented the PRIority Medicines (PRIME) scheme, which supports dialog between the EMA and the pharmaceutical industry to accelerate evaluation processes.[108,122,133] The EMA's Scientific Advice Working Party (SAWP) has also been established to provide scientific advice or protocol assistance as well as information on scientific and regulator expectations and requirements. This service can be provided in parallel with the US FDA.[122] EU member states and Australia have established Managed Entry Agreements (MEAs) between the pharmaceutical industry and regulatory agencies that allow conditional access to the market for novel drugs with unclear efficacy and safety profiles.[129,133]

In the UK, 'hospital exemption' and 'specialised' schemes, as well as 'commissioning through evaluation (CtE)' offer accelerated access to innovative therapies that are lacking in clinical and cost-effectiveness evidence, whilst facilitating further evidence generation as the

therapy is used in practice.[42] The FDA have introduced four distinct approaches to accelerate adoption of innovative therapies that address unmet medical need, namely: 'Fast Track', 'Breakthrough Therapy', 'Accelerated Approval', 'Priority Review' and Fast Track'. These approaches expedite review of innovative therapies and impose less stringent standards than regular procedures to accelerate adoption. In Japan, reimbursement licensing schemes have been developed for innovative therapies where conditional regulatory approvals may be granted based on early phase clinical trials that demonstrate safety and are likely to predict efficacy.[110,122] Therapies that receive conditional approval are eligible for reimbursement by the Japanese national health system, transferring economic and health risks of experimental innovative therapies to the health system.[122] Whilst this innovative scheme can improve patient access to innovative therapies, it requires patients and tax payers to assume significant personal and economic risks, considering the high failure rate in Phase II trials.[122] Such schemes may also negatively impact the collection of efficacy data for final regulatory decisions, in part, because patients with access to therapies have less incentive to enrol in clinical trials.[122]

Orphan drug frameworks such as the EU orphan drug framework have also been developed by authorities to incentivise the development and translation of therapies for rare diseases.[122] Incentives include reduced development costs through tax credits for clinical trial expenses, research grants, waived administrative fees for regulatory approvals, higher cost-effectiveness thresholds, priority approval programs, specialist advice and assistance on therapy development and approval, and once released to market, orphan drugs can be granted market exclusivity, protecting from direct competition for 8–10 years (10 years in the EU; 8 years in Canada).[122]

Recognising that targeted innovative therapies may be indicated for smaller patient populations, regulatory agencies are also experimenting with adaptive clinical trial designs, permitting smaller and shorter clinical trials as well as use of surrogate outcomes.[38,64,122,163] However, these designs require payers to extrapolate long-term health benefits from short trials, which may be problematic for curative therapies and for assessing long term side effects.[122]

Regulatory harmonisation initiatives have been developed across countries to help synchronise regulatory processes, streamline requirements for global market approval and reduce the costs of innovative therapy development and implementation.[125] The International Horizon Scanning (Beneluxa) Initiative involves 8 European countries and encourages collaboration on pharmaceutical policy to 'harmonise' approval processes.[134] This initiative uses a central database to continuously gather data, analyse research and facilitate information sharing about new and developing therapies, aiming to help policymakers identify future challenges, set priorities, forecast costs, and facilitate timely decision making as well as negotiations for lower prices.[134]

Cost-effectiveness analyses *(Cost-effectiveness analyses may unfavourably impact value assessments of innovative therapies)*

- Innovative therapies are often permitted higher cost-effectiveness thresholds. However, this may represent an unfair assessment of opportunity costs.
- Cost-effectiveness analyses for innovative therapies are commonly conducted by industry, with concerns over potential bias.
- Alternative methods to assess innovative therapy value have been proposed but are in their infancy.

Cost-effectiveness analyses are the main tool used to assess value for money of new healthcare interventions.[122–124,138,139,165,170,176,177] However conducting cost-effectiveness analyses for innovative therapies are challenging, particularly for those requiring one-off dosing, with life-long, potentially curative benefits and targeting small populations; since in these cases, data is often from small clinical trials with limited follow-up data, and potentially no comparator.[108,122,129] Cost-effectiveness analyses may also unfavourably impact value assessments of innovative therapies, typically only including direct healthcare costs (omitting social costs including social care costs, rehabilitation and unemployment) and potentially having limited time horizons[108,119] that fail to offset the sizeable upfront costs of innovative therapies.[110,120,163,176,177] Health economic models for innovative therapies also tend to carry considerable uncertainty due to paucity of available data, particularly long-term effectiveness and safety data, thereby increasing reliance on assumptions and reducing reliability.[108,120,122,124,163,176–178] These factors can impact the

confidence of reimbursement decisions and reduce the likelihood of innovative therapy adoption.[119,122]

To account for this, innovative therapies targeting rare or orphan conditions often carry a higher cost-effectiveness threshold.[108,165] The ICER (Institute for Clinical and Economic Review) has suggested a cost-effectiveness threshold of $150,000 per QALY gained for ultra-rare diseases. In the UK, NICE, has allocated gene therapies a cost-effectiveness threshold of up to £300,000 per QALY.[108,122] However these thresholds are controversial and some experts argue that this 'special treatment' of innovative therapies represents an unfair assessment of opportunity cost.[108]

Cost-effectiveness analyses for innovative therapies are generally conducted and submitted by industry to regulatory bodies for appraisal, with concerns that such analyses can be biased in favour of positive recommendations.[108] Regulators can work to minimise these biases; for instance, NICE have published measures taken to identify biases of submitted models as well as adjust analyses to reduce uncertainty.[64,140,179,180]

A number of organisations such as the European Network for Health Technology Assessment (EUnetHTA), Advance HTA, The International Society Pharmacoeconomics and Outcomes Research (ISPOR) Rare Disease Group and others have suggested that more comprehensive value assessments are required for innovative therapies, extending beyond direct costs and effects, factoring-in multiple social value criteria with a focus on patient priorities.[64,163,176,177] Agent-based modelling (ABM) has been suggested as a possible approach having the potential to capture a spectrum of consequences and effects by simulating changing states and activities of individual 'agents' in a system.[149,177] Multi-criteria decision analysis (MCDA) has also been suggested as an alternative tool, providing a methodological infrastructure that adds interests, values and concerns from stakeholders to the decision making process, allowing decision makers to incorporate these perspectives in their decision making.[176]

Ethical and legal considerations *(Ethical considerations will influence adoption and implementation)*

- Innovative therapies will most likely be delivered at centralised hospitals, potentially leading to ethical concerns around equal access to services.
- The capture of genotypical and phenotypical data for innovative therapy delivery will require careful data governance considerations.

Innovative therapies introduce a range of ethical concerns and considerations dependant on the nature of the therapy.[108,142,181] It is important for developers of innovative therapies to appraise the public's ethical perception of an innovative therapy before development, including potential trade-offs that are willing to be made by patients and the public (e.g. whether an effective therapy addressing an area of unmet need may overcome ethical concerns around gene editing).[142,156] Decision makers can appraise the public's ethical perception before therapy entry into the market.[142,156]

Innovative therapies will most likely be delivered at centralised, specialist hospitals, potentially leading to ethical concerns around equal access to services.[134,138,182] Therapies deemed too costly to be provided by government healthcare systems may only be available in the private sector creating further inequalities.[138,142] Decision makers will need to carefully design patient pathways and referral routes with input from patients to avoid inequalities in patient access.[134]

The development of digital health tracking technologies and comprehensive patient registries with genotype and phenotype data has been suggested as an effective strategy to fairly identify patients that are eligible for innovative therapies as well as monitor patient access.[38,182] However, the capture and sharing of such data will be accompanied by data governance issues.[38,147,149] A potential solution may be gaining consent from patients to make their data freely available.[38]

The patient-specific genetic and biological data required to administrate innovative therapies can lead to issues of discrimination and stigmatisation for purposes of healthcare, insurance, employment or educational opportunities.[138,182] The development of expert panels with an in-depth understanding of the science and ethical implications of innovative therapies may be necessary to guide policy decisions in this complex field.[181]

Consequences *(Consequences following the adoption of an innovative therapy)*

Resource requirements *(The resources required by the innovative therapy will influence adoption and implementation)*

- The high direct and indirect costs of innovative therapies represent a barrier to adoption.
- Payment strategies must be carefully considered so that innovative therapies can be affordable.

Innovative therapies typically carry high prices[42,136,173] and may require precision diagnostic tests, specialist facilities, specialist clinicians, and information systems, incurring further costs.[41,125,137,138,151,153,163,170,174] These high costs represent a major barrier to adoption; particularly for therapies indicated for large patient populations.[38,42,108,118,122,124,134,137,139,155,163,174,183]

Whilst high resource requirements may be overcome by high income countries, this may not be the case for lower income countries,[131] and payment strategies must be carefully considered so that innovative therapies can be affordable and accessible (see element 'Payment strategies').[134] Decision makers will need to consider whether the therapy is affordable to the healthcare system[58] and the distinction between affordability and cost-effectiveness must be carefully considered in this context.[41] Cost-effectiveness describes assessment of value for money (see element 'Cost-effectiveness analyses'), whilst affordability describes ability to pay. A number of therapies that have been found to represent good value for money, have experienced poor uptake owing to insufficient resources to pay for the therapy.[41]

Raising investment (*Raising investment for innovative therapy research, development and procurement will facilitate adoption and implementation)*

- Targeted government investment into innovative therapies can stimulate further private investment.
- Regulatory and payment strategies are being developed to boost private investment.

Targeted government investment into innovative therapy research and development can stimulate further private investment and help drive adoption into healthcare systems.[109] The UK government provides an example, investing in the Cell and Gene Therapy Catapult in 2012 and the UK Cell Therapy Manufacturing Centre in 2018, which appears to have attracted considerable additional private investment with subsequent increases in numbers of active trials, manufacturing facilities, number of staff employed and number of manufacturers.[109]

For the field to continue to attract commercial investment, companies must have a degree of confidence that their investment will generate a return. To help boost this confidence, government decision makers are adopting regulatory and payment strategies that facilitate uptake of innovative therapies (see elements 'Regulatory and decision making processes' and 'Payment strategies').[110]

Payment strategies

- Reimbursement appears to be one of the key barriers to the adoption of innovative therapies.
- Novel payment strategies are being developed and tested, aiming to accelerate patient access. However, barriers to these novel strategies should be noted.

Challenges

Reimbursement represents one of the key barriers to the adoption of innovative therapies.[110,161] Concerns have been raised that current reimbursement models are not well suited to innovative therapies which typically involve considerable high upfront costs, and offer potentially one-off curative treatments carrying life-long benefits, making assessment of value-for-money difficult.[108,125,129,134,136,153,161,178,184] Moreover, upon regulatory approval, the long term effects of innovative therapies are not well-captured by clinical trials and due

to their novelty, there will be a lack of real world data, resulting in uncertainty in long term benefits. Payers can be reluctant to pay high sums in the face of this uncertainty.[134,136,161,178,184] Developers of innovative therapies also face uncertainly. Healthcare systems around the world vary significantly in available resources, decision making models and reimbursement strategies; making the area complex for navigate.[42,136]

In private healthcare systems where patients can change insurers,[161] payers may be less inclined to cover the high upfront costs of innovative therapies owing to concerns that patients will move to a different insurer, meaning that the initial insurer will bear the costs but not realise the long-term savings afforded.[153,161,173] Adding innovative therapies to government provider programs can also be challenging. Government providers usually make payments using payment codes; and the costs incurred by innovative therapies will not usually be adequately captured by these codes, with the development of new codes resulting in considerable delays.[161]

To help address these challenges, novel payment strategies are being developed and tested, aiming to accelerate patient access and allow payers to manage uncertainty, financial risk and plan for high upfront costs, whilst providing sufficient incentives for innovation.[161,184]

Potential solutions

1) Outcomes-based or pay for performance contracts reimburse companies once the therapy successfully achieves a predetermined clinical endpoint, within a pre-set time period.[41,129,136,153] This is particularly helpful when the long-term benefits of a therapy at launch are unclear and reduces the risk of high upfront payments for therapies that may be less effective than promised, sharing risk between companies and payers.[136,154,161,178]

2) Over-time payments or high-cost drug mortgages, help to address the potentially large upfront costs of innovative therapies.[173,178,185] The total cost of a therapy is separated into milestones and can follow the patient across multiple payers and over a predetermined time period. This is an attractive model for both high-cost therapies, as well as for healthcare systems where patients can change insurers.[161,173] Over-time payments can also

be linked to effectiveness, whereby if the prescribed health outcomes set forth in clinical trials are not realised, milestone payments could be stopped before the payment for a full course of the therapy.[173,178]

3) Risk-pooling or reinsurance describes a payment strategy where public and/or private payers pay into a dedicated fund that would reimburse innovative therapies.[109,161,173,185] In this model, the high costs of an innovative therapy for an individual patient are borne by a risk pool of multiple payers, alleviating concerns around financial risk as well as insurer-switching.[173,185]

4) A subscription, or "Netflix" payment model has also been developed where the payer pays an annual subscription fee to the company for unlimited access to the innovative therapy.[161] The main benefit of this model is that it provides certainty of outlays for payers, helping to plan budgets.[161]

5) High-cost patient rebates involve rebates by a healthcare payer to patients with cost-sharing burdens for their innovative therapy. In this model, rebates are made from payers to patients after the completion of, or milestones along, a course of treatment.[173] As patients demonstrate that they are adhering to the therapy, their co-payment would decrease over time to reward patients for actively participating in their medical care. If health outcomes are not being realised, the patient's care could be reviewed to determine if a different therapy may be more appropriate.[173]

6) Flexible pricing that enables prices to be adjusted over time to reflect changes in value has been promoted to fairly reward innovative therapies that add value, but also provide assurances to the payer that prices can be reduced should future data demonstrate reductions in value.[64]

7) Increased cooperation between payers internationally and companies developing innovative therapies will help anticipate where novel payment strategies are needed. This cooperation will also help improve transparency on prices paid for therapies including

confidential discounts, helping payers make informed decisions as well as assist in negotiations.[108,136,184]

Barriers to novel payment strategies

These payments strategies, whilst promising, have barriers to their use. Payment models that rely on the collection of accurate, real world data, will require the development of an appropriate data infrastructure, that are lacking in the majority of healthcare systems and are expensive and time-consuming to establish.[41,136,184] Moreover, in the event that generated data urges the discontinuation of funding, this can be difficult in reality to implement owing to existing patient expectations and public pressure.[136]

Outcomes-based models will require payer and company agreement on outcome measures for innovative therapy performance, clinical milestones for payments, as well as payment schedule, which may be challenging to reach.[161] The method for triggering payment for achieving the milestone would also need to be designed and agreement reached on what happens should a patient switch insurer.[161,173]

Legal and regulatory frameworks within healthcare systems will also need to evolve to accommodate novel payment strategies.[173,184] This includes the development of governance frameworks on data sharing and establishing quality standards on data collection as well as data analysis and interpretation.[184]

Change in clinician roles *(Changes in clinician roles can facilitate implementation)*

- Primary care clinicians will play a key role in referring patients for innovative therapies and executing long-term management plans.
- The role of surgeons may become increasingly multifaceted.

Primary care clinicians, including GPs appear to play a key role in the implementation of innovative therapies, identifying eligible patients, referring patients to centres providing innovative therapies, and carrying out longer term management plans as well outcomes monitoring.[109,126,138] Innovative therapies frequently offer non-surgical approaches and may

result in the role of a surgeon becoming increasingly multifaceted and blurred with that of other professionals. Surgeons may have more of a non-surgical role, with more time spent on diagnosis, non-surgical interventions and monitoring.[142] This is already the case in some surgical specialties including cardiothoracic surgery, neurosurgery, vascular surgery and urology.[142] With genomic testing becoming available for a wider proportion of conditions, surgeons will assume a greater role in acquiring tissue for testing, in diagnosing disease, assessing risk within the multidisciplinary team and discussing genomic analysis with patients.[110,142]

Discussion

Summary of findings

In this study, by performing an extensive hermeneutic review, I was able to place the findings from Chapter 3 in context with the literature on innovative therapy adoption and implementation across healthcare specialties and systems. This has provided me with deeper insights into the elements that influence the adoption and implementation of IHTs, including an understanding of elements not identified in Chapter 3.

More specifically, this review provided me with new insights on how companies developing IHTs may benefit from collaborating with companies in different healthcare specialities, enabling learning from case studies of implementation, and sharing knowledge on trial delivery, regulatory frameworks as well as payment and market access strategies. Engaging with patients from the early stages of product development can help companies developing IHTs assess whether their therapy has the potential to address unmet need and attract patient and public support. The findings from this review suggest that IHT companies may be able to benefit from gaining input from external experts, rather than having all expertise 'in-house', reducing costs whilst obtaining targeted expertise. It may also be advantageous for companies developing IHTs and precision diagnostics to establish co-development strategies, accelerating the development of precision diagnostics, which appear crucial for IHT implementation. Regulators recognise the benefits of co-development strategies and are simplifying shared regulatory pathways.

This review also provided me with insights into how healthcare systems with decentralised decision making processes and early alert systems may be better placed to adopt IHTs owing to increased flexibility to manage budgets and ability to support forward planning. Moreover, that healthcare systems with established collaborations between industry, university and healthcare providers, centralised datasets, experienced clinical trial units and clinical trial networks may facilitate IHT uptake by supporting evidence generation and long-term monitoring. I learnt that constructing detailed patient journey maps may be helpful for companies trying to implement IHTs, assisting in identifying areas of unmet need and where opportunities lie, as well as contributing to business case development. Further that the centralisation of IHTs in specialised delivery centres may promote implementation by increasing efficiencies, fostering partnerships between healthcare organisations and industry, accelerating clinician skillset development and facilitating real world data collection. Additional discoveries include how decentralised manufacturing strategies appear best suited to innovative therapies and that IHT companies may benefit from automation of unit operations as well as implementing intelligent systems that can responsively coordinate supply chains. It also appears important for future IHT manufacturers to plan for storage and transportation requirements early, including establishing links with specialist hospitals that can act as cell or tissue procurement services. The literature suggests that accelerator organisations can assist with developing innovative therapy manufacturing and distribution strategies as well as help support clinical trialing, develop health economic and business models, and lobby decision makers. Utilising such organisations will likely be of considerable benefit to IHT companies. I also learnt that the underlying characteristics of clinicians and patients may influence IHT uptake. Younger, specialist and research-oriented clinicians appear more likely to use innovative therapies. Younger patients, with higher socioeconomic status and unsatisfactory response to existing therapies appear more likely to receive an innovative therapy.

Implications

The insights gained from this hermeneutic review can be used by stakeholders across the translational pathway to facilitate adoption and implementation of innovative therapies within and outside of the hearing field. They can be used by companies to inform their

implementation strategies, providing information on how different healthcare system infrastructures as well as clinician and patient characteristics can influence innovative therapy uptake. They can also be used to provide companies and decision makers with strategies to increase patient involvement in innovative therapy development and policy making, promoting the development and adoption of therapies that address patient needs. Decision makers can use my findings to help assess the potential for innovative therapies to 'fit' into patient pathways and construct models of service provision that encourage successful implementation. They can also use my findings to help plan for direct and indirect resource requirements as well as explore novel payment strategies that can increase affordability and patient access, whilst stimulating further private investment into innovative therapy development. Important insights were gained into clinician education that can help inform the content of effective training programmes, promoting innovative therapy uptake amongst clinicians. Additional insights were gained on new regulatory initiatives that can be used to streamline regulatory processes, incentivise and reduce the costs of therapy development and accelerate adoption and patient access. My results can also help inform company manufacturing strategies, including planning for manufacturing challenges as well as storage and distribution requirements. Stakeholders can use my findings to explore potential data governance concerns that could arise following the collection of patient specific genetic and biologic data as well as potential strategies to overcome these concerns.

Strength and limitations

Carrying out a hermeneutic review enabled me to flexibly search articles in both the scientific and grey literature, enabling me to enhance my understanding of the elements that influence innovative therapy uptake, rather than perform a descriptive summary of studies. Another key strength was that the coding framework used to extract data from the literature was developed from empirical data (Chapter 3). I also had the flexibility to be able to adapt this coding framework as needed to take into account new findings from the literature, broadening my understand of the elements that influence adoption and implementation. I acknowledge that the scope of this review has meant that it has incorporated a range of therapies across healthcare specialities and systems, and that there is likely to be variation in elements that influence therapies according to setting, therapies

and stakeholders involved. I also recognise that since I was the only author performing data extraction and coding, this process may have been subject to interpretive bias.

Conclusion

This hermeneutic review builds upon my findings from Chapter 3 and provides further insights into the elements that influence the adoption and implementation of innovative therapies. These insights can be used by stakeholders across healthcare specialities and systems to facilitate adoption and implementation of innovative therapies.

CHAPTER 5: Framework development

Introduction

This chapter presents my framework of adoption and implementation for IHTs. Please note that I have written this chapter in a language that is understandable and useful for professionals who develop, will use and pay for IHTs.

My findings in Chapters 2, 3 and 4 of this thesis have contributed to a detailed understanding of the elements that influence the adoption and implementation of IHTs and have also outlined practical strategies to facilitate their uptake. In Chapter 2, I constructed an early health economic model which can be used to inform IHT development and decision making. The construction of this model also provided me with insights into the perspectives of stakeholders trying to steer the adoption of IHTs as well as their perspectives on health economic modelling. These insights informed the topic guide and coding framework of my study in Chapter 3, where I carried out semi-structured interviews with experts and following analysis, identified and explained the elements that influence the adoption and implementation of IHTs in the UK healthcare system. In my hermeneutic review in Chapter 4, I contextualised these empirically derived insights across healthcare specialities and systems and advanced my understanding of the elements that influence the adoption and implementation of IHTs.

In this chapter, I structure and integrate the findings from my thesis into a framework that can be easily used by stakeholders to gain an understanding of the elements that influence IHT adoption and implementation, and to identify strategies to facilitate their uptake.

Objective: To integrate the findings from my thesis into a framework of adoption and implementation for IHTs.

Methods

The construction of my framework consisted of two parts: 1) developing a map of constructs that summarises the elements that influence the adoption and implementation of IHTs in the UK healthcare system and 2) creating a table that provides a summary of the practical strategies discovered in this thesis that can facilitate IHT uptake.

Developing a map of constructs

I drew upon my understanding of the elements explained in Chapters 3 and 4 and developed overarching constructs that incorporate the elements that influence the successful adoption and implementation of IHTs. I also produced a brief narrative that explained each construct and that contained signposts to elements in my thesis which can provide more in-depth explanations. I then created a diagram that maps how these constructs relate to one-another to influence IHT adoption and implementation.

Creating a table of practical strategies

To develop this table, I reviewed the results sections from both Chapters 3 and 4, and extracted practical strategies discussed under each element that could be used to facilitate the adoption and implementation of IHTs. I then allocated these practical strategies into the same constructs as above, and inserted signposts to where each strategy is discussed in this thesis.

Results

I developed the following overarching constructs that incorporate the elements discovered in this thesis:

- Context
- Preparing
- Driving
- Decision making mechanisms
- Consequences

- Monitoring

Table 16 shows which elements from Chapters 3 and 4 contributed to each construct and provides page numbers which signpost to where each element is explained in this thesis.

Table 16: The elements which make up each construct in my framework of adoption and implementation.

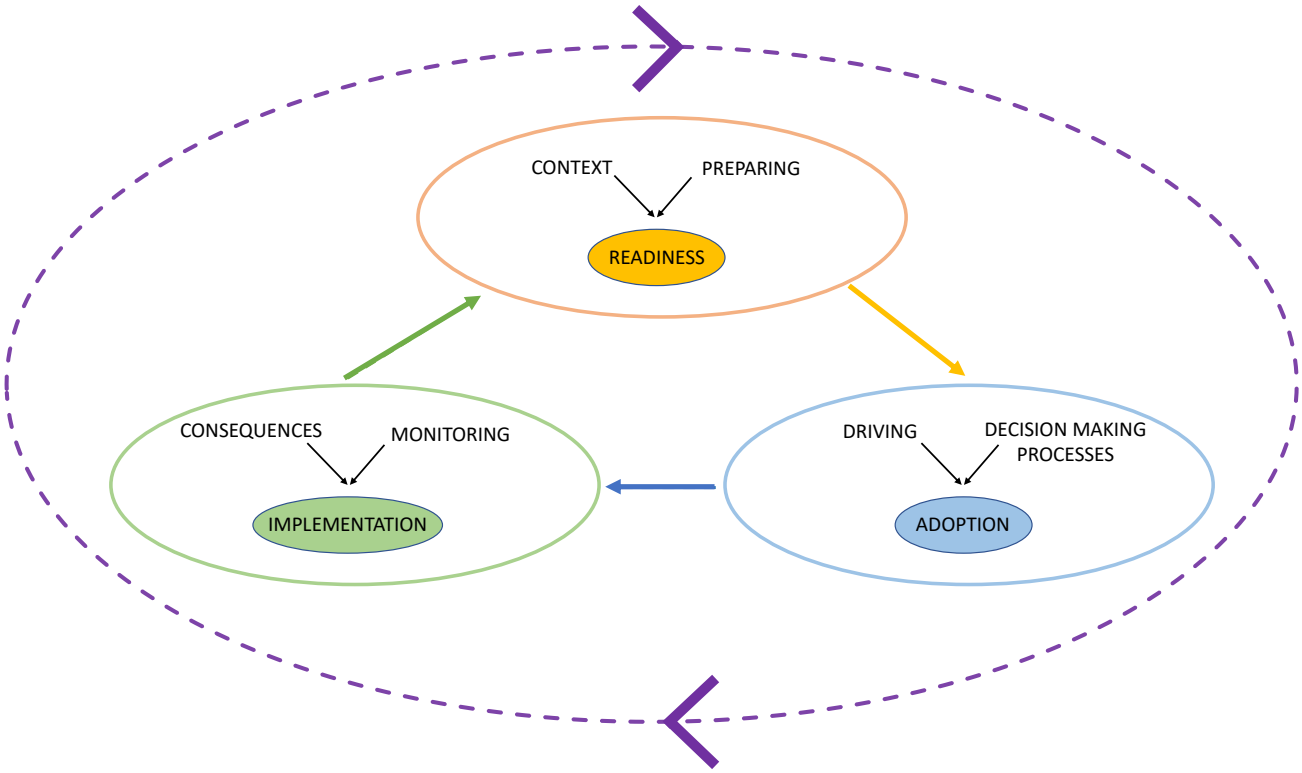
CONTEXT	PREPARING	DRIVING	DECISION MAKING PROCESSES	CONSEQUENCES	MONITORING
Complexity of the UK healthcare system p.52	Developing alliances between clinicians, scientists and industry p.61; p.126	Providing patient and public information p.79; p.136	Sense making p.89; p.139	Resource requirements p.99; p146	Collecting real world data p.77; p.135
Current infrastructure p.122	Developing alliances amongst healthcare professionals and scientists p.65; p.126	Working with accelerator organisations p.81; p.137	Regulatory and decision making processes p.89; p.140	Raising investment for research, development and procurement p.101; p.146	
Current practices p.53	Early evaluation and evidence of effectiveness and safety p.66; p.128	Developing a business case p.85	Cost-effectiveness analyses p.92; p.143	Impact on hearing healthcare services p.107	
Clinician perspectives p.55; p.124	Education and training p.69; p.130	Payment strategies p.103; p147	Ethical considerations p.97; p144	Minimising impedance p.109	
Patient perspectives p.56	Patient pathway p.131			Change in clinician roles p.104; p150	
Motivations for adoption and implementation p.58; p.125	Manufacture and distribution p.134				
Route of administration p.72; p.132	Developing coalitions between companies p.83; p.126				
Indication p.74	Developing precision diagnostics p.86; p.138				
Characteristics of clinicians and patients p.133					

Figure 14 shows my framework of adoption and implementation for IHTs, consisting of 1) a map of constructs and 2) a table of practical strategies discovered in this thesis that can

facilitate IHT uptake, allocated to each construct. The discussion section provides an explanation of each construct and how they relate. It also provides instructions on how this framework can be used by stakeholders.

Figure 14: Framework of adoption and implementation of IHTs, consisting of 1) map of constructs and 2) table of practical strategies.

1) Map of Constructs



2) Table of practical strategies

Context	Developers of IHTs to work with accelerator organisations p.53, p.81	Establish alliances with groups with an understanding of the healthcare system and its decision making processes p.53, p.89	Developers of IHTs to work with clinicians and patients to target areas of unmet need p.53	Collect real world data p.55	Develop relationships with patient groups and charities p.57, p.66	Gain an understanding of, and target stakeholder motivations for IHTs p.58, p.73, p.125	
Preparing	Develop early alliances between clinicians, scientists and biotechnology companies p.61, p.65	Form diffusion networks with clinicians p.63	Prepare for challenges to alliance formation between clinicians, scientists and biotechnology companies p.65	Collaborate, learn from, and pool resources with clinicians and biotechnology companies outside the hearing field p.66, p.127	Develop collaborations between existing hearing technology and biotechnology companies to share resources, knowledge and market access p.83, p.138	Companies to sponsor clinician education and develop KOLs p.64, p.130	Utilise training ENT surgeons to raise awareness of IHTs, increasing referrals to specialist centres p.70
	Carry out early and tailored clinician education p.56, p.69, p.89, p.130, p.139	Provide advanced training to a sub-group of expert ENT surgeons and audiologists p.71	Utilise KOL's to deliver clinician education p.70	Stimulate patient demand to drive clinician education p.70	Involve patient representatives from the beginning of the research process p.58	Involve clinicians in trial development and utilise clinicians for information dissemination p.64, p.130	For IHT trials, use strict inclusion criteria, close to the preclinical model p.68, p.74
	Perform early health economic modelling p.67	Clinicians and decision makers to reach agreement on what constitutes sufficient evidence of effectiveness to warrant regulatory approval p.128	Embed genomic medicine and cell biology into clinician education programmes p.130	Engage with decision making groups, including commissioners at an early stage of IHT development p.81	Use and develop outcome measures that are easily understandable to patients and decision makers p.67, p.128	Gain input from external experts rather than having all expertise 'in house' p.127	Foster partnerships between biotechnology companies, companies developing precision diagnostics for co-development p.127, p.138

	Utilise streamlined regulatory processes for co-development of precision diagnostics p.140	Centrally collect patient genotypical and phenotypical data to assist patient selection for trials and the development of precision diagnostics p.87	Develop patient journey maps to identify unmet need and opportunities for pathway integration p.132	Plan manufacturing, storage and delivery strategies early and seek assistance from accelerator organisations p.134			
Driving	Clearly articulate unmet need p.53	Seek patient input in dissemination of findings p.57	Establish alliances with patient groups and charities p.71, p.79, p.127	Provide patient information p.80, p.89	Involve patients in decision making and industry committee structures p.127	Companies to sponsor patient charity events and contribute to patient charity research funding p.80 p.127	Work with accelerator organisations p.81, p.89, p.137
	Develop targeted business cases p.85, p.96	Make decision makers aware of upcoming IHTs (e.g. utilising early alert systems) p.81, p.123	Be aware of novel payment strategies p.103, p.147	Collect real world data p.68, p.77, p.90 p.128, p.135			
Decision making processes	Carry out clinician education p.89, p.140	Provide easy-to-understand information on the IHT to patients and decision makers p.89, p.136, p.140	Construct and validate economic models p.92, p.102, p.110	Utilise strategies to streamline decision making processes p.125, p.140	Commission independent academic organisations to perform cost-effectiveness analyses p.95	Collect real world data p.95, p.135	Lobby the public, highlighting dangerous impacts of hearing loss (e.g. dementia) p.96, p.97, p.101
Consequences	Develop efficient patient pathways p.55, p.107, p.145	Plan for indirect and direct resource requirements early p.100 p.132, p.146	Key stakeholder groups to effectively communicate the case for IHTs to raise investment p.101	Patient groups to lobby decision makers p.96, p.98, p.101	Biotechnology companies to establish relationships with patient groups and charities p.101	Be aware of and utilise novel payment strategies p.103, p.146, p.147	Train clinicians for potential change in roles p.104, p.150

	Develop collaborations between existing hearing technology and biotechnology companies to minimise impedance p.109	Realign incentives for scientists with a focus on translation rather than publications or grants p.110	Centralise IHT delivery in specialist delivery centres p.132				
Monitoring	Develop centralised registries p.79	Harness national trainee collaboratives and research infrastructure p.123, p.136	Utilise digital health tracking technologies p.145				

Discussion

Explanation of constructs within the framework

Context

(Healthcare system infrastructure, areas of unmet need, as well stakeholder perspectives that can guide IHT development and influence uptake)

Successful adoption and implementation of an IHT into a healthcare system requires an understanding of the target healthcare system, its infrastructure, areas of unmet need, as well as underlying stakeholder motivations and perspectives. This understanding should ideally be developed before IHT development. This includes an appreciation of the complexity of the target healthcare system and its decision making processes as well as specific strategies that can be used help navigate it (see element 'Complexity of the UK healthcare system'). In Chapters 3 and 4 I discuss the importance of having an understanding of how existing healthcare system infrastructures can be used to promote uptake; and to have an awareness of stakeholder perspectives on existing hearing devices, on areas of unmet need and where opportunities lie for IHTs within the patient pathway

(see elements ‘Clinician perspectives’, Patient perspectives’, ‘Current infrastructure’, Current practices’, ‘Flexibility of staff’). Similarly, to have an awareness of clinician and patient perspectives on what type of IHT they would be more willing to take-up, on the type of evidence they would be most convinced by, as well as on how to influence clinician and patient perspectives to maximise IHT uptake (see elements ‘Clinician perspectives, Patient perspectives’). My results from Chapters 3 and 4 suggest that having an appreciation of the underlying motivations of different stakeholders to take-up IHTs, as well as having an understanding on how clinician and patient characteristics can influence routine use, can help develop strategies to facilitate implementation (see elements ‘Motivations’ and ‘Characteristics of clinicians and patients’). My findings also highlight the importance of appreciating how an IHT’s indication(s) and route of administration may impact resource requirements, the delivery setting, as well as decision making processes of clinicians, patients and regulators (see elements ‘Indication’ and ‘Route of administration’).

Preparing

(Preparing to increase chances of successful adoption and implementation before the therapeutic is released onto the market)

Specific actions can help prepare for IHT adoption and implementation before the therapy is ready to be released onto the market. My results from Chapter 3 suggest that the development of alliances between clinicians, scientists and companies can help pool skillsets and resources to accelerate translation, whilst helping to establish trustworthy clinician diffusion networks that can be utilised once the therapy is developed. Strategies to develop these alliances are also discussed (see elements ‘Developing alliances between clinicians, scientists and industry’ and ‘Developing alliances amongst healthcare professionals and scientists’). In Chapter 3 I found that early evaluation of IHTs, before or during development, via early health economic modelling, can help inform product development to increase chances of uptake, and can also provide important insights into the potential cost-effectiveness of IHTs in their intended context, helping to inform decision making (see element ‘Early evaluation and evidence of effectiveness and safety’). I discussed in both Chapters 3 and 4, that demonstrating evidence of effectiveness and safety is crucial for securing regulatory approval as well as support from clinicians and patients. Reaching early

agreement between clinicians and decision makers on what constitutes sufficient evidence to warrant regulatory approval can facilitate uptake, as can developing outcome measure(s), such as PROMs, that are easily understood by patients and decision makers (see element 'Early evaluation and evidence of effectiveness and safety'). My findings also suggest that early introduction of IHTs into clinician education programmes, prior to release onto the market, can help increase clinician uptake of IHTs, and industry can invest in clinician education to develop alliances with clinicians and stimulate information spread (see element 'Education and training'). Further that industry can invest in raising awareness of IHTs amongst patient groups to generate patient interest which appears to be a powerful driver to stimulate clinician training (see element 'Education and training'). In Chapter 4 I found that companies developing IHTs should consider decentralised manufacturing strategies early and explore opportunities to leverage existing healthcare system infrastructure to facilitate future IHT distribution (see element 'Manufacture and distribution'). I also found that that early dialogue between stakeholders as well as the development of patient journey maps can assist in planning for how an IHT can be best incorporated into the healthcare system and patient pathway (see element 'Patient pathway'). As discussed in Chapter 3, IHT companies can consider developing mutually beneficial coalitions with existing hearing technology companies to pool resources, explore combination opportunities and improve market access, including sharing access to well established networks within the clinical community and patient groups (see element 'Developing coalitions between companies). In Chapters 3 and 4 I emphasise that precision diagnostics can be crucial for facilitating optimal patient selection for trials and in therefore demonstrating clinical effectiveness, whilst reducing research and development costs; and that their development should ideally take place alongside innovative therapy development using co-development strategies (see element 'Developing precision diagnostics').

Driving

(Activities that can help drive adoption once the IHT is ready for assessment by decision makers and regulators)

Strategic activities can help accelerate IHT uptake once the therapy is ready for assessment by decision makers and regulators. In Chapters 3 and 4, I found that effective provision of

information to patients, patient groups and the public on an IHT and the unmet need it hopes to address can help boost patient demand to receive it, which appears a powerful lever to influence decision makers and clinicians (see element 'Providing patient and public information'). My results also suggest that publicly funded accelerator organisations (e.g., the Cell and Gene Therapy Catapult) can assist in developing strategies to optimise market access including lobbying for regulatory and policy adjustments to accelerate therapy uptake (see element 'Working with accelerator organisations'). In Chapter 3 I outlined that reimbursement appears one of the key barriers to future IHT implementation, and the development of effective business cases can help decision makers plan for IHT procurement by redirecting funds early. Business cases appear particularly important in the NHS, where insufficient resources delay innovative therapy adoption even if deemed to be cost-effective with a funding mandate from NICE (see element 'Developing a business case'). In Chapter 4, I provide detailed information on novel payment strategies, including on how they can be used to help make IHT procurement affordable, thereby promoting uptake (see element 'Payment strategies').

Decision making processes

(Processes of decision making that need to take place for IHT adoption)

Clinicians, patients, and decision makers will need to make decisions on whether to take-up IHTs and my results from Chapters 3 and 4 suggest that in order to make these decisions, it is helpful to have an understanding of how the IHT differs to existing interventions, what it is specifically looking to address and how it could fit into the current hearing healthcare system and pathway. It appears that successfully making sense of these aspects can help increase IHT uptake and a number of strategies are proposed to facilitate this (see element 'Sense making'). In Chapter 4, I outline that regulatory processes play a critical role in innovative therapy uptake and are frequently considered to delay adoption as well as incur significant costs. Further that regulatory bodies recognise this and have implemented a range of strategies to streamline their decision making processes. A good awareness of regulatory decision making processes as well as strategies available to streamline these can facilitate IHT adoption (see element 'Regulatory and decision making processes'). My results also suggest that cost-effectiveness analyses form an important tool for decision making

and can be influential in determining national uptake, particularly in the NHS. However, concerns over uncertainty of economic models developed for IHTs may limit their influence on regulators and clinicians. Strategies are discussed to help increase confidence in the outputs of economic models (see element 'Cost-effectiveness analyses). In Chapters 3 and 4, I emphasise that economic models typically do not provide information on affordability, with concerns that they may drive the implementation of unaffordable, but cost-effective IHTs, potentially slowing uptake. Demonstrating affordability can be achieved via use of business cases (e.g., outline budget impacts and how the IHT can result in wider, long-term savings) as well as novel payment strategies (payments can be packaged to fit into healthcare budgets). My results from Chapter 3 suggest that an IHT found to be cost-ineffective, may still enter the NHS and private markets if specific mechanisms and levers are used (see element 'Cost-effectiveness'). Ethical considerations also appear to influence IHT adoption and implementation. Therapies interfering with natural mechanisms, such as genetic manipulation, may stimulate ethical controversy, and sufficient public opinion against an IHT on ethical grounds may influence policy decisions and impede adoption. In Chapter 3 I found that clear evidence of effectiveness and safety can sway ethical considerations and regulatory bodies can inadvertently take ethical decisions away from stakeholders within a healthcare market following approving a therapy (see element 'Ethical considerations').

Consequences

(Consequences following the adoption of an IHT that influence implementation processes)

Once an IHT is adopted into the healthcare system, consequent impacts and activities may influence implementation processes. In Chapter 3 I highlight that some IHTs will be costly and raise concerns around affordability, patient access as well as impact on other healthcare services that may need to incur consequent savings. However, if indicated for a small proportion of patients, this could limit the overall cost burden to a healthcare system and facilitate uptake (see element 'Resource requirements'). My results from Chapter 3 suggest that following approval of an IHT by regulators, key stakeholder groups can work together to lobby and raise investment from decision makers to increase access. Effectively communicating the case for IHTs, competing with other diseases and treatments, appears

important for raising this investment, with anxiety or fear being powerful levers to motivate public and political opinions (see element 'Raising investment for research, development and procurement'). My findings also suggest that the introduction of IHTs may require the development of new treatment pathways, influenced by the therapy's delivery mechanism, indication and degree of effectiveness. For example, an effective IHT delivered via an injection through the ear drum, indicated for a large proportion of patients may require the establishment of new referral pathways to centralised day units that perform high volumes of these procedures (see element 'Impact on hearing healthcare services'). In Chapter 3 I also found that IHT implementation may be impeded by groups within the healthcare service owing to perceived threat. Forming coalitions between hearing technology and biotechnology companies, developing robust business cases and demonstrating clear evidence of comparative effectiveness may mitigate resistance (see element 'Minimising impedance'). My results from both Chapters 3 and 4 show that healthcare professionals may need to be flexible and change their roles to facilitate implementation. This may include GPs, commercial hearing aid providers, care of the elderly doctors, old age psychiatrists, paediatricians, neurologists, emergency doctors and oncologists playing a role in identifying and referring patients. Audiologists may need to carry out novel precision diagnostic tests and potentially prescribe or administer IHTs. ENT surgeons would likely be responsible for formulating management plans, administering IHTs and monitoring patient outcomes. Specialist nurse practitioners may be needed to perform minimally invasive, high volume procedures (see element 'Change in clinician roles').

Monitoring

(Collecting and reviewing real world data once the IHT is introduced in the healthcare system)

Once the IHT is introduced in the healthcare system, ongoing monitoring via collection of data from routine clinical practice (collecting real world data) will be crucial to embed the IHT. Chapters 3 and 4 found that prospectively collected data from real world settings, on effectiveness and safety appears particularly convincing to clinicians and patients, promoting uptake. This data can also be used to develop and refine business cases, support regulator decision making processes, early access programmes, novel payment strategies

(e.g. outcomes based contracts), and help develop and validate cost-effectiveness analyses. Chapter 3 highlights that establishing centralised independent registries appears critical to generating meaningful real world data for innovative therapies; and have the additional benefit of supporting precision diagnostics development via the collection of geno- and phenotype data (see element 'Collecting real world data').

Explanation of diagram that maps how constructs relate to one-another

Figure 14 maps how the constructs explained above relate to one-another. In this figure, I propose that having an appreciation of the healthcare system infrastructure, areas of unmet need, as well stakeholder perspectives (Context); and carrying out activities to prepare for IHT adoption and implementation (Preparing) will provide the foundations for a healthcare system to become ready for IHT uptake ('Readiness'). Strategic activities can then be carried out to help drive (Driving) decision making mechanisms (Decision making processes) towards adoption. Following the decision to adopt the IHT, successful implementation will be influenced by consequent impacts and activities (Consequences), as well as the collection of real world data (Monitoring). There is an important feedback loop where ongoing, long-term monitoring of the IHT (Monitoring) will contribute to an evolving understanding of the healthcare system (Context), inform preparing (Preparing) and pushing (Driving) activities as well as facilitate decision making mechanisms (Decision making processes). This process of ongoing monitoring can also provide information on resource requirements for IHT adoption and implementation as well as impact on hearing healthcare services (Consequences). This map therefore represents a cyclical process where information gained from ongoing monitoring feeds back into other constructs.

How my framework can be used in practice.

Whilst users can use my framework (Figure 14) intuitively, I recommend that it is used starting with the map of constructs. Users can read this map in a clockwise manner, starting with the construct 'Context', and read the accompanying text explaining each construct. Guided by their information needs, users can refer to signposted elements (page numbers located in Table 16) which provide more in-depth information. Alongside this, users can refer to the table of practical strategies, and where relevant refer to signposted page

numbers to obtain further information. Users can then read the explanation of relationships within the framework to gain an appreciation of how constructs interact to influence adoption and implementation of IHTs. This approach will enable users to gain a tailored and in-depth understanding of the elements that influence IHT adoption and implementation whilst identifying practical strategies that can be mobilised to facilitate uptake.

This framework has been purposely constructed so that it can be easily used by IHT stakeholders to navigate through complex adoption and implementation processes. However, whilst this map is designed in a simple cyclical manner, with a flow from construct to construct, it is important to note that within each construct is a web of interacting elements. By referring to signposted elements (Table 16) readers can appreciate this web and gain an appreciation of how these adoption and implementation processes resemble a tangled intersection characterised by multiple elements.

CHAPTER 6: Discussion

Summary of PhD journey.

This PhD fellowship was triggered by my experiences as an ENT clinician and researcher, where I gained insights into the field of IHTs. I learnt about their considerable potential and gained an appreciation that their implementation into healthcare systems would present significant and distinct challenges. With expert supervision in the fields of IHTs, early health economic modelling and implementation science, I secured funding for a PhD project that could help prepare the UK healthcare system for the successful uptake of IHTs. Specifically, I set out to provide stakeholders who develop, will use and pay for IHTs, with a detailed understanding of the elements that influence their adoption and implementation and with practical strategies to facilitate their uptake. To achieve this, I carried out 4 studies that built upon one another to result in a practical framework that can be used to facilitate IHT uptake. To inform product development and decisions on value for money, I constructed the first early health economic model for IHTs (Chapter 2). Drawing upon insights from this early health economic model I carried out a qualitative study to characterise and understand the elements that influence the adoption and implementation of IHTs (Chapter 3). To add to this understanding, I performed a hermeneutic review of elements that influence the adoption and implementation of innovative therapies across healthcare systems and specialties (Chapter 4). Finally, to integrate the findings from my thesis, I constructed a framework that maps the elements that influence IHT adoption and implementation, and that summarises practical strategies to facilitate uptake (Chapter 5).

Implications

Given the international perspectives of informants interviewed and the international nature of included articles in the hermeneutic review, my framework is relevant to and can be used across developed healthcare systems to facilitate IHT adoption and implementation. It can be used by stakeholders who develop, will use and pay for IHTs to gain an understanding of the elements that influence their adoption and implementation and to access practical strategies to facilitate IHT uptake. More specifically, my framework can be used to provide an understanding of how healthcare system environments can influence adoption and

implementation and on how to navigate environments to facilitate uptake. It also provides an understanding of stakeholder perspectives and motivations on IHTs and how these can be influenced. It can be used to explore activities that can help prepare for IHT adoption and implementation before the therapy is ready to be released onto the market, as well as activities that can accelerate IHT uptake once the therapy is ready for assessment by decision makers. Stakeholders can use my framework to gain information on decision making processes that need to take place for IHT adoption as well as strategies to facilitate these processes. They can also use my framework to explore potential impacts and activities that can influence implementation processes once an IHT is introduced into the healthcare system. Importantly, my framework also provides information on how real world data collection can be used to promote uptake and routine use.

Initiatives are underway to support and accelerate the adoption and implementation of innovative therapies into the UK healthcare system. These include for example the NHS Accelerated Access Collaborative (AAC),[186] the NHS innovation Accelerator (NIA),[187] and London Advanced Therapies (LAT).[188] The AAC and NIA initiatives identify specific areas of health need within the NHS that should be targeted by researchers, innovators and funders, and scan for new promising innovations that can benefit from support, including helping innovators access the NHS's research infrastructure, as well as develop funding strategies. They also bring together industry, government, regulators, patients and the NHS to help remove barriers and develop strategies to accelerate the introduction of new treatments and diagnostics. The LAT works towards bringing together the London scientific community in the field of gene and cell therapies aiming to foster collaborative research, facilitate commercial partnerships and develop educational programmes to train the next generation of healthcare professionals in gene and cell therapies. Toolkits have also been developed to faciliate the uptake of innovative therapies into healthcare systems. The Advanced Therapy Treatment Centres (ATTC) Institutional Readiness Toolkit[189] is an example, developed to assess the capacity of an institution to adopt advanced therapies and involves identifying the gaps that hospitals must address to deliver advanced therapies to patients. My framework of adoption and implementation is distinct and complementary to these initiatives. It provides empirically based information and strategies that can be used to support these initiatives and also characterises and explains a wide range of elements and

strategies that influence adoption and implementation processes across the innovative therapy translational pathway that are not explored by these initiatives. Moreover, my framework explains how these elements influence one-another, rather than focusing on specific elements in isolation.

Originality of research and contribution to the literature

This is the first study that has provided information on the potential cost-effectiveness of IHTs. It is also the first study that has investigated implementation processes for IHTs, resulting in a framework that can be practically used to gain an understanding of the elements that influence IHT adoption and implementation as well as strategies that can accelerate uptake.

This framework is distinct to other implementation theories in its construction and end-product, offering a novel contribution to the literature. As discussed by Per Nilsen,[54] the majority of implementation theories or models that specify determinants of uptake provide limited "how-to" support for carrying out implementation endeavours since determinants usually are too generic to provide sufficient detail for guiding an implementation process. My framework is specific to IHTs, providing in-depth and practical information on elements and strategies that influence adoption and implementation within this field. It has also been developed by a clinician embedded within the NHS, and purposely constructed and explained in a way that can be easily understood and used by IHT stakeholders. Moreover, the elements investigated span across the translational pathway, providing information on adoption and implementation processes from before IHT development through to after the decision to adopt. This means that the framework can be of value to stakeholders across the IHT translational pathway. Another difference to other implementation theories is that the construction of my framework uniquely drew upon health economics. During the construction of the early health economic model, my interviews with 26 participants provided me with insights on their perspectives on IHTs, on health economic models and on how health economic models can be used to influence IHT uptake into healthcare systems. These insights informed the topic guide and coding framework of my interview study, contributing to a broad exploration of elements that influence adoption and implementation, and resulting in health economics forming an important component of my

framework. The conduct of the hermeneutic review *after* the interview study is another unique feature. This approach helped me carry out a more focussed and meaningful literature review and helped me contextualise the findings from my interview study across healthcare systems and specialities. As a result, I was able to gain a deeper insight and understanding into elements discussed in the interview study, as well as discover new elements, contributing to the development of a robust framework. This approach, drawing upon both health economics and implementation science and carrying out a hermeneutic review after an empirical study may be a valuable approach that can be adopted outside the field of IHTs.

Distinct from other implementation theories, my framework places particular emphasis on how different types of evidence can influence decision making processes. Specifically, that clinicians, patients and decision makers may be unconvinced by safety and efficacy data generated from RCTs owing to apprehensions over trial design and external validity. Real world data (data collected from routine delivery of care) on IHT safety and effectiveness can be more influential, increasing confidence amongst clinicians, patients and decision makers to take-up IHTs; and can also validate and increase the confidence in outputs from health economic models. Importantly, real world data can also support payment strategies and early access programs as well as help fulfil regulatory monitoring requirements. My framework also emphasises the importance of generating patient demand and motivation for IHTs, recognising that patients are a powerful lobbying group to clinicians and decision makers, driving decision makers to take up, and convincing clinicians to train and use these therapies. Anxiety or fear appears a powerful tool to motivate public opinion, and generate demand, and arguments for IHTs could be framed to highlight the consequences of untreated hearing loss, such as dementia, mental health problems and unemployment. Another distinct feature of my framework is the emphasis that precision diagnostics appear critical to the development and uptake of IHTs; and that co-development strategies and novel regulatory pathways can help accelerate their development. Similarly, strategic alliances between clinicians, scientists, patients, biotechnology and existing technology companies appear crucial for adoption and implementation, benefitting from pooled resources, diffusion networks and established market access.

Plans for future work

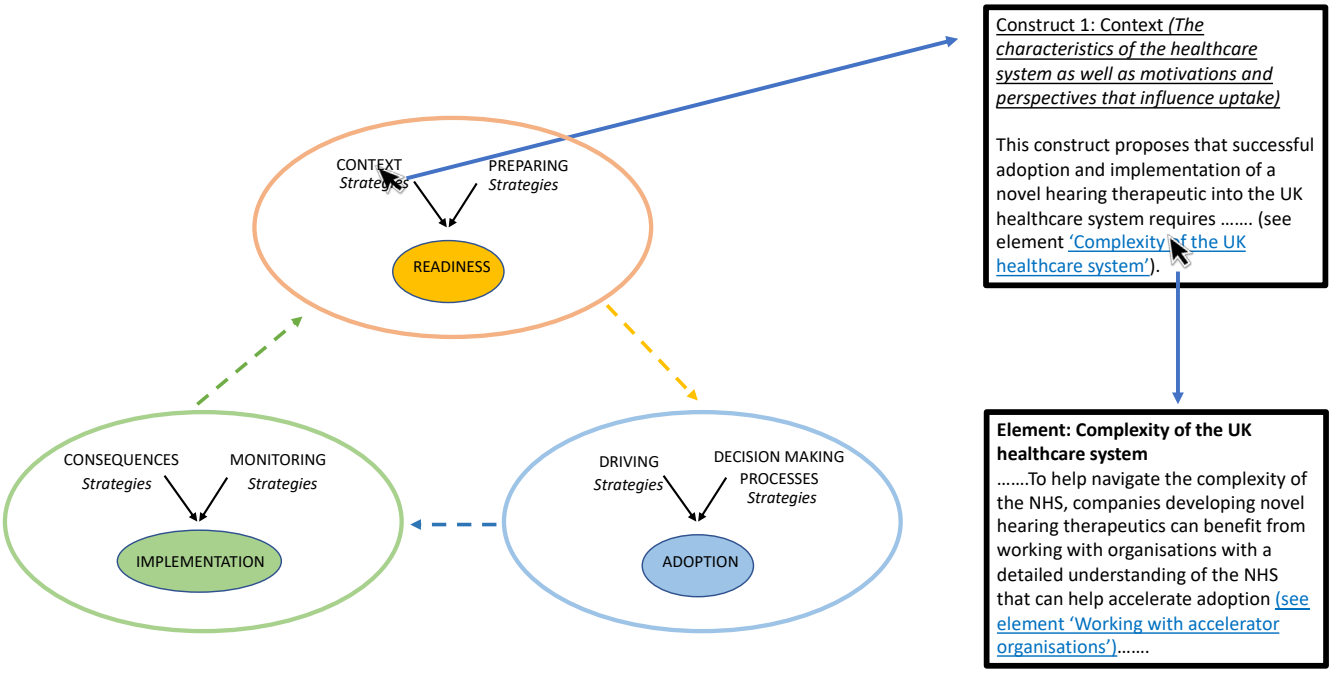
Following completion of my PhD fellowship I aim to secure funding to develop an electronic toolkit that can be used by professional stakeholders across the innovative therapy translational pathway to navigate my framework and use it to facilitate adoption and implementation of innovative therapies, including therapies outside the hearing domain.

The development of this toolkit will involve: the assembly of a round table working group, the validation and refinement of my framework following its use in practice, and the construction of an electronic toolkit. A round table working group, consisting of: industry representatives, researchers, clinicians, patients, regulators and commissioners, will receive training on my framework of adoption and implementation and be tasked to use this framework to help guide the adoption and implementation of a specific therapy. Alongside this process, a validation study can be carried out, assessing the use of my framework in practice, involving semi-structured interviews amongst working group members exploring the utility of my framework in guiding adoption and implementation and exploring how the framework can evolve to increase its utility and ease of use.

Following this validation process, a refined framework of adoption and implementation can be developed and translated into an accessible electronic toolkit, freely available on the NIHR-University College London Hospitals (UCLH) Biomedical Research Centre (BRC) website: https://www.uclhospitals.brc.nihr.ac.uk/content/biomedical-research-centre

I envisage that this toolkit will consist of a landing page with the map of constructs visible (see Figure 15). Users will be able to click on individual constructs within the framework which will direct them to a page summarising the selected construct. Users can read these summaries, and guided by their information needs, can click on elements referred to in the text, directing them to a page providing more in-depth information on the selected element. Users can also click on 'Strategies' links which will direct them to strategies, specific to each construct that can facilitate uptake. This process will enable users to flexibility obtain an understanding of the elements that influence innovative therapy adoption and implementation.

Figure 15: Illustration of how a future electronic toolkit can be used



Conclusion

This is the first research project that has investigated adoption and implementation processes in the field of IHTs. My research has uniquely drawn upon health economics and implementation science and has resulted in the development of a framework that can accelerate patient access to IHTs and help reduce waste and disruption commonly associated with the implementation of innovative medical therapies. Stakeholders can use my framework to gain detailed information on the processes that need to take place for adoption and implementation of IHTs as well as strategies to facilitate these processes.

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APPENDICES

Appendix 1: ISPOR Consolidated Health Economic Evaluation Reporting Standards [CHEERS], checklist[68]

Section/topic	#	Recommendation	Reported on page
TITLE AND ABSTRACT			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	17
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	This has been completed for published version.
INTRODUCTION			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	17-18
METHODS			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	18
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	18
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	27
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	22-23
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	23
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	26
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	26
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Not applicable
	11b	*Synthesis-based estimates*: Describe fully the methods used	24-26

		for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	20-22
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	27-31
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	31-32
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	22-24
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	20
Analytical models	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	32-33
RESULTS			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters/ Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	25-29, 31
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	34

		applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	34-36
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	35-36
Section/topic	**#**	**Checklist item**	**Reported on page #**
DISCUSSION			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	37-39
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	vii-viii
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	viii

Appendix 2: Study information sheet for Economic Model (professionals)

Study Information Sheet

UCL Research Ethics Committee Approval ID Number: 12241/001

Development of an early health economic model for innovative hearing therapies

Dear Expert,

You are being invited to take part in a research study. We are developing an early health economic model for innovative hearing therapies and are looking for input from professional stakeholders to ensure that the model reflects current practices as closely as possible. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask a member of the research team.

What is the purpose of this study?
Hearing loss impacts peoples' ability to communicate and function in society. It can cause both physical and mental health problems and has been directly linked to dementia. The World Health Organization estimates that approximately 500 million people worldwide suffer from hearing loss, and from an economic standpoint, the annual cost of untreated hearing loss is $750 billion globally, primarily due to unemployment.

In most adults, hearing loss is sensorineural indicating an abnormality of the cochlea, the auditory nerve, or higher central auditory pathways. Current management of sensorineural hearing loss is mainly limited to hearing aids and cochlear implants which do not treat the underlying cause. Biotechnology and pharmaceutical companies as well as private investors and venture capitalists have recognised this unmet need, and, equipped with recent discoveries in the genetic and molecular pathways that underlie sensorineural hearing loss, are increasingly developing innovative hearing therapies, that promise to protect, restore or regenerate the hearing system. These include a variety of drug, gene and cell therapies, some of which are undergoing clinical testing in humans. If proven effective, these therapies are set to radically change hearing services within the next 5-10 years.

It is essential to start planning for the implementation of innovative hearing therapies now to prevent unintended consequences including failed or delayed integration into healthcare systems, resulting in poor patient access to care, suboptimal outcomes and financial inefficiencies.

The proposed study works towards addressing this, by developing an early health economic model to assess the potential added value of innovative hearing therapies. To develop the economic model, we will be using sudden onset sensorineural hearing loss (SSNHL) as a case study, recognising that this is a lead indication for several novel innovative therapies in development.

Why have I been invited?
We are inviting professional stakeholders with expertise in: 1) managing patients with SSNHL; and 2) innovative hearing therapies, to ensure that the model reflects current practices as closely as possible.

Do I have to take part?
No. You are under no obligation to participate in this study. You may also withdraw from the study at any time by contacting the researcher and without giving any reasons.

What would I be asked to do if I took part?
You will be asked to participate in an audio-recorded interview, assessing your views on an economic model on SSNHL.

The interview will take place either face-to-face at a venue that is convenient for you or over the telephone at a time that is suitable for you. The interview will take approximately 20-30 minutes. When we write about the results of the research, all personal details will be removed so that no one will know who you are.

Will my taking part in this study be kept confidential?
Your signed consent form will be kept separately in a locked filing cabinet, only accessed by the researcher. All the information will be handled in confidence. The audio recording of your interview will be kept on a password-protected computer at the university. Once the recording is transcribed it will be erased. All data will be anonymised and stored separately from your contact details. The findings will include anonymised quotations and no information that can identify you personally will be published. Please note that assurances on confidentiality will be strictly adhered to unless evidence of wrongdoing or potential harm is uncovered. In such cases the University may be obliged to contact relevant statutory bodies/agencies.

What are the risks and benefits of being involved?
There are no known risks associated with being involved. Whilst there are no immediate benefits for those people participating in the project, the information you provide will help develop an early health economic model to assess the potential added value of innovative hearing therapies

What will happen when this research study stops?
If you would like to know the findings of the research study, please indicate on the consent form. Once the data collection is complete, a summary of the findings will be sent to you. No personal information will be presented in the results. All data has to be stored anonymously by the University for a minimum of five years. This data may need to be looked at by auditors during this time. After this period, it will be confidentially destroyed.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If they are unable to resolve

your concern or if you wish to make a complaint regarding the study, please contact a University Research Ethics Co-ordinator on 020 7679 8717 or by email to ethics@ucl.ac.uk

What do I do now?
If you decide you would like to take part in this study, please email Mr Rishi Mandavia

Who is organising and funding this research?
The research funding is provided by the University College London and this study is being conducted by evidENT (Evidence based Ear, Nose, Throat), organised by the University College London.

Further information and contact details
If you have any further questions or would like additional information, please contact:
Mr Rishi Mandavia
Prof Anne Schilder

Many thanks for your help and for taking the time to read this information sheet.

Appendix 3: Study information sheet for Economic Model (patients)

Participant Information Sheet for patients

UCL Research Ethics Committee Approval ID Number: 12241/001

Development of a health economic model for innovative hearing therapies

Dear Sir/Madam,

You are being invited to take part in a research study. We are investigating the costs that are involved in hearing loss as well as patient experiences of hearing loss care. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask a member of the research team, who will try to answer any questions you may have.

What is the purpose of this study?
Hearing loss impacts people's ability to communicate and function in society. It can cause both physical and mental health problems as well as being associated with dementia. The World Health Organization estimates that approximately 500 million people worldwide suffer from hearing loss, with a global economic burden of 750 billion dollars. This cost is set to increase as the world's population ages. In most adults, hearing loss is caused by loss of hair cells in the inner ear. At the moment, the treatment for this includes hearing aids for patients with mild to moderate hearing loss and cochlear implants for patients with severe hearing loss. These devices do not however treat the cause of hearing loss. Therefore, there is an urgent need for entirely new hearing therapies. Biotechnology, pharmaceutical and device companies, as well as private investors, have recognised this and are increasingly investing in developing innovative hearing therapies (e.g. gene / pharmaceutical / cell therapies). It is important that these innovative hearing therapies are affordable and can be successfully brought into a healthcare system, so that patients can benefit from them. In order to decide whether these innovative therapies reflect value for money, it is essential to establish estimates of the current costs for treating patients as well as understand the pathway of patient care.

Why have I been invited?
We are inviting patients with hearing loss to share their views and experience of their treatment for hearing loss.

Do I have to take part?
No. You are under no obligation to participate in this study. You may withdraw from the study prior to analysis of data by contacting the researcher and without giving any reasons. This will have no impact on the care or services you receive.

What would I be asked to do if I took part?

You will be asked to participate in an audio-recorded interview exploring your views and experiences of your treatment for hearing loss.

The interview will take place at The Ear Institute, University College London at a time that is convenient for you and will last between 30-60 minutes. When we write about the results of the research, all personal details will be removed so that no one will know who you are.

Will my taking part in this study be kept confidential?
Your signed consent form will be kept separately in a locked filing cabinet, only accessed by the researcher. All the information will be handled in confidence. The audio recording will be kept on a password-protected computer at the university. Once the recording is transcribed it will be erased. All data will be anonymised and stored separately from your contact details. The findings will include anonymised quotations and no information that can identify you personally will be published. Please note that assurances on confidentiality will be strictly adhered to unless evidence of wrongdoing or potential harm is uncovered. In such cases the University may be obliged to contact relevant statutory bodies/agencies.

What are the risks and benefits of being involved?
There are no identified risks of taking part in this study.
Whilst there are no immediate benefits for those people participating in the project, the information that you provide will help to increase our understanding of the costs associated with hearing loss, which in turn will aid future research into hearing loss therapies.

What will happen when this research study stops?
If you would like to know the findings of the research study, please indicate on the consent form. Once the data collection is complete, a summary of the findings will be sent to you. No personal information will be presented in the results. All data has to be stored anonymously by the University for a minimum of five years. This data may need to be looked at by auditors during this time. After this period, it will be confidentially destroyed.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researcher (using the contact details provided below), who will do their best to answer your questions. If they are unable to resolve your concern or if you wish to make a complaint regarding the study, please contact a University Research Ethics Co-ordinator on 020 7679 8717 or by email to ethics@ucl.ac.uk

What do I do now?
If you decide you would like to take part in this study, please email Dr Rishi Mandavia at the email address given below.

Who is organising and funding this research?
The research funding is provided by the University College London and this study is being conducted by evidENT (Evidence based Ear, Nose, Throat), organised by the University College London.

Further information and contact details
If you have any further questions or would like additional information, please contact:
Dr Rishi Mandavia
Prof Anne Schilder

Many thanks for your help and for taking the time to read this information sheet

Appendix 4: Initial topic guide for semi-structured interview for economic model

Initial topic guide for economic model

Thank you for agreeing to take part in this study. As per the study information sheet, hearing loss is a major public health problem, and the most common type of hearing loss is SNHL. Current management of SNHL is limited. Biotechnology and pharmaceutical companies as well as private investors and venture capitalists have recognised this unmet need, and are increasingly developing innovative hearing therapies, including a variety of drug, gene and cell therapies, some of which are undergoing clinical testing in humans. If proven effective, these therapies are set to radically change hearing services within the next 5-10 years. It is essential to start planning for the implementation of future innovative hearing therapies now to prevent unintended consequences including failed or delayed integration into healthcare systems, resulting in poor patient access to care, suboptimal outcomes and financial inefficiencies.

The proposed study works towards addressing this, by developing an early health economic model to assess the potential added value of innovative hearing therapies. To develop the economic model, we will be using idiopathic sudden onset sensorineural hearing loss (SSNHL) as a case study, recognising that this is a lead indication for several innovative hearing therapies in development.

To help develop the model I am looking for input from experts and patients in the field to ensure that my developing model reflects current practices as closely as possible. I will start by providing you with a brief overview of my evolving model before gaining your input.

Decision tree

This decision tree maps the costs and outcomes of the treatment pathway for patients presenting with SSNHL; for both the current standard of care in the NHS and for innovative hearing therapies (not yet in clinical use).

For the current standard of care, patients with different severities of hearing loss have been mapped to receive oral steroids, followed by up to three intratympanic steroid injections (in the event that hearing does not recover to baseline). Patients not recovering to baseline (hearing level within 10dB of contralateral/unaffected ear) following steroid treatment have been mapped to undergo a Magnetic Resonance Imaging (MRI) scan, and laboratory testing to exclude identifiable causes of SSNHL. Only patients who recover to baseline or who have no identifiable cause (idiopathic SSNHL) enter the state transition model.

For the innovative hearing therapy, patients have been mapped to receive the innovative therapy; and in the event that hearing does not recover to baseline, patients undergo an MRI scan and laboratory testing to exclude identifiable causes of SSNHL. Only patients recovering to baseline and those with idiopathic SSNHL enter the state transition model.

State transition model

The state-transition Markov model follows from the decision tree. The state transition model calculates the long term costs and outcomes for patients that have 'entered' the state transition model with idiopathic SSNHL. The model is only looking at idiopathic SSNHL. In the state transition model, patients enter the hearing health state that corresponds to their terminal node in the decision tree. Following the first cycle, patients can move to a 'hearing loss with amplification health state' or stay in the same health state. Patients can also move from a 'hearing loss with amplification health state' back to their initial hearing loss state, recognising compliance issues with hearing aids. Patients from all health states are able to move to "death". This model spans the patient's lifetime until death, owing to the life-long costs and effects of hearing loss. The study takes the perspective of the NHS.

Specific questions for stakeholders (remember to explore why they have said that):

- Please confirm your current role and interest in the field.
- What are your initial thoughts on the decision tree/ state transition model?
- Is there anything unclear?
- We felt that it is relatively rare for patients to receive **no** treatment following onset of SSNHL. Therefore, we did not include this possibility in the decision tree. What are your thoughts on this?
- We have only included unilateral SSNHL owing to the rarity of bilateral SSNHL. What are your thoughts on this?
- We have not included recurrent SSNHL. So patients only get the SSNHL once. What are your thoughts on this?
- We have specified that the 'current strategy' for SSNHL is: oral steroids, followed by up to three intratympanic steroid injections in the event that hearing does not recover to baseline (hearing level in contralateral/unaffected ear). Patients not recovering to baseline following steroid treatment were mapped to undergo Magnetic Resonance Imaging, and laboratory testing to exclude identifiable causes of SSNHL. This is based on national guidance and a review of the literature. What are your thoughts on this?
- Should the MRI IAM have contrast or no contrast? (This affects the costs)
- Which specific blood tests would you do (if any)?
- The effectiveness of steroid therapy in the decision tree was independent of type of steroid used. What are your thoughts on this?
- Which specific oral steroid is most common? What regimen do you use?
- Should we cost for PPI e.g., omeprazole?
- Which specific IT steroid is most common? Do you give analgesia/local anaesthetic?
- How many IT injections should we cost for?
- Should we account for complications of steroids?
- We assume that patients receive the innovative therapy before any investigations (except for hearing tests), similar to the current pathway. What are your thoughts on this?
- At the moment, for patients receiving an innovative hearing therapy, they do not receive steroid therapy as well. Do you agree with this, or do you think these patients should also receive steroid therapy (oral and/or IT).
- If they should receive steroid therapy as well, should they have the IT's as a salvage.

- Baseline hearing is defined as the hearing level in the contralateral (unaffected) ear. Do you agree?
- We assume that patients have a baseline of symmetrical hearing. Do you agree?
- Patients treated with the current pathway or innovative hearing therapy could stay at the same level of hearing, recover to a better hearing state or recover to baseline. We have not modelled for them to return to 'normal' hearing (<20dB) if this was not their baseline. Do you agree with this?
- Response to treatment is assumed to be the same for both sexes for the purpose of this study. What are your thoughts on this?

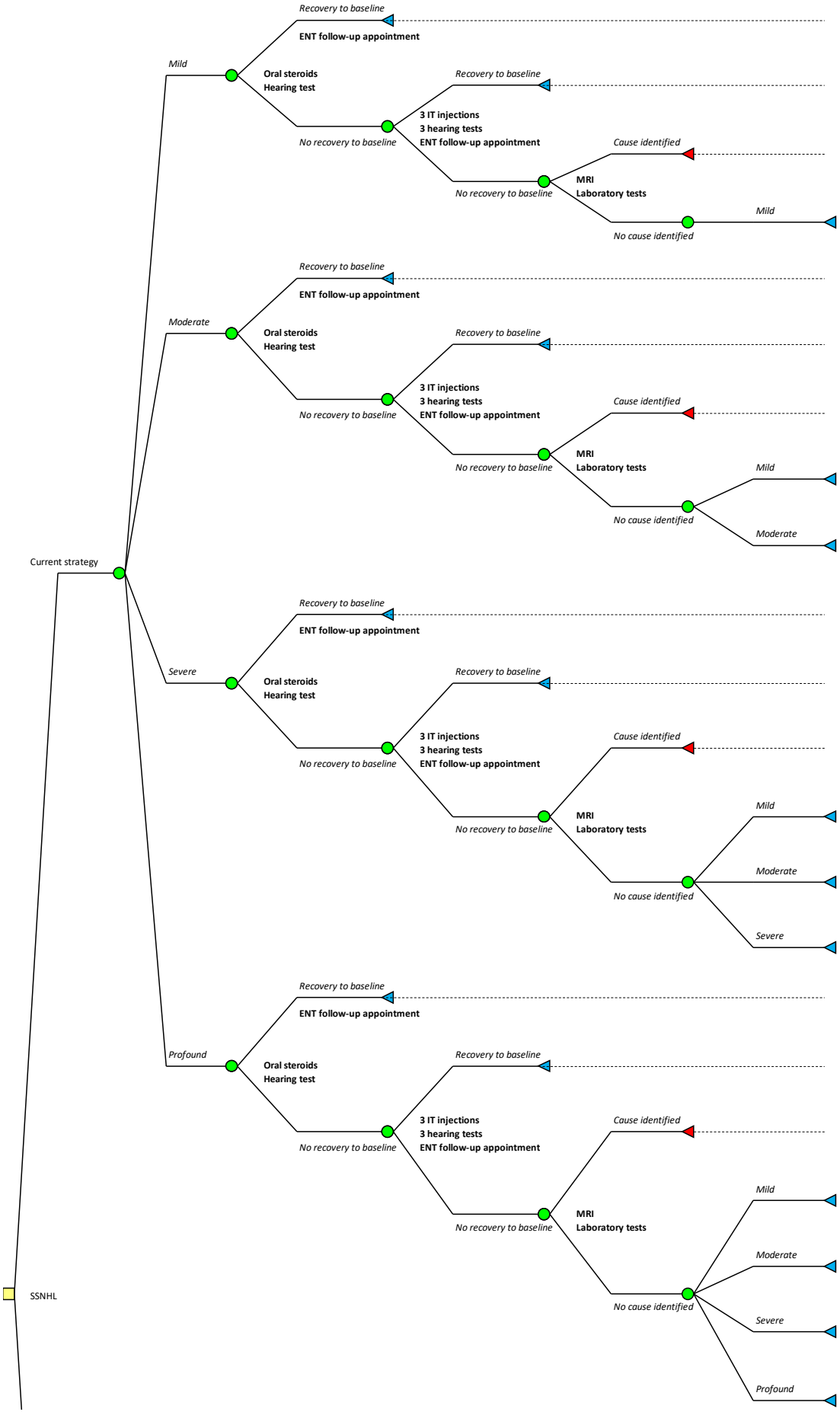
<u>State transition model:</u>

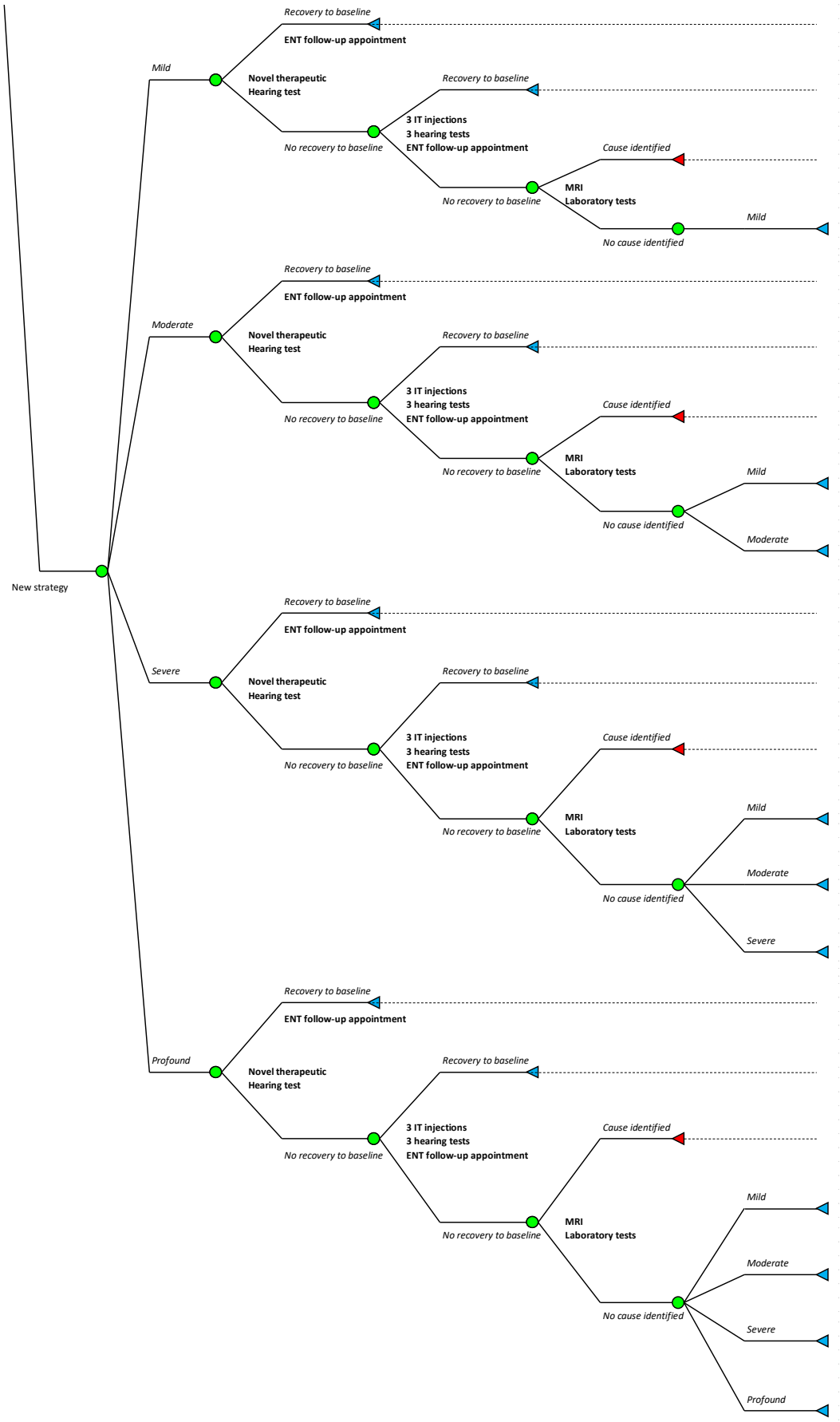
- Following entering the state transition model, patients with SSNHL of a specific hearing level, stay in the same hearing level up to death. Age related decline in hearing or other causes of hearing loss are not taken into account since we only want to model SSNHL. What are your thoughts on this?
- In the hearing loss with amplification box, do you think we should include Contralateral Routing of Signal (CROS) aids/ Bone Conduction Hearing Devices/ MEI/ CIs?
- Should this be specific for level of hearing loss eg:
    - Mild and mod – hearing aids
    - Severe and profound – HA/ CROS / BCHD/ CI
- In the state transition model, hearing aids can be modelled to be fitted monaurally or binaurally. What are your thoughts?
- Hearing aid duration (that is, the time between provision of a hearing aid and it needing to be replaced) has been set at 3 years. Do you agree with this?

<u>General questions:</u>

- What are the main questions you want answered from the model
- Anyone you recommend I get in touch with?

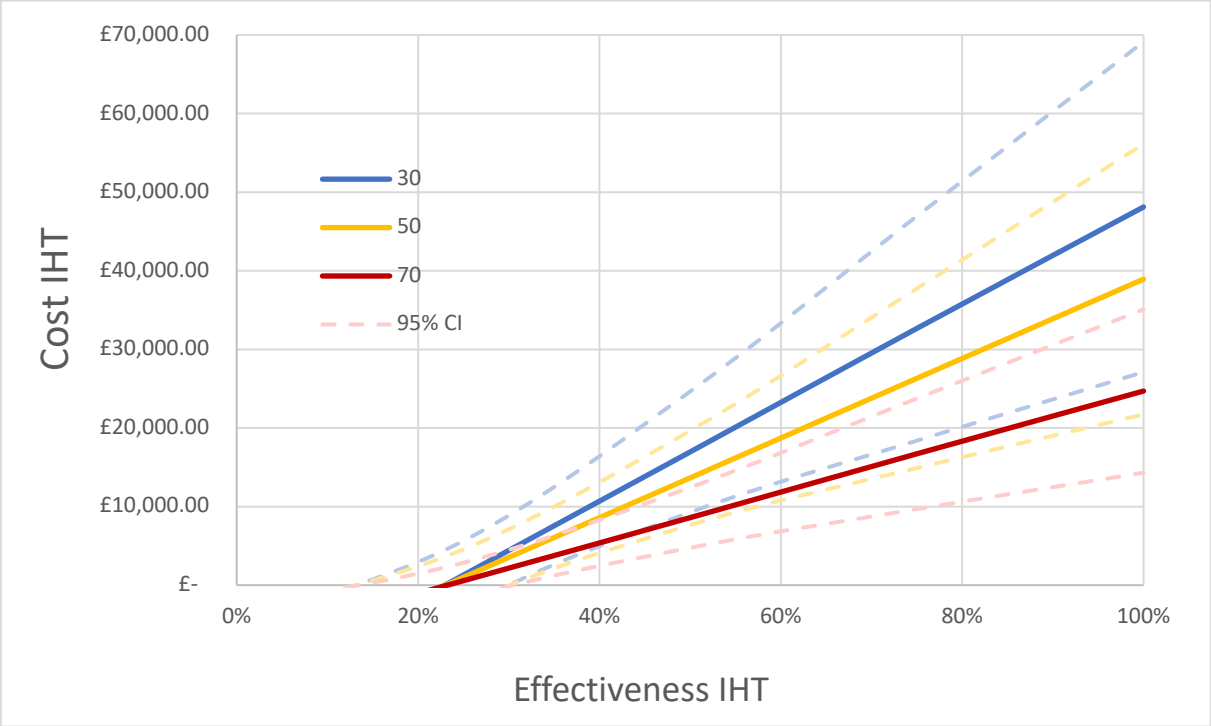
Appendix 5: Full decision tree for early health economic model





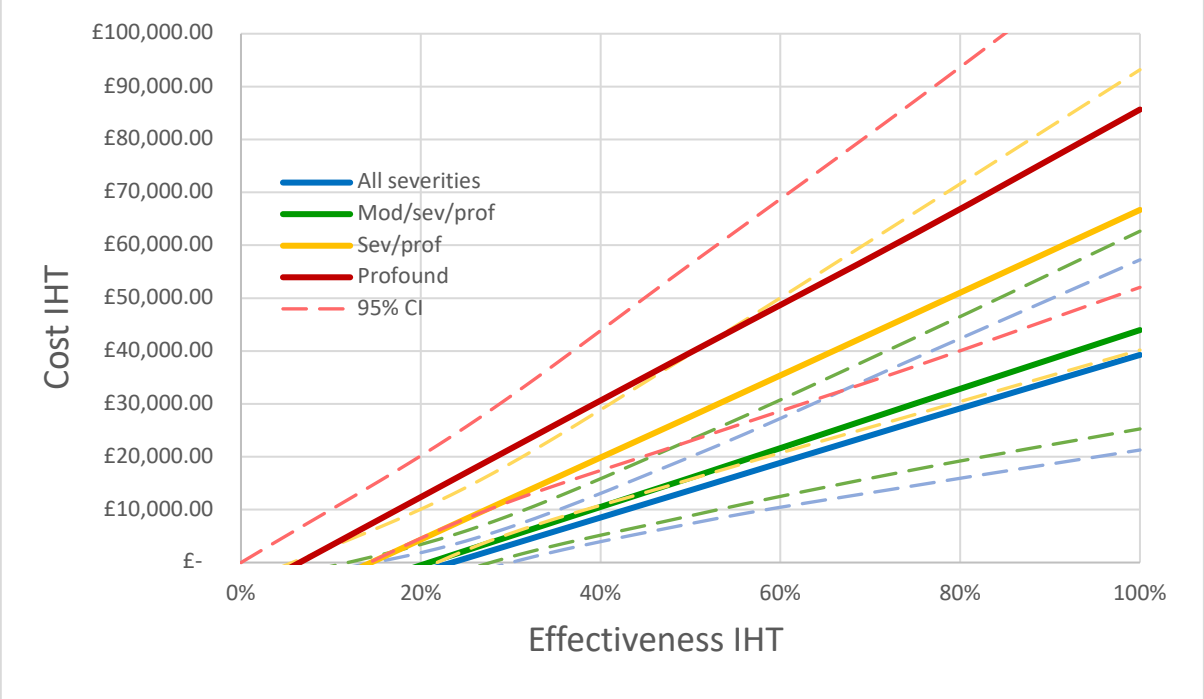
IT, intratympanic; MRI, magnetic resonance imaging

Appendix 6: Threshold analysis with 95% confidence intervals for starting age



Threshold analysis – starting age including confidence intervals

Appendix 7: Threshold analysis with 95% confidence intervals for severity of hearing loss. M, moderate; S, severe; P, profound.



Threshold analysis - severity of hearing loss. Mod, moderate; Sev, severe; Prof, profound. Dotted lines illustrate the confidence intervals for these data

Appendix 8: Study information sheet for Interview Study

Study Information Sheet

UCL Research Ethics Committee Approval ID Number: 11965/001

The PATH study: Preparing for the Adoption of innovative hearing THerapies

Dear Expert,

You are being invited to take part in a research study. We are investigating professional stakeholders' views on the adoption of innovative hearing therapies into healthcare systems. Participation in this research study is voluntary. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask a member of the research team, who will try to answer any questions you may have.

What is the purpose of this study?
Hearing loss is a growing worldwide problem requiring urgent response. The most common form of hearing loss is sensorineural hearing loss (SNHL), which accounts for 90% of cases. The mainstay of treatments for SNHL - hearing aids and cochlear implants, are not meeting the needs of patients as they make sounds louder but not clearer and do not treat the underlying cause.

Biotechnology and pharmaceutical companies as well as private investors and venture capitalists have recognised this unmet need, and, equipped with recent discoveries in the genetic and molecular pathways that underlie SNHL, are increasingly developing innovative hearing therapies, that promise to protect, restore or regenerate the hearing system. Between 2011 and 2015 alone, 34 patents were granted for new therapy and delivery approaches for inner ear disorders and a recent review identified 43 companies working in the field, contending to be the first to deliver effective strategies. These novel approaches, which include a variety of drug, gene and cell therapies, are rapidly progressing along the translational pathway to the stage of clinical testing for safety and efficacy in humans. Examples include the ongoing EU Horizon 2020 supported REGAIN phase I/II trial, and the US Novartis supported phase I/II trial, assessing the safety and efficacy of a small molecule drug and gene therapy respectively in regenerating inner ear (cochlear) hair cells. Many other therapies are approaching the clinical domain, and if proven effective are set to radically change hearing services within the next 5 to 10 years.

It is essential to start planning for these innovative hearing therapies now so that valuable ones can be successfully integrated into healthcare services. This will improve patient access to care, and prevent unintended consequences including suboptimal patient outcomes and financial inefficiencies, which have occurred in other specialities such as Ophthalmology. Crucial to planning for these innovative hearing therapies, is to identify and understand the many factors that influence whether a new therapy can be successfully adopted into a healthcare system.

The PATH study works to directly address this. Using implementation science and by engaging with experts, we will build a toolkit that will identify the factors that influence the adoption of innovative hearing therapies in healthcare systems.

Do I have to take part?
No. You are under no obligation to participate in this study. You may withdraw from the study at any time prior to data analysis by contacting the researcher and without giving any reasons.

What would I be asked to do if I took part?
You will be asked to participate in an audio-recorded interview exploring your views on the factors that influence whether innovative therapies can be successfully adopted into healthcare systems. The interview will take place either face-to-face at a venue that is convenient for you or over the telephone at a time that is suitable for you. The interview will take approximately 30 minutes. When we write about the results of the research, all personal details will be removed so that no one will know who you are.

Will my taking part in this study be kept confidential?
Your signed consent form will be kept separately in a locked filing cabinet, only accessed by the researcher. All the information will be handled in confidence. The audio recording of your interview will be kept on a password-protected computer at the university. Once the recording is transcribed it will be erased. All data will be anonymised and stored separately from your contact details. The findings will include anonymised quotations and no information that can identify you personally will be published. Please note that assurances on confidentiality will be strictly adhered to unless evidence of wrongdoing or potential harm is uncovered. In such cases the University may be obliged to contact relevant statutory bodies/agencies.

What are the risks and benefits of being involved?
There are no known risks associated with being involved. Whilst there are no immediate benefits for those people participating in the project, your input will help plan for the adoption of novel hearing therapies in healthcare systems.

What will happen when this research study stops?
If you would like to know the findings of the research study, please indicate on the consent form. Once the data collection is complete, a summary of the findings will be sent to you. No personal information will be presented in the results. All data has to be stored anonymously by the University for a minimum of five years. This data may need to be looked at by auditors during this time. After this period, it will be confidentially destroyed.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If they are unable to resolve your concern or if you wish to make a complaint regarding the study, please contact a University Research Ethics Co-ordinator on 020 7679 8717 or by email to ethics@ucl.ac.uk

What do I do now?
If you decide you would like to take part in this study, please email Mr Rishi Mandavia.

Who is organising and funding this research?
The research funding is provided by the University College London and this study is being conducted by evidENT (Evidence based Ear, Nose, Throat), organised by the University College London.

Further information and contact details
If you have any further questions or would like additional information, please contact:
Mr Rishi Mandavia
Prof Anne Schilder

Many thanks for your help and for taking the time to read this information sheet.

Appendix 9: Initial topic guide (interview study)

Social Structural Resources

- When a novel therapy is developed (for example a new tablet/IV treatment/Injection) that could protect, restore, or regenerate the hearing system, do you think/ how do you think practices could change?
    - How could it change how a GP/audiologist/ENT surgeon manages their patients?
    - How could it change the patient pathway?
    - How could it impact the organisations that regulate treatments for patients with hearing loss?
    - How could it impact hearing aid companies or implant companies?
    - How could it impact private providers of hearing services or private practice? Could they provide the new treatment?

- When these novel therapies are developed, do you think/how could they change your colleagues' roles or the roles of people in the field?
    - How would it change an audiologists role – e.g., from doing tests to doing interventions.
    - How would it change an ENT doctor's role. e.g., less surgery/more prescribing/coordinating care?
    - How would it change a GP's role – from sign posting to prescribing and actually treating?
    - What type of healthcare professional would provide these new therapies?
    - Could nurse practitioners or audiologists have more of a role? Will there need to be a new type of hearing healthcare professional?

- When these novel therapies are developed how could they change what resources are needed (for your colleagues) to treat patients? (Resources e.g.: financial, time, staffing levels, technological)
    - For example, how could it change what resources are needed for an ENT surgeon/audiologist to carry out their role of improving hearing?

- When these novel therapies are developed how do you think they could affect what your colleagues need to know (knowledge base) in order to treat their patients?
    - E.g. basic science knowledge/pathophysiology/procedural knowledge
    - Would there need to be changes to training programmes? – GP's/ENT/Audiology trainees
    - How about training those already fully trained? ENT consultant? GP's?

Social Cognitive Resources

- When these novel therapies are developed, to what extent would their use and success depend people's motivation or discretion to roll them out/use them?
    - For example, motivation of commissioners, regulators, ENT surgeons, audiologists, private providers?

- When these novel therapies are developed, to what extent would their use depend on people's attitudes towards them?
    - For example, attitudes of ENT surgeons, audiologists, GPs, hearing aid and implant companies, private providers?

<u>Capability: interactions between people and things</u>

- When these novel therapies are developed, to what extent would their use depend on groups working together (coalition forming).
    - For example, novel companies (e.g. biotechnology companies), clinicians, existing implant/hearing aid companies, patients, patient charities, researchers, regulators, for common goals
    - Which groups do you think would work together?
    - Could groups work together to hinder/impede the use of new therapies – e.g., existing implant companies and implant surgeons may work together to block novel therapies?

- When a novel therapy is developed, what would be needed for it to become successfully integrated ('make it fit') within the UK health system?
    - E.g., user friendly
    - Length of procedure/number of follow-up visits
    - Work with existing implant/ hearing aid companies, engage with clinicians.
    - The research base. E.g., evidence of cost-effectiveness/cost-effectiveness analysis?
    - Favourable assessment by guideline developers/commissioners etc

- What role would research into cost-effectiveness play in this field. How would it affect whether novel therapies would be implemented/embedded in the UK healthcare system?
    - What are your thoughts on health economic analysis? – Are they useful/appropriate/sufficiently accurate? Are they worth-while?
    - How do cost-effectiveness analysis results influence you/your colleagues?
    - Can they (their development and the way they are interpreted) be influenced by people in the field. I.e., to what extent can they be influenced by intentions of different stakeholders, and their values.

- What if it is not found to be cost-effective. What happens then?

<u>Contribution: the things that people do</u>

- (On an individual basis), when a novel therapy is developed what do people within the UK hearing healthcare system need to do for the novel therapy to become implemented?
    - Identify how it is different to existing strategies
    - Understand the novel therapy and its role within the hearing healthcare system.
    - Form groups to use the novel therapies/to help them come into practice.
    - Understand their own role to implement the novel therapy

- Could you imagine that people may resist the novel therapy? If so how and why?
    - E.g., form groups/coalitions
    - Conduct research

- If a novel therapy were developed, what would be needed for participants to be skilled in using the novel therapy?
    - E.g., part of training curriculum
    - Part of national guidance/protocol
    - Changes made by educational bodies

- If a novel therapy were developed, how should it be monitored/evaluated?
    - Outcome measure
    - Registries
    - Study design

Do you have any questions?

Can you recommend anyone to speak to with expertise in this field?

Appendix 10: Overview of articles included in Hermeneutic review

Authors and year	Healthcare field	Country/Region of focus	Relevance of article to review	Type of therapy	Elements that influence adoption and implementation of innovative therapies
Iglesias-Lopez et al 2019[107]	Not specific to one healthcare field	US and Europe	Discusses the differences in regulatory frameworks between EU and US and how this impacts adoption of ATMPs	ATMPs	Regulatory and decision making processes
IQVIA 2020[128]	Not specific to one healthcare field	UK	Discusses the obstacles and opportunities for the UK to foster innovation in the life sciences	Innovative therapies in general	Developing collaborations between stakeholders; raising investment for research, development and procurement; motivations for adoption and implementation; providing patient and public information
Heffron 2020[178]	Not specific to one healthcare field	Europe	Discusses regulatory and payment challenges and solutions	Gene	Regulatory and decision making processes; payment strategies

The Royal College of Surgeons 2019[142]	Surgery	UK	Discusses how to prepare surgery for new medical innovations including innovative therapies	Cell and gene	Education and training; collecting real world data; developing collaborations between stakeholders; ethical and legal considerations
Scavone et al 2019[133]	Not specific to one healthcare field	US and Europe	Discusses factors that can assist and limit the adoption of innovative therapies	Innovative therapies in general	Regulatory and decision making processes; payment strategies; evidence of effectiveness and safety; resource requirements; route of administration; providing patient and public information; education and training
Gonçalves 2020[108]	Not specific to one healthcare field	US and Europe	Discusses decision making processes around innovative therapies	ATMPs	Regulatory and decision making processes; patient pathway; cost-effectiveness analyses; ethical and legal considerations; collecting real world data; evidence of effectiveness and safety
Sola et al 2019[126]	Family medicine	Spain	Discusses attitudes of family doctors towards innovative therapies	Innovative therapies in general	Ethical considerations; education and training; clinician perspectives; change in clinician roles

Kurnat-Thoma 2020[190]	Not specific to one healthcare field	US	Discusses workforce training to promote adoption of gene therapies	Gene	Education and training
Efpia 2020[184]	Not specific to one healthcare field	Not specific	Discusses new pricing and payment models for innovative therapies	Innovative therapies in general	Payment strategies
Kariyawasam et al 2020[134]	Neurology	Not specific	Discusses preparing for the implementation of innovative therapies in neurology	Gene	Resource requirements; patient pathway; regulatory and decision making processes; patient pathway; evidence of effectiveness and safety; precision diagnostics; payment strategies; providing patient and public information; ethical and legal considerations; collecting read-world data; cost-effectiveness analyses
Stainthorpe et al 2020[140]	Oncology	England and Wales	Discusses NICE processes in decision making and in appraising cost-effectiveness analyses produced by industry	Drug	Regulatory and decision making processes; cost-effectiveness analyses

Misra et al 2019[146]	Renal medicine	Canada	Discusses factors that can assist the adoption of innovative therapies	Kidney organoids from stem cells	Evidence of effectiveness and safety; providing patient and public information; developing collaborations between stakeholders; collecting real world data
Sheinholtz and Safari 2020[135]	Not specific to one healthcare field	Not specific	Discusses how health services can plan for innovative therapies	Innovative therapies in general	Providing patient and public information; developing collaboration between stakeholders; patient pathway
Relling et al 2020[172]	Not specific to one healthcare field	Not specific	Discusses use of genetic tests results to facilitate implementation of innovative therapies	Gene	Developing precision diagnostics
Rose et al 2015[42]	Ophthalmology	Canada and UK	Describes and explains the factors that influence the adoption and implementation of cell therapies	Cell	Regulatory and decision making processes; current infrastructure; clinician perspectives; resource requirements
Jena et al 2019[161]	Not specific to one healthcare field	US	Discusses payment strategies to increase access to innovative therapies	Innovative therapies in general	Regulatory and decision making processes; payment strategies; collecting real world data

Macpherson et al 2019[181]	Not specific to one healthcare field	Not specific	Discusses ethical challenges of gene therapies	Gene	Ethical and legal considerations
Schilder et al 2019[12]	Hearing and Deafness	Not specific	Discusses factors that influence adoption of novel hearing therapies	Innovative therapies in general	Developing precision diagnostics; evidence of effectiveness and safety; collecting real world data; cost-effectiveness analyses; developing collaboration between stakeholders
Sergouniotis 2019[143]	Ophthalmology	Not specific	Discusses evidence requirements for the implementation of innovative therapies	Gene	Cost-effectiveness analyses; evidence of effectiveness and safety; collecting real world data
Saadeh et al 2019[151]	Oncology	Not specific	Discusses adoption of precision medicine in Oncology	Innovative therapies in general	Evidence of effectiveness and safety; education and training; resource requirements
Mensah et al 2019[182]	Cardiovascular medicine	Not specific	Discusses ethical challenges of innovative therapies	Innovative therapies in general	Collecting real world data; ethical and legal considerations; evidence of effectiveness and safety

Webster and Gardner 2019[58]	Not specific to one healthcare field	Not specific	Discusses 'readiness' as it relates to adoption of innovation with example from regenerative medicine	Examples of regenerative therapies provided	Manufacture and distribution; regulatory and decision making processes; sense making; education and clinicians; evidence of effectiveness and safety; resource requirements; change in clinician roles; patient pathway
Lasalvia et al 2019[176]	Orphan drugs	Not specific	Discusses approaches to assess value of orphan drugs	Orphan drugs	Cost-effectiveness analyses
Low and Nakamura 2019[191]	Oncology	Not specific	Discusses the use of artificial intelligence to facilitate implementation	Personalised immunotherapy	Collecting real world data
Thielen 2019[179]	Oncology	England and Wales	Discusses NICE processes in decision making and in appraising cost-effectiveness analyses produced by industry	Drug	Regulatory and decision making processes; cost-effectiveness analyses
Cannizzo et al 2018[177]	Not specific to one healthcare field	Not specific	Discusses adoption of innovative therapies targeting orphan diseases	Innovative therapies targeting orphan diseases	Cost-effectiveness analyses; collecting real world data; evidence of effectiveness and safety

Pappalardo et al 2018[149]	Not specific to one healthcare field	Not specific	Discusses use of in silico clinical trials to facilitate implementation of innovative therapies	Innovative therapies in general	Evidence of effectiveness and safety; collecting real world data; ethical and legal considerations
Raez et al 2018[131]	Oncology	Latin America	Provides a low and middle income perspective on adoption of innovative therapies	Innovative therapies in general	Resource requirements; patient pathway; developing precision diagnostics; regulatory and decision making processes; education and training; developing collaboration between stakeholders
Harrison et al 2018[43]	Not specific to one healthcare field	Not specific	Discusses manufacturing strategies of innovative therapies and impact on implementation	Gene and cell	Manufacture and distribution
Nakashima 2018[124]	Oncology	Canada	Discusses factors that influence adoption of innovative therapies in oncology	Innovative therapies in general	Evidence of effectiveness and safety; resource requirements; regulatory and decision making processes; cost-effectiveness analyses; providing patient and public information; current infrastructure
Webster 2017[154]	Not specific to one healthcare field	UK	Discussed challenges faced by regenerative medicine field and provides proposals for responsible acceleration to the clinic	Regenerative	Manufacture and distribution; sense making; collecting real world data; patient pathway; sense making; payment strategies

Ritchie et al 2017[137]	Care of the elderly	UK	Discusses how healthcare services can plan for innovative therapies for Alzheimer's disease.	Drug and biological agents	Precision diagnostics; current infrastructure; sense making; providing patient and public information; evidence of effectiveness and safety; collecting real world data; developing collaborations between stakeholders; ethical and legal considerations; resource requirements; regulatory and decision making processes; cost-effectiveness analyses; education and training; clinician perspectives; change in clinician roles; patient pathway
Gardner and Webster 2017[39]	Not specific to one healthcare field	UK	Discusses the role of accelerator agencies and potential tensions in their motivations	Gene and cell	Manufacture and distribution; regulatory and decision making processes; patient pathway; working with accelerator agencies; motivations for adoption and implementation
Webster 2017[109]	Not specific to one healthcare field	UK	Discusses challenges and potential solutions of cell and gene therapy adoption	Regenerative	Manufacture and distribution; sense making; regulatory and decision making processes; payment strategies; patient pathway; change in clinician roles
Dheda et al 2018[155]	Infectious diseases	Not specific	Discusses implementation of innovative therapies for tuberculosis	Drug	Route of administration; resource requirements; evidence of effectiveness and safety

Harrington et al 2017[152]	Oncology	Europe	Discusses implementation of a novel gene therapy for patients with melanoma	Gene	Manufacture and distribution; regulatory and decision making processes; route of administration; patient pathway; change in clinician roles; developing collaborations between stakeholders
Harrison et al 2017[158]	Not specific to one healthcare field	Not specific	Discusses challenges and potential solutions of innovative therapy manufacturing	Cell and gene	Manufacture and distribution; cost-effectiveness analyses
Corbett et al 2017[129]	Not specific to one healthcare field	EU	Discusses barriers and facilitators to adoption of innovative therapies	Regenerative	Collecting real world data; evidence of effectiveness and safety; manufacture and distribution; working with accelerator organisations; regulatory and decision making processes; developing collaborations between stakeholders; cost-effectiveness analyses; payment strategies; current infrastructure
Bando 2017[175]	Oncology	Japan and Europe	Discusses challenges of delivering innovative therapies in Japan and Europe	Innovative therapies in general	Evidence of effectiveness and safety; regulatory and decision making processes

Inokuma 2017[157]	Not specific to one healthcare field	Japan	Discusses monitoring of innovative therapies by regulators	Regenerative	Regulatory and decision making processes
Harada et al 2017[132]	Cardiovascular medicine	US	Discusses an implementation framework developed using genotype-guided antiplatelet therapy as an example.	Gene	Developing collaboration between stakeholders; developing precision diagnostics; education and training; collecting real world data
Vogler et al 2017[136]	Not specific to one healthcare field	Europe	Discusses use of pricing policies to influence access to therapies	Drug	Payment strategies; current infrastructure; cost-effectiveness analyses; developing collaboration between stakeholders
Gardner and Webster 2016[119]	Not specific to one healthcare field	EU	Explores the attempts of stakeholders to overcome adoption challenges for regenerative medicines	Regenerative	Current infrastructure; manufacture and distribution; regulatory and decision making processes; cost-effectiveness analyses

Farrar et al 2016[169]	Neurology	Not specific	Discusses challenges that novel therapy strategies will bring into clinical practice	Innovative therapies in general	Evidence of effectiveness and safety; precision diagnostics; collecting real world data
Walko et al 2016[150]	Oncology	US	Discusses the use precision diagnostic boards to guide use of innovative therapies	Innovative therapies in general	Precision diagnostics; education and training
Nguyen et al 2016[144]	Cardiovascular medicine	Not specific	Discusses challenges for implementation of stem cell therapies	Cell	Precision diagnostics; evidence of effectiveness and safety
Gardner et al 2015[120]	Not specific to one healthcare field	UK	Discusses translational challenges in regenerative medicine	Regenerative	Current infrastructure; evidence of effectiveness and safety; collecting real world data; regulatory and decision making processes; manufacture and distribution; cost-effectiveness analyses; working with accelerator organisations; patient pathway
Neofytou et al 2015[156]	Not specific to one healthcare field	Not specific	Discusses challenges facing translation of stem cell therapies	Cell	Ethical and legal considerations; manufacture and distribution; regulatory and decision making processes

Bubela et al 2015[122]	Regenerative medicine	UK	Reports on discussions from 2 workshops on adoption on innovative therapies	Innovative therapies in general	Cost-effectiveness analyses; developing collaborations between stakeholders; payment strategies; evidence of effectiveness and safety; current infrastructure; regulatory and decision making processes; collecting real world data; resource requirements
Stegemann et al 2016[159]	Not specific to one healthcare field	Not specific	Discusses advances in pharmaceutical manufacturing	Drug	Manufacture and distribution
Terzic et al 2015[125]	Not specific to one healthcare field	US	Discusses barriers and facilitators to the implementation of regenerative medicines	Regenerative	Education and training; resource requirements; evidence of effectiveness and safety; regulatory and decision making processes; developing collaboration between stakeholders; payment strategies; developing precision diagnostics
Slater et al 2015[163]	Oncology	Canada	Discusses the barriers to implementation of innovative therapies in the Canadian healthcare system	Precision therapies	Providing patient and public information; education and training; sense making; regulatory and decision making processes; collecting real world data; cost-effectiveness analyses; resource requirements; developing precision diagnostics; developing collaborations between stakeholders

Mazur et al 2015[148]	Respiratory medicine	Not specific	Discusses challenges to development and implementation of innovative therapies for respiratory syncytial virus	Innovative therapies in general	Evidence of effectiveness and safety; collecting real world data
Price-Haywood 2015[145]	Not specific to one healthcare field	US	Discusses clinical comparative effectiveness research through the lens of decision makers	Innovative therapies in general	Evidence of effectiveness and safety; collecting real world data
Kleinke and McGee 2015[173]	Not specific to one healthcare field	US	Discusses potential financing models for innovative therapies	Innovative therapies in general	Resource requirements; sense making; payments strategies; route of administration
Mostofian et al 2015[192]	Not specific to one healthcare field	Not specific	Discusses methods to change physician practices	Innovative therapies in general	Education and training
Lublóy 2014[141]	Not specific to one healthcare field	Not specific	Discusses how behaviour of medical professionals influences diffusion of novel drugs	Drug	Clinician perspectives; characteristics of clinicians and patients; education and training; providing patient and public information; developing precision diagnostics
Meadows et al 2014[63]	Mainly oncology	US and Europe	Discusses barriers to adoption	Stratified (personalised) medicines	Developing precision diagnostics; resource requirements

Zumla et al 2014[130]	Infectious diseases	Not specific	Discusses adoption of novel drug therapies for Tuberculosis	Drug	Collecting real world data; developing collaborations between stakeholders; regulatory and decision making processes
Lima-Dellamora et al 2014[123]	Not specific to one healthcare field	Brazil	Discusses adoption of innovative therapies in university hospitals in Brazil	Drug	Motivations for adoption and implementation; evidence of effectiveness and safety; education and training; cost-effectiveness analyses; clinician perspectives; developing collaborations between stakeholders
Godman et al 2013[138]	Not specific to one healthcare field	Not specific	Discusses factors that influence adoption of innovative therapies	Targeted therapies	Developing precision diagnostics; resource requirements; ethical and legal considerations; change in clinician roles; patient pathway; evidence of effectiveness and safety; cost-effectiveness analyses; developing collaboration between stakeholders; collecting real world data; providing patient and public information; developing coalitions between stakeholders; education and training
McCarthy et al 2013[147]	Not specific to one healthcare field	Not specific	Discusses challenges and opportunities for innovative therapies	Innovative therapies in general	Collecting real world data; evidence of effectiveness and safety; education and training; patient pathway; ethical and legal considerations; sense making

Jönsson 2013[165]	Oncology	Not specific	Discusses technology assessment for innovative therapies in oncology	Targeted therapies	Regulatory and decision making processes; cost-effectiveness analyses; evidence of effectiveness and safety; developing precision diagnostics
Hems et al 2012[183]	Not specific to one healthcare field	Scotland	Discusses mechanisms in Scotland to manage the introduction of innovative therapies	Innovative therapies in general	Regulatory and decision making processes; resource requirements
Mittra and Tait 2012[166]	Not specific to one healthcare field	Not specific	Discusses how to align precision diagnostic and novel therapy development to facilitate successful adoption.	Targeted therapies	Regulatory and decision making processes; developing precision diagnostics
Eichler et al 2012[162]	Not specific to one healthcare field	Not specific	Discusses adaptive licensing approaches for innovative therapies	Innovative therapies in general	Collecting real world data; regulatory and decision making processes

Dawe and Ellis 2012[170]	Oncology	Canada	Discusses challenges in implementation of targeted therapies for lung cancer	Targeted therapies	Cost-effectiveness analyses; developing precision diagnostics; resource requirements
Bollyky et al 2010[160]	Infectious diseases	Not specific	Discusses challenges to adoption of innovative therapies	Innovative therapies in general	Collecting real world data; regulatory and decision making processes
Greenhalgh et al 2009[180]	Oncology	England and Wales	Discusses NICE processes in decision making and in appraising cost-effectiveness analyses produced by industry	Drug	Regulatory and decision making processes; cost-effectiveness analyses
Abrahams and Silver 2009[168]	Not specific to one healthcare field	Not specific	Discusses role of precision diagnostics in novel therapy adoption	Innovative therapies in general	Developing precision diagnostics
Chauhan and Mason 2008[118]	Not specific to one healthcare field	UK	Explores the determinants of uptake of new drugs in secondary care	Drugs	Education and training; providing patient and public information; characteristics of clinicians and patients; resource requirements; clinician perspectives; route of administration; evidence of effectiveness and safety; current infrastructure; sense making

Mason 2008[127]	Family medicine	UK	Explores the determinants of uptake of new drugs in primary care	Drug	Education and training; evidence of effectiveness and safety; clinician perspectives
Bergethon and Wasfy 2019[139]	Cardiovascular medicine	US	Discusses strategies to increase adoption of novel drugs in cardiology	Drug	Education and training; sense making; providing patient and public information; resource requirements; cost-effectiveness analyses; collecting real world data; payment strategies
Nakagawa 2014[167]	Hearing and Deafness	Not specific	Discusses importance of developing diagnostic tests for adoption of novel hearing therapies	Innovative therapies in general	Developing precision diagnostics
Khakoo et al 2019[174]	Cardiovascular medicine	US	Discusses implementation barriers for innovative therapies for cardiovascular disease	Innovative therapies in general	Resource requirements; developing collaboration between stakeholders; sense making
Rapp 2020[164]	Not specific to one healthcare field	Not specific	Discusses importance of understanding the target market to facilitate adoption	Cell and gene	Sense making, sense making, patient pathway

The Royal Society 2018[38]	Not specific to one healthcare field	UK	Discusses how to prepare for innovative therapies	Innovative therapies in general	Manufacture and distribution; regulatory and decision making processes; resource requirements; patient pathway; evidence of effectiveness and safety; developing precision diagnostics; ethical and legal considerations; cost-effectiveness analyses; education and training; collecting real world data.
DiMichele 2018[193]	Haematology	Not specific	Discusses importance of establishing safety for novel therapy adoption.	Gene	Evidence of effectiveness and safety
McCormack et al 2014[171]	Not specific to one healthcare field	Not specific	Discusses co-development of precision diagnostics with innovative therapies to facilitate adoption	Innovative therapies in general	Developing precision diagnostics
Gardner et al 2018[41]	Not specific to one healthcare field	UK	Discusses barriers and facilitators to the implementation of regenerative therapies	Regenerative	Clinician perspectives; current infrastructure; developing collaborations between stakeholders; motivations for adoption and implementation; sense making; evidence of effectiveness and safety; resource requirements; manufacture and distribution; payment strategies; patient pathway
Elverum and Whitman 2020[153]	Not specific to one healthcare field	US	Discusses strategies to facilitate uptake of cell and gene therapies	Cell and gene	Manufacture and distribution; patient pathway; change in clinician roles; ethical and legal considerations; payment strategies; resource requirements

The Academy of Medical Sciences 2013[64]	Not specific to one healthcare field	UK and EU	Discusses barriers and solutions for the use of targeted drugs	Drug	Current infrastructure; manufacture and distribution; developing precision diagnostics; regulatory and decision making processes; payments strategies; education and training; developing collaborations between stakeholders; patient and public information; cost-effectiveness analyses; collecting real world data
House of Commons Science and Technology Committee 2017[110]	Not specific to one healthcare field	UK	Discusses barriers and facilitators to adoption of innovative therapies in the UK	Regenerative	Regulatory and decision making processes; payment strategies; raising investment for research, development and procurement; manufacture and distribution; cost-effectiveness analyses; patient pathway; change in clinician roles
Accelerated Access 2016[121]	Not specific to one healthcare field	UK	Makes recommendations to Government on how to accelerate access for NHS patients to innovative medicines	Innovative medicines	Current infrastructure; regulatory and decision making processes; collecting real world data; patient pathway