STARFISH Trial Summary

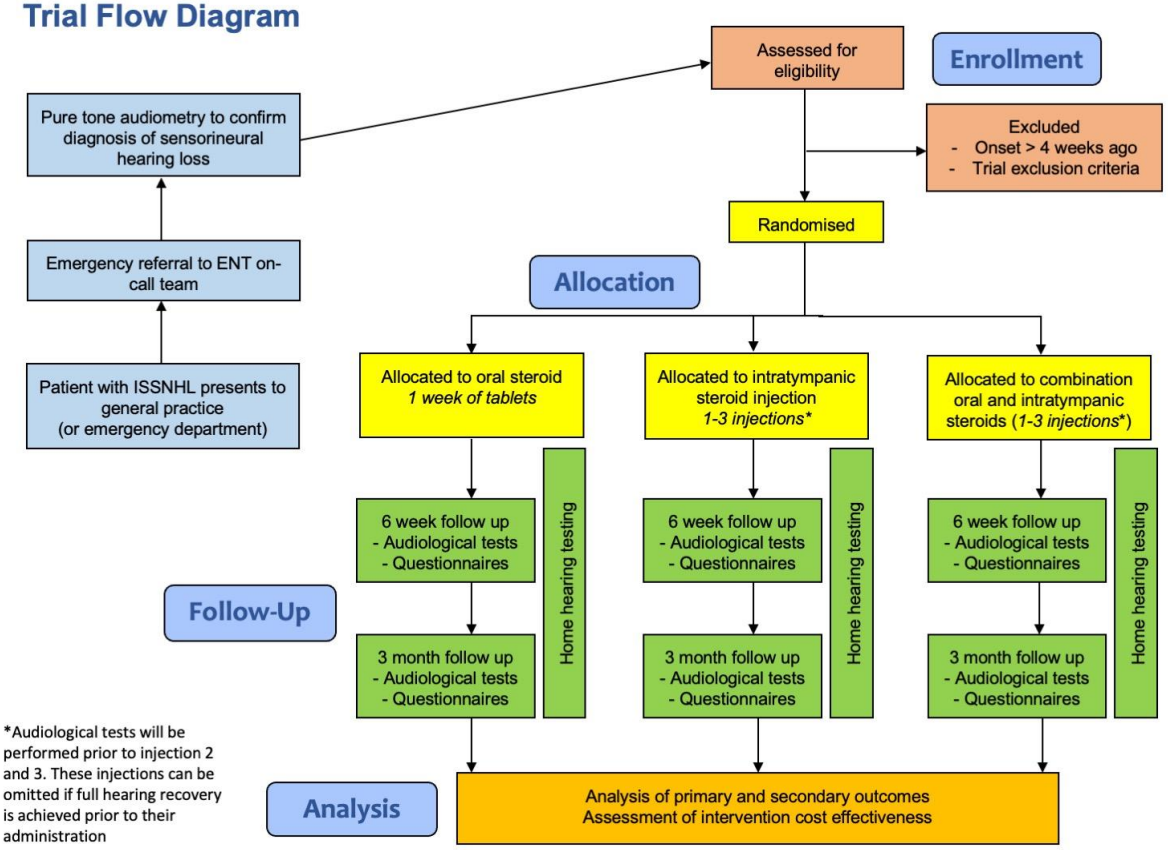
Title	STARFISH: A randomised controlled trial of STeroid Administration Routes For Idiopathic Sudden sensorineural Hearing loss
Trial Design	A pragmatic, multicentre, assessor-blinded, parallel 3-arm intervention, superiority, randomised controlled trial (1:1:1) with a 9-month internal pilot.
Interventions	• Oral steroid (Prednisolone) 1mg/Kg/day up to 60mg/day for 7 days; Or • Intratympanic steroid (Dexamethasone) three intratympanic injections 3.3mg/ml or 3.8mg/ml spaced 7±2 days apart*; Or • Combined oral (Prednisolone) and intratympanic (Dexamethasone) steroid as described above, with the first intratympanic injection occurring within 4 days of the start of oral steroids. **injections 2&3 may be withheld in the event of full hearing recovery prior to administration*

Outcome Measures	**Primary Outcome**
	• The absolute improvement in pure tone audiogram average at 12-weeks following treatment initiation (calculated at 0.5, 1.0, 2.0, 4.0 Kilohertz (kHz))
	
	Secondary Outcomes (all at 6 and 12 weeks from randomisation unless stated)
	• Functional hearing:
	  ○ Hearing related to speech: using The Speech, Spatial and Qualities of hearing scale (SSQ)
	  ○ Absolute improvement in hearing threshold at six weeks (calculated at 0.5, 1.0, 2.0, 4.0 kHz)
	  ○ Actual hearing thresholds at six and twelve weeks (calculated at 0.5, 1.0, 2.0, 4.0 kHz).
	  ○ High frequency hearing threshold across 4.0, 6.0 and 8.0 kHz
	  ○ Recovery of speech perception: using Arthur Boothroyd (AB) word lists scored by phoneme
	  ○ Extent of hearing recovery: using an established classification of recovery
	• Associated symptoms: dizziness and tinnitus (Vestibular Rehabilitation Benefit Questionnaire & Tinnitus Functional Index)
	• Adverse Events
	Optional
	• Weekly home hearing tests (speech and pure tone thresholds)
	Health Economic Assessment
	• Health Utility Index 3
	• ICEpop CAPability measure for Adults
	• Resource usage

Trial duration per participant	Overall trial period 12 weeks: clinic follow up at 6 weeks to collect secondary outcomes, and 12 weeks to collect primary and secondary outcomes. Optional weekly home hearing test using online testing.

Estimated total trial duration	41 months (6 months setup, 25 months recruitment, 3 months follow up, 7 months analysis and write up)
Recruitment start date	Anticipated September 2022
Setting	Approximately 75 NHS hospital ENT units in the UK
Sample Size	525 participants
Eligibility Criteria	**Inclusion Criteria** • Adults aged 18 years or over • Diagnosis of new-onset ISSNHL: a new increase in sensorineural thresholds of 30 decibels (dBHL) or greater affecting each of 3 contiguous pure-tone frequencies (out of 0.5, 1.0, 2.0, 4.0 kilohertz (kHz)) confirmed with a pure tone audiogram, having an onset over a period of 3 days or less according to the patient's history* • Onset of hearing loss within four weeks of randomisation. • English spoken as a first or second language *Where audiometry is not available prior to the ISSNHL and there is a history is of equal hearing in both ears prior to the sudden loss, hearing loss will be defined in relation to the opposite ear's thresholds. Where audiometry is not available prior to the ISSNHL and there is a history of different hearing in both ears prior to the sudden loss, then the candidate can only be included if the ISSNHL occurred in the better hearing ear and the measured thresholds are at least 30dB below the contralateral ear at 3 contiguous pure-tone frequencies (out of 0.5, 1.0, 2.0, 4.0 kilohertz (kHz)) confirmed with a pure tone audiogram. **Exclusion Criteria** • Identified cause for hearing loss (not idiopathic) e.g. Meniere's • Bilateral ISSNHL • Received prior steroid treatment for the same episode of ISSNHL* • Medical contraindication to high dose systemic steroids • Previous history of psychosis • On oral steroid therapy for another condition • Known adrenocortical insufficiency other than exogenous corticosteroid therapy • Hypersensitivity to the active substance or to any of the excipients • Has a systemic infection unless specific anti-infective therapy is employed • Has ocular herpes simplex • Has ipsilateral acute or chronic active middle ear disease (including acute otitis media, chronic suppurative otitis media and cholesteatoma, excluding dry perforation) • Does not have the capacity to provide written informed consent *This includes steroid topical drops or combination steroid and antibiotic drops if given in the presence of a perforated ear drum in the absence of a middle ear infection e.g. for otitis externa.

Trial Flow Diagram



*Audiological tests will be performed prior to injection 2 and 3. These injections can be omitted if full hearing recovery is achieved prior to their administration

Schedule of Assessments

	Visits						
			From first injection		From randomisation		
Assessments	**Screening**	**Baseline**	**2nd injection (week 1 ±2 days)**	**3rd injection (week 2 ±2 days)**	**Weekly**	**Week 6 ±7 days**	**Week 12 ±7 days**
Eligibility check	All						
Valid informed consent		All					
Relevant medical history taken		All					
Concomitant medication		All					
Demographic information		All					
Randomisation		All					
Otoscopy		All	2,3	2,3		All	All
Pure tone audiogram (0.5-8.0kHz range)		All*	2,3	2,3		All	All
AB phoneme speech testing		All**				All	All
Online digits-in-noise test #					All#		
Online pure tone audiogram test #					All#		
Speech, Spatial and Qualities of hear scale (SSQ)		All				All	All
Vestibular Rehabilitation Benefit Questionnaire (VRBQ)		All				All	All
Tinnitus Functional Index (TFI)		All				All	All
Health Utilities Index 3 (HUI3)		All				All	All
ICECAP-A		All				All	All
Resource usage						All	All
Adverse Events monitoring						All	All
Compliance reporting						2,3	2,3&
Oral steroid provision		1,3					
Intratympanic injection		2,3	2,3	2,3			

1 = for arm 1 (oral steroid), 2 = for arms 2 (intratympanic injection), 3 = for arm 3 (combined treatment)

 # optional, for individual participants and participating sites.

** should be performed within three days prior to commencement of treatment*

*** recommended to be performed on same day as pure tone audiogram or if not practicable within next working day*

& only persistent perforation of the tympanic membrane will be recorded at 12 weeks