

## Additional File 1: Methodology

### Appendix 1a. Defining clinical questions using the P.I.C.O methodology

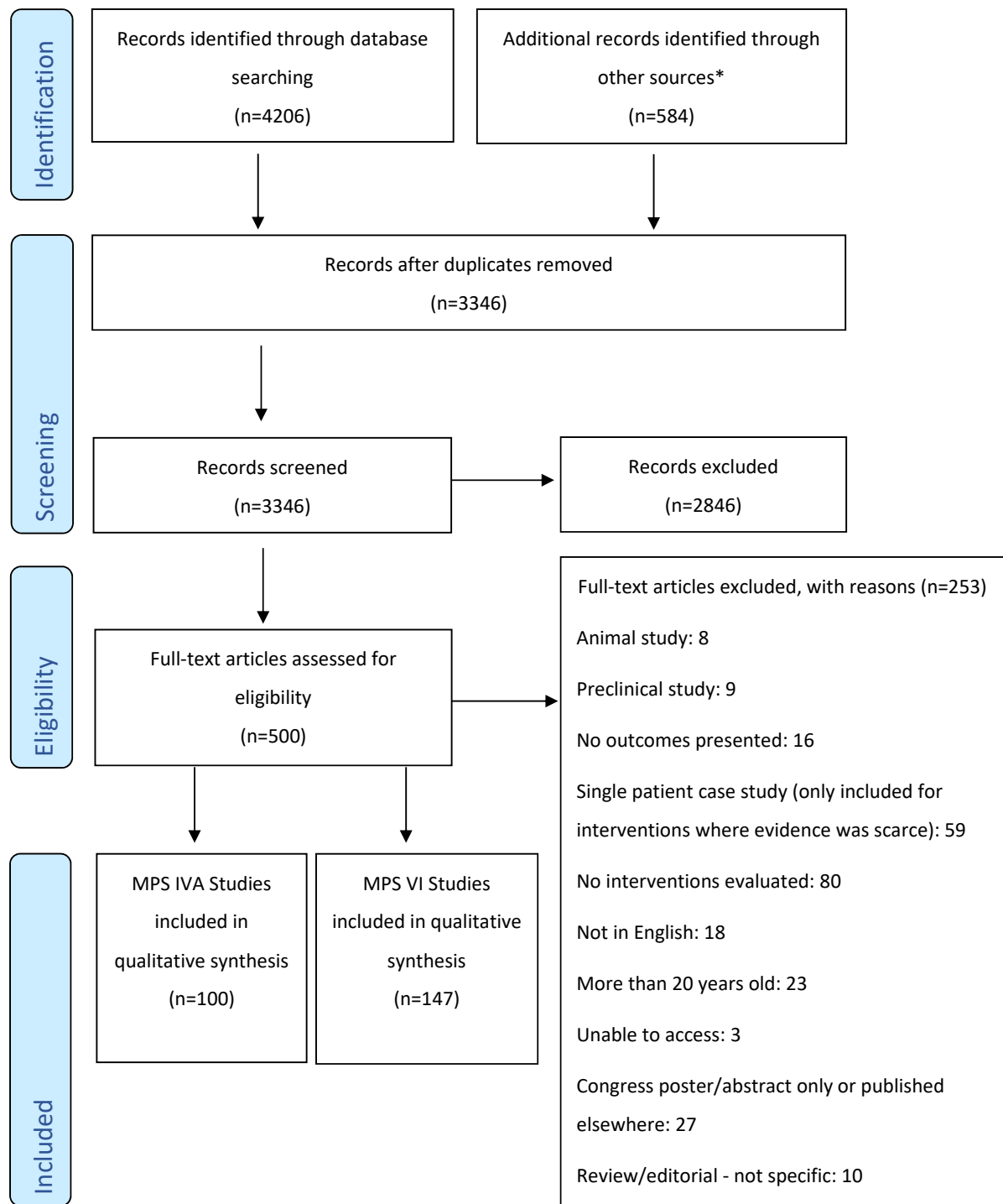
Patients	Interventions	Comparison	Outcomes
<ul style="list-style-type: none"> <li>• Paediatric and adult patients with a confirmed diagnosis of MPS IVA</li> <li>• Paediatric and adult patients with a confirmed diagnosis of MPS VI</li> </ul>	<p><b>Disease-modifying interventions</b></p> <ul style="list-style-type: none"> <li>• ERT</li> <li>• HSCT</li> </ul> <p><b>Interventions to manage symptoms</b></p> <ul style="list-style-type: none"> <li>• Respiratory and sleep disorders (e.g. continuous positive airway pressure [cPAP]/non-invasive positive pressure ventilation [NIPPV], oxygen supplementation and hypercapnia monitoring)</li> <li>• Anaesthesia</li> <li>• Surgical procedures:               <ul style="list-style-type: none"> <li>○ Spinal surgery (e.g. spinal cord decompression, spinal instability stabilization and fusion, spinal deformity correction)</li> <li>○ Limb surgery (e.g. hip reconstruction and/or total hip replacement, total knee replacement, guided growth procedures/hemiepiphysiodesis [ankle joint], osteotomy around the knee, carpal tunnel decompression)</li> <li>○ Ear-nose-throat (ENT) surgery (e.g. tonsillectomy and adenoidectomy [T&amp;A] tracheostomy and insertion of ventilation tubes)</li> <li>○ Cardiac surgery (e.g. heart valve replacement)</li> <li>○ Ophthalmic surgery (e.g. corneal transplantation)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• No treatment</li> <li>• No surgical intervention</li> </ul>	<p>Note that the domains below will cover clinician- and patient-reported outcomes:</p> <p><b>Physical function/performance:</b></p> <ul style="list-style-type: none"> <li>• Survival/mortality</li> <li>• Growth/skeletal involvement</li> <li>• Mobility/balance</li> <li>• Grip/reach</li> <li>• Breathing</li> <li>• Hearing</li> <li>• Speech</li> <li>• Vision</li> <li>• Chewing/swallowing</li> <li>• Heart function</li> <li>• Energy</li> <li>• Sleep quality</li> <li>• Reproduction</li> </ul> <p><b>Mental/emotional outcomes</b></p> <ul style="list-style-type: none"> <li>• Mood</li> <li>• Quality of life</li> <li>• Pain</li> </ul> <p><b>Socioeconomic outcomes:</b></p> <ul style="list-style-type: none"> <li>• Social/peer relationships</li> <li>• School/work</li> <li>• Healthcare utilization (hospitalization and surgical interventions)</li> <li>• Compliance with therapy</li> </ul>

**Appendix 1b. Search strategy recording form**

Database	Date of search	Limits	Search terms/search strings	Number of articles	Notes (please provide reasons for amends to search terms)
PubMed	13/07/2017	None	(mucopolysaccharidos* OR mucopolysaccharidoses[MeSH Terms] OR Morquio A syndrome OR Morquio syndrome OR Maroteaux-Lamy syndrome OR mucopolysaccharidosis IVA OR mucopolysaccharidosis VI) AND (carpal tunnel syndrome OR Vascular Access Devices[MeSH Terms] OR totally implantable vascular access device OR cardiac OR valve replacement OR ophthalmic surgery OR corneal transplant OR dental procedures OR tooth extraction OR occipito OR Surgical Procedures, Operative[MeSH Terms] OR surgery[MeSH Terms] OR hematopoietic stem cell transplant* OR HSCT OR bone marrow transplant OR BMT OR hemiepiphysiodesis OR spinal cord compression OR spinal surgery OR hip replacement OR hearing aid[MeSH Terms] OR hearing [MeSH Terms] OR respiration, artificial[MeSH Terms] OR tracheostomy OR orthopedic surgery OR anesthesia OR enzyme replacement therapy[MeSH Terms] OR enzyme replacement therapy OR ERT OR tonsillectomy OR adenoidectomy OR GALNS protein, human[Supplementary Concept] OR galsulfase[Supplementary Concept] OR vimizim OR naglazyme OR elosulfase alfa[Title/abstract] OR Treatment Outcome [MeSH Terms] OR clinical outcomes)	2270	

Web of Science	13/07/2017		(mucopolysaccharidos* OR mucopolysaccharidoses[MeSH Terms] OR Morquio A syndrome OR Morquio syndrome OR Maroteaux-Lamy syndrome OR mucopolysaccharidosis IVA OR mucopolysaccharidosis VI) AND (carpal tunnel syndrome OR Vascular Access Devices[MeSH Terms] OR totally implantable vascular access device OR cardiac OR valve replacement OR ophthalmic surgery OR corneal transplant OR dental procedures OR tooth extraction OR occipito OR Surgical Procedures, Operative[MeSH Terms] OR surgery[MeSH Terms] OR hematopoietic stem cell transplant* OR HSCT OR bone marrow transplant OR BMT OR hemiepiphyodesis OR spinal cord compression OR spinal surgery OR hip replacement OR hearing aid[MeSH Terms] OR hearing [MeSH Terms] OR respiration, artificial[MeSH Terms] OR tracheostomy OR orthopedic surgery OR anesthesia OR enzyme replacement therapy[MeSH Terms] OR enzyme replacement therapy OR ERT OR tonsillectomy OR adenoidectomy OR GALNS protein, human[Supplementary Concept] OR galsulfase[Supplementary Concept] OR vimizim OR naglazyme OR elosulfase alfa[Title/abstract] OR Treatment Outcome [MeSH Terms] OR clinical outcomes)	1902	
Google scholar	2017/07/07 (12:00)	Limited number of search terms per search query	mucopolysaccharidosis OR mucopolysaccharidosis IVA OR mucopolysaccharidosis VI OR Morquio syndrome OR Maroteaux-Lamy syndrome AND enzyme replacement therapy OR HSCT OR surgery OR treatment outcome OR clinical outcome	14	The total number of hits was 4820, but out of the first 12 pages (as advised by our mentor) only 13 were not appearing in the above-mentioned databases, specifically web of science
LDN World	13/07/2017	Years 2012–2017	mucopolysaccharidosis	20	Articles found are all included in the molecular genetics and metabolism online journal

## Appendix 1c. Results of the systematic literature review according to PRISMA



\*Includes relevant articles from Journal of Inherited Metabolic Disease, Molecular Genetics and Metabolism, Genetics in Medicine, Society for Inherited Metabolic Disorders (SIMD), Society for the Study of Inborn Errors of Metabolism (SSIEM), American College of Medical Genetics and Genomics (ACMG), Lysosomal Disease Network We're Organizing Research on Lysosomal Diseases (LDN WORLD), SCOPUS and Cochrane.

## Appendix 2. The oxford centre for evidence-based medicine criteria

Table 1. Oxford Evidence Level Criteria

	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"i)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; eg, <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies

3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on economic theory or “first principles”

**Table 2. Oxford evidence grade criteria**

Grade	Rationale
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies <b>or</b> extrapolations from level 1 studies
C	Level 4 studies <b>or</b> extrapolations from level 2 or 3 studies
D	Level 5 evidence <b>or</b> troublingly inconsistent or inconclusive studies of any level

### Appendix 3. AGREE II evaluation

Total number of Appraisers	Review round 1				Review round 2			
	Appraiser				Appraiser			
3	1	2	3*		1	2	3*	
<b>Domain 1: scope and purpose</b>								
Q1. The overall objective(s) of the guideline is (are) specifically described	3	6	3	12	5	7	6	18
Q2. The health question(s) covered by the guideline is (are) specifically described	6	4	3	13	7	6	5	18
Q3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	5	6	6.5	17.5	5	7	7	19
	14	16	12.5	42.5	17	20	18	55
	62%				85%			
<b>Domain 2: stakeholder involvement</b>								
Q4. The guideline development group includes individuals from all relevant professional groups	5	7	3	15	5	7	3	15
Q5. The views and preferences of the target population (patients, public, etc.) have been sought	7	6	3	16	7	6	6	19
Q6. The target users of the guideline are clearly defined	5	5	5	15	7	7	7	21
	17	18	11	46	19	20	16	55
	69%				85%			
<b>Domain 3: Rigour of development</b>								
Q7. Systematic methods were used to search for evidence	4	5	2	11	7	7	5.5	19.5
Q8. The criteria for selecting the evidence are clearly described	6	4	2.5	12.5	7	5	4	16
Q9. The strengths and limitations of the body of evidence are clearly described	4	4	3	11	4	4	3	11
Q10. The methods for formulating the recommendations are clearly described	7	6	3.5	16.5	7	7	4	18
Q11. The health benefits, side effects, and risks have been considered in formulating the recommendations	6	4	5	15	6	4	5	15
Q12. There is an explicit link between the recommendations and the supporting evidence	7	6	6	19	7	6	6	19
Q13. The guideline has been externally reviewed by experts prior to its publication	6	2	7	15	6	2	7	15
Q14. A procedure for updating the guideline is provided	3	6	7	16	3	6	7	16
	43	37	36	116	47	41	41.5	129.5
	64%				73%			

<b>Domain 4: clarity of presentation</b>								
Q15. The recommendations are specific and unambiguous	7	6	7	20	7	6	7	20
Q16. The different options for management of the condition or health issue are clearly presented	7	4	7	18	7	4	7	18
Q17. Key recommendations are easily identifiable	1	6	3	10	4	6	3	13
	15	16	17	48	18	16	17	51
	72%				78%			
<b>Domain 5: applicability</b>								
Q18. The guideline describes facilitators and barriers to its application	7	3	1	11	7	3	2	12
Q19. The guideline provides advice and/or tools on how the recommendations can be put into practice	5	2	1	8	5	2	1	8
Q20. The potential resource implications of applying the recommendations have been considered	2	1	1	4	5	1	1.5	7.5
Q21. The guideline presents monitoring and/or auditing criteria	4	2	3	9	4	2	3	9
	18	8	6	32	21	8	7.5	36.5
	28%				34%			
<b>Domain 6: editorial independence</b>								
Q22. The views of the funding body have not influenced the content of the guideline	7	5	6	18	7	5	6	18
Q23. Competing interests of guideline development group members have been recorded and addressed	4	4	3	11	4	4	3	11
	11	9	9	29	11	9	9	29
	64%				64%			
<b>Overall guideline assessment</b>								
1. Rate the overall quality of this guideline. Scoring: 1 (lowest quality) – 7 (highest quality)	5	4	4		6	5	5	
2. I would recommend this guideline for use. Scoring: "Yes", "Yes, with modifications", "No"	Yes	Yes, with modifications			Yes	Yes, with modifications		

\*Average scores calculated from two assessments carried out by three independent appraisers.