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Toward a Core Outcome Set for Head, Neck, and Respiratory Disease in Mucopolysaccharidosis Type II: Systematic Literature Review and Assessment of Heterogeneity in Outcome Reporting

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Abstract

The mucopolysaccharidoses (MPS) are a relatively uncommon group of inherited metabolic disorders, with significant negative implications for life span and aspects of quality of life. Their rarity means that producing evidence to guide best practice has often entailed assimilating findings from multiple studies. Core outcome sets (COS) are being increasingly used across medicine as a potential solution to the problems arising from heterogeneous reporting of outcomes in effectiveness studies. A COS is a recommended minimum set of outcomes that should be measured for a given condition in an effectiveness study, with the ultimate aim of increasing the value of clinical information by enabling meaningful comparison and combination of data from various sources. A systematic review identified 41 outcomes measured in published studies and ongoing and completed clinical trials, with individual outcomes being measured using a variety of measurement instruments/tools. This work represents the important initial steps in the development of COS for head, neck, and respiratory disorders in MPS type II, raising awareness of the extent of heterogeneity in outcome reporting and determining the scope of outcomes and corresponding instruments currently used. The next step will be to use the generated "longlist" of outcomes to develop an electronic Delphi prioritization exercise with the intention of reaching a consensus regarding the most important outcomes to measure in effectiveness studies for head, neck, and respiratory disease in MPS type II.

Keywords

core outcome set, systematic review, mucopolysaccharidosis, outcome domain, outcome measure instrument

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Background

The mucopolysaccharidoses (MPS) are a family of inherited metabolic disorders, caused by specific lysosomal enzyme deficiencies, with resultant accumulation of partially degraded glycosaminoglycans (GAG) within tissues.[1] The ubiquitous nature of GAG within the body means that a number of different organ systems can be affected. Eleven distinct types of MPS disorders have been classified, according to the particular enzyme that is deficient.[1–3]

Involvement of the upper and lower respiratory tract in MPS type II results in significant airway compromise, with progressive airway obstruction being responsible for a significant proportion of the morbidity and mortality associated with this condition.[4] Airway disease is characterized by adenotonsillar hypertrophy, macroglossia, recurrent upper respiratory tract infections, thickened nasal mucosa, airway deposits, and tracheomalacia.[5–7] These changes within the airway are considered to result from GAG accumulation in soft tissues.[5] Sleep disordered breathing, or obstructive sleep apnoea, has been reported in 90% (27/30 patients) of patients with MPS type II when tested using polysomnography.[8] Obstructive events during sleep can lead to learning impairment, behavioral problems, developmental, and learning delay as well as cardiovascular disease (pulmonary hypertension and right ventricular hypertrophy).[9] Skeletal abnormalities (eg, small ribs and short neck), enlarged internal organs, restrictive lung disease, neurocognitive impairment, and cardiac disease may further compound multilevel upper airway involvement, leading to respiratory compromise that may significantly restrict lifestyle and ultimately lead to death.[5,6]

Hearing loss is a universal finding in MPS, with a third of patients having severe profound hearing loss.[10] More is understood about the hearing loss in MPS type II in comparison with the other subtypes, due to the publication of hearing data from an international observational study (The Hunter outcome survey [HOS]).[11] At the time of reporting, 84% (70/83) of the children surveyed had a hearing loss; 24% (20/83) had a mild hearing loss, 31% (26/83) a moderate loss, 22% (18/83) a severe loss, and 7% (6/83) a profound loss (WHO-ICIDH criteria). The conductive component of the hearing loss in MPS type II is predominantly related to an increased tendency toward the development and persistence of otitis media with effusion (OME, glue ear) and recurrent acute otitis media (rAOM). In MPS type II, GAG deposits are believed to accumulate within the nasopharynx contributing to Eustachian tube dysfunction (ETD) and the development and persistence of OME. The increased tendency toward upper respiratory tract infections in MPS may manifest as chronic adenoiditis, further contributing to ETD and AOM. The tendency toward OME may last into adolescence and adulthood in MPS. Long- and short-term ventilation tubes and hearing aids have been used in the management of persistent OME with hearing loss,[10,12,13] with greater emphasis now being placed on hearing aids due to the anticipated longevity of OME and the attendant risk of recurrent general anaesthesia.

There is an unmet need for strong clinical evidence to guide treatment of head, neck, and respiratory disease in MPS disorders, with much of the published evidence reflecting the experience of larger centres based on the retrospective analysis of patient outcomes.

A Core Outcome Set (COS) describes the minimum outcome data that should be measured in a clinical study for a particular condition.[14] The lack of an agreed COS for MPS type II in general, and specifically respiratory/head and neck disease, crucially hinders comparison between studies. In addition, purchasers and regulatory bodies are likely to prefer evidence from clinical studies that adhere to an agreed set of outcome measures. There is also a paucity of information detailing patient and parent perspectives on the symptomatology of MPS disorders. The ideal COS for respiratory/head and neck disease associated with MPS type II would combine both patient/parent and clinician opinion and could be used in the design of all subsequent clinical studies. Currently, the tendency to only report those findings that researchers consider to be significant or positive can lead to outcome reporting bias (ORB).[15] The development of a COS can help to negate the effect of ORB in future study designs and limit heterogeneity of chosen outcomes in studies investigating different interventions in the same organ system.

The aim of this systematic literature review was to generate a "long list" of *outcome measures* and corresponding list of *outcome measurement instruments* reported in the MPS type II literature for respiratory/head and neck disease. This information would help to determine the extent of heterogeneity of outcome reporting in this MPS subtype and enable the subsequent development of a COS specific for respiratory/head and neck disease.

Methods

Literature Search

Studies were identified using a systematic search strategy applied to EMBASE, MEDLINE, and CINAHL (using http://www.library.nhs.uk/hdas) over the 24-year period (1990-2014). The time period selected represents contemporary practice and current understanding of the disease, reflecting the introduction of disease-modifying therapies, along with centralized, coordinated, and multidisciplinary care.

Multiple databases were used to maximize the sensitivity of the search. Within EMBASE, MEDLINE, and CINAHL a Medical Subject Headings (MeSH) search (mapped to the Thesaurus) was performed. Within the Thesaurus, the subject heading was "exploded" and the "OR" setting applied. The general MeSH headings (Table 1) was subsequently combined with the mucopolysaccharidosis (MPS) II MeSH heading using the "AND" option.

The COS being developed is specifically for 2 interrelated body systems (respiratory and head and neck) within MPS type

Table 1. MeSH headings for systematic review search.

	1. Otolaryngology
2. Otorhinolaryngologic Disease	3. Adenoidectomy
4. Positive pressure respiration OR continuous positive airway pressure (CPAP) OR sleep apnoea syndrome OR sleep apnoea or obstructive or polysomnography or airway obstruction or pharynx/or apnoea	5. Deafness
6. Positive pressure respiration	7. Conductive hearing loss
8. Continuous positive airway pressure	9. Sensorineural hearing loss
10. Sleep apnoea syndrome	11. Hearing aids
12. Sleep apnoea	13. Bone conduction/cochlear implant
14. Obstructive	15. Cochlear implant
16. Polysomnography	17. Bone conduction
18. Airway obstruction	19. Chronic disease/psychology
20. Pharynx	21. Psychology
22. Apnoea	23. Health service research
24. Snoring	25. Qualitative research
26. Tracheostomy	27. Questionnaire
28. Respiratory sounds	29. Value of life
30. Rhinitis	31. Health Care surveys
32. Sinusitis	33. Empirical research
34. Nasal polyps	35. Quality of Life
36. Chronic Disease	37. Enzyme replacement therapy (ERT)
38. Otitis media with effusion or otitis media or child or child preschool or middle ear ventilation or ear middle or adenoidectomy	39. Hematopoietic stem cell therapy (HSCT) Or bone marrow replacement or cord blood stem cell transplantation
40. Otitis media with effusion	41. Hematopoietic stem cell therapy
42. Otitis media	43. Bone marrow replacement
44. Child	45. Cord blood stem cell transplantation
46. Child preschool	47. Quality of life OR quality-adjusted life years
48. Middle ear ventilation	49. Quality-adjusted life years

Abbreviation: MESH, Medical Subject Headings.

II. Reflecting our understanding of the literature, it was considered necessary to include a range of study types in order to achieve a meaningful summary of outcomes used in studies related to these 2 body systems. We were concerned that the information contained in abstracts for less formal study designs might be insufficient to appropriately screen, and formal studies may not include all outcomes in the abstract. As such, a search strategy using additional general MESH headings considered relevant to these body systems was chosen with the aim of limiting reliance upon the quality of abstracts at the screening stage.

The following limits were applied to the search strategy:

- 1990 to 2014
- English language only
- Human only

Clinical Trials Registry Search

The World Health Organization (WHO) International Clinical Trials Registry Portal (http://apps.who.int/trialsearch/, last accessed January 02 2018) and ClinicalTrials.Gov (https://clinicaltrials.gov/, last accessed January 02 2018) were searched for Mucopolysaccharidosis II. This search revealed 45 and 10 results from the ClinicalTrials.gov and WHO databases, respectively. Both open and closed trials were included.

Inclusion Criteria

Any otolaryngology surgical or medical intervention in patients with MPS II was included, along with studies focusing on ERT and HSCT. We also included all systematic reviews with/without meta-analyses, randomized controlled trials, case-controlled trials, case series, prospective cohorts, and review articles.

Exclusion Criteria

We excluded studies that were not specifically related to MPS type II, studies that did not investigate or report respiratory/head and neck disease in patients with MPS type II (the exception to this were papers looking at bone marrow transplant [BMT] and HSCT), case series with fewer than 3 patients, expert opinion papers, discussion papers, and consensus papers.

Study Selection

Two researchers (J.M. and N.B.) independently reviewed the abstracts produced by the above-mentioned literature search strategy, and a comprehensive list of studies was obtained. The full-text articles of studies that appeared to fit the inclusion criteria and those that have insufficient information in the title and abstract were obtained. The articles were assessed independently by the 2 reviewers (J.M. and N.B.). Any disagreement between the reviewers regarding including the inclusion of a paper was resolved through discussion. Where agreement was not reached, a third reviewer was consulted (I.A.B.).

The reference section of each paper was cross-referenced to identify any further relevant papers. Outcomes relevant to respiratory/head and neck disease were identified in published studies involving patients with MPS type II, receiving either medical or surgical interventions. Clinical trials were reviewed by one researcher (A.M.) and were included if they measured outcomes relevant to respiratory/head and neck disease in patients with MPS type II.

Results

The systematic review of relevant literature was performed. Databases EMBASE, MEDLINE, and CINAHL were searched from 1990 to 2014. Literature search yielded 228 results which subsequently were reduced to 90 records following the removal of 138 duplicates. Of 90 publications following the thorough screening process of abstracts against inclusion and exclusion criteria, further 68 results were excluded. Consequently, 22 publications were left. Full-text articles were collected for those 22 results, and they were assessed using the inclusion and exclusion criteria. The total of 10 full-text articles were excluded for the following reasons: 7 results had less than 3 patients, 1 result was a consensus paper, 1 result was a review article, and 1 publication was a duplicate study published in 2 different journals under a different name. Ultimately 12 publications were identified and reviewed for outcomes (Figure 1).

A total of 55 clinical trials were identified following a clinical trials registry search for "Mucopolysaccharidosis II." Five trials were duplicated between the databases. Of the remaining 50 clinical trials, 7 studies did not investigate MPS type II. Among the remaining 43 trials, 4 studies were already included in the literature search, and 33 studies did not consider any respiratory/head and neck disease outcomes. Following the review process, 6 clinical trials were identified and outcomes measured were included in this review (Figure 1). Of particular note, the clinical trial NCT03292887 reported data from the Hunter Outcome Survey (HOS). The HOS collects a wealth of data on patients with MPS type II who are or have been treated with ERT (Elaprase) or those who receive no treatment at all. Data collection began in 2005, and it is anticipated to continue for a minimum of 17 years. In addition to general outcomes (eg, GAG status and mobility), HOS collects information about respiratory and ENT outcomes. One publication identified during the systematic literature search have reported on HOS findings relating to otological outcomes.[11]

A total of 41 outcomes were extracted (Table 2). The HOS collects 26 outcomes, and the remaining studies reported between 1 and 8 outcomes. The most frequently reported outcome was exercise tolerance, which was reported by 9 out of 17 studies, followed by pulmonary function, which was reported by 8 of the 16 reviewed studies, while sleep apnoea and hearing were assessed in 4 and 5 research studies, respectively (see Table 2 for references). Identified outcomes were subsequently organized according to the most recent COS taxonomy (Table 3).[16] Such classification of outcomes will be presented to stakeholders in the next stage of this project of COS identification, the electronic Delphi (eDelphi) exercise.

Discussion

Mucopolysaccharidosis type II is rare with an incidence of approximately 1 per 100 000 male births. In the period between 1992 and 2002, 52 babies with Hunter syndrome were born in the United Kingdom (http://www.mpssociety.org.uk/diseases/mps-diseases/mps-ii/). The rarity of this condition makes it difficult to obtain sufficient amounts of good-quality data to guide practice and decision-making, both for clinicians and for carers alike. Currently, we are reliant on case series from larger tertiary referral centers to support evidence-based practice, with only limited conformity in choice of outcome reporting. Pathology found in MPS type II may affect both the lower and the upper aerodigestive tract, and we suggest that combining assessments of both has direct clinical application. Mucopolysaccharidosis type II is an expensive disease to treat; ERT has been reported by de Bitencourt to cost over £100 000 per year for a child and twice as much for an adult.[26] It is difficult to assess "value for money" when the evidence for efficacy is so limited.

The core outcome measures in effectiveness trials (COMET) initiative (http://www.comet-initiative.org) promotes standardization of outcome reporting in research, supporting researchers in developing COS. A COS is an agreed standardized collection of outcomes, which should, as a minimum, be measured and reported in all trials in a specific clinical area. Core outcome measures in effectiveness trials also provide a database resource for researchers and patients, detailing what COS have been, or are being developed for a particular medical condition or intervention. This study was the first step toward determining a COS for head, neck, and respiratory disease for patients with MPS type II. This systematic literature review highlights the extent of heterogeneity in outcome reporting, in terms of both outcome measures and corresponding outcome measurement instruments.

It is important to note that only 2 publications and 2 clinical trials considered QoL as an outcome.[20,24] One of the publications was a systematic review that established QoL as one of its

Table 2. Long-list of outcome measures and corresponding outcome measurement instruments (OMI).

Outcome	Paper/Clinical Trial Using the Outcome	Outcome Measurement Instrument	Time Point	Study Type
Pulmonary function	Muenzer J, et al. *Molecular Genetics and Metabolism*. 2007;90:329-337[17]	Forced Expiratory Volume in the first second[a] (FEV1), Forced vital capacity[a] (FVC)	Baseline and 53 weeks posttreatment	Prospective
	Muenzer J, et al. *Genetics in Medicine August*. 2006;8(8)[18]	FVC[a]	Baseline and 18, 36, and 53 weeks posttreatment	Prospective
	Sohn, et al. *Orphanet Journal of Rare Diseases*. 2013;8:42[19]	FVC[a]	Baseline and 12 and 24 weeks posttreatment	Prospective
	da Silva EMK, et al. *Cochrane Database Syst Rev*. 2011[20]	FEV1[a], FVC[a]	Baseline and 18, 36 and 53 weeks posttreatment	Retrospective
	Glamuzina E, et al. *J. Inher. Metab. Dis*. 2011;34(3):749-754[21]	FVC[a]	Baseline and yearly thereafter	Retrospective
	Wooten W, et al. *The Journal of Paediatrics*. 162(6):1210-1215[8]	FEV1[a], FVC[a]; Total lung capacity[b] (TLC), Ratio of residual volume to TLC[b] (RV/TLC)	1 measurement time point[c]	Prospective
	NCT02663024	FVC[c]	Baseline and 25 weeks posttreatment	Prospective
	NCT03292887[d]	FEV1[c], FVC[c], TLC[c]	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Dyspnoea	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Chronic Cough	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Bronchitis	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Pneumonia	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Prevalence of pulmonary-related hospitalizations	NCT03292887[d]	Occurrence of hospitalization due to pulmonary symptoms	At time of entry into HOS database. No set points for data collection thereafter	Prospective
Blood Gas	Muenzer J, et al. *Molecular Genetics and Metabolism*. 2007;90:329-337[17]	O_2 desaturation events[e]	Baseline and 53 weeks posttreatment	Prospective
	Wooten W, et al. *The Journal of Paediatrics*. 162(6):1210-1215	Minimum SpO_2[e], mean sleep SpO_2[e], Oxygen desaturation index[e], $ETCO_2$[e]	1 measurement time point[c]	Prospective
	NCT03292887[d]	Respiratory rate, SpO_2	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Need for oxygen therapy	NCT03292887[d]	Diagnosed Y/N	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective

(continued)

Table 2. (continued)

Outcome	Paper/Clinical Trial Using the Outcome	Outcome Measurement Instrument	Time Point	Study Type
Sleep apnoea	Muenzer J, et al. *Molecular Genetics and Metabolism*. 2007;90:329-337	Apnoea-hypopnoea index (AHI)[ef]	Baseline and 53 weeks posttreatment	Prospective
	da Silva EMK, et al. *Cochrane Database Syst Rev*. 2011	Overnight AHI[e]	Not reported	Retrospective
	Wooten W, et al. *The Journal Of Paediatrics*. 162(6):1210-1215	AHI[ef]	1 measurement time point[c]	Prospective
	NCT03292887[d]	Diagnosed Y/N	At time of entry into HOS database. No set points for data collection thereafter	Prospective and retrospective
Exercise tolerance	Muenzer J, et al. *Molecular Genetics and Metabolism. 2007*;90:329-337	6-minute walk test (6MWT)	Baseline and 53 weeks posttreatment	Prospective
	Muenzer J, et al. *Genetics in Medicine*. 2006;8(8)	6MWT	Baseline and 18, 36 and 53 weeks posttreatment	Prospective
	Sohn, et al. *Orphanet Journal of Rare Diseases*. 2013;8:42	6MWT	Baseline and 12 and 24 weeks posttreatment	Prospective
	da Silva EMK, et al. *Cochrane Database Syst Rev*. 2011	6MWT	Baseline and 18, 36 and 53 weeks posttreatment	Retrospective
	Glamuzina E, et al. *J. Inher. Metab. Dis*. 2011;34(3):749-754	6MWT	Baseline and yearly thereafter	Retrospective
	NCT02663024	6MWT	Baseline and 25 weeks posttreatment	Prospective
	NCT02455622	6MWT	Baseline to minimum 5 years post enrolment	Prospective
	NCT03292887[d]	6MWT	At time of entry into HOS database. No set points for data collection thereafter	Prospective and retrospective
	NCT02044692	6MWT	Baseline and every 6 months up to 5 years	Prospective
Hearing	da Silva EMK, et al. *Cochrane Database Syst Rev*. 2011	Audiologic assessment, details not provided	Not reported	Retrospective
	Vellodi A, et al. *J. Inher. Metab. Dis*. 1999;22:638-648[22]	Griffiths Mental Development Scales (GMDS)	Pre (2 weeks to several months prior) and posttransplant (6-12 months)	Prospective
	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343–353[11]	Database review- Hunter Outcome Survey (HOS): 1. PTA air conduction thresholds at 250, 500, 1000, 2000, 4000, 8000 Hz 2. PTAs bone conduction 250, 500, 1000, 2000, 4000 and 8000 Hz 3. Auditory brainstem response (ABR)[g]	From registration to the last follow-up	Retrospective
	Cho Y, et al. *Audiol Neurotol*. 2008;13:206-212[23]	Click-evoked ABR, Pure tone audiogram (PTA)	1 measurement time point[c]	Prospective
	NCT03292887[d]	Word recognition test[c], Bone conduction[α]	From registration to the last follow-up	Prospective

(continued)

Table 2. (continued)

Outcome	Paper/Clinical Trial Using the Outcome	Outcome Measurement Instrument	Time Point	Study Type
QOL	da Silva EMK, et al. *Cochrane Database Syst Rev*. 2011	Not reported	Not reported	Retrospective
	Raluy-Callado, et al. *Orphanet Journal of Rare Diseases*. 2013;8:101[24]	1. The Hunter Syndrome-Functional Outcomes for Clinical 2. Understanding Scale (HS-FOCUS) 3. The Childhood Health Assessment Questionnaire (CHAQ) 4. The Child Health Questionnaire (CHQ) 5. The Health Utilities Index (HUI)	At the time of enrolment to a clinical trial	Retrospective
	NCT02455622	HS-FOCUS	Baseline to minimum 5 years post enrolment	Prospective
	NCT03292887[d]	Hunter Syndrome on Health-related Quality of Life HS-FOCUS	At time of entry into HOS database. No set points for data collection thereafter	Prospective and retrospective
Intelligence	Vellodi A, et al. *J. Inher. Metab. Dis*. 1999;22:638-648	The Wechsler Intelligence Scale for Children[h], Third Edition UK (W PPSI-R)	Pre (2 weeks to several months prior) and posttransplant (6-12 months)	Prospective
	Cho Y, et al. *Audiol Neurotol* 2008;13:206-212	Korean Educational Development Institute-Wechsler Intelligence Scale or Developmental Test of Visuomotor Integration and the Picture Vocabulary Test or Social Maturation Test	1 measurement time point[α]	Prospective
	NCT01870375	Depending on age: 1. Mullen Scales of Early Learning 2. Wechsler Preschool and Primary Scale of Intelligence III 3. Wechsler Abbreviated Scale of Intelligence 4. Wechsler Intelligence Scale for Children IV (controls) 5. Wechsler Adult Intelligence Scale III (controls)	1 measurement time point[c]	Prospective
Psycho-social development	Vellodi A, et al. *J. Inher. Metab. Dis*. 1999;22:638-648	GMDS[i]	Pre- (2 weeks to several months prior) and posttransplant (6-12 months)	Prospective
Need for surgical intervention to ears	Vellodil A, et al. *J. Inher. Metab. Dis*. 1999;22:638-648	Ventilation tubes insertion	Any time after treatment	Prospective
	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—Hunter Outcome Survey: Ventilation tubes insertion	From registration to the last follow up	Retrospective
	Cho Y, et al. *Audiol Neurotol* 2008;13:206-212	Ventilation tubes insertion	1 measurement time point[c]	Prospective
	NCT03292887[d]	Ventilation tubes insertion	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Chronic nasal discharge	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Instrument not reported/retrospective case note review	Any time during disease	Retrospective
Airway obstruction	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Instrument not reported/retrospective case note review	Any time during disease	Retrospective

(continued)

Table 2. (continued)

Outcome	Paper/Clinical Trial Using the Outcome	Outcome Measurement Instrument	Time Point	Study Type
Voice quality	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Instrument not reported / retrospective case note review	Any time during disease	Retrospective
Complication of surgical treatment	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Instrument not reported /retrospective case note review	Any time after treatment	Retrospective
	Jeong H, et al. *Int J Pediatr Otorhinolaryngol*. 2006;70(10):1765-1769[25]	Review in clinic: complication present/ absent	Up to 12 months following the procedure	Retrospective
Need for noninvasive ventilatory support	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Use of CPAP (prior to insertion of tracheostomy tube)	Any time during disease	Retrospective
	Wooten W, et al. *The journal of pediatrics*. 162(6):1210-1215	Use of CPAP	Any time during disease	Prospective
	Muenzer j, et al; *Molecular Genetics and Metabolism*. 2007;90:329-337[17]	Use of CPAP	At baseline	Prospective
	NCT03292887[d]	Use of CPAP, BIPAP	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Enlarged tonsils	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Tosillectomy	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Enlarged Adenoids	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Adenoidectomy	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Swallowing difficulties	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Tracheotomy	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Survival	Malik V, et al. *Int J Pediatr Otorhinolaryngol*. 2013;77(7):1204-1208	Age at death	In the event	Retrospective
	NCT03292887[d]	Age at death	In the event	Prospective and Retrospective
Acute Otitis Media (AOM)	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—HOS: present/ absent	At time of entry into HOS database. No set points for data collection thereafter	Retrospective
Tinnitus	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—HOS: present/ absent	At time of entry into HOS database. No set points for data collection thereafter	Retrospective
Tympanic membrane perforation	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—HOS: present/ absent	At time of entry into HOS database. No set points for data collection thereafter	Retrospective
	Cho Y, et al. *Audiol Neurotol*. 2008;13:206-212	Otoscopy	1 measurement time point[c]	Prospective
Vertigo	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—HOS: present/ absent	At time of entry into HOS database. No set points for data collection thereafter	Retrospective

(continued)

Table 2. (continued)

Outcome	Paper/Clinical Trial Using the Outcome	Outcome Measurement Instrument	Time Point	Study Type
Chronic Otitis Media (COM)	Keilmann A, et al. *J Inherit Metab Dis*. 2012;35:343-353	Database review—HOS: present/absent	At time of entry into HOS database. No set points for data collection thereafter	Retrospective
Turbulent Ear Discharge	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Middle ear function	Cho Y, et al. *Audiol Neurotol* 2008;13:206-212	Impedance audiometry	1 measurement time point[α]	Prospective
Language development and communication skills	Cho Y, et al. *Audiol Neurotol*. 2008;13:206-212	1. Preschool Language Scale, Picture Vocabulary Test, Test of Language Development – Primary 2. Evaluating Acquired Skills in Communication – Revised	1 measurement time point[c]	Prospective
	NCT02455622	Vineland Adaptive Behaviour Scales (domain: communication)	Baseline to minimum 5 years post enrolment	Prospective
	NCT03333200	No details available on ClinicalTrials.gov	15 years total: 3 months the first year, every 6 months the second year and once a year thereafter	Prospective
Nonsurgical intervention to ears	Cho Y, et al. *Audiol Neurotol*. 2008;13:206-212	Hearing aid: present/absent	1 measurement time point[α]	Prospective
	NCT03292887[d]	Hearing aid: present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Temporal Bone status	Cho Y, et al. *Audiol Neurotol*. 2008;13:206-212	CT	1 measurement time point[α]	Prospective
Nasal congestion/ obstruction	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Rhinorrhea	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Nasal polyps	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective
Sinus involvement	NCT03292887[d]	Present/absent	At time of entry into HOS database. No set points for data collection thereafter	Prospective and Retrospective

[a]Measured by spirometry.
[b]Measured by plethysmography.
[c]Not standardized for the group.
[d]Hunter Outcome Survey.
[e]Measured by polysomnography.
[f]No definition of AHI in the paper.
[g]No details provided about the test stimulus.
[h]Verbal IQ, performance IQ and an overall general IQ.
[i]Include the following areas: locomotor, personal-social, hearing and language, eye and hand co-ordination, performance, practical reasoning.

Table 3. Long-list of outcome measures organised according to COMET COS taxonomy.

Outcome Area	Outcome Domain	Outcome
Death	1. Mortality/survival	Survival
Physiological/clinical	2. Blood and lymphatic system outcomes	Blood Gas
	6. Ear and labyrinth outcomes	Acute Otitis Media (AOM)
		Tinnitus
		Tympanic membrane perforation
		Vertigo
		Chronic Otitis Media (COM)
		Middle ear function
		Hearing
		Turbulent Ear Discharge
	15. Musculoskeletal and connective tissue outcomes	Temporal Bone status
	22. Respiratory, thoracic, and mediastinal outcomes	Pulmonary function
		Sleep apnoea
		Chronic nasal discharge
		Airway obstruction
		Dyspnoea
		Chronic Cough
		Bronchitis
		Pneumonia
		Enlarged tonsils
		Enlarged adenoids
		Swallowing difficulties
		Nasal Congestion/obstruction
		Rhinorrhoea
		Nasal Polyps
		Sinus involvement
Life impact	25. Physical functioning	Exercise tolerance
	26. Social functioning	language development and communication skills
		Intelligence
		Psycho-social development
	30. Global quality of life	QOL
Resource use	36. Need for intervention	Need for surgical intervention to ears
		Need for noninvasive ventilatory support
		Nonsurgical intervention to ears
		Tonsillectomy
		Adenoidectomy
		Tracheotomy
		Need for oxygen therapy
		Prevalence of pulmonary-related hospitalizations
Adverse events	38. Adverse events/effects	Voice quality
		Complication of surgical treatment

Abbreviation: QoL, quality of life.

secondary outcomes. However, only 1 publication subsequently fulfilled the criteria to be included in the systematic review[18] and in that study QoL was not measured. The second publication which considered the QoL used 4 different questionnaires of which only 1 was MPS type II specific (HS-FOCUS). Mucopolysaccharidosis type II has been shown to be associated with significant impact on the QoL of both patients and their families.[24,27] Raluy-Callado et al used the Health Utility Index (HUI) which specifically investigated the impact of disease on hearing. They have shown that hearing is the biggest deficiency suffered by patients with MPS type II in agreement with previous publications.[5] Inclusion of hearing in the HUI makes it particularly relevant for studies involving the head and neck. It is difficult to predict why it was not considered in any of the studies reviewed in this work, although the cost of purchasing a license for use may be a barrier.[28] Another tool to consider when evaluating head and neck and respiratory-related QoL is HS-FOCUS which measures patient and parental views in 6 areas, including breathing.[29] The use of QoL scales in complex diseases such as MPS type II presents additional challenges to clinicians and researchers: (1) *generic* scales may not be sufficiently sensitive or specific to detect meaningful change in the patient cohort, that is, ask the wrong questions and (2) *bespoke* disease-specific scales may not be validated and we do not understand their utility.

The next step in this project is to use the outcomes "long list" in an eDelphi prioritization and consensus exercise to

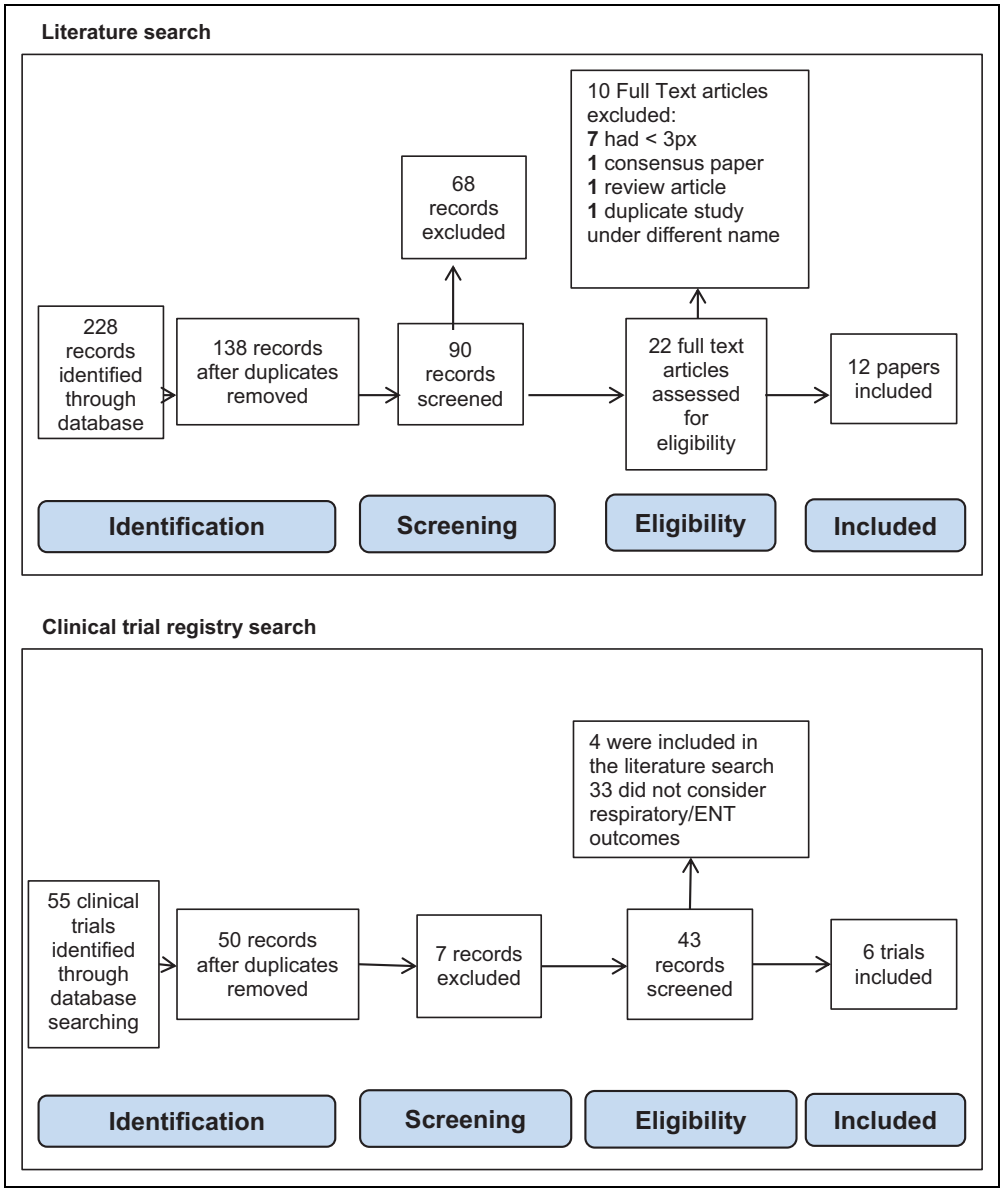

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart illustrating the review of methodology.

reach agreement between clinical stakeholder groups (ear, nose, and throat surgeons, metabolic physicians, clinical geneticists, specialist nurses, physiotherapists, and respiratory pediatricians) and patients and parents/carers regarding the most important outcomes to be measured in clinical studies of MPS type II. Involvement of a variety of stakeholders will help ensure that the resultant COS will be inclusive, helpful, and provide a valuable resource for any future clinical studies investigating the head, neck, and respiratory manifestations of MPS type II. Additionally, this study provides a component of the information needed to develop a "general" COS for studies involving patients with MPS type II. Finally, the prioritization and consensus seeking involved in COS development could be used to inform review of the existing HOS database for MPS type II.

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