European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea

Supplementary Material

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Key words: Mandibular advancement device, positional therapy, muscle stimulation, pharmaceutical therapy, maxillo-mandibular osteotomy, bariatric surgery

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Sources of financial support

The participants of the project received funding for travel and meetings from the European Respiratory Society (no TF-2018-01).

Conflict of interest

Winfried Randerath reports personal fees and travel grants from Weinmann, Heinen & Löwenstein, Resmed, Philips Respironics, Inspire and Bioprojet; Johan Verbraecken reports institutional fees and educational grants from Accuramed, Agfa-

Gevaert, AirLiquide, AstraZen, Bekaert Deslee Academy, Bioprojet, Desitin, Fisher & Paykel, Heinen & Löwenstein, Idorsia, Inspire, Jazz Pharmaceutics, Medidis, Mediq Tefa, NightBalance, OSG, Philips Respironics, ResMed, Sanofi, SomnoMed, Springer, Total Care, UCB Pharma, Vivisol, Wave Medical, and Westfalen Medical; Jan Hedner reports Grants from ResMed and ERS; Jean Louis Pepin reports Grants and research funds from (payments made to the institutions) : Air Liquide Foundation, Agiradom, AstraZeneca, Fisher and Paykel, Mutualia, Philips, Resmed, Vitalaire; Fees from: Agiradom, AstraZeneca, Boehringer Ingelheim, Jazz pharmaceutical, Night Balance, Philips, Resmed, Sefam; Nicole Skoets reports Grants or contracts from Cochrane; Joerg Steier reports research grants from the British Lung Foundation and a pending patent for Guy's & St Thomas' NHS Foundation Trust and King's College London (WO2016124739A1), Thomy Tonia acts as ERS Methodologist, Wojciech Trzepizur reports travel grants from Asten.

Christel de Raaf, Simon Herkenrath, Winfried Hohenhorst, Tina Jakob, Oreste Marrone, Marie Marklund, Walter T. McNicholas, Rebecca Morgan, Sofia Schiza, Dan Smyth, Piet-Heijn van Mechelen, and Peter Wijkstra report no conflict of interest related to the manuscript.

Abbreviations

AE	Adverse event
AHI	Apnoea-Hypopnoea Index
BMI	Body Mass Index
BP	Blood Pressure
BPAP	Bilevel Positive Airway Pressure
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
DISE	Drug-induced Sleep Endoscopy
ENT	Ear Nose Throat
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
h	Hour
HNS	Hypoglossal Nerve Stimulation
HrQoL	Health-related Quality of Life
IQR	Inter Quartile Range
ITT	Intention-to-treat
MA	Meta-analysis
MAD	Mandibular advancement device
MMO	Maxillo mandibular osteotomy
N	Number
NICE	National Institute for Health and Care Excellence
ODI	Oxygen Desaturation Index
OSA(S)	Obstructive Sleep Apnoea (syndrome)
p	Probability
PICO	Population, Intervention, Control, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography
PT	Positional Therapy
RCT	Randomised Controlled Trial
RYGB	Roux-en-Y Gastric Bypass Surgery

SAE	Severe adverse event
SD	Standard Deviation
SEI	Sleep Efficiency
SF-36	Short-form Questionnaire 36
STAR	Stimulation Therapy for Apnea Reduction
TENS	Transcutaneous electrical nerve stimulation
TESLA	Domiciliary Transcutaneous Electrical Stimulation in Obstructive Sleep Apnoea
TF	Task Force
USA	United States of America

Flow diagrams

Figure e1: PICO 1: In adult obese patients with OSA, should laparoscopic Roux-en-Y gastric bypass surgery (RYGB) or weight reducing diet be used?

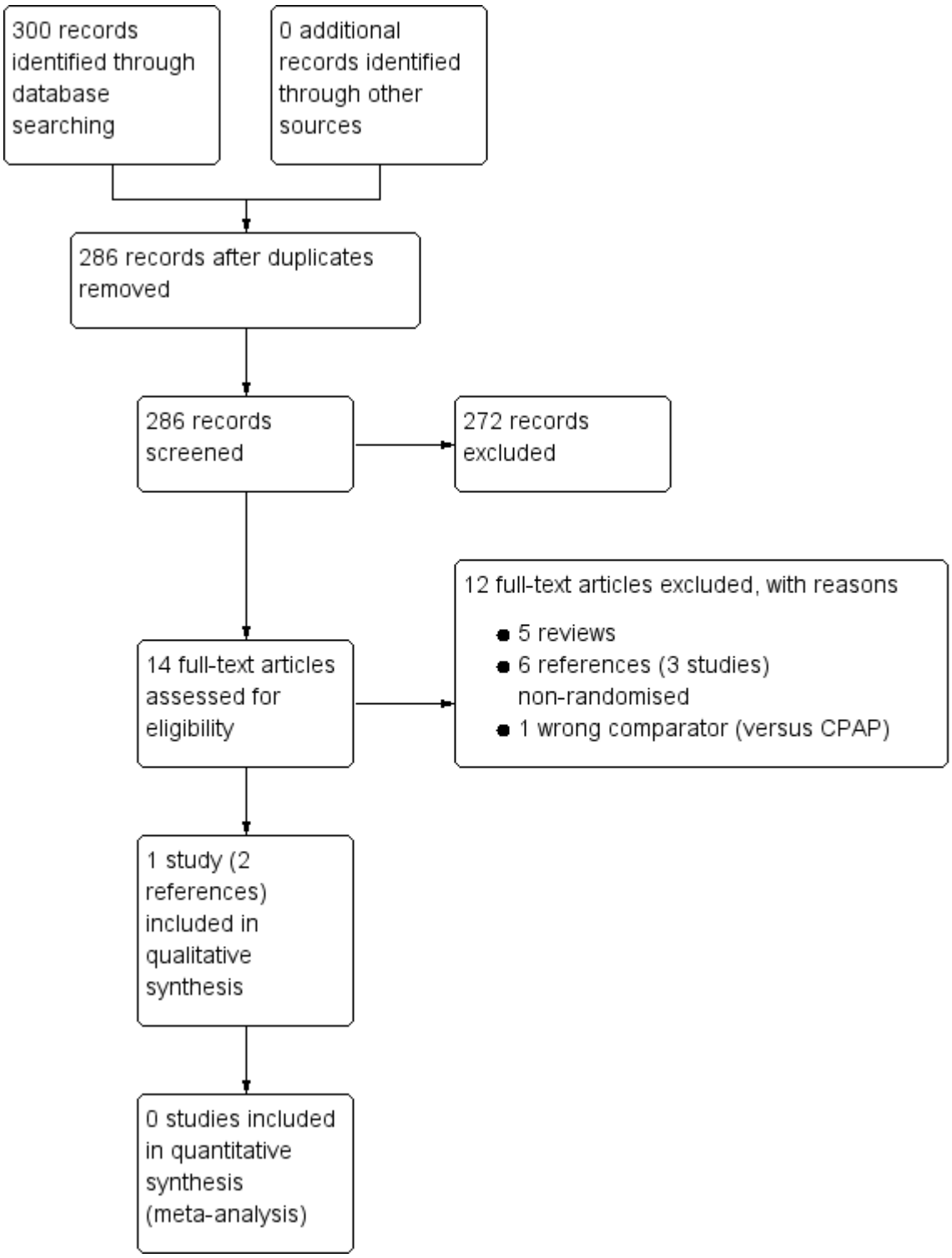


Figure e2: PICO 2: Should a custom-made dual-block mandibular advancement device or CPAP be used for adult patients with obstructive sleep apnoea?

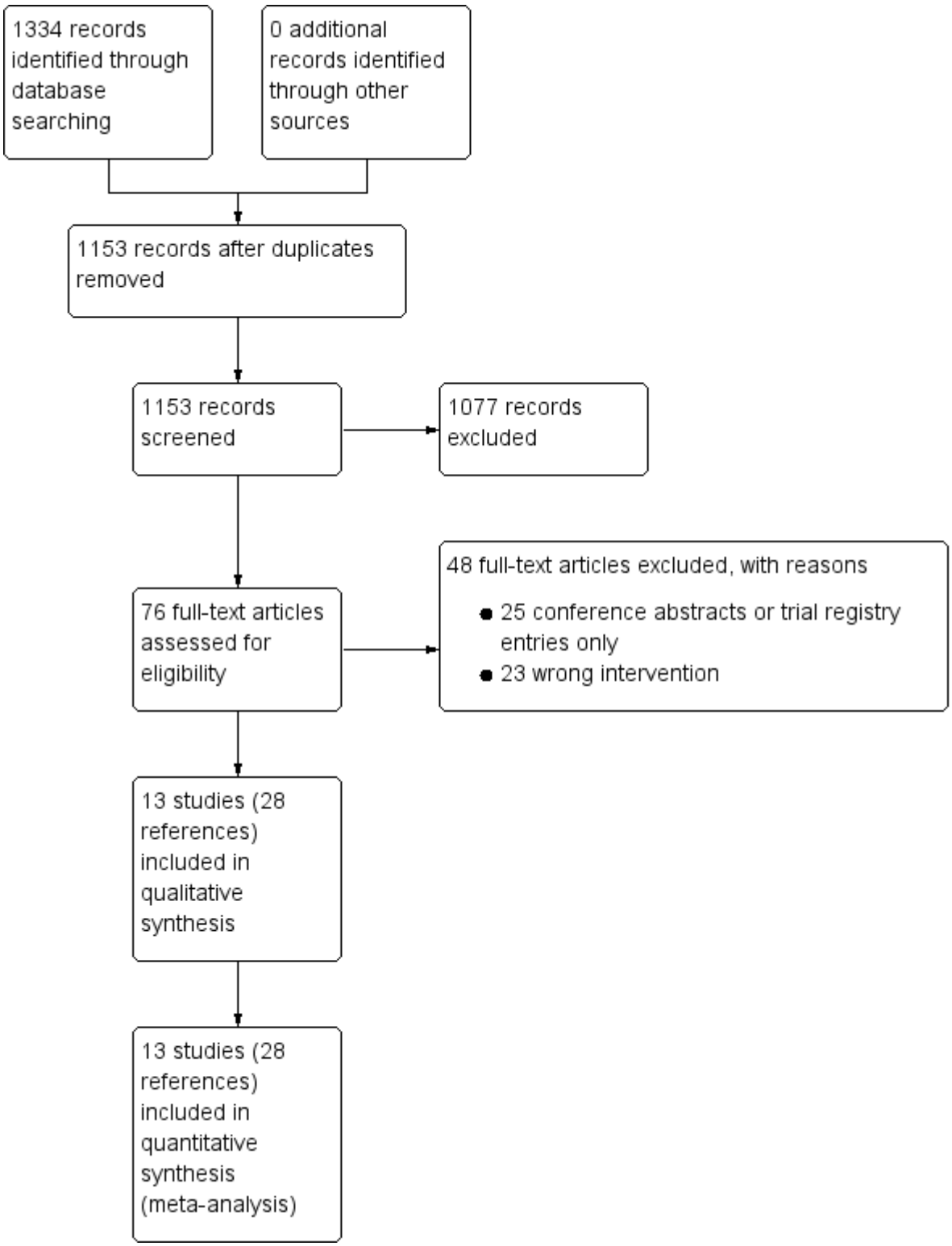


Figure e3: PICO 3: Should hypoglossal nerve stimulation during sleep or no treatment be used for adult patients with obstructive sleep apnoea?

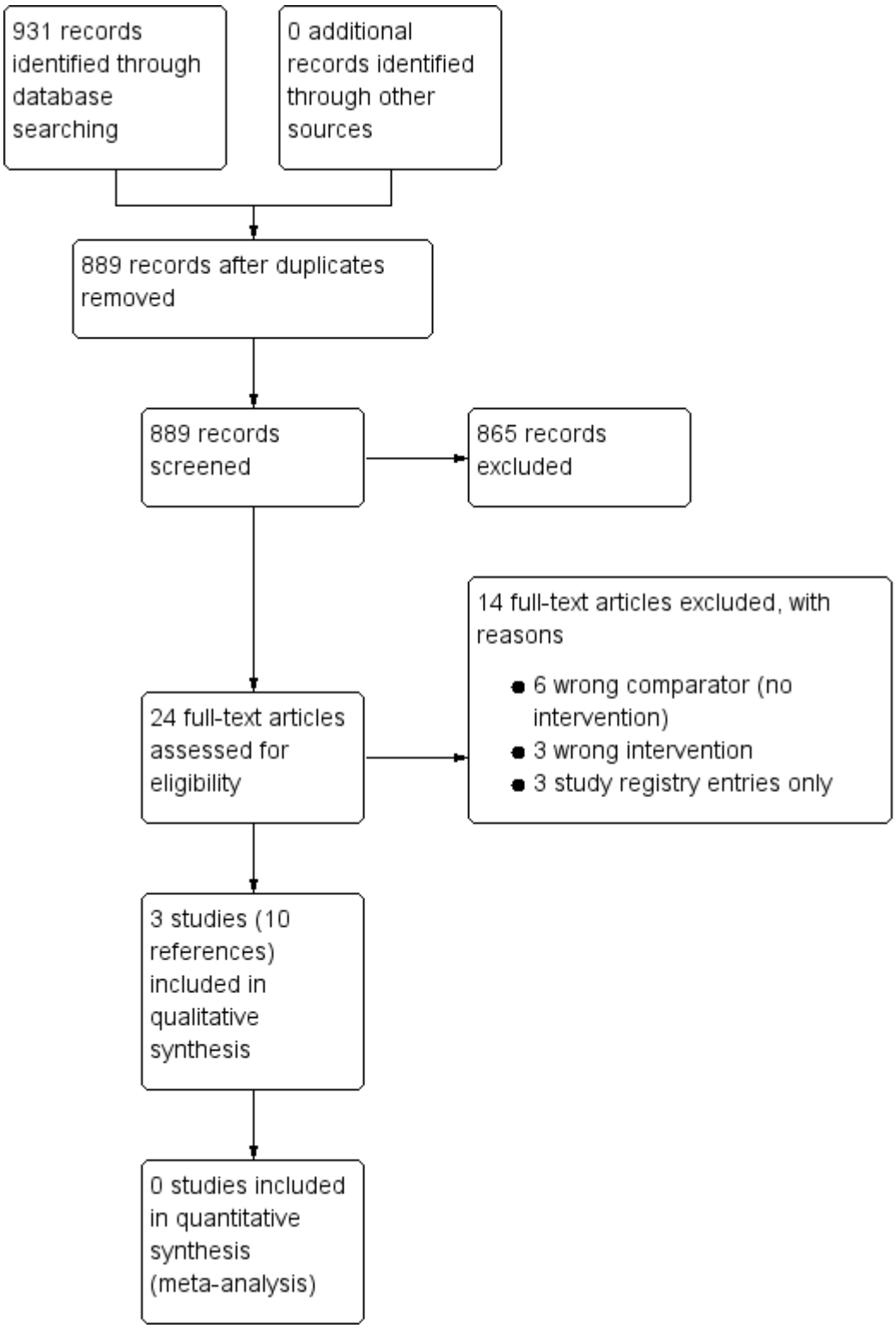


Figure e4: PICO 4 a: In adult patients with OSA, should myofunctional therapy or no treatment be used?

PICO 4 b: Should myofunctional therapy or CPAP be used for adult patients with obstructive sleep apnoea?

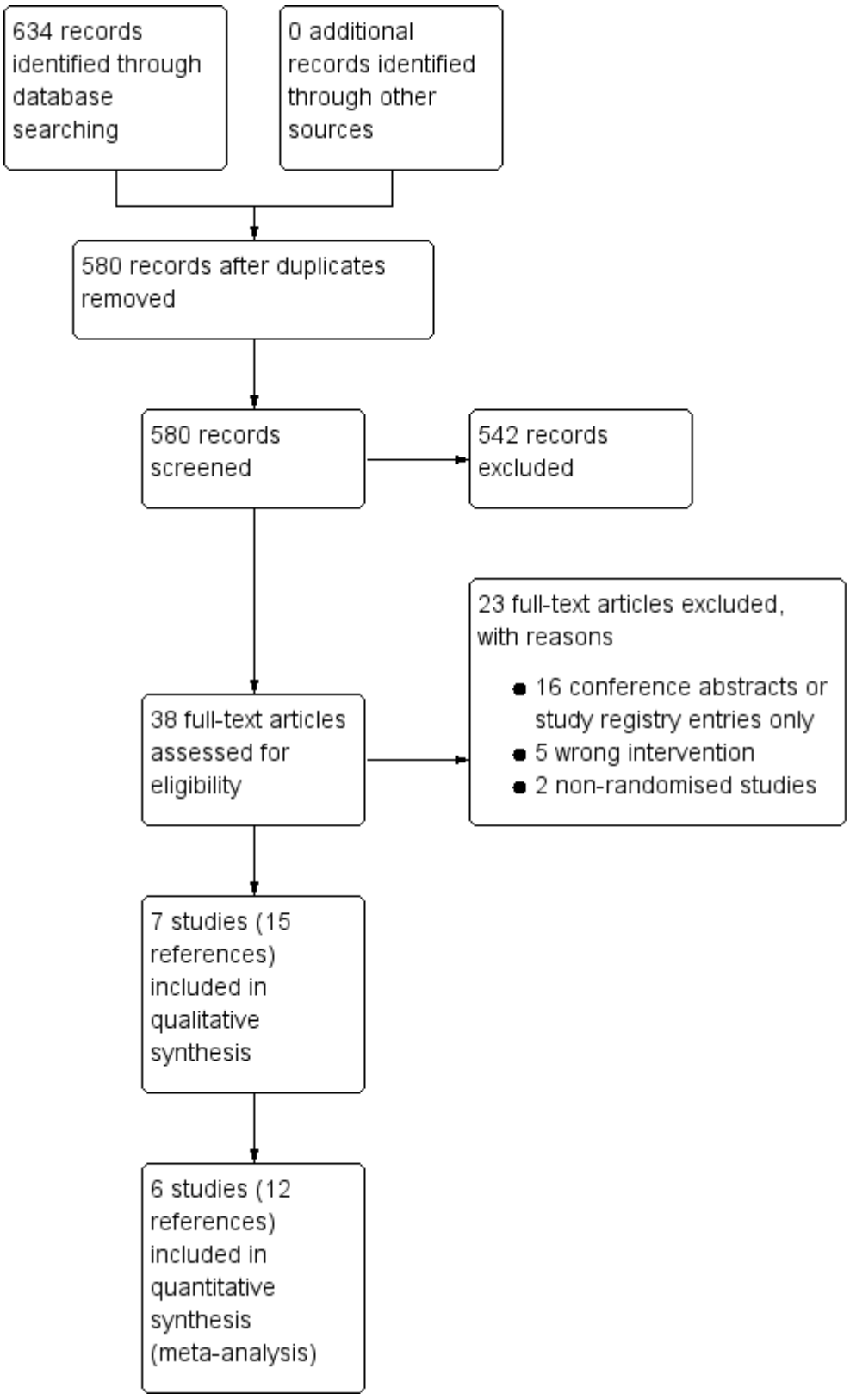


Figure e5: PICO 5: Should maxillo-mandibular osteotomy or CPAP be used for adult patients with obstructive sleep apnoea?

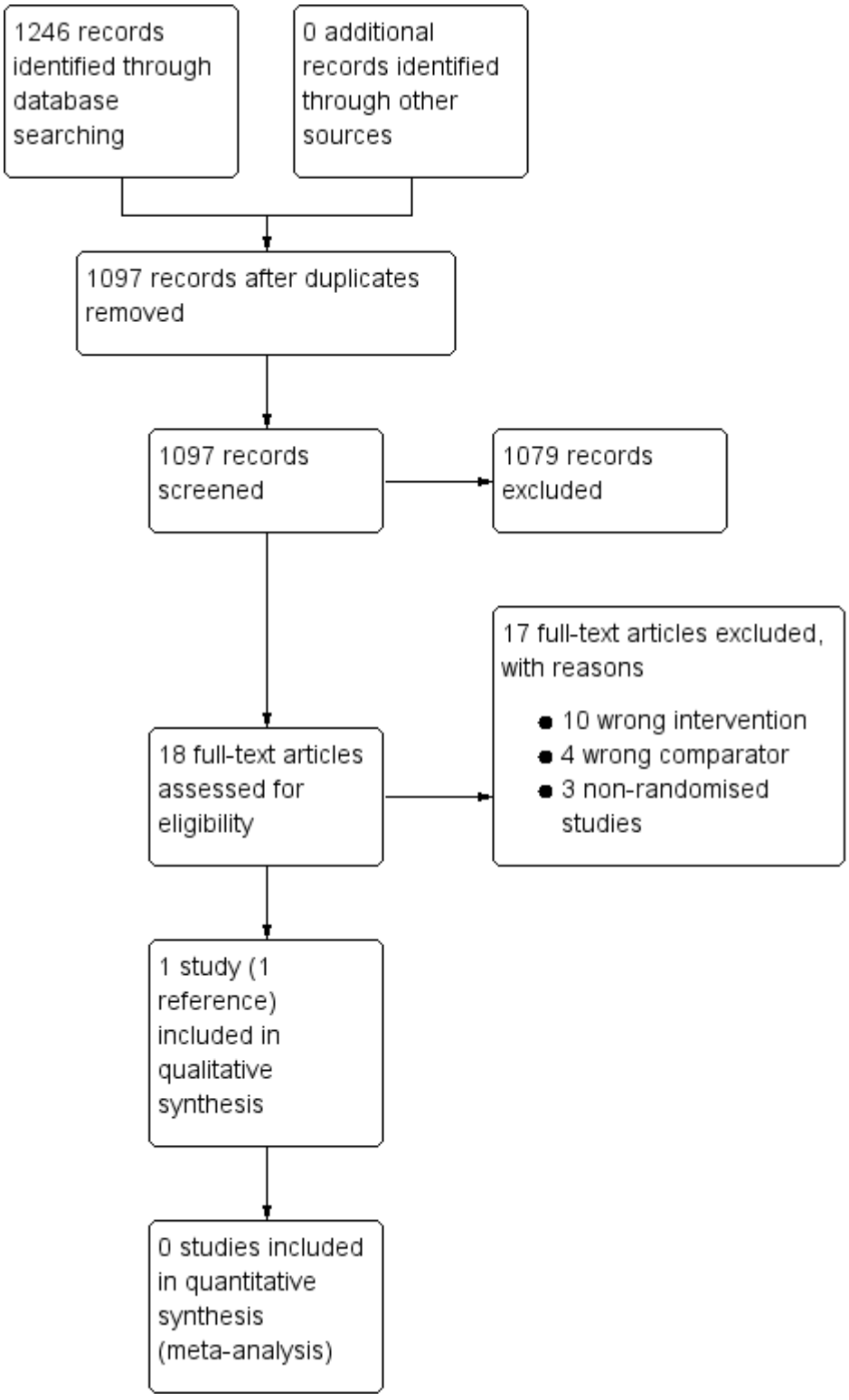


Figure e6: PICO 6: Should carbonic anhydrase inhibitors (compared to placebo) be used for adult patients with obstructive sleep apnoea?

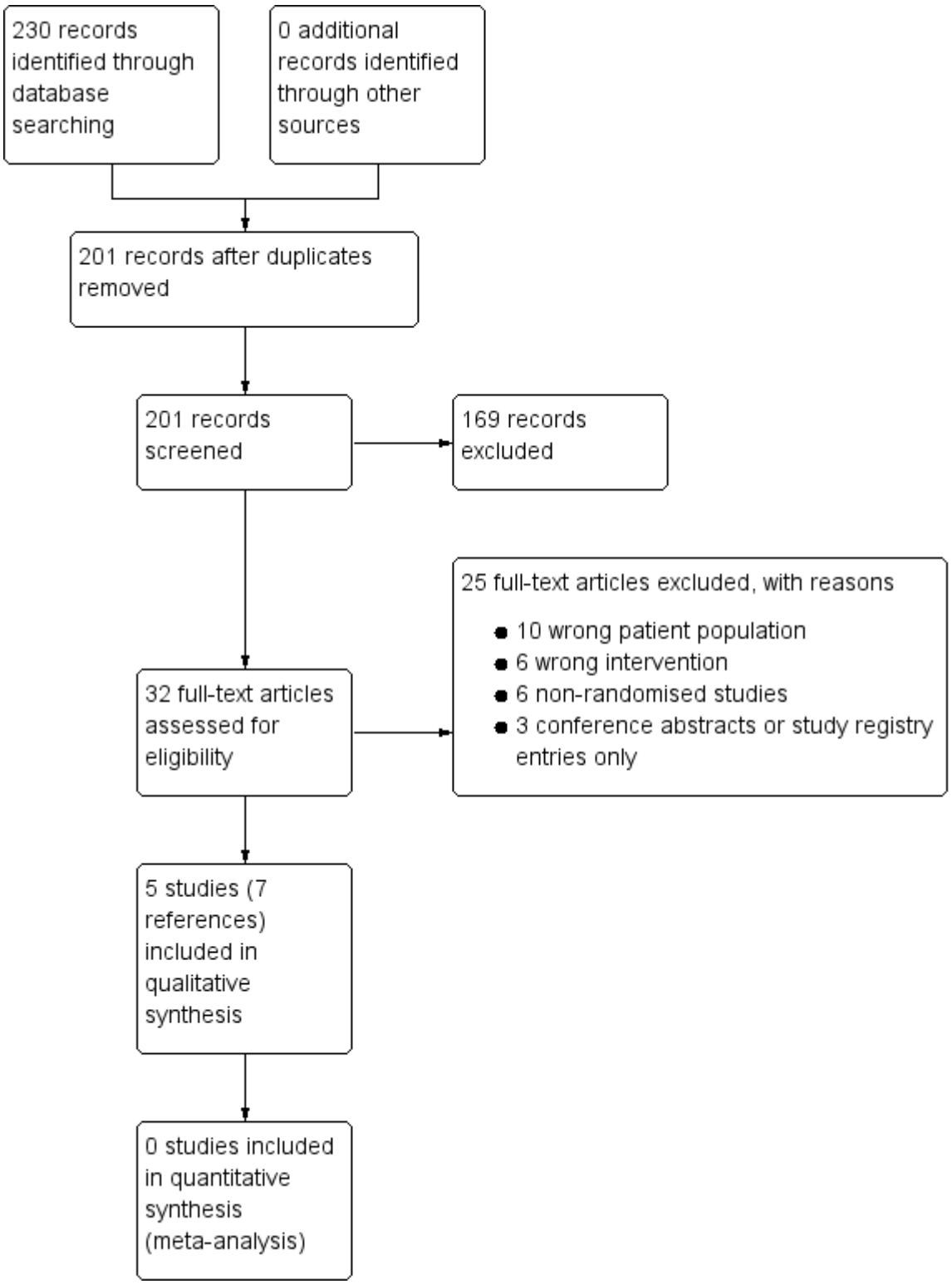


Figure e7: PICO 7: Should positional therapy or CPAP be used for adult patients with position-dependent obstructive sleep apnoea?

PICO 8: Should positional therapy (intervention) or custom made dual-block mandibular advancement devices (control) be used for adult patients with position-dependent obstructive sleep apnoea?

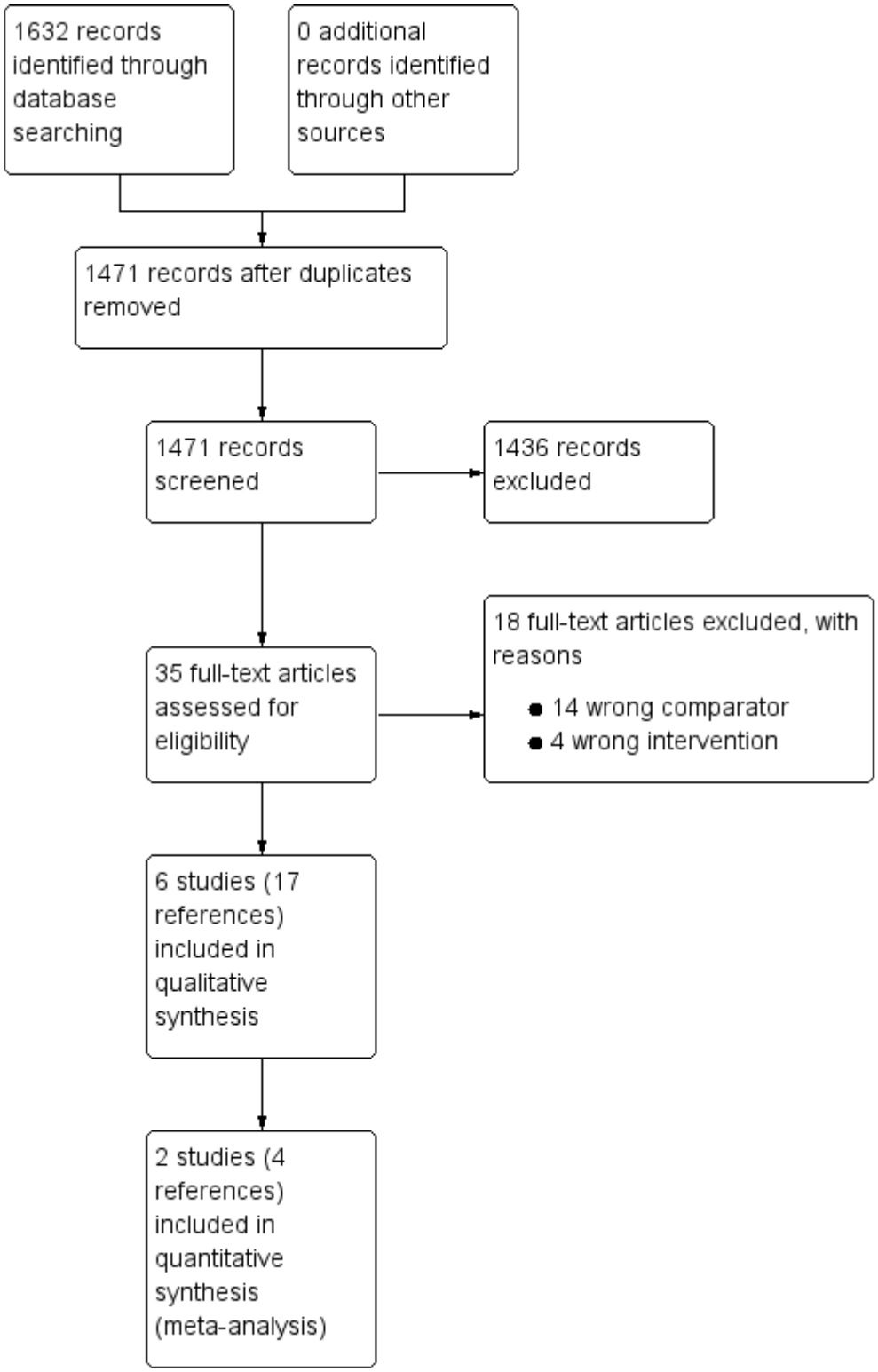
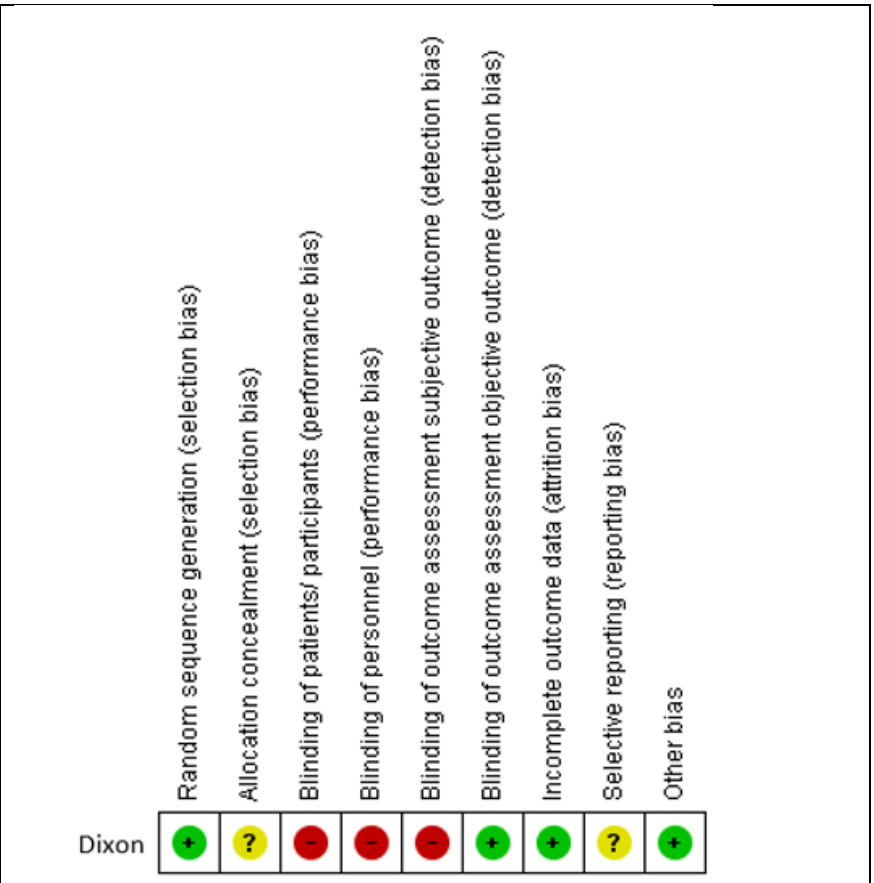
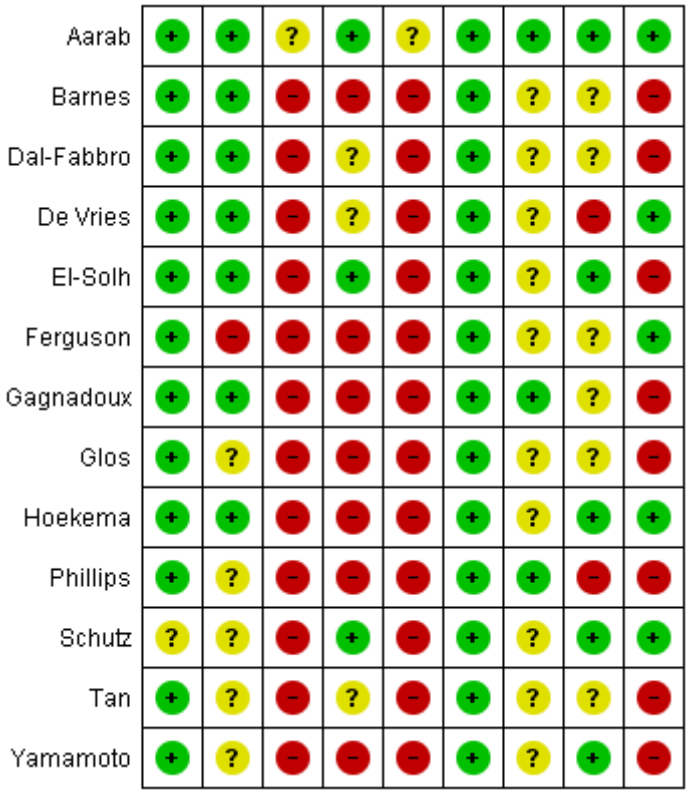
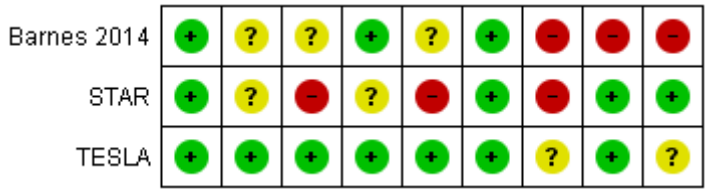
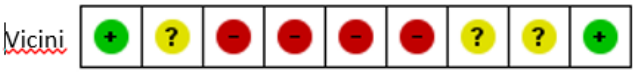
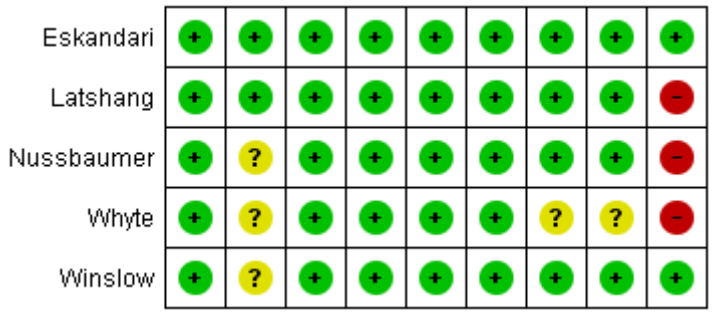
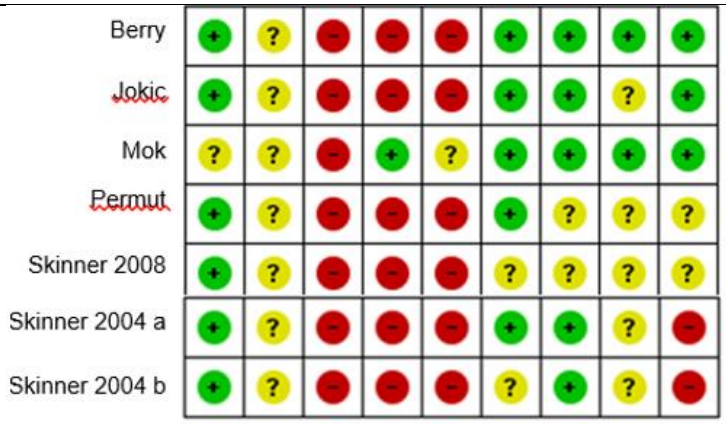
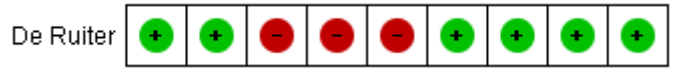


Figure e8: Overview of included RCTs with RoB judgement for each PICO

PICO 1	[1, 2]	
PICO 2	[3-23]	 (Footnote to Aarab: Patients were blinded to the nature of the

		assigned therapy (placebo or active). After evaluating the therapy, all patients were asked if they were of the opinion that they had received an active or placebo treatment. As indicated below, blinding of the analyst was ascertained by assigning codes to data sets and by analyzing these sets in random blocks.
PICO 3	[24-29]	
PICO 4	[30-39]	
PICO 5	[40, 41]	
PICO 6	[42-48]	

PICO 7	[49-55]	
PICO 8	[56, 57]	

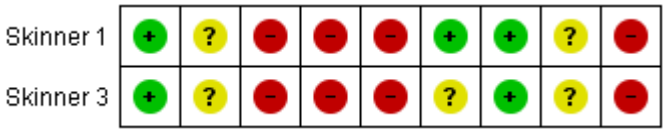
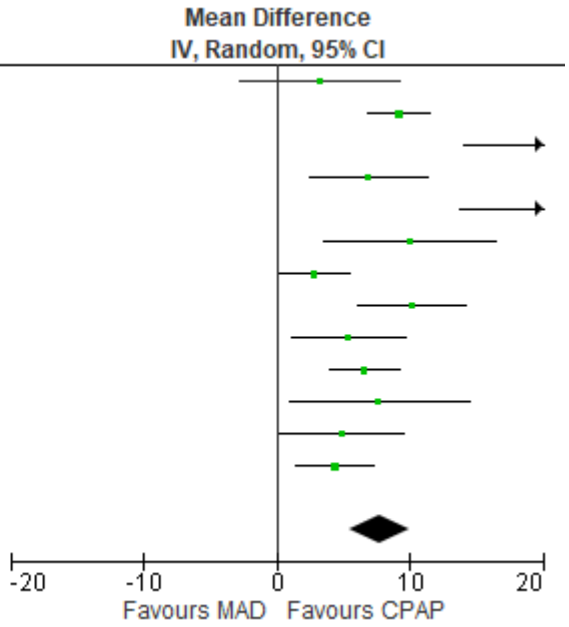


Figure e9: PICO 2 – Meta-Analyses

AHI

Study or Subgroup	MAD Mean	MAD SD	MAD Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Random, 95% CI
Aarab	-16.3	10.3	20	-19.5	8.7	18	6.4%	3.20 [-2.84, 9.24]
Barnes	14	9.8387	80	4.8	4.4721	80	10.5%	9.20 [6.83, 11.57]
Dal-Fabbro	26.7	25.8488	29	3.2	2.1541	29	3.9%	23.50 [14.06, 32.94]
De Vries	9.7	11.4	28	2.8	3.9	35	8.1%	6.90 [2.48, 11.32]
El-Solh	26.3	25.6	35	3.9	4.8	35	4.4%	22.40 [13.77, 31.03]
Ferguson	14.2	14.7	20	4.2	2.2	20	6.0%	10.00 [3.49, 16.51]
Gagnadoux	7.9	6.4	56	5.1	7.8	56	10.2%	2.80 [0.16, 5.44]
Glos	13.7	12	40	3.5	5.2	40	8.6%	10.20 [6.15, 14.25]
Hoekema	7.8	14.4	47	2.4	4.2	47	8.3%	5.40 [1.11, 9.69]
Phillips	11.1	12.1	108	4.5	6.6	108	10.2%	6.60 [4.00, 9.20]
Schutz	9.6	10.3	9	1.9	1.2	9	5.7%	7.70 [0.93, 14.47]
Tan	8	10.9	23	3.1	2.8	22	7.9%	4.90 [0.29, 9.51]
Yamamoto	8.9	7.7	40	4.5	5.5	40	9.9%	4.40 [1.47, 7.33]
Total (95% CI)			**535**			**539**	**100.0%**	**7.76 [5.49, 10.02]**

Heterogeneity: Tau² = 11.31; Chi² = 46.04, df = 12 (P < 0.00001); I² = 74%
Test for overall effect: Z = 6.71 (P < 0.00001)

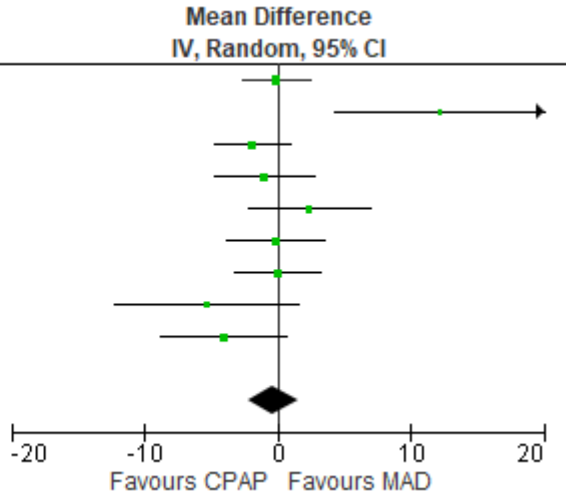


Sleep efficiency

Study or Subgroup	MAD Mean	MAD SD	MAD Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Random, 95% CI
Barnes	82	8.9443	80	82.1	7.1554	80	16.5%	-0.10 [-2.61, 2.41]
El-Solh	82.9	13.7	35	70.7	19.4	35	4.7%	12.20 [4.33, 20.07]
Ferguson	87.9	5.5	20	89.8	3.4	20	15.3%	-1.90 [-4.73, 0.93]
Gagnadoux	82.7	12	56	83.7	8.2	56	12.0%	-1.00 [-4.81, 2.81]
Glos	88.2	9.4	40	85.8	11.6	40	9.8%	2.40 [-2.23, 7.03]
Hoekema	86.1	8.1	47	86.2	10	47	12.4%	-0.10 [-3.78, 3.58]
Phillips	82	12	108	82	12	108	14.0%	0.00 [-3.20, 3.20]
Schutz	84.2	8.8	9	89.5	5.8	9	5.8%	-5.30 [-12.19, 1.59]
Tan	83.2	8.1	23	87.2	8.1	22	9.5%	-4.00 [-8.73, 0.73]
Total (95% CI)			**418**			**417**	**100.0%**	**-0.32 [-2.23, 1.59]**

Heterogeneity: $Tau^2 = 4.11$; $Chi^2 = 16.72$, df = 8 (P = 0.03); $I^2 = 52\%$

Test for overall effect: Z = 0.33 (P = 0.74)



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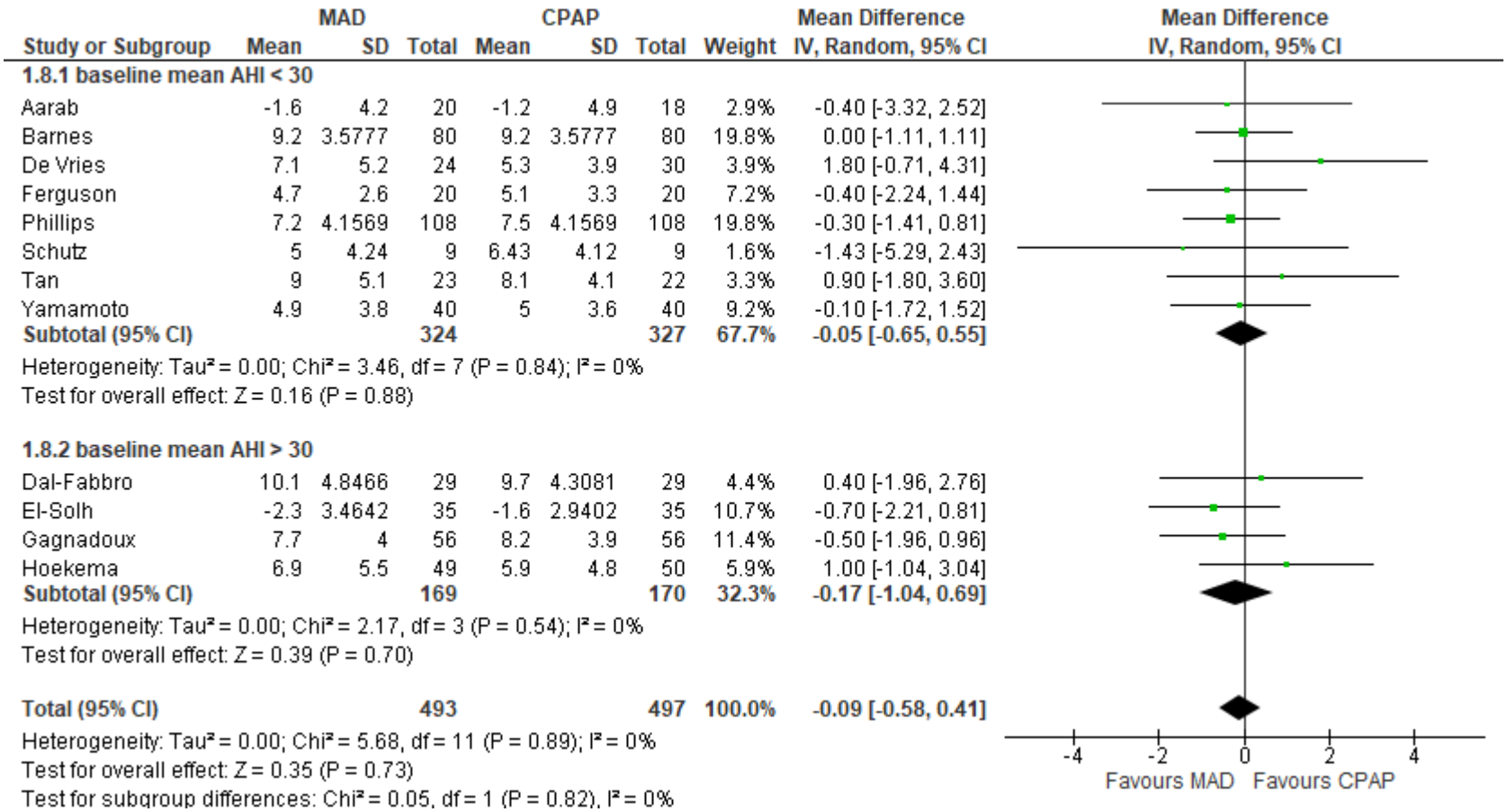
MAD
CPAP
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.8.1 baseline mean AHI < 30
Aarab -1.6 4.2 20 -1.2 4.9 18 2.9% -0.40 [-3.32, 2.52]
Barnes 9.2 3.5777 80 9.2 3.5777 80 19.8% 0.00 [-1.11, 1.11]
De Vries 7.1 5.2 24 5.3 3.9 30 3.9% 1.80 [-0.71, 4.31]
Ferguson 4.7 2.6 20 5.1 3.3 20 7.2% -0.40 [-2.24, 1.44]
Phillips 7.2 4.1569 108 7.5 4.1569 108 19.8% -0.30 [-1.41, 0.81]
Schutz 5 4.24 9 6.43 4.12 9 1.6% -1.43 [-5.29, 2.43]
Tan 9 5.1 23 8.1 4.1 22 3.3% 0.90 [-1.80, 3.60]
Yamamoto 4.9 3.8 40 5 3.6 40 9.2% -0.10 [-1.72, 1.52]
Subtotal (95% CI) 324 327 67.7% -0.05 [-0.65, 0.55]
Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 7 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.88)
1.8.2 baseline mean AHI > 30
Dal-Fabbro 10.1 4.8466 29 9.7 4.3081 29 4.4% 0.40 [-1.96, 2.76]
El-Solh -2.3 3.4642 35 -1.6 2.9402 35 10.7% -0.70 [-2.21, 0.81]
Gagnadoux 7.7 4 56 8.2 3.9 56 11.4% -0.50 [-1.96, 0.96]
Hoekema 6.9 5.5 49 5.9 4.8 50 5.9% 1.00 [-1.04, 3.04]
Subtotal (95% CI) 169 170 32.3% -0.17 [-1.04, 0.69]
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)
Total (95% CI) 493 497 100.0% -0.09 [-0.58, 0.41]
Heterogeneity: Tau² = 0.00; Chi² = 5.68, df = 11 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%
-4
-2
0
2
4
Favours MAD
Favours CPAP

SF36 physical functioning

Study or Subgroup	MAD Mean	MAD SD	MAD Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 baseline mean AHI < 30								
Aarab	0	0	0	0	0	0		Not estimable
Barnes	80	15.2053	80	81	13.4164	80	37.4%	-1.00 [-5.44, 3.44]
De Vries	81.9	21.7	29	81.8	19.7	37	7.2%	0.10 [-10.03, 10.23]
Phillips	84.7	19.7454	108	83.7	19.7454	108	26.6%	1.00 [-4.27, 6.27]
Schutz	85	13.04	9	82.14	11.85	9	5.6%	2.86 [-8.65, 14.37]
Subtotal (95% CI)			**226**			**234**	**76.8%**	**0.08 [-3.02, 3.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 3 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
1.9.2 baseline mean AHI > 30								
El-Solh	65	17.2031	35	66.62	17.2031	35	11.4%	-1.62 [-9.68, 6.44]
Hoekema	78.8	21.5	49	80.6	18.5	50	11.8%	-1.80 [-9.71, 6.11]
Subtotal (95% CI)			**84**			**85**	**23.2%**	**-1.71 [-7.36, 3.93]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.59 (P = 0.55)								
Total (95% CI)			**310**			**319**	**100.0%**	**-0.34 [-3.06, 2.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 5 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.24 (P = 0.81)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%								

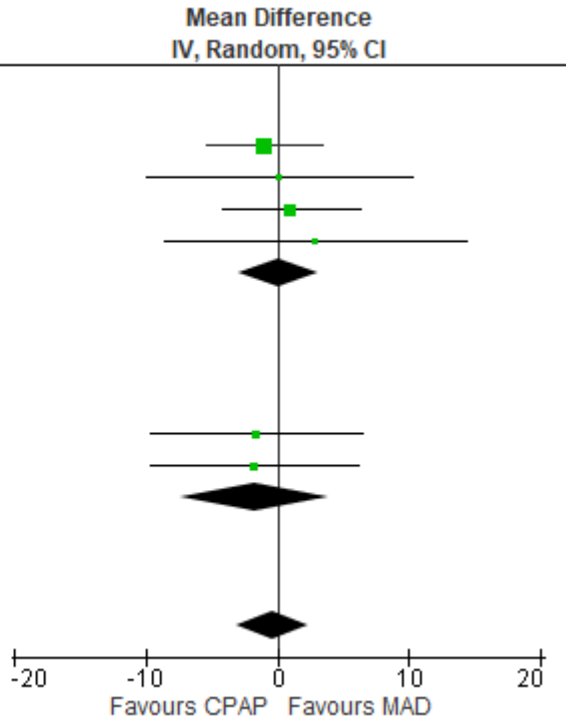

Figure e10: PICO 4 a and b – Meta-Analyses

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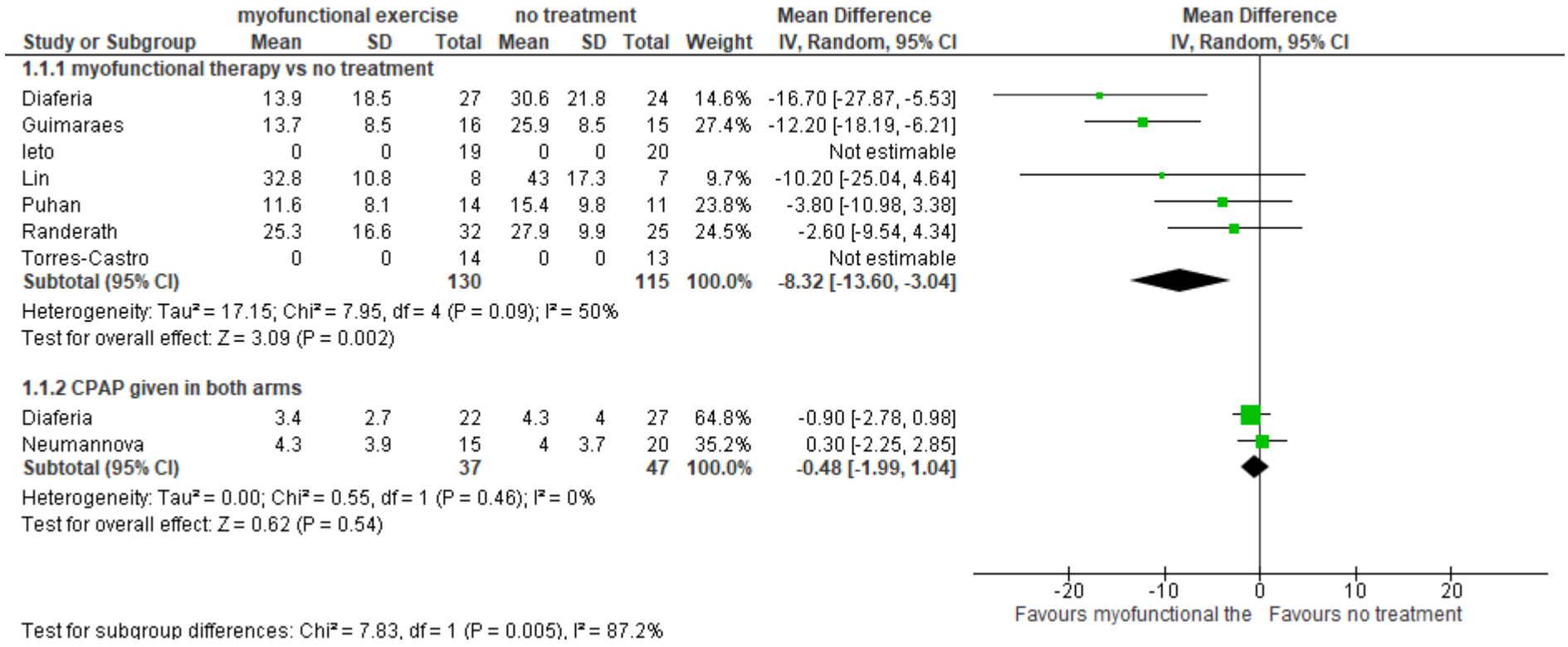
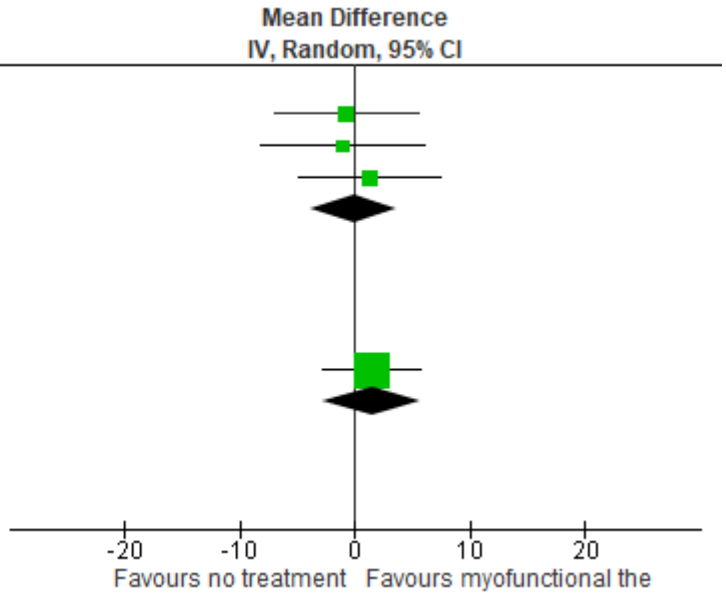
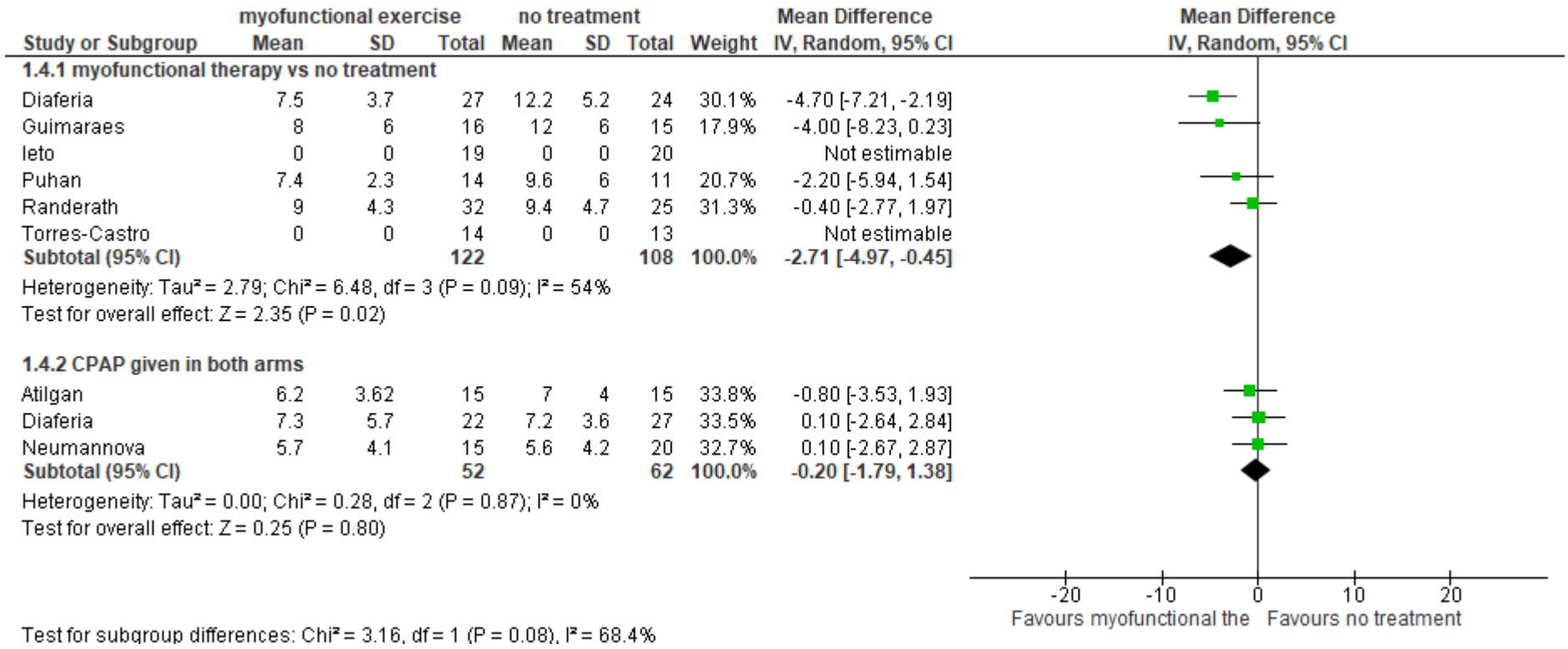


Sleep efficiency

Study or Subgroup	myofunctional exercise Mean	SD	Total	no treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 myofunctional therapy vs no treatment								
Diaferia	84.5	13.1	27	85.2	9.3	24	36.4%	-0.70 [-6.89, 5.49]
Guimaraes	86	9	16	87	11	15	27.6%	-1.00 [-8.10, 6.10]
Ieto	86.3	8.6	19	85	11.1	20	36.0%	1.30 [-4.91, 7.51]
Subtotal (95% CI)			**62**			**59**	**100.0%**	**-0.06 [-3.79, 3.67]**
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.97)								
1.2.2 CPAP given in both arms								
Diaferia	88.1	7.5	22	86.6	7.8	27	100.0%	1.50 [-2.80, 5.80]
Subtotal (95% CI)			**22**			**27**	**100.0%**	**1.50 [-2.80, 5.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.49)								
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%								



Sleepiness ESS



Sleep quality Pitsburgh

Study or Subgroup	myofunctional exercise Mean	SD	Total	no treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 myofunctional therapy vs no treatment								
Guimaraes	6.9	2.5	16	10.8	3.7	15	30.1%	-3.90 [-6.14, -1.66]
Ieto	4	2.6	19	6.4	3.9	20	33.4%	-2.40 [-4.47, -0.33]
Puhan	4.3	2.1	14	5.6	2.7	11	36.5%	-1.30 [-3.24, 0.64]
Subtotal (95% CI)			**49**			**46**	**100.0%**	**-2.45 [-3.91, -0.99]**
Heterogeneity: Tau² = 0.54; Chi² = 2.96, df = 2 (P = 0.23); I² = 33%								
Test for overall effect: Z = 3.29 (P = 0.001)								
1.5.2 CPAP given in both arms								
Atilgan	4.68	2.33	15	5.93	3.51	15	100.0%	-1.25 [-3.38, 0.88]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**-1.25 [-3.38, 0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.15 (P = 0.25)								

Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%

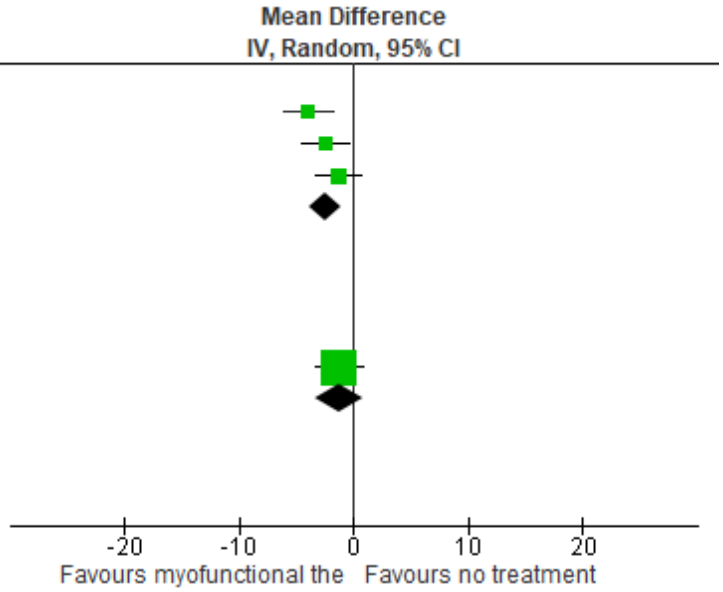
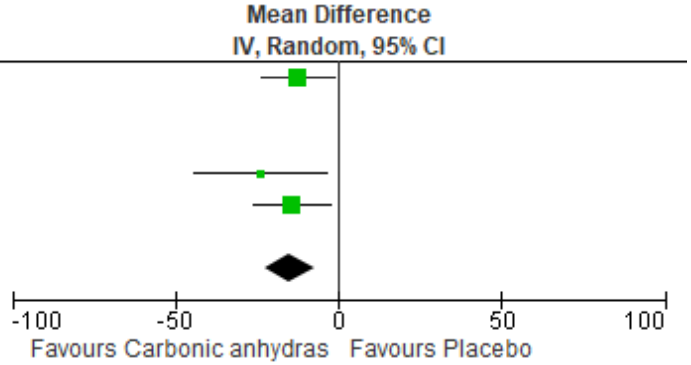


Figure e11: PICO 6 – Meta-Analyses

AHI

Study or Subgroup	Carbonic anhydrase inhibi Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eskandari	-8.7	12.9076	13	4	17.5159	15	44.2%	-12.70 [-24.01, -1.39]
Latshang	0	0	0	0	0	0		Not estimable
Nussbaumer	0	0	0	0	0	0		Not estimable
Whyte	26	20	10	50	26	10	13.7%	-24.00 [-44.33, -3.67]
Winslow	-32	18.4653	19	-17.7	18.893	21	42.1%	-14.30 [-25.89, -2.71]
Total (95% CI)			**42**			**46**	**100.0%**	**-14.92 [-22.44, -7.40]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)



Sleepiness (ESS)

Study or Subgroup	Carbonic anhydrase inhibi Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eskandari	1.4	3.3096	13	-0.3	3.6115	15	48.6%	1.70 [-0.86, 4.26]
Whyte	0	0	0	0	0	0		Not estimable
Winslow	-1.9	3.923	19	-1.8	4.1243	21	51.4%	-0.10 [-2.59, 2.39]
Total (95% CI)			**32**			**36**	**100.0%**	**0.78 [-1.01, 2.56]**

Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)

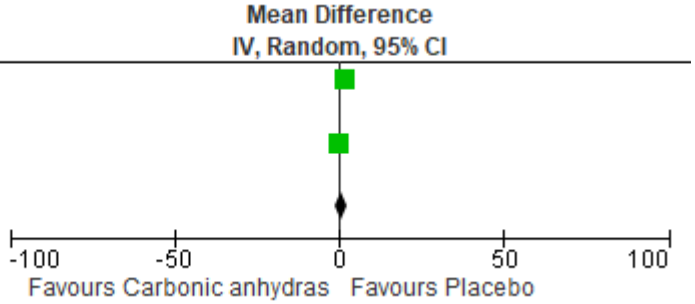
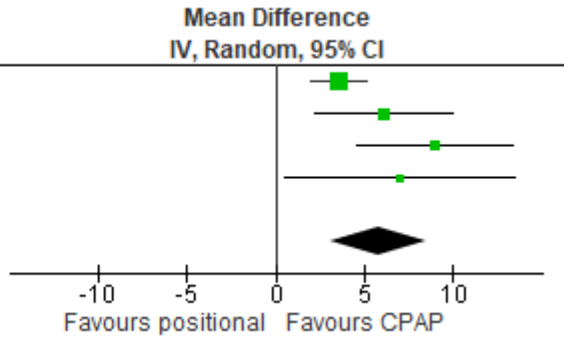


Figure e12: PICO 7 – Meta-Analyses

AHI

Study or Subgroup	positional Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berry	7.29	6.8	110	3.71	5.1	110	41.4%	3.58 [1.99, 5.17]
Jokic	9.5	6.85	13	3.4	1.8	13	24.5%	6.10 [2.25, 9.95]
Mok	13	13.8	40	4	3.2	40	21.3%	9.00 [4.61, 13.39]
Skinner 2	12	14.5	20	5	3	20	12.8%	7.00 [0.51, 13.49]
Total (95% CI)			**183**			**183**	**100.0%**	**5.79 [3.08, 8.50]**

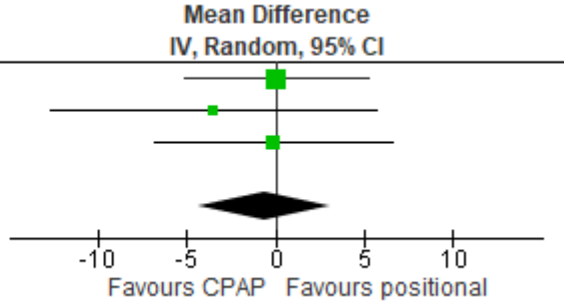
Heterogeneity: Tau² = 3.95; Chi² = 6.55, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 4.19 (P < 0.0001)



SF-36 physical functioning

Study or Subgroup	positional Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berry	83.82	19.42	110	83.78	19.89	110	52.0%	0.04 [-5.15, 5.23]
Mok	77.1	22.7	40	80.6	18.9	40	16.7%	-3.50 [-12.65, 5.65]
Skinner 2	44.5	11	20	44.6	10.6	20	31.3%	-0.10 [-6.79, 6.59]
Total (95% CI)			**170**			**170**	**100.0%**	**-0.60 [-4.34, 3.15]**

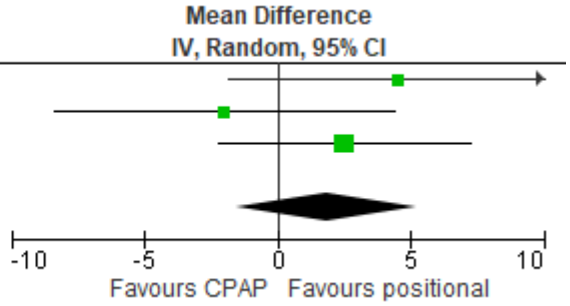
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)



Sleep efficiency

Study or Subgroup	positional Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berry	85.47	31.82	110	80.96	12.16	110	26.8%	4.51 [-1.86, 10.88]
Jokic	82	7.6	13	84	9	13	26.5%	-2.00 [-8.40, 4.40]
Mok	85.4	9.3	40	82.9	12.1	40	46.6%	2.50 [-2.23, 7.23]
Total (95% CI)			**163**			**163**	**100.0%**	**1.85 [-1.54, 5.23]**

Heterogeneity: Tau² = 0.58; Chi² = 2.13, df = 2 (P = 0.34); I² = 6%
Test for overall effect: Z = 1.07 (P = 0.29)



Sleepiness (ESS)

Study or Subgroup	positional Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berry	8.27	4.98	110	7.37	3.98	110	64.3%	0.90 [-0.29, 2.09]
Mok	10.9	4	40	8.9	4.5	40	26.2%	2.00 [0.13, 3.87]
Skinner 2	11.6	5.8	20	10.4	4.1	20	9.4%	1.20 [-1.91, 4.31]
Total (95% CI)			**170**			**170**	**100.0%**	**1.22 [0.26, 2.17]**

Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)

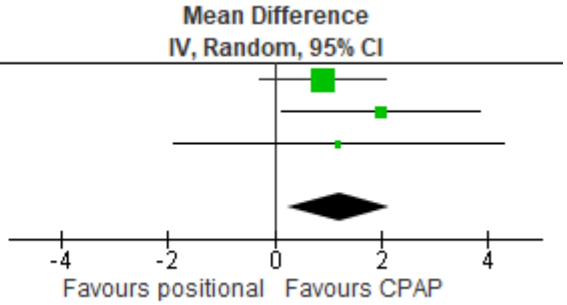


Table e1: Meetings of the ERS Non-CPAP therapies in obstructive sleep apnoea (2018-2020)

		Paris 17/08/2018 (kick-off meeting)	**Düsseldorf** 01/07/2019	**Madrid** 01/10/2019	**Consensus meeting** 23/11/2020 (virtual)
Winfried Randerath	Solingen (Germany)	Present	Present	Present	Present
Johan Verbraecken	Antwerp (Belgium)	Present	Present	Present	Present
Christel de Raaff	Amsterdam (The Netherlands)	Excused	Excused	Present	Present
Nicole Skoetz	(Cologne, Germany)	Excused	Present	Present	Present
Tina Jacobs	(Cologne, Germany)	Excused	Excused	Present	Present
Rebecca Morgan	(Hamilton, Canada)	N/A	Present	N/A	N/A
Simon Herkenrath	(Solingen, Germany)	Present	Present	Present	Present
Oreste Marrone	(Palermo, Italy)	Present	Excused	Present	Present
Jean-Louis Pepin	(Grenoble, France)	Excused	Present	Excused	Present
Jan Hedner	(Gothenburg, Sweden)	Present	Excused	Present	Present

		Paris 17/08/2018 (kick-off meeting)	**Düsseldorf** 01/07/2019	**Madrid** 01/10/2019	**Consensus meeting** 23/11/2020 (virtual)
Marie Marklund	(Umea, Sweden)	Present	Excused	Excused	Present
Walter McNicholas	(Dublin, Ireland)	Present	Excused	Excused	Present
Peter Wijkstra	(Groningen, The Netherlands)	Excused	Present	Present	Present
Sofia Schiza	(Heraklion, Greece)	Present	Present	Present	Present
Wojciech Trzepizur	(Anger, France)	Present	Present	Present	Excused
Winfried Hohenhorst	(Essen, Germany)	Present	Present	Present	Present
Jörg Steier	(London, UK)	Excused	Excused	Excused	Present
Dan Smyth	(Sheffield, UK)	Present	Present	Excused	Excused
Mark De Quidt	(Sheffield, UK)	Present	Present	Present	Withdrawn
Barbara Johnson	(Sheffield, UK)	Excused	Excused	Present	N/A
Piet-Heijn van Mechelen	(Sheffield, UK)	N/A	N/A	N/A	Present
Claire Williams	(Sheffield, UK)	N/A	N/A	N/A	Present
Tomy Tonia	(Bern, Switzerland)	Present	Excused	Excused	Present

Table e2: PICO questions

Number	Name	Population	Intervention	Comparison	Outcome	Recommendation
1	In adult obese patients with OSA, should laparoscopic Roux-en-Y gastric bypass surgery (RYGB) or weight loss diet be used?	Obese patients with OSA	Laparoscopic Roux-en-Y gastric bypass surgery (RYGB)	Weight reducing diet	AHI; sleep efficiency; health-related quality of life; sleepiness; hypertension; compliance; adverse events	Conditional recommendation for the intervention, very low quality of evidence
2	Should custom-made dual-block mandibular advancement device or CPAP be used for adult patients with obstructive sleep apnoea?	Adult patients with OSA	Custom-made dual-block mandibular advancement device	CPAP	AHI; sleep efficiency; oxygen desaturation; sleepiness; physical functioning; arterial hypertension; compliance; adverse events.	Conditional recommendation against the intervention, very low quality of evidence
3	Should hypoglossal nerve stimulation during sleep or no treatment be used for adult patients with obstructive sleep apnoea?	Adult patients with OSA	Hypoglossal nerve stimulation	No treatment	AHI; sleep efficiency; oxygen desaturation; sleepiness; physical functioning; arterial hypertension; compliance; adverse events.	Conditional recommendation against the intervention, very low quality of evidence.

Number	Name	Population	Intervention	Comparison	Outcome	Recommendation
4a	In adult patients with OSA, should myofunctional therapy or no treatment be used?	Adult patients with OSA	Myofunctional therapy	No treatment	AHI; sleep efficiency; sleepiness; physical functioning; compliance; adverse events.	Conditional recommendation for either the intervention or the comparison, low quality of evidence
4b	Should myofunctional therapy or CPAP be used for adult patients with obstructive sleep apnoea?	Adult patients with OSA	Myofunctional therapy	CPAP	AHI; sleep efficiency; sleepiness; physical functioning; compliance; adverse events.	Conditional recommendation against the intervention, low quality of evidence
5	Should maxillo-mandibular osteotomy or CPAP be used for adult patients with obstructive sleep apnoea?	Adult patients with OSA	Maxillo-mandibular osteotomy	CPAP	AHI; sleepiness; satisfaction; adverse events.	Conditional recommendation for either the intervention or the comparison, very low quality of evidence
6	Should carbonic anhydrase inhibitors (compared to placebo) be used for adult patients with obstructive sleep apnoea	Adult patients with OSA	Carbonic anhydrase inhibitors	Placebo	AHI; sleep efficiency; oxygen desaturation; sleepiness; arterial hypertension; compliance; adverse events.	Conditional recommendation for the intervention, low quality of evidence

Number	Name	Population	Intervention	Comparison	Outcome	Recommendation
7	Should positional therapy or CPAP be used for adult patients with position-dependent obstructive sleep apnoea?	Adult patients with position-dependent obstructive sleep apnoea.	Positional therapy	CPAP	AHI; sleep efficiency; oxygen desaturation; sleepiness; health-related quality of life; energy level scores; compliance; adverse events	Conditional recommendation for either the intervention or the comparison, very low certainty of evidence
8	Should positional therapy (intervention) or custom made dual-block mandibular advancement devices (control) be used for adult patients with position-dependent obstructive sleep apnoea?	Adult patients with position-dependent obstructive sleep apnoea.	Positional therapy	Custom-made dual-block mandibular advancement device	AHI; sleep efficiency; oxygen desaturation; sleepiness; arterial hypertension; adherence; adverse events; Quality of life.	Conditional recommendation for either the intervention or the comparison, very low certainty of evidence

Table e3: Reasons for the definition of the PICOs

PICO 1: In adult obese patients with OSA, should laparoscopic Roux-en-Y gastric bypass surgery (RYGB) or weight reducing diet be used?

Obesity is the most important risk factor of OSA. Weight reducing has been discussed in the 2011 ERS statement and is an unequivocal part of OSA treatment. However, we asked for the relevance of bariatric surgery and decided to analyse the most frequently performed technique. The accepted weight reducing diet was chosen as a comparator as the standard treatment.

PICO 2: Should a custom-made dual-block mandibular advancement device or CPAP be used for adult patients with obstructive sleep apnoea?

Custom-made dual-block mandibular advancement device are the accepted standard of mandibular advancement technique. They have been mentioned in the 2011 ERS statement. There is an increasing interest in mandibular advancement leading to reimbursement in some health systems. The body of evidence is growing, asking for a renewed view on the comparison between custom-made dual-block mandibular advancement device and CPAP.

PICO 3: Should hypoglossal nerve stimulation during sleep or no treatment be used for adult patients with obstructive sleep apnoea?

Recent advances on the pathophysiology of OSA have shown the relevance of upper airway muscle responsiveness and activity. This stresses the question of direct or indirect stimulation of muscle activity. Hypoglossal nerve activity has raised growing interest due to the availability of devices and surgical techniques. Therefore, an independent evaluation of the scientific basis of the therapy seemed necessary. We chose “no treatment” as a comparator as the expert panel was –a priori- not aware of placebo-controlled or longer-term CPAP-controlled studies.

PICO 4a: In adult patients with OSA, should myofunctional therapy or no treatment be used?

PICO 4b: Should myofunctional therapy or CPAP be used for adult patients with obstructive sleep apnoea?

In addition to PICO 3, myofunctional therapies are discussed as approaches to improvement of muscle activity. These techniques do not require surgery or technical devices. Their efficacy was analysed alone (comparator “no treatment”) and in comparison to the gold standard CPAP. A placebo-control is not possible is these procedures, which cannot be blinded.

PICO 5: Should maxillo-mandibular osteotomy or CPAP be used for adult patients with obstructive sleep apnoea?

Maxillo-mandibular osteotomy represents an intervention at the facial skeleton, which is considered being the most effective surgical treatment of OSA. However, a re-evaluation of available data in comparison to the standard therapy of CPAP seemed timely to the panel.

PICO 6: Should carbonic anhydrase inhibitors (compared to placebo) be used for adult patients with obstructive sleep apnoea?

In general, drug therapy is a well-known and often preferred therapeutical option for patients and clinicians. Therefore, the panel intended to include pharmaceutical therapies in the guideline. According to the target of the guideline, we selected drugs intending to directly influence OSA. The evaluation of drugs (or other options) in pre-clinical stages or substances focussing on consequences such as residual sleepiness might be the target of future guidelines or statements. The comparator placebo seems adequate for pharmaceutical interventions.

PICO 7: Should positional therapy or CPAP be used for adult patients with position-dependent obstructive sleep apnoea?

Positional therapy has risen broad interest due to the development of new, more comfortable devices. However, there is a huge uncertainty on the efficacy of these approaches as compared to the gold standard CPAP.

PICO 8: Should positional therapy (intervention) or custom made dual-block mandibular advancement devices (control) be used for adult patients with position-dependent obstructive sleep apnoea?

In addition to PICO 7, positional therapy can be compared to other accepted therapeutical options, especially the custom-made dual-block mandibular

advancement devices. This analysis may also guide to future additional analyses to combined therapies.

Table e4: Search strategies PICO 1

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)** 1946 to June 12, 2020

Search Strategy:

#	Searches	Results	Annotations
1	sleep apnoea syndromes/	14597	
2	exp Sleep Apnoea, Obstructive/	20693	
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.	37738	
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.	133173	
5	3 and 4	30224	2 and 3
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.	22588	
7	1 or 2 or 3 or 5 or 6	50267	
8	Gastric Bypass/	9332	
9	(bypass* adj3 (gastric* or gastroileal* or roux-en-y gastric*)).tw,kf,ot.	11803	
10	astrojejunostom*.tw,kf,ot.	1	
11	or/8-10	13913	
12	Anastomosis, Roux-en-Y/	3491	
13	(roux en y or roux y).tw,kf,ot.	11646	
14	(RYGB or LRYGB or B-RYGB).tw,kf,ot.	3794	
15	or/12-14	12913	
16	7 and (11 or 15)	460	
17	meta analysis.pt.	115768	
18	meta analysis.mp.	187180	
19	review.pt.	2656587	
20	search*.tw.	459682	
21	or/17-20	3002410	
22	exp clinical pathway/	6706	
23	exp clinical protocol/	167108	

24	exp consensus/	12857	
25	exp consensus development conference/	11962	
26	exp consensus development conferences as topic/	2836	
27	critical pathways/	6706	
28	exp guideline/	34048	
29	guidelines as topic/	39665	
30	exp practice guideline/	27110	
31	practice guidelines as topic/	117410	
32	health planning guidelines/	4086	
33	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.	43409	
34	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.	33103	
35	(standards or guideline or guidelines).ti,kf,kw.	109877	
36	((practice or treatment* or clinical) adj guideline*).ab.	39949	
37	(CPG or CPGs).ti.	5730	
38	consensus*.ti,kf,kw.	26154	
39	consensus*.ab. /freq=2	25204	
40	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.	20215	
41	recommendat*.ti,kf,kw.	41112	
42	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.	58764	
43	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.	7620	
44	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.	9843	
45	or/22-44	613690	
46	randomized controlled trial.pt.	507458	
47	controlled clinical trial.pt.	93712	
48	randomi?ed.ab.	577230	

49	placebo.ab.	208492	
50	drug therapy.fs.	2210650	
51	randomly.ab.	335022	
52	trial.ab.	508651	
53	groups.ab.	2056514	
54	or/46-53	4739084	
55	exp animals/ not humans/	4706928	
56	54 not 55	4112484	
57	16 and (21 or 45 or 56)	193	

Cochrane Central Register of Controlled Trials (Central, 2020, Issue 06) in the Cochrane Library (searched 15 June 2020)

ID Search

#1 MeSH descriptor: [Sleep Apnoea Syndromes] explode all trees

#2 MeSH descriptor: [Sleep Apnoea, Obstructive] explode all trees

#3 ((apnoea* or apnoea*) near/3 sleep*)

#4 (hypopnoea* or hypopnoea* or obstructive*)

#5 #3 and #4

#6 (OSA or OSAS or OSAHS or SHS or SAHS)

#7 #1 or #2 or #3 or #5 or #6

#8 MeSH descriptor: [Gastric Bypass] explode all trees

#9 (bypass* near/3 (gastric* or gastroileal* or roux-en-y gastric*))

#10 astrojejunostom*

#11 #8 or #9 or #10

#12 MeSH descriptor: [Anastomosis, Roux-en-Y] explode all trees

#13 (roux en y or roux y)

#14 (RYGB or LRYGB or B-RYGB)

#15 #12 or #13 or #14

#16 #7 and (#11 or #15)

Table e5: Search strategies PICO 2

Medline (Ovid) search strategy

#	Searches
1	sleep apnoea syndromes/
2	exp Sleep Apnoea, Obstructive/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	"upper airway resistance sleep apnoea syndrome".mp.
7	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
8	1 or 2 or 3 or 5 or 6 or 7
9	Mandibular Advancement/
10	(mandibular* adj2 advancement*).tw,kf,ot.
11	exp orthodontic appliances/
12	((oral* or orthodontic*) adj2 appliance*).tw,kf,ot.
13	Orthodontic Appliance Design/
14	(functional* adj2 appliance*).tw,kf,ot.
15	(mandibular* adj3 (splint* or positioning* or appliance*)).tw,kf,ot.
16	*splints/
17	block*.tw,kf,ot.
18	(duo* or twin* or two-piece).tw,kf,ot.
19	17 and 18
20	((twin-block* or TB) adj2 appliance*).tw,kf,ot.
21	herbst*.tw.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 19 or 21
23	8 and 22
24	meta analysis.mp.
25	meta analysis.pt.
26	review.pt.
27	search*.tw.

28 or/24-27

29 exp clinical pathway/

30 exp clinical protocol/

31 exp consensus/

32 exp consensus development conference/

33 exp consensus development conferences as topic/

34 critical pathways/

35 exp guideline/

36 guidelines as topic/

37 exp practice guideline/

38 practice guidelines as topic/

39 health planning guidelines/

40 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

41 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

42 (standards or guideline or guidelines).ti,kf,kw.

43 ((practice or treatment* or clinical) adj guideline*).ab.

44 (CPG or CPGs).ti.

45 consensus*.ti,kf,kw.

46 consensus*.ab. /freq=2

47 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

48 recommendat*.ti,kf,kw.

49 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

50 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

51 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

52 or/29-51

53 randomized controlled trial.pt.

54 controlled clinical trial.pt.

55 randomi?ed.ab.

56 placebo.ab.

57 drug therapy.fs.

58 randomly.ab.

59 trial.ab.

60 groups.ab.

61 or/53-60

62 exp animals/ not humans/

63 61 not 62

64 23 and 28

65 23 and 52

66 23 and 63

67 23 and (28 or 52 or 63)

Cochrane Central Register of Controlled Trials (Central, 2020, Issue 06) in the Cochrane Library (searched 15 June 2020)

ID Search

#1 MeSH descriptor: [Sleep Apnoea Syndromes] explode all trees

#2 MeSH descriptor: [Sleep Apnoea, Obstructive] explode all trees

#3 ((apnoea* or apnoea*) near/3 sleep*)

#4 (hypopnoea* or hypopnoea* or obstructive*)

#5 #3 and #4

#6 (OSA or OSAS or OSAHS or SHS or SAHS)

#7 #1 or #2 or #3 or #5 or #6

#8 MeSH descriptor: [Mandibular Advancement] explode all trees

#9 (mandibular* near/2 advancement*)

#10 MeSH descriptor: [Orthodontic Appliances] explode all trees

#11 ((oral* or orthodontic*) near/2 appliance*)

#12	MeSH descriptor: [Orthodontic Appliance Design] explode all trees
#13	(functional* near/2 appliance*)
#14	(mandibular* near/3 (splint* or positioning* or appliance*))
#15	MeSH descriptor: [Splints] explode all trees
#16	block*
#17	(duo* or twin* or two-piece)
#18	#16 and #17
#19	((twin-block* or TB) near/2 appliance*)
#20	herbst*
#21	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #18 or #19 or #20
#22	#7 and #21
#23	#22 in Trials

Table e6: Search strategies PICO 3

Medline / Ovid Search Strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/
2	exp SLEEP APNOEA, OBSTRUCTIVE/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
7	1 or 2 or 3 or 5 or 6
8	HYPOGLOSSAL NERVE/
9	(nerve* adj2 (hypoglossal* or hypoglossus* or XII or XIIS)).tw,kf,ot.
10	(nervus adj2 (hypoglossal* or hypoglossus* or XII or XIIS)).tw,kf,ot.
11	(cranial adj2 nerve* adj2 (twelfth or XII or XIIS or "12")).tw,kf,ot.
12	CARDIOSA*.tw,kf,ot.
13	exp ELECTRIC STIMULATION THERAPY/

14	(stimulation* adj2 therap*).tw,kf,ot.
15	ELECTRIC STIMULATION/
16	TRANSCUTANEOUS ELECTRIC NERVE STIMULATION/
17	exp IMPLANTABLE NEUROSTIMULATORS/
18	(neurostimulator* or nerve stimulation*).tw,kf,ot.
19	inspire.tw,kf,ot.
20	ImThera.tw,kf,ot.
21	Nyxoah.tw,kf,ot.
22	TESLA.tw,kf,ot.
23	(hypoglossal nerve* or hypoglossal nervus or upper-airway or transcutaneous or submental* or cranial nerve* or cranial nervus or genioglossus or electronic*).tw,kf,ot.
24	(stimulation* or stimulator*).tw,kf,ot.
25	23 and 24
26	(HGNS or UAS).tw,kf,ot.
27 or	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 22 or 25 or 26
28	7 and 27
29	exp ANIMALS/ not HUMANS/
30	28 not 29

Cochrane Central Register of Controlled Trials (Central, 2020, Issue 06) in the Cochrane Library (searched 15 June 2020)

ID	Search
#1	MeSH descriptor: [Sleep Apnoea Syndromes] explode all trees
#2	MeSH descriptor: [Sleep Apnoea, Obstructive] explode all trees
#3	((apnoea* or apnoea*) near/3 sleep*)
#4	(hypopnoea* or hypopnoea* or obstructive*)
#5	#3 and #4
#6	(OSA or OSAS or OSAHS or SHS or SAHS)
#7	#1 or #2 or #3 or #5 or #6

#8	MeSH descriptor: [Hypoglossal Nerve] explode all trees
#9	(nerve* near/2 (hypoglossal* or hypoglossus* or XII or XIIS))
#10	(nervus near/2 (hypoglossal* or hypoglossus* or XII or XIIS))
#11	(cranial near/2 nerve* near/2 (twelfth or XII or XIIS or "12"))
#12	CARDIOSA*
#13	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#14	(stimulation* near/2 therap*)
#15	MeSH descriptor: [Electric Stimulation] explode all trees
#16	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#17	MeSH descriptor: [Implantable Neurostimulators] explode all trees
#18	(neurostimulator* or nerve stimulation*)
#19	inspire
#20	ImThera
#21	Nyxoah
#22	TESLA
#23	(hypoglossal nerve* or hypoglossal nervus or upper-airway or transcutaneous or submental* or cranial nerve* or cranial nervus or genioglossus or electronic*)
#24	(stimulation* or stimulator*)
#25	#23 and #24
#26	(HGNS or UAS)
#27	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #25 or #26
#28	#7 and #27

Table e7: Search strategies PICO 4

Medline (Ovid) search strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/

2 exp SLEEP APNOEA, OBSTRUCTIVE/

3 ((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.

4 (hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.

5 3 and 4

6 (OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.

7 1 or 2 or 3 or 5 or 6

8 SNORING/

9 snoring*.tw,kf,ot.

10 upper airway resistance syndrome*.tw.

11 or/8-10

12 7 or 11

13 MYOFUNCTIONAL THERAPY/

14 myofunctional*.tw,kf,ot.

15 (myo-therap* or myotherap*).tw,kf,ot.

16 (myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.

17 (oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.

18 myofascial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70 30 and (35 or 59 or 70)

Medline (Ovid) search strategy:

Searches

1 SLEEP APNOEA SYNDROMES/

2 exp SLEEP APNOEA, OBSTRUCTIVE/

3 ((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.

4 (hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.

5 3 and 4

6 (OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.

7 1 or 2 or 3 or 5 or 6

8 SNORING/

9 snoring*.tw,kf,ot.

10 upper airway resistance syndrome*.tw.

11 or/8-10

12 7 or 11

13 MYOFUNCTIONAL THERAPY/

14 myofunctional*.tw,kf,ot.

15 (myo-therap* or myotherap*).tw,kf,ot.

16 (myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.

17 (oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.

18 myofascial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70	30 and (35 or 59 or 70)

Table e8: Search strategies PICO 5

Medline (Ovid) search strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/
2	exp SLEEP APNOEA, OBSTRUCTIVE/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
7	1 or 2 or 3 or 5 or 6
8	SNORING/
9	snoring*.tw,kf,ot.
10	upper airway resistance syndrome*.tw.
11	or/8-10
12	7 or 11
13	MYOFUNCTIONAL THERAPY/
14	myofunctional*.tw,kf,ot.
15	(myo-therap* or myotherap*).tw,kf,ot.
16	(myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.
17	(oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.
18	myofascial reeducation*.tw,kf,ot.
19	(upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.
20	SPEECH THERAPY/
21	speech therap*.tw,kf,ot.
22	EXERCISE THERAPY/
23	TONGUE/
24	22 and 23
25	((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70 30 and (35 or 59 or 70)

Medline (Ovid) search strategy:

Searches

1 SLEEP APNOEA SYNDROMES/

2 exp SLEEP APNOEA, OBSTRUCTIVE/

3 ((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.

4 (hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.

5 3 and 4

6 (OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.

7 1 or 2 or 3 or 5 or 6

8 SNORING/

9 snoring*.tw,kf,ot.

10 upper airway resistance syndrome*.tw.

11 or/8-10

12 7 or 11

13 MYOFUNCTIONAL THERAPY/

14 myofunctional*.tw,kf,ot.

15 (myo-therap* or myotherap*).tw,kf,ot.

16 (myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.

17 (oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.

18 myofascial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64	drug therapy.fs.
65	randomly.ab.
66	trial.ab.
67	groups.ab.
68	or/60-67
69	exp ANIMALS/ not HUMANS/
70	30 and (35 or 59 or 70)

Table e9: Search strategies PICO 6

Medline (Ovid) search strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/
2	exp SLEEP APNOEA, OBSTRUCTIVE/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
7	1 or 2 or 3 or 5 or 6
8	SNORING/
9	snoring*.tw,kf,ot.
10	upper airway resistance syndrome*.tw.
11	or/8-10
12	7 or 11
13	MYOFUNCTIONAL THERAPY/
14	myofunctional*.tw,kf,ot.
15	(myo-therap* or myotherap*).tw,kf,ot.
16	(myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.
17	(oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.
18	myofascial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70 30 and (35 or 59 or 70)

Medline (Ovid) search strategy:

Searches

1 SLEEP APNOEA SYNDROMES/

2 exp SLEEP APNOEA, OBSTRUCTIVE/

3 ((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.

4 (hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.

5 3 and 4

6 (OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.

7 1 or 2 or 3 or 5 or 6

8 SNORING/

9 snoring*.tw,kf,ot.

10 upper airway resistance syndrome*.tw.

11 or/8-10

12 7 or 11

13 MYOFUNCTIONAL THERAPY/

14 myofunctional*.tw,kf,ot.

15 (myo-therap* or myotherap*).tw,kf,ot.

16 (myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.

17 (oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.

18 myofacial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.
59	or/36-58
60	randomized controlled trial.pt.
61	controlled clinical trial.pt.
62	randomi?ed.ab.
63	placebo.ab.
64	drug therapy.fs.
65	randomly.ab.
66	trial.ab.
67	groups.ab.
68	or/60-67
69	exp ANIMALS/ not HUMANS/
70	30 and (35 or 59 or 70)

Table e10: Search strategies PICO 7 and 8

Medline (Ovid) search strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/
2	exp SLEEP APNOEA, OBSTRUCTIVE/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
7	1 or 2 or 3 or 5 or 6
8	SNORING/
9	snoring*.tw,kf,ot.
10	upper airway resistance syndrome*.tw.
11	or/8-10

12 7 or 11

13 MYOFUNCTIONAL THERAPY/

14 myofunctional*.tw,kf,ot.

15 (myo-therap* or myotherap*).tw,kf,ot.

16 (myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.

17 (oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.

18 myofacial reeducation*.tw,kf,ot.

19 (upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.

20 SPEECH THERAPY/

21 speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70 30 and (35 or 59 or 70)

Medline (Ovid) search strategy:

#	Searches
1	SLEEP APNOEA SYNDROMES/
2	exp SLEEP APNOEA, OBSTRUCTIVE/
3	((apnoea* or apnoea*) adj3 sleep*).tw,kf,ot.
4	(hypopnoea* or hypopnoea* or obstructive*).tw,kf,ot.
5	3 and 4
6	(OSA or OSAS or OSAHS or SHS or SAHS).tw,kf,ot.
7	1 or 2 or 3 or 5 or 6
8	SNORING/
9	snoring*.tw,kf,ot.
10	upper airway resistance syndrome*.tw.
11	or/8-10
12	7 or 11
13	MYOFUNCTIONAL THERAPY/
14	myofunctional*.tw,kf,ot.
15	(myo-therap* or myotherap*).tw,kf,ot.
16	(myolog* adj3 (oro-facial* or orofacial*)).tw,kf,ot.
17	(oropharyngeal* or oropharingeal* or orofaringeal*).tw,kf,ot.
18	myofacial reeducation*.tw,kf,ot.
19	(upper airway adj3 (exercise* or remodeling*)).tw,kf,ot.
20	SPEECH THERAPY/
21	speech therap*.tw,kf,ot.

22 EXERCISE THERAPY/

23 TONGUE/

24 22 and 23

25 ((pharyngeal* or pharingeal*) adj3 (muscle* or musculatur*)).tw,kf,ot.

26 (tongue* adj3 (task* or exercise*)).tw,kf,ot.

27 MUSIC THERAPY/

28 didgeridoo*.tw,kf,ot.

29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28

30 12 and 29

31 meta analysis.mp.

32 meta analysis.pt.

33 review.pt.

34 search*.tw.

35 or/31-34

36 exp CLINICAL PATHWAY/

37 exp CLINICAL PROTOCOL/

38 exp CONSENSUS/

39 exp CONSENSUS DEVELOPMENT CONFERENCE/

40 exp CONSENSUS DEVELOPMENT CONFERENCES AS TOPIC/

41 CRITICAL PATHWAYS/

42 exp GUIDELINE/

43 GUIDELINES AS TOPIC/

44 exp PRACTICE GUIDELINE/

45 PRACTICE GUIDELINES AS TOPIC/

46 HEALTH PLANNING GUIDELINES/

47 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

48 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.

49 (standards or guideline or guidelines).ti,kf,kw.

50 ((practice or treatment* or clinical) adj guideline*).ab.

51 (CPG or CPGs).ti.

52 consensus*.ti,kf,kw.

53 consensus*.ab. /freq=2

54 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.

55 recommendat*.ti,kf,kw.

56 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.

57 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.

58 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.

59 or/36-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomi?ed.ab.

63 placebo.ab.

64 drug therapy.fs.

65 randomly.ab.

66 trial.ab.

67 groups.ab.

68 or/60-67

69 exp ANIMALS/ not HUMANS/

70 30 and (35 or 59 or 70)

GRADE evidence profiles and evidence-to-decision frameworks

Table e11: PICO 1

QUESTION

Should Laparoscopic Roux-en-Y gastric bypass surgery or weight reducing diet be used for adult obese patients with obstructive sleep apnoea?	
POPULATION:	Adult obese patients with obstructive sleep apnoea.
INTERVENTION:	Laparoscopic Roux-en-Y gastric bypass surgery.
COMPARISON:	Weight reducing diet.
MAIN OUTCOMES:	Apnoea-Hypopnoea-Index; Sleep efficiency; Health-related quality of life; Sleepiness; Hypertension; Compliance; Adverse events (only listed for each arm).
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	There is an increasing evidence of obesity, associated with increasing risk of OSA. Weight reduction is mandatory to treat the underlying cause. Despite dietary interventions, bariatric surgery is increasingly popular. Thus, the question arises if gastric bypass surgery is as effective as CPAP therapy.	The technique of Roux-en-Y surgery is the most frequently performed procedure.

○ Don't know		

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Compared to weight reducing diet, impact of gastric banding on AHI, sleep quality and sleepiness is small and non-significant. However, health-related quality of life improved 3.5 points more on the SF-36 physical scale after gastric banding. *See Appendix 1*.	Reviewed the beneficial outcomes and the panel determine the benefit to be small. Some concern with the length of follow-up. Because of the patient population - in real life - may expect to see less success with the weight reducing group. Need longer-term studies on outcomes from surgery studies.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Intervention: serious (leading to direct hospitalisation): 5 in 5 participants, Acute LAGB pouch dilatation requiring surgical repositioning (1); Pneumonia (1); Acute cholecystitis with pancreatitis (1); Strangulated umbilical hernia (1); Duodenal Ulcer (1); Severe headaches (1). Control: serious (leading to direct hospitalisation) 5 in 5 participants, Chest pain – angina (1); Cardiac and renal failure; (1); Acute abdomen (1) Peri-anal abscess and fistula (1); Asthma (1). *See Appendix 1.*	Adverse events - concern if any occurred within the 4 patients that switched to the control arm. Determined to be trivial - many SAEs not related to the surgical intervention.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is very low.	Based on very low certainty of evidence for the citiclal outcomes.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not look for evidence on patient values.	Perhaps some trade off between the beneficial outcomes related to symptoms. Excessive daytime sleepiness/symptoms - more willing to accept surgical intervention and related adverse events. Perhaps variability introduced by age, occupation, severity of underlying condition, comorbidities. Severe symptoms - less uncertainty. Minimally symptomatic - more uncertainty.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Direct evidence shows the desirable effects to be small, and there were some concerns regarding long-term outcome. Undesirable effects were considered trivial, since many serious adverse events were not related to the surgical intervention.	Very low certainty - possibly important uncertainty The trial with gastric banding versus CPAP may underestimate the benefit of an intervention with gastric bypass surgery. Additional evidence is needed to demonstrate sustained benefit from gastric bypass surgery & weight loss diet** Overall, weight-loss is less after gastric banding than after other bariatric procedures, which argues to perform bariatric surgery type RYGB.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for evidence on resources.	It is difficult to compare the cost within Europe. Coverage varies across patients/countries, etc.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not look for evidence on resources.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not look for evidence on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for evidence on equity.	Reimbursement may not be possible and make intervention less attainable.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not look for evidence on acceptability.	This intervention is acceptable for clinicians. On the other hand, there is some variability in acceptability for patients. However, mostly the intervention is acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for evidence on feasibility.	There is some variability in availability.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderu neeate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In adult obese patients with OSA, we suggest bariatric surgery evaluation or weight reducing diet when weight has not improved despite participating in a comprehensive weight reduction program and if no contraindications (conditional recommendation, very low certainty of evidence).

Comorbidites should be considered when making surgical decisions (in favor or against).

Patients´ values and preference may weigh heavily in their decision for surgery/against surgery.

Justification

There was no RCT on RYGB available in OSA patients. The described study did not exactly match our PICO question (only included gastric banding), so that there is only indirect evidence for this PICO. Based on the presented RCT with evidence to use gastric banding surgery as an intervention, the panel determined the benefit to be small, and there were some concerns regarding long-term outcome. Side effects were considered trivial, since many serious adverse events were not related to the surgical intervention. Given overall weight loss is less after gastric banding than after other bariatric procedures, the panel proposes to perform bariatric surgery type RYGB.

Very low certainty of evidence was given due to concerns about imprecision (only 60 patients included, compliance only described for intervention arm) and high risk of bias (unblinded study design and subjectively reported outcomes).

Subgroup considerations

The beneficial outcomes have to be balanced related to symptoms. In case of excessive daytime sleepiness or other symptoms, patients may be more willing to accept surgical intervention and related adverse events. In addition, variability could be introduced by age, occupation, severity of the underlying condition and comorbidities.

Implementation considerations

The intervention is usually acceptable for clinicians, and is mostly acceptable for patients. For health insurers, this depends on the clinical situation.

Monitoring and evaluation

For reassessment, a follow-up poly(somno)graphy should be considered one year after the intervention. This has to be balanced versus the weight reduction obtained and dependency on CPAP therapy.

Research priorities

More RCT studies in adult obese patients with OSA are warranted to demonstrate sustained benefit from surgery and weight reducing diet on AHI, blood pressure, sleepiness and compliance.

PICO 1 APPENDICES

PICO 1 Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with weight reducing diet	Risk with gastric banding				
Apnoea-Hypopnoea-Index (AHI) assessed with: Polysomnography Scale from: 0 (best) to higher (worst) follow up: mean 2 years	The mean apnoea-Hypopnoea-Index was **43.2** events/hour	mean **3.7 events/hour fewer** (1.4 fewer to 6.5 fewer)	-	60 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]	Intervention: AHI decreased by 25.5 events/hour (95% CI, 14.2 to 36.7 events/hour) from 65.0 events/hour to 39.5 (28.4 to 50.5) events/hour - - - control: AHI decreased by 14.0 events/hour (95% CI, 3.3 to 24.6 events/hour) from 57.2 events/ hour to 43.2 (34.9 to 51.9) events/hour - - - difference between change scores −11.5 (−28.3 to 5.3); p = 0.18
Sleep efficiency assessed with: PSG (%) Scale from: 0 (worst) to 100 (best)	The mean sleep efficiency was **72.4** %	mean **7.4 % higher** (4.2 higher to 10.5 higher)	-	60 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]	Intervention: 2 year score: 79.8 % (75.8 to 83.8) / change 1.6 % (-3.4 to 6.6) - - - control: 2 year score: 72.4 % (65.3 to 79.6) / change -3.04 (-9.7 to 3.7) - - - difference between change scores: 4.7 % (-4.6 to 13.9); p = 0.32
Health-related quality of life assessed with: SF-36 physical Scale from: 0 (worst) to 100 (best) follow up: mean 2 years	The mean health-related quality of life was **44.5** points	mean **3.5 points more** (3.1 more to 3.8 more)	-	60 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	Intervention: 2-year score: 48.0 (43.9 to 52.1) / change at 2 years +12.6 (7.3 to 17.9) - - - control: 2-year score: 44.5 (40.1 to 49.0) / change at 2 years 3.4 (-1.6 to 8.4)- - - difference between change scores 9.3 (0.5 to 18.0); p = 0.04 favouring intervention arm
Sleepiness (ESS) assessed with: Epworth Sleepiness Scale	The mean sleepiness was **8.8** points	mean **2.4 points lower** (1.8 lower to 2.9 lower)	-	60 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	Intervention: 2 year score: 6.4 (4.7 to 8.1) / change at 2 years -6.8 (-9.4 to -4.2) - - - control: 2 year score: 8.8 (6.5 to 11.0) / change at 2 years -3.6 (-6.0 to -1.2) - - - P = 0.12

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with weight reducing diet	Risk with gastric banding				
Scale from: 0 (best) to 24 (worst) follow up: mean 2 years						
Hypertension	baseline - intervention group: 15/50 - control group: 17/57 - - - intervention: 2-year score syst. 130.1 mmHg (124 to 137) change score: -7.25 (-15.9 to 0.69) - - - control: 2-year score syst. 136 (131 to 142) change score: -5.9 (-12.1 to 0.34) - - - difference between change scores (syst.): -1.4 (-11.7 to 9.0) p = 0.80 - - - intervention: 2-year score diast. 82.0 mmHg (78.4 to 85.7) change score -1.1(-5.1 to 3.0) - - - control: 2-year score diast. 83.3 (79.4 to 87.1) change score: -3.5 (-8.2 to 1.2) - - - difference between change scores: 2.4 (-4.6 to 9.4) p = 0.375		-	60 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	
Compliance	"In the surgical group, 4 participants did not consent to surgery but continued in the study and received conventional therapy" - - - CPAP adherence: no difference between groups		-	60 (1 RCT)	⨁◯◯◯ VERY LOW[a,c,d]	
Adverse events (only listed for each arm)	intervention: serious (leading to direct hospitalisation): 5 in 5 participants, Acute LAGB pouch dilatation requiring surgical repositioning (1); Pneumonia (1); Acute cholecystitis with pancreatitis (1); Strangulated umbilical hernia (1); Duodenal Ulcer (1); Severe headaches (1); - - - minor: 16 in 12 participants, Elective arthroplasties (2), Shoulder (1), hip (1); LAGB replacement (1); Spinal stimulator placement for pain (1); Nasal surgery (1); Knee reconstruction (1); Knee pain (1); Shoulder pain (2); Back Pain (1); Syncope episode (dehydration) (1); Epilepsy (1) - - - control: serious (leading to direct hospitalisation)5 in 5 participants, Chest pain – angina (1); Cardiac and renal failure; (1); Acute abdomen (1) Peri-anal abscess and fistula (1); Asthma (1); - - - minor: 11 in 9, Hand surgery (1); Heel surgery (1); Joint pain (3); Back (1), shoulder (1); knee (1); Kidney stone (1); Diarrhea with very low calorie diet (1); Depression (1); Cold, Flu & sinusitis (3 in 3)		-	60 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	

a. Downgraded one for indirectness: trial does not evaluate Roux-en-Y gastric bypass but gastric banding.
b. Downgraded two for imprecision: only 60 participants included.
c. Downgraded one for study limitations: outcomes are self-reported, 2 domains high risk of bias (performance bias and detection bias due to unblinded study design and subjectively reported outcomes).
d. Downgraded two for imprecision: only 60 participants included; only described for intervention arm, compliance of control treatment not reported.

PICO 1 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-Hypopnoea-Index assessed with: Polysomnography Scale from: 0 (best) to higher (worst) follow up: mean 2 years	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Sleep efficiency assessed with: PSG (%) Scale from: 0 (worst) to 100 (best)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Health-related quality of life assessed with: SF-36 physical Scale from: 0 (worst) to 100 (best) follow up: mean 2 years	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Sleepiness assessed with: Epworth Sleepiness Scale Scale from: 0 (best) to 24 (worst) follow up: mean 2 years	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Hypertension	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Compliance	CRITICAL	⨁◯◯◯ VERY LOW[a,c,d]
Adverse events (only listed for each arm)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

a. Downgraded one for indirectness: trial does not evaluate Roux-en-Y gastric bypass but gastric banding.
b. Downgraded two for imprecision: only 60 participants included.
c. Downgraded one for study limitations: outcomes are self-reported, 2 domains high risk of bias (performance bias and detection bias due to unblinded study design and subjectively reported outcomes).
d. Downgraded two for imprecision: only 60 participants included; only described for intervention arm, compliance of control treatment not reported

Table e12: PICO 2

QUESTION

Should a custom made dual-block mandibular advancement device or CPAP be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Custom made dual-block mandibular advancement device.
COMPARISON:	CPAP.
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/h); Sleep efficiency %; <3% and <4% oxygen desaturation (events/h); Sleepiness ESS; Physical functioning; Arterial hypertension - 24h systolic blood pressure; Arterial hypertension - 24h diastolic blood pressure; Nighttime systolic blood pressure; Nighttime diastolic blood pressure; Adherence / Compliance; Adverse events.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is an increasing group of patients treated with mandibular advancement therapy. Some national scientific societies recommend the use of MADs as an alternative (first or second line) to CPAP. Therefore, a formal European recommendation is urgently required.	It is of interest not only to focus on AHI, but also on other outcome parameters, including quality of life, comorbidities, and oxygenation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Sleep efficiency, ESS and quality of life (SF-36), systolic and diastolic 24-BP did not differ between treatments in the whole group and in all severity subgroups. Similarly, no significant differences were found regarding night-time systolic and diastolic BP's in the whole group.	Difference in compliance and patient preference in favour of MAD. This has moderate to large relevance for patients with moderate sleep apnoea, but smaller relevance for patients with severe apnoea (AHI more relevant).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	AHI decreased more with CPAP than with MAD among all studied patients. Significant differences in favour of CPAP were found in all severity groups. CPAP had a higher impact on night-time systolic BP in moderate to severe OSA patients and in the study with a mean baseline AHI > 30/h. *See Appendix 1*	AHI is especially relevant for patients with severe obstructive sleep apnoea. A significant difference was found for subgroups moderate and severe OSA regarding nighttime blood pressure (small number of patients).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall quality of evidence was low.	There is a lack of long-term RCTs with higher number of patients, including different levels of OSA severity, various comorbidities and weight categories.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or	The intervention is usually acceptable for clinicians, patients and health insurers. There are huge differences in patients´ preferences and knowledge and experience of sleep physicians and dentists.	The prediction of outcome is only partly feasible.

variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		There are differences in the recognition and acceptance of the various side-effects. Outcome depends on the different devices applied by various actors, also leading to various values.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	CPAP has in general a greater impact on AHI decrease and a higher impact on systolic night-time BP decrease in severe OSA. It is also advantageous with increasing severity of OSA, comorbidities, as well as odontological concerns.	However, in mild and moderate OSA, the AHI under MAD treatment is usually low and close to the normal range. Furthermore, there is some evidence of a better compliance and patient's preference in favour of MAD as compared to CPAP and similar impact on sleepiness and quality of life.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not look for studies on cost-effectiveness.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for studies on health equity.	The availability of MAD treatment might highly differ between countries due to different healthcare systems, including costs and to different levels of training and interest of dentists to sleep disorders. Indeed, MAD treatment requires a coordinated cooperation between dentists and sleep physicians for MAD initiation and long-term follow-up. As this is not given in all countries nor regions, equity is probably reduced.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not look for studies assessing acceptability.	Concerns on oral health, bite and craniofacial changes have to be taken into account. The intervention is usually acceptable for clinicians, patients and health insurers. Many patients prefer non-surgical alternatives. Treatment is acceptable if local side-effects are not overwhelming.

Feasibility

Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not look for studies assessing feasibility	The feasibility depends on the availability of the device, dedicated dentists, and reimbursement. These aspects vary substantially. There are technical limitations according to oral health, anatomical abnormalities and a sufficient number of teeth.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

In adult patients with OSA, we suggest that CPAP should be used as compared to MAD (conditional recommendation, low quality of evidence).

This recommendation does not differentiate regarding the severity of the disease. This is because most studies did not focus on specific subgroups in their inclusion criteria. However, most publications presented with mild to moderate OSA, while only a minor proportion with severe cases. In mild-moderate OSA, the difference in AHI becomes less important and therefore, due to equal effects on sleepiness and quality of life, both devices can be considered equally.

Justification

This recommendation is mainly based on the higher decrease of the AHI with CPAP over MAD. CPAP has a greater impact on AHI decrease, independently of OSA severity. This consideration, in addition to the higher impact of CPAP on systolic night-time BP decrease in severe OSA, leads the panel to a conditional recommendation in favour of CPAP in patients with OSA. However, in mild and moderate OSA, the AHI under MAD treatment is usually low and close to the normal range. Furthermore, there is some evidence of a better compliance and patient's preference in favour of MAD as compared to CPAP and similar impact on sleepiness and quality of life. Altogether, those considerations lead the panel to recommend CPAP and MAD equally in patients with mild to moderate OSA. With increasing severity of OSA, taking into account comorbidities, as well as odontological concerns, CPAP should be considered also in this group of patients.

Subgroup considerations

AHI less important in mild OSA.
Patients with nighttime hypertension benefit more from CPAP.

Implementation considerations

Availability differs due to different healthcare systems.

Training and interest of dentists, and long-time follow-up, cooperation between dentists and sleep physicians.

Monitoring and evaluation

Regular at least yearly follow-up with evaluation of adherence, symptoms, quality of life, efficacy (AHI, oxygenation), contraindications (oral health), side effects.

Research priorities

Studies with a higher number of patients, different severity categories, unbiased studies (no selection of patients), for other outcomes than AHI, studies including patients with all levels of weight/BMI, studies with cardiovascular outcome parameters needed, level of symptoms / symptomatic suffers (since it is the symptoms that brings patients to doctors), studies that take co-morbidities into account, long-time follow-up, objective compliance measurements, comparable cost-effectiveness studies in European countries; different types of devices, some are still entering the market; combination therapies (with positional therapy and CPAP)

PICO 2 APPENDICES

PICO 2 Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with custom made dual-block mandibular advancement device				
Apnea-hypopnea index (events/h) (AHI) assessed with: PSG at different time points (range 1 months - 12 months); Scale from 0 (best) to higher (worse)	The mean apnea-hypopnea index (events/h) was **3.7** events/hour	MD **7.76 events/hour more** (5.49 more to 10.02 more)	-	1110 (13 RCTs)	⨁⨁◯◯ LOW[a,b]	
Sleep efficiency % (SEI) assessed with: PSG at different time points (range: 1 month to 4 months); Scale from 0 (worst) to 100 best)	The mean sleep efficiency % was **84.1** %	MD **0.32 % lower** (2.23 lower to 1.59 higher)	-	871 (9 RCTs)	⨁⨁◯◯ LOW[a,b]	
<3% and <4% oxygen desaturation (events/h) assessed with: PSG at different time points (range 1-3 months), 0 (best) to higher (worse)	Five studies reported measures of oxygen desaturation (286 patients included and treated with MAD and CPAP in cross-over design). Four studies reported statistical significant results favouring CPAP. One study failed to show a statistically significant result.		-	286 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	
Sleepiness ESS assessed with: Epworth Sleepiness Scale at different time points (range 1 month to 12 months); Scale from 1 (best) to 24 (worst)	The mean sleepiness ESS was **7.0** points	MD **0.09 points lower** (0.58 lower to 0.41 higher)	-	990 (12 RCTs)	⨁⨁◯◯ LOW[c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with custom made dual-block mandibular advancement device				
Physical functioning assessed with: SF36-domain at different time points (range: 1 to 6 months) Scale 0-100, higher is better	The mean physical functioning was **79.3** points	MD **0.34 points lower** (3.06 lower to 2.38 higher)	-	667 (7 RCTs)	⨁⨁◯◯ LOW[c]	Additional evidence: Aarab: "The changes in the domains of the SF-36 were not significantly different between the three groups"
Arterial hypertension - 24h systolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 140mmHg	The mean arterial hypertension - 24h systolic blood pressure was **125.7** mmHg	MD **0.3 mmHg lower** (2.19 lower to 1.59 higher)	-	514 (4 RCTs)	⨁⨁⨁◯ MODERATE[a]	
Arterial hypertension - 24h diastolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 90mmHg	The mean arterial hypertension - 24h diastolic blood pressure was **77.9** mmHg	MD **0.12 mmHg lower** (1.41 lower to 1.16 higher)	-	514 (4 RCTs)	⨁⨁⨁◯ MODERATE[a]	
Nighttime systolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 140mmHg	The mean nighttime systolic blood pressure was **112.9** mmHg	Mean **1.56 mmHg more** (2.19 fewer to 5.3 more)	-	354 (3 RCTs)	⨁⨁◯◯ LOW[a,b]	
Nighttime diastolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 90mmHg	The mean nighttime diastolic blood pressure was **70.55** mmHg	Mean **0.99 mmHg lower** (3.08 lower to 1.09 higher)	-	514 (4 RCTs)	⨁⨁◯◯ LOW[a,b]	
Adherence / Compliance	Nine studies reported compliance (measured variously). Of these, compliance was statistically significant better with MAD compared to CPAP in 5 cases. In the other 4 cases no statistically significant difference could be shown or no information on statistics were given. - - - - - - Six studies Reported patients preferences. In one study CPAP was preferred, in the other five MAD was		-	499 (9 RCTs)	⨁⨁◯◯ LOW[c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with custom made dual-block mandibular advancement device				
	preferred - see supporting material.					
Adverse events	Six studies reported adverse events. Frequency was described as similar and intensity as mostly mild.		-	264 (6 RCTs)	⨁⨁◯◯ LOW[c]	

a. Minus 1 point for study limitations due to 2 or more domains at high risk of bias (mostly cross-over design and unblinded personnel)
b. Minus 1 point for inconsistency due to I2 results and not overlapping confidence intervals
c. Minus 2 points for study limitations due to 2 or more domains at high risk of bias (undblinded design with subjectively reported outcome and cross-over study design)

PICO 2 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/h) assessed with: PSG at different time points (range 1 months - 12 months); Scale from 0 (best) to higher (worse)	CRITICAL	⨁⨁◯◯ LOW[a,b]
Sleep efficiency % assessed with: PSG at different time points (range: 1 month to 4 months); Scale from 0 (worst) to 100 best)	CRITICAL	⨁⨁◯◯ LOW[a,b]
<3% and <4% oxygen desaturation (events/h) assessed with: PSG at different time points (range 1-3 months), 0 (best) to higher (worse)	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Sleepiness ESS assessed with: Epworth Sleepiness Scale at different time points (range 1 month to 12 months); Scale from 1 (best) to 24 (worst)	CRITICAL	⨁⨁◯◯ LOW[c]
Physical functioning assessed with: SF36-domain at different time points (range: 1 to 6 months) Scale 0-100, higher is better	CRITICAL	⨁⨁◯◯ LOW[c]
Arterial hypertension - 24h systolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 140mmHg	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Arterial hypertension - 24h diastolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 90mmHg	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Nighttime systolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 140mmHg		⨁⨁◯◯ LOW[a,b]
Nighttime diastolic blood pressure assessed with: PSG at different time points (1 to 3 months); hypertension above 90mmHg		⨁⨁◯◯ LOW[a,b]
Adherence / Compliance	CRITICAL	⨁⨁◯◯ LOW[c]

Outcomes	Importance	Certainty of the evidence (GRADE)
Adverse events	CRITICAL	⨁⨁◯◯ LOW[c]

a. Minus 1 point for study limitations due to 2 or more domains at high risk of bias (mostly cross-over design and unblinded personnel).
b. Minus 1 point for inconsistency due to 2 results and not overlapping confidence intervals.
c. Minus 2 points for study limitations due to 2 or more domains at high risk of bias (undblinded design with subjectively reported outcome and cross-over study design).

Table e13: PICO 3

QUESTION

Should hypoglossal nerve stimulation during sleep or no treatment be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Hypoglossal nerve stimulation during sleep.
COMPARISON:	No treatment.
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/hour); Sleep efficiency %; 4% oxygen desaturation; Sleepiness; Quality of life; Arterial hypertension (blood pressure systolic above 140mmHg and diastolic above 90mmHg); Compliance/adherence; Adverse events.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is an increasing group of patients with implanted HNS, particularly in the USA and Germany. Some national healthcare systems support HNS as an alternative (first or second line) to CPAP. However, there is limited evidence from prospective RCTs despite growing evidence from cohort follow up.	It is of interest to have more evidence on prospective AHI, ODI and ESS improvements, as well as compliance/adherence and impact on measures of quality of life.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The STAR trial provided evidence in a therapy withdrawal design (improvement of AHI/ODI and ESS), while the TESLA trial provided only short-term evidence on the primary outcome, the 4%ODI, which improved significantly, not the AHI. Responders to treatment were identified prior to inclusion in the STAR trial, not in the TESLA trial. However, 17/36 patients were labelled responders in the non-invasive approach (TESLA) revealing significant improvements in 4%ODI and AHI. *See Appendix 1*	Information from cohort studies reporting on the follow up over now >5 years reveal evidence that AHI, ODI and ESS significantly improve with ongoing efficacy and safety of the treatment.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Undesirable effects related to the invasive HNS are predominantly intervention/procedure related; the total SAE's in the follow up period of the STAR trial was about 2%. The non-invasive approach (TESLA) has no reported SAE's, but improves mouth-dryness. Claustrophobia was reported in the study by one patient for both intervention and sham-control stimulation. *See Appendix 1*	The severity and invasiveness of undesirable effect depends on the method (invasive procedures vs transcutaneous/non-invasive intervention). Follow up and compliance should be reported separately, as it is likely that SAE's, side effects and compliance will significantly differ between the methods.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence from prospective RCTs was low. More data have become available in long-term follow up studies of cohorts established on HNS. *See Appendix 2.*	There are sparse data on long-term prospective RCTs with higher number of patients, including different levels of OSA severity, various comorbidities and weight categories/ genders.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Except for the transcutaneous method, the procedure of HNS is considered invasive for clinicians, patients and health insurers. There are differences in patients' preferences and knowledge and experience of sleep physicians and ENT surgeons using the implantable HNS. The transcutaneous approach (TESLA/non-invasive) entails low costs (TENS machine) and has a low side effect profile. Patients are interested in these innovative approaches, where less sleepy patients are more likely to choose less invasive techniques [29].	HNS is not applied in Belgium / other countries as well, not largely applied. The USA and Germany employ the invasive method, while the UK has developed the non-invasive approach (TESLA) which is less expensive (currently undergoing domiciliary RCT/TESLA home). It is thought that the invasive HNS is too expensive in Europe. NICE has developed a guidance for HNS, but it is not used in the UK yet, and reimbursement remains unclear. As long as HNS is available in some countries only, but not all, it is thought to remain available only to a few patients.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	CPAP has in general a greater impact on the AHI/ODI, particularly in obese patients with very severe OSA. CPAP has proven efficacy on long-term outcomes, quality of life and cost-efficacy.	In a specific group of patients, HNS may be considered: non-responders to CPAP and MAD who remain sleepy may benefit from this treatment. In addition, non-compliant patients who do not continue with first line therapy, such as CPAP/MAD< may benefit from this approach. On other hand, HNS remains not easily available, although this may change in future and with the availability of a non-invasive approach. The current prospective evidence from RCTs does not show statistically significant improvements between groups, although follow up cohorts and recent meta-analysis may add to this evidence.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not look for studies on cost-effectiveness.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased	We did not look for studies on health equity.	The availability of HNS treatment may differ significantly between countries, as in some countries this treatment is supported by the healthcare system (e.g. USA/Germany), while it remains unavailable in many other countries. Not all

○ Increased ○ Varies ○ Don't know		patients can access it as HNS and TESLA are typically available in centres only. Therefore, equity is reduced.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing acceptability, but quote the patient feedback in the TESLA trial (with good acceptability and low side effect spectrum).	From patients' perspective, there are high expectations, alternative therapies to CPAP/ MAD may appeal as very popular and very acceptable. However, the invasive approach is not easily reversible, which limits acceptability. This may be helped in a wider availability of a non-invasive approach in future (e.g. TESLA home RCT).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	The feasibility depends on the availability of the device, sleep laboratory, ENT surgeon (with DISE experience) and operating theatre. It needs to be differentiated between the invasive (STAR) and non-invasive (TESLA) approach, as transcutaneous electrical stimulation is widely available and requires less sophisticated titration / follow up. However, there remains uncertainty about outcomes, risks, costs, and availability between countries.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest that hypoglossal nerve stimulation should not be used as first line treatment for OSA patients in general (conditional recommendation, low quality of evidence). However, we suggest that hypoglossal nerve stimulation compared to no treatment should be used as a salvage treatment in patients with symptomatic obstructive sleep apnoea, who cannot be sufficiently treated with positive airway pressure treatment (CPAP, BPAP) or MAD, and who have an AHI below 50/hour and a BMI <32 kg/m2 (conditional recommendation, very low quality of evidence).

Justification

This recommendation is mainly based on the limited evidence available for this intervention; No RCT in HNS in unselected patients is available.No significant reduction in AHI or sleepiness was found with TESLA, while quality of life improved. For some patients seeking for alternative treatment, it might be an acceptable treatment option.

Subgroup considerations

It is important to consider subgroups of responders and non-responders to this treatment, which is also defined by OSA severity and BMI, neck circumference. The outcomes have also to be balanced related to the underlying pathophysiological traits of OSA. Some patients may be more willing to accept surgical intervention if intolerant to CPAP or reluctant to use it. Future study designs should compare this method against usual care (CPAP/MAD) and include longer follow-up periods and markers for quality of life / symptoms. Furthermore, consideration needs to be given to the various different methods of HNS, particularly the invasive vs transcutaneous (non-invasive) approach.

Implementation considerations

Availability differs due to different healthcare systems and approvals / lack of approvals. The required training of staff in the sleep laboratory, ENT surgeon, anaesthetist and titration of the devices in the invasive approach of HNS limit implementation in any other setting than centres.

In contrast, the non-invasive approach (TESLA) using TENS machines may become more widely available, although comfortable settings (current) and effective intensity need to be considered when establishing patients on this treatment.

Monitoring and evaluation

Regular and at least annual follow-up should be performed just as in CPAP / other treatments to demonstrate efficacy (AHI/ODI, symptoms, quality of life), adherence, safety and long-term implications.

Research priorities

Prospective RCT using HNS / TESLA with CPAP or MAD in the control arm should be undertaken, ideally with longer follow up periods, to prove the efficacy on outcomes (AHI/ODI, symptoms, quality of life, compliance). Responders and non-responders, as well as the different levels of efficacies dependent on the OSA severity, BMI and gender require further attention. Health-related cost-efficacy studies would be useful for various healthcare settings and methods. Combination therapies with CPAP and MAD may be useful.

Additional outcomes to study: effect on hypertension, metabolic effects, symptomatic improvement.

Cohorts of interest: patients with conditions that may not allow for the use of facial masks due to required care (or dexterity), e.g. neuromuscular conditions, post-stroke, learning disability, anxiety.

PICO 3 APPENDICES

PICO 3 Appendix 1

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Apopnea-hypopnea index (events/hour) (AHI) assessed with: PSG at different follow-up points (range: 1 night to 6 months)	Two out of three included studies showed no statistical difference between groups at 1 night and 6 months follow-up, while one study showed statistically significant difference favouring the intervention after 1 week therapy withdrawal in previous responders.	103 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]
Sleep efficiency % assessed with: PSG (follow-up 1 night)	One study reported sleep efficiency for the one night of each intervention and showed no statistically significant difference between arms.	36 (1 RCT)	⨁◯◯◯ VERY LOW[a,d]
4% oxygen desaturation (ODI) assessed with: PSG at different follow-up time points (range: 1 night to 6 months)	Two out of three included studies showed no statistical difference between groups after 1 week and 6 months follow-up, while one study showed statistically significant difference favouring the intervention at the one night of treatment.	103 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b,e]
Sleepiness assessed with: Stanford (1x) and Epworth (2x) Sleepiness Scale (range: 1 night to 6 months)	None of the studies showed a statistical significant effect for sleepiness (assessed with ESS by Barnes and STAR and Stanford Sleepiness Scale by TESLA).	103 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire "scores range from 5.0 to 20.0, with higher scores indicating greater functioning" and Beck Depression Inventar (0 points (best) to 63 (worst)) follow-up range: 1 week to 6 months	Two studies reported outcomes relating to quality of life (1 week and 6 months follow-up) and both showed statistical significant effects favouring the intervention.	67 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]
Arterial hypertension (blood pressure systolic above 140mmHG and diastolic above 90mmHg)	One study reported no statistical significant differences between intervention and control looking at systolic and diastolic blood pressure after 1 week of therapy withdrawal.	46 (1 RCT)	⨁◯◯◯ VERY LOW[a,d]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
assessed with: PSG (follow-up 1 week withdrawal)			
Compliance/adherence assessed with: follow-up 1 night	Only one study reported the outcome 'compliance' after the 1 night of treatment: TESLA: "The patients' device acceptance was good with patients reporting no skin discomfort or unpleasant sensations at night. There was no difference in patients' perceived sleep quality. There was a 59% reduction in mouth dryness after active treatment compared to sham-stimulation. There were no severe adverse events"	36 (1 RCT)	⨁◯◯◯ VERY LOW[a,d]
Adverse events assessed with: (range: 1 night to 1 week withdrawal in RCT, but 13 month cohort study)	Two studies reported adverse events narratively. STAR (in total cohort 126, over 13 months of follow up): 2 serious adverse events device-related, another 33 serious adverse events not device-related. Most non serious adverse events implantation-related. See supporting material for further info. TESLA (transcutaneous): The only significant side effect observed was one patient who complained about claustrophobia at night; this was during both treatment nights. The total count of mild side effects occurred in 2.8% of the studied cohort and there were no severe adverse events.	162 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]

a. Minus 1 for strongly suspected publication bias due to two terminated trials with unpublished/only partly published data
b. Minus 2 for imprecision due limited number of patients and pooling was not possible
c. Minus 1 for inconsistency since 2 studies show stat. sign. effect and one doesn't
d. Minus 2 due to very limited number of patients
e. Minus 1 for inconsistency since 2 studies show no stat. sign. effect and one does

PICO 3 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Appnoea-hypopnoea index (events/hour) assessed with: PSG at different follow-up points (range: 1 night to 6 months)	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Sleep efficiency % assessed with: PSG (follow-up 1 night)	CRITICAL	⨁◯◯◯ VERY LOW[a,d]
4% oxygen desaturation assessed with: PSG at different follow-up time points (range: 1 night to 6 months)	CRITICAL	⨁◯◯◯ VERY LOW[a,b,e]
Sleepiness assessed with: Stanford (1x) and Epworth (2x) Sleepiness Scale (range: 1 night to 6 months)	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire "scores range from 5.0 to 20.0, with higher scores indicating greater functioning" and Beck Depression Inventar (0 points (best) to 63 (worst)) follow-up range: 1 week to 6 months	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Arterial hypertension (blood pressure systolic above 140mmHg and diastolic above 90mmHg) assessed with: PSG (follow-up 1 week withdrawal)	CRITICAL	⨁◯◯◯ VERY LOW[a,d]
Compliance/adherence assessed with: follow-up 1 night	CRITICAL	⨁◯◯◯ VERY LOW[a,d]
Adverse events assessed with: (range: 1 night to 1 week withdrawal in RCT, but 13 month cohort study)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

a. Minus 1 for strongly suspected publication bias due to two terminated trials with unpublished/only partly published data.
b. Minus 2 for imprecision due limited number of patients and pooling was not possible.
c. Minus 1 for inconsistency since 2 studies show stat. sign. effect and one doesn't.
d. Minus 2 due to very limited number of patients.

e. Minus 1 for inconsistency since 2 studies show no stat. sign. effect and one does.

Table e14: PICO 4a

QUESTION

Should myofunctional therapy or no treatment be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Myofunctional therapy.
COMPARISON:	No treatment.
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/hour) (AHI); Sleep efficiency %; Sleepiness ESS; Quality of life ; Adherence / Compliance measured subjectively with diary entries or objectively (Randerath); Adverse events.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is a need for new or complementary therapeutic modalities for OSA. Therefore, a formal European recommendation is urgently required.	Other reasons for this are the percentage of patients who do not respond satisfactorily to available treatments, the reduced adherence to CPAP and the possible complications of surgical procedures.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	After intervention, small improvement in AHI, ESS and quality of life, no statistically significant results in all studies. *See Appendix 1.*	Effect might be only temporary. AHI : although statistically significant, potentially not from moderate to mild. More than 2 points for ESS means a clinically significant change: symptomatic improvement.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No reported or limited. *See Appendix 1*.	Mild symptoms of erythema, skin irritation and facial pain.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall quality of evidence was low. *See Appendix 2.*	Myofunctional therapy is not suggested as a standard/regular treatment of OSA, but only for specific cases seeking alternative treatments and who are reluctant to surgical or mechanical strategies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability	There is limited evidence available for this intervention, based on only six small RCTs.	Different types of patients might be an opportunity for some

● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Moreover, this treatment offers only a small and probably temporary advantage over existing treatments and patients might reject other proven effective treatment options.	of them. Some concerns: acceptance of the chronic condition, upset with maintstream therapies. Some might look for the most effective treatments, other for alternative treatments like this one.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	This treatment offers only a small and probably temporary advantage over existing treatments with limited undesirable effects.	Data on adverse events was reported in two studies (82 patients). One reported no adverse or unexpected events in either group and the other reported mild erythema, skin irritation and facial pain compared to placebo patients.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not look for studies on health equity	Less problems with costs of the device compared to other PICO interventions. Health insurance might not cover this treatment, depends on the health care system and whether speech therapy is reimbursed.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not look for studies assessing acceptability.	For many patients it might be acceptable as they seek for alternatives. Acceptable for professionals (e.g. speech therapists). Acceptability for physicians might be reduced (currently no large clincially relevant effects, low certainty of the evidence).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	Not enough trained speech therapists available, experience for sleep apnoea are lacking.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
			comparison				
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We do not suggest myofunctional therapy as a standard/regular treatment of OSA, but only for specific cases who seek for alternative treatments and who are reluctant to surgical or mechanical strategies (conditional recommendation, low quality of evidence).

Justification

There is limited evidence available for this intervention, based on only six small RCTs. Moreover, this treatment offers only a small and probably temporary advantage over existing treatments and patients might reject other proven effective treatment options. Nevertheless, for many patients seeking for alternative treatment, it might be an acceptable treatment option rejecting effective treatment options. In this case, regular follow-up should be performed, similar to other treatments, in order to demonstrate efficacy. The therapy is limited by cost, feasibility and missing long-term data.

Subgroup considerations

There are not enough trained professionals (e.g. speech therapists) and there is a concern regarding adequate training on OSA patients. Furthermore, health insurance might not cover this type of treatment, depending on the health care system and reimbursement policies.

Implementation considerations

Availability differs due to different healthcare systems.

Trained professionals are needed in cooperation with sleep physicians as well as long-time follow-up time.

Monitoring and evaluation

Regular at least yearly follow-up with evaluation of adherence, symptoms, quality of life, efficacy (AHI, oxygenation), contraindications (oral health), side effects.

Research priorities

More RCTs are warranted involving a larger number of patients and longer treatment periods to determine if the beneficial effects of myofunctional therapy can be sustained over prolonged periods of time.

APPENDICES PICO 4 A

PICO 4a Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with myofunctional therapy				
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG at between 6 weeks and 4 months of follow-up; Scale from 0 (best) to higher (worst)	The mean apnoea-hypopnoea index (events/hour) (AHI) was **24.95** events/hour	mean **8.19 events/hour lower** (14.27 lower to 2.11 lower)	-	230 (6 RCTs)	⨁⨁◯◯ LOW[a,b]	Additional evidence: Ieto and Torres-Castro reported results as median + interquartile ranges. For Ieto, AHI decreased in both arms (no info about significant differences between groups). For Torres-Castro, AHI increased in both arms (also no info about significant differences between groups). See supporting material for details
Sleep efficiency % assessed with: PSG at 3 months of follow-up; scale 0 (worst) to 100% (best)	The mean sleep efficiency % was **85.73** %	mean **0.06 % lower** (3.79 lower to 3.67 higher)	-	121 (3 RCTs)	⨁⨁◯◯ LOW[c]	
Sleepiness ESS assessed with: Epworth Sleepiness Scale at between 6 weeks and 4 months follow-up; Scale from 1 (best) to 24 (worst)	The mean sleepiness ESS was **10.8** points	mean **2.71 points lower** (4.97 lower to 0.45 lower)	-	230 (6 RCTs)	⨁⨁◯◯ LOW[b,d]	Additional evidence: Ieto and Torres-Castro reported results as median + interquartile ranges. For Ieto sleepiness kept steady in the intervention arm and non-significantly, slightly improved in the control arm (not sign. between groups). Torres-Castro found similar results.
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire (FOSQ) + Quebec Sleep Questionnaire + SF-36 functional capacity	see comment	see comment	-	135 (3 RCTs)	⨁⨁◯◯ LOW[e]	QoL improved in the myofunctional therapy arm in one study. In two other studies it improved in both arms (Diaferia (SF-36): "functional capacity domain of the SF-36 improved in the speech therapy group (P < 0.03)" - - - - Randerath: "A similar pretraining to posttraining increase was observed in both groups in the score of the Functional Outcome of Sleep Questionnaire score" - - - - - Torres-Castro: Quebec Sleep Questionnaire: Increased slighty (non-sign.) in both arms.)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with myofunctional therapy				
Adherence / Compliance measured subjectively with diaiy entries or objectively (Randerath)	see comment	see comment	-	123 (5 RCTs)	⨁⨁◯◯ LOW[e]	Diaferia: myofunctional therapy 63%; sham control 55% - - - Guimares: intervention: exclusion of 3 pts due to low compliance, in control 5 pts - - - Ieto: "The % of adherence to the exercises according to the weekly diaries was > 75% for all pts and was on average 85% ± 8%." - - - Puhan: pts practised an average of 5.9 days a week (SD 0.86) for 25.3 minutes (SD 3.4) (were asked to do it at least 5 days a week for 20min) - - - Randerath obj.:"There were no differences in the duration of use"[f]
Adverse events	see comment	see comment	-	82 (2 RCTs)	⨁⨁◯◯ LOW[e]	Puhan: "There were no adverse or unexpected events in either group." - - - Randerath: "On a scale of 0 (minimum) to 6 (maximum), treated patients scored the symptoms erythema (treated patients, 0.4; ± 0.7; placebo, 0.2 ± 1.0; P< .05), skin irritation (treated patients, 0.7 ± 1.4; placebo, 0.3 ± 1.2; P< .05), and facial pain (treated patients, 1.1 ± 1.8; placebo, 0.3 ± 1.0; P< .05) higher than did placebo patients"

a. Minus 1 for inconsistency since the statistical I^2 > 60%.
b. Minus 1 for imprecision due to low number of included patients.
c. Minus 2 for imprecision since the 95% CI suggest the possibility of both benefit and harm; only 121 patients included.
d. Minus 1 for inconsistency since the results which were reported as 'median' only and could not be included in the statistical analysis show results potentially favouring potentially favouring the direction of control, which is contrary to the result of the meta-analysis.
e. Minus 2 for imprecision: data not able to be analysed quantitatively, due to heterogenous reporting of results; low number of included patients.
f. * Randerath: in control group 9 pts lost to follow up, in intervention group 1 pt; but reasons given transparently (due to medical, professional, personal reasons).

PICO 4a Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG at between 6 weeks and 4 months of follow-up; Scale from 0 (best) to higher (worst)	CRITICAL	⨁⨁◯◯ LOW[a,b]
Sleep efficiency % assessed with: PSG at 3 months of follow-up; scale 0 (worst) to 100% (best)	CRITICAL	⨁⨁◯◯ LOW[c]
Sleepiness ESS assessed with: Epworth Sleepiness Scale at between 6 weeks and 4 months follow-up; Scale from 1 (best) to 24 (worst)	CRITICAL	⨁⨁◯◯ LOW[b,d]
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire (FOSQ) + Quebec Sleep Questionnaire + SF-36 functional capacity	CRITICAL	⨁⨁◯◯ LOW[e]
Adherence / Compliance measured subjectively with dairy entries or objectively (Randerath)	CRITICAL	⨁⨁◯◯ LOW[e]
Adverse events	CRITICAL	⨁⨁◯◯ LOW[e]

a. Minus 1 for inconsistency since the statistical I^2 > 60%.
b. Minus 1 for imprecision due to low number of included patients.
c. Minus 2 for imprecision since the 95% CI suggest the possibility of both benefit and harm; only 121 patients included.
d. Minus 1 for inconsistency since the results which were reported as 'median' only and could not be included in the statistical analysis show results potentially favouring the direction of control, which is contrary to the result of the meta-analysis.
e. Minus 2 for imprecision: data not able to be analysed quantitatively, due to heterogeneous reporting of results; low number of included patients.

Table e15: PICO 4b

QUESTION

Should myofunctional therapy or CPAP be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Myofunctional therapy.
COMPARISON:	CPAP.
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/hour) (AHI); Sleep efficiency %; Sleepiness ESS; Quality of life; Adherence / Compliance.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	CPAP is effective in the treatment of severe as well as of mild OSA, but its acceptability may be more problematic for patients with mild to moderate forms of this disorder. Myofunctional therapy is still a poorly known alternative therapy for these patients.	Technique of administration of myofunctional terapy is not standardised. Outcomes could differ depending on administration modality.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	AHI and subjective sleepiness improved with both therapies. Quality of life improved with myofunctional therapy but not with CPAP. Subjectively reported good adherence with myofunctional therapy. *See Appendix 1.*	Single RCT, potentially underpowered. Both arms improved. Difference between treatment effects not analysed.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Residual AHI after therapy apparently higher with myofunctional therapy (difference in effect non tested statistically). *See Appendix 1.*	A limited correction of AHI could result in insufficient protection against OSA complications.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall quality of evidence was low. *See Appendix 2*	Only one RCT is available, with a small number of patients.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or	Although some patients may prefer myofunctional therapy to CPAP, average compliance to myofunctional therapy may not be better than with CPAP. On the other hand, in compliant patients correction of respiratory disorders with myofunctional therapy is unlikely to be as good as with CPAP. The panel assumes possible uncertainty/ variability There is uncertainty how	See PICO 4a. Predictors of better compliance with one therapy should be

variability ○ No important uncertainty or variability	patients and physician value myofunctional therapy. Some may prefer a non-CPAP approach, while others may prefer the more effective suppression of respiratory disturbances under CPAP.	identified.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Myofunctional therapy offers symptomatic and quality of life improvement, with limited undesirable effects, while residual AHI is apparently higher compared to CPAP:	Effects of myofunctional therapy on blood pressure of OSA patients are not yet studied.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not look for studies on health equity.	See PICO 4a.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	We did not look for studies assessing acceptability.	See PICO 4a.

○ Probably yes ○ Yes ● Varies ○ Don't know		Long term adherence to CPAP: not unsubstantial numbers 25% after 3 months, after 12 months: 50% non-adherence to CPAP 30% in RCT might not reflect current practice, people in the trial might be highly selected.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	See Pico 4a. No problem with CPAP.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest using CPAP instead of myofunctional therapy for adult patients (conditional recommendation, low quality of evidence)

Justification

Currently, limited evidence is available for this intervention based on one RCT only. In this RCT, the panel determined that the benefit of the intervention as compared to CPAP was of similar effect size for sleepiness, but lower for AHI with no statistical tests performed to compare the in-group differences. However, no significant side effects were reported. The low objective compliance to CPAP could explain the significant but limited beneficial effects in the CPAP arm; adequate CPAP adherence, as in standard practice, could even further contribute to the benefits observed. The panel concluded that in summary of the above the comparison group (CPAP) was favoured.

Subgroup considerations

Specific subcohorts of patients could value several outcomes of the intervention, particularly when they have discontinued CPAP therapy. The intervention has a limited feasibility due to insufficient availability of trained speech therapists who, in addition, often lack experience for sleep apnoea. Health insurance might not cover this treatment. It is currently not clear whether, and if so for how long, any interventional treatment effects are maintained.

Implementation considerations

Training and interest of physiotherapists, as well as cooperation between physiotherapists and sleep physicians, need to be implemented.

Monitoring and evaluation

Regular follow-up to re-inforce adherence to therapy and evaluate its efficacy over time.

Research priorities

Long-term studies to evaluate feasibility of long-term treatment by myofuncttional therapy and RCTs to explore effects of therapy not only on sleep variables, but also on the natural history of patients with obstructive sleep apnea under different treatments are needed.

APPENDICES PICO 4B

PICO 4b Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with myofunctional therapy				
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG at 3 months follow-up; Scale from 0 (best) to higher (worst)	see comment	see comment	-	54 (1 RCT)	⨁⨁◯◯ LOW[a]	speech therapy: decrease from 28 ± 22.7 to 13.9 ± 18.5; p<0.001 - - - CPAP: decrease from 34.4 ± 22.4 to 4.3 ± 4.0; p<0.001 - - - between group difference: not given
Sleep efficiency % assessed with: PSG at 3 months follow-up; Scale from 0 (worst) to 100 (best)	see comment	see comment	-	54 (1 RCT)	⨁⨁◯◯ LOW[a]	speech therapy: decrease from 85.7 ± 9.5 to 84.5 ± 13.1 - - - CPAP: slight decrease from 86.9 ± 9.9 to 86.6 ± 7.8 - - - between groups: not sign.
Sleepiness ESS assessed with: Epworth Sleepiness Scale at 3 months follow-up; Scale from 1 (best) to 24 (worst)	see comment	see comment	-	54 (1 RCT)	⨁⨁◯◯ LOW[a]	speech therapy: decrease from 13.7 ± 3.2 to 7.5 ± 3.7; p < 0.001 - - - CPAP decrease from 12.0 ± 2.1 to 7.2 ± 3.6; p < 0.001 - - - between group differences not given
Quality of life assessed with: SF-36 functional capacity at 3 months follow-up; scale 0 = worst to 100 = best	see comment	see comment	-	54 (1 RCT)	⨁⨁◯◯ LOW[a]	"functional capacity domain of the SF-36 improved in the speech therapy group (P < 0.03)"
Adherence / Compliance	see comment	see comment	-	54 (1 RCT)	⨁⨁◯◯ LOW[a]	speech therapy: 63% (subjectively); CPAP: 30% (objectively)

a. Minus 2 for imprecision due to low number of patients and due of reporting of results quantitative analysis was not possible.

PICO 4b Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG at 3 months follow-up; Scale from 0 (best) to higher (worst)	CRITICAL	⨁⨁◯◯ LOW[a]
Sleep efficiency % assessed with: PSG at 3 months follow-up; Scale from 0 (worst) to 100 (best)	CRITICAL	⨁⨁◯◯ LOW[a]
Sleepiness ESS assessed with: Epworth Sleepiness Scale at 3 months follow-up; Scale from 1 (best) to 24 (worst)	CRITICAL	⨁⨁◯◯ LOW[a]
Quality of life assessed with: SF-36 functional capacity at 3 months follow-up; scale 0 = worst to 100 = best	CRITICAL	⨁⨁◯◯ LOW[a]
Adherence / Compliance	CRITICAL	⨁⨁◯◯ LOW[a]

a. Minus 2 for imprecision due to low number of patients and due of reporting of results quantitative analysis was not possible.

Table e16: PICO 5

QUESTION

Should maxillo- mandibular osteotomy or CPAP be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Maxillo-mandibular osteotomy.
COMPARISON:	CPAP.
MAIN OUTCOMES:	Apnoea-hypopnoea index; Sleepiness; Satisfaction; Adverse events.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	MMO has been pointed out as a highly effective therapy for abolishing obstructive apnoeas, but most of the present knowledge on its effects is based on uncontrolled studies on case series. Besides, invasiveness and complexity of the technique have prevented its widespread use.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Improvement in AHI and sleepiness did not differ between MMO and CPAP. Average degree of satisfaction was similar as well. *See Appendix 1*	Occasionally, dissatisfaction with MMO could derive from moderate to severe side effects, which are less likely to occur with CPAP.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	One acute episode of dyspnoea due to tracheotomy tube crusting after surgery. Minor side effects of variable duration in all patients. *See Appendix 1.*	Additional orthodontic work may be required. The TF prioritised the magnitude of the AEs when making the judgment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of evidence was very low. *See Appendix 2.*	Only 1 RCT was available. Trial includes only patients with high AHI (>30). In patients with less severe disease, efficacy would likely be the same as what was observed in the trial, but evidence is indirect.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or	Intervention assesed as satisfactory by most patients, but large interindividual differences cannot be excluded.	Variability could be introduced by age (younger may prefer surgery), underlying unfavourable profile of the face. Also important uncertainty when considering patients with

variability ○ No important uncertainty or variability		high AHI (>30) and lower AHI (<30). Lower AHI might value potential for AEs as more important (similar to patients who are not experiencing sleepiness).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Resolution of nocturnal respiratory disorders substantially similar with MMO and CPAP, but moderate side effects during the trial observed only with MMO.	Probably favours CPAP, because trivial desirable but moderate undesirable. Recognises some variability in values and preferences.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not look for studies on cost-effectiveness.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for studies on health equity.	Availability and cost may be a problem for MMO.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing acceptability.	Patients: May vary. Clinicians: Yes. Health insurers: Yes.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	In some locations, limited specialists are available. Accessibility varies on location.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

In adult patients with OSA, the TF suggests using either MMO or CPAP (conditional recommendation, very low quality of evidence).

Justification

In the presented RCT, the panel determined differential benefits between MMO and CPAP to be trivial. Moderate adverse effects were associated with MMO, which could also require additional orthodontic work. Initially, patients may prefer CPAP because it is less invasive than MMO, but some patients may find MMO an acceptable alternative if they value not using CPAP or have other rationale for facial surgery. Patients who value the potential for adverse events or potential esthetical concerns more, may find MMO less acceptable. For patients experiencing CPAP failure, MMO is an effective alternative. Altogether, balance of effects may favour CPAP, but younger people and patients with high AHI may be more prone to accept MMO. Availability and cost may be a problem for MMO.

Subgroup considerations

The intervention is usually acceptable for clinicians and health insurers, but its acceptability may largely vary among patients. There are age limitations in some countries.

Implementation considerations

A greater involvement of maxillo-facial surgeons in the management of obstructive sleep apnoea is advisable to improve the multidisciplinary approach to this disorder, increase number and quality of studies on surgical treatment, and augment availability of maxillo-facial surgery when it could be appropriate.

Monitoring and evaluation

Short-term and long-term follow-ups are indicated to evaluate efficacy of treatment, side-effects and possible relapses.

Research priorities

At present, evidence from RCT is extremely limited. More studies are needed. They should also address aspects that were not considered in the available RCT study, like changes in blood pressure and in objective sleep quality.

PICO 5 APPENDICES

PICO 5 Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with maxillo-mandibular osteotomy				
Apnoea-hypopnoea index (AHI) assessed with: polysomnography (at home) Scale from: 0 (best) to higher (worst) follow up: mean 1 years	The mean apnoea-hypopnoea index was **6.3** events/hour	mean **1.8 events/hour more** (3.3 fewer to 6.9 more)	-	50 (1 RCT)	⨁⨁◯◯ LOW[a,b]	Change with MMO: decrease from 56.8 (SD 16.5) to 8.1 (SD 7.0); Change score: 48.7 events/hour- - - change with CPAP: decrease from 50.3 (SD 12.4) to 6.3 (SD 1.9); Change score: 44.0 events/hour- - - p = 0.21
Sleepiness assessed with: Epworth Sleepiness Scale Scale from: 0 (best) to 24 (worst) follow up: mean 1 years	The mean sleepiness was **5.9** points	mean **1.8 points more** (1.5 more to 2.1 more)	-	50 (1 RCT)	⨁⨁◯◯ LOW[b,c]	Intervention arm: decrease from 11.6 (2.8) to 7.7 (1.3) - - - control arm: decrease from 11.2 (2.6) to 5.9 (1.6) - - - p = 0.20
Satisfaction assessed with: visual analogue scale in % Scale from: 0 (worst) to 100 (best) follow up: mean 1 years	The mean satisfaction was **90** %	mean **4 % higher** (0 to 0)	-	50 (1 RCT)	⨁◯◯◯ VERY LOW[b,c]	"No statistically significant difference"

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with maxillo-mandibular osteotomy				
Adverse events	MMO arm: (1) acute episode of tracheotomy tube crusting with sudden dyspnoea; All patients had transient paresthesias in infraorbital and mandibular areas; (7) persistent but not disturbing paresthesia around the chin; (6) slight to minimal malocclusion; (1) minimal orthodontic correction was required - - - CPAP: (4) patients required more than 3 consultations to stabilize the full fruition of the ventilation device; (1) lesion to the facial skin (overcome with a new type of mask)		-	50 (1 RCT)	⨁◯◯◯ VERY LOW[b,c]	Complaints from patients: CPAP arm: almost all patients complained of minor discomfort, whereas 3 requested to stop the treatment& entered the surgical group

a. Downgraded two for imprecision: 95% CI suggest the possibility of both benefit and harm; only 50 participants included"From a methodological point of view, the true limit of this study is its low power. The power calculation suggests that a well-designed study would need to be extremely large and would almost certainly require multi-institutional collaboration for collecting larger surgical serie", baseline scores differ.
b. Downgraded one for study limitations: 2 domains of high risk of bias due to unblinded study (blinding not possible). Home-based instead of clinical polysomnography not determined to introduce bias.
c. Downgraded two for imprecision: only 50 participants included"From a methodological point of view, the true limit of this study is its low power. The power calculation suggests that a well-designed study would need to be extremely large and would almost certainly require multi-institutional collaboration for collecting larger surgical serie", baseline scores differ.

PICO 5 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index assessed with: polysomnography (at home) Scale from: 0 (best) to higher (worst) follow up: mean 1 years	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Sleepiness assessed with: Epworth Sleepiness Scale Scale from: 0 (best) to 24 (worst) follow up: mean 1 years	CRITICAL	⨁◯◯◯ VERY LOW[b,c]
Satisfaction assessed with: visual analogue scale in % Scale from: 0 (worst) to 100 (best) follow up: mean 1 years	CRITICAL	⨁◯◯◯ VERY LOW[b,c]
Adverse events	CRITICAL	⨁◯◯◯ VERY LOW[b,c]

a. Downgraded two for imprecision: 95% CI suggest the possibility of both benefit and harm; only 50 participants included"From a methodological point of view, the true limit of this study is its low power. The power calculation suggests that a well-designed study would need to be extremely large and would almost certainly require multi-institutional collaboration for collecting larger surgical serie", baseline scores differ.
b. Downgraded one for study limitations: 2 domains of high risk of bias due to unblinded study (blinding not possible).
c. Downgraded two for imprecision: only 50 participants included"From a methodological point of view, the true limit of this study is its low power. The power calculation suggests that a well-designed study would need to be extremely large and would almost certainly require multi-institutional collaboration for collecting larger surgical serie", baseline scores differ.

Table e17: PICO 6

QUESTION

Should carbonic anhydrase inhibitors (compared to placebo) be used for adult patients with obstructive sleep apnoea?	
POPULATION:	Adult patients with obstructive sleep apnoea.
INTERVENTION:	Carbonic anhydrase inhibitors.
COMPARISON:	Placebo.
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/hour) (AHI); Sleep efficiency %; 4% oxygen desaturation index (events/hour) (ODI); Sleepiness ESS / Karolinska sleepiness scale; Arterial hypertension; Adherence / Compliance; Adverse events.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Due to a high prevalence of CPAP non-adherence there is also a high demand for pharmaceutical therapies.There is still a sparsity of data, especially from RCTs, on the efficacy of a pharmacological therapy in OSA. Several studies in the field deal with drugs with carbonic anhydrase inhibitory properties. The positioning for such therapies is unclear and a formal European recommendation is urgently needed.	In the determination of efficacy, it is of interest to not only focus on the AHI but also on other outcomes like oxygenation, comorbidities and quality of life.

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	Efficacy may be expressed in terms of reduced sleepiness, improved cognition, reduced blood pressure, potential primary preventive effects or improvement of metabolic disease. The majority of these outcomes have not been explored after carbonic anhydrase inhibitors in OSA. Phase II data suggest approximately 50% AHI reduction in half the population although patients may exhibit both smaller and bigger effects.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	The clinical effect needs to be assessed with respect to dose dependency and duration. Effects: dose-dependent Could result in polypharmacy in patients with co-morbidities (no data) Undesirable effects can be more important in patients with severe obstructive sleep apnoea and hypoxia Discussion: small to moderate
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ● Low ○ Moderate ○ High ○ No included studies	*See Appendix 2*	Only few studies available but the bulk of data suggests a substantial but variable effect. Several candidate drugs are under investigation. No drug with a label including OSA has yet undergone regulatory evaluation (except medications aimed to reduce overweight or obesity).

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Only very limited data available. Tolerability important for compliance. Probably no important variability.	Drug therapies may be considered in various combination strategies. It is likely that the efficacy of various types of medication (pharmacological therapies in OSA) will vary with respect to phenotype. Tools to predict the best therapeutic alternative in a given patient, potentially based on biomarkers, need to be developed. This need might be higher after various drugs compared with eg. CPAP in OSA.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Very limited data available. Favors intervention.	Small studies only and RCTs needed. High variability in terms of tolerance expected.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not look for studies on cost-effectiveness	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for studies on health equity.	All drugs should be available, but off-label, patients might have to cover costs.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing acceptability.	Limitation: physicians might not be aware of this possibility. Patients might prefer compared to CPAP.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	Off label use. As the certainty of the evidence is low, physicians might have some concerns to prescribe

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention

○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest the use of carbonic anhydrase inhibitors only in the context of an RCT, as there is no drug in this category with an approved label for OSA (conditional recommendation, low quality of evidence).

Justification

The acute effects of carbonic anhydrase inhibitors in OSA are reasonably well documented and there is biological plausibility, although the amount of evidence is limited. The effect on bordering co-morbid conditions is incompletely studied and there is concern regarding long-term outcome due to missing data. The only drug in this class with more extensive documentation is acetazolamide, but there is no approved label on this drug for use in OSA. Side effects seem to be class specific for drugs with carbonic anhydrase inhibitory effect and proper mapping of safety should be performed over longer-term therapy. Excessive daytime sleepiness has not been shown to decrease after therapy. Cognitive symptoms are not uncommon for drugs with a carbonic anhydrase inhibitory effect including topiramate and zonisamide. In addition, it remains that variability in the response to drug could be introduced by age, occupation, severity of the underlying condition and comorbidities. Putting these aspects together, the panel decided to make a recommendation for use under research conditions.

Subgroup considerations

Drug therapy is familiar, acceptable for clinicians, and frequently preferred by patients. There is no prior art on the regulatory concerns that may be applied on the approval of a drug to be used in OSA, particularly with respect to relevant outcomes, efficacy and side effects. In addition, the endpoints that would justify a willingness to pay for this type of therapy in OSA are still uncertain.

Implementation considerations

Cost is not a limiting factor, given acetazolamide is a cheap drug out of patent, and available in most European countries.Side effects are usually minor and dose-dependent (paresthesias, nocturia), but the drug should preferably not be prescribed in patients with nephrocalcinosis. Newer carbo-anhydrase inhibitors should be used more carefully, given wide-spread use is lacking.

Monitoring and evaluation

Regular follow-up with evaluation of subjective improvement, symptoms, side effects, and eventually electrolyte balance. Polysomnographic reassessment is useful on the short-run and long-run, given effectiviness is only present in 50% of the cases, and long-term data are lacking.

Research priorities

Large RCTs as part in conventional drug development programs in various forms of OSA are warranted. Biomarkers useful for identification of candidates for drug therapy should be developed. The possibility to combine drug therapy with various forms of mechanical therapy in OSA should be explored. Finally, a better understanding of the effects of carbonic anhydrase inhibitors in comorbidities typical in OSA, such cardiovascular and metabolic disorders and obesity, would be useful when exploring this field of therapy in OSA. The potential influence of drugs with a carbonic anhydrase inhibitory effect suggests that comorbidities in OSA, such as insulin resistance and diabetes, dyslipidemia, systemic hypertension and cardiovascular disease, should be specifically addressed in trials as there is experimental data suggesting that their appearance in patients with OSA may be influenced to the pathomechanism.

APPENDICES PICO 6

PICO 6 Appendix 1

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG; Scale from 0 (best) to higher (worst); range of follow-up: 6 days to 28 weeks of intervention	Meta-analysis of 3 studies (78 patients) showes a statistically significant effect favouring carbonic anhydrase inhibitors over placebo treatment (mean difference -14.92 95% CI [-22.44, -7.40]; range of follow-up: 2 - 28 weeks). Two further studies tested carbonic anhydrase inhibitors in two different altitudes and reported results as median (2x3 days of treatment). They showed statistically significant results at both altitudes in one study. In the other study, only the results at the higher altitude showed a statistically significant result.	(5 RCTs)	⨁⨁◯◯ LOW[a,b]
Sleep efficiency % assessed with: PSG; Scale from 0 (worst) to 100% (best); 6 days to 4 weeks of intervention	3 studies reported sleep efficiency of which two showed statistically significant results favouring the intervention (both at both measured altitudes, only median reported) and one did not.	(3 RCTs)	⨁⨁◯◯ LOW[a,b]
4% oxygen desaturation index (events/hour) (ODI) assessed with: PSG, range of follow-up: 6 days to 4 weeks of intervention	Meta-analysis of 2 studies (38 patients) showed a statistically significant effect favouring carbonic anhydrase inhibitors (mean difference -9.43 95% CI [-16.40, -2.47]. One other study reported ODI <3% and also showed a statistically significant effect favouring the intervention.	(3 RCTs)	⨁⨁◯◯ LOW[a,b,c]
Sleepiness ESS / Karolinska sleepiness scale assessed with: Epworth Sleepiness Scale from 1 (best) to 24 (worst) and Karolinska sleepiness scale ranging from 1 (very awake) to 9 (very tired); range of follow-up: 6 days to 28 weeks of intervention	Neither the meta-analysis of 2 studies analysing sleepiness via ESS (mean difference 0.78 95% CI [-1.01, 2.56]) nor the results of two additional studies using the Karolinska sleepiness scale found statistically significant results.	(4 RCTs)	⨁⨁◯◯ LOW[a,b]
Arterial hypertension assessed with: PSG; systolic above 140mmHG and diastolic above 90mmHG; range of follow-up: 6 days to 28 weeks of intervention	Meta-analysis of 2 studies (68 patients) studies showed no statistically significant effect regarding systolic and diastolic blood pressure (mean difference -4.63 95% CI [-9.84, 0.59] and mean difference 1.28 95% CI [-2.23, 4.78] respectively). One other study showed a statistically significant effect looking at the mean blood pressure favouring the intervention at both altitudes. One other study showed a statistically significant effect looking at systolic, but not diastolic blood pressure at both altitudes.	(4 RCTs)	⨁⨁◯◯ LOW[a,b]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Adherence / Compliance	In one study (N=10) patients were asked for preferences: "Seven subjects expressed no preference and three subjects prefered acetazolamide((intervention)". In another study (N=28), compliance was determined by tablet count at 4 weeks: 90.1 ± 6.9% in intervention group and 90.6 ± 8.3% in control group.	(2 RCTs)	⨁⨁◯◯ LOW[d]
Adverse events	Adverse events were not reported homogeneous enough to calculate meta-analysis (see supplementary materials). Most reported AEs were paraesthesia, unpleasant taste, vertigo and dry mouth and they occurred more often in the intervention group.	(5 RCTs)	⨁⨁◯◯ LOW[a,b]

a. Minus 1 for indirectness, due to the fact that 1-2 studies were conducted in altitude, which is very specific and not specifically covered by the PICO definition.
b. Minus 1 for imprecision due to the limited number of patients.
c. Minus 1 for inconsistency would be reasonable since the results of the studies differ, however, since for the study in altitude certainty in the evidence was already downgraded 1 for indirectness it was not downgraded for inconsistency as well.
d. Minus 2 for imprecision due to the very limited number of patients.

PICO 6 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/hour) (AHI) assessed with: PSG; Scale from 0 (best) to higher (worst); range of follow-up: 6 days to 28 weeks of intervention	CRITICAL	⨁⨁◯◯ LOW[a,b]
Sleep efficiency % assessed with: PSG; Scale from 0 (worst) to 100% (best); 6 days to 4 weeks of intervention	CRITICAL	⨁⨁◯◯ LOW[a,b]
4% oxygen desaturation index (events/hour) (ODI) assessed with: PSG, range of follow-up: 6 days to 4 weeks of intervention	CRITICAL	⨁⨁◯◯ LOW[a,b,c]
Sleepiness ESS / Karolinska sleepiness scale assessed with: Epworth Sleepiness Scale from 1 (best) to 24 (worst) and Karolinska sleepiness scale ranging from 1 (very awake) to 9 (very tired); range of follow-up: 6 days to 28 weeks of intervention	CRITICAL	⨁⨁◯◯ LOW[a,b]
Arterial hypertension assessed with: PSG; systolic above 140mmHg and diastolic above 90mmHg; range of follow-up: 6 days to 28 weeks of intervention	CRITICAL	⨁⨁◯◯ LOW[a,b]
Adherence / Compliance	CRITICAL	⨁⨁◯◯ LOW[d]
Adverse events	CRITICAL	⨁⨁◯◯ LOW[a,b]

a. Minus 1 for indirectness, due to the fact that 1-2 studies were conducted in altitude, which is very specific and not specifically covered by the PICO definition.
b. Minus 1 for imprecision due to the limited number of patients.
c. Minus 1 for inconsistency would be reasonable since the results of the studies differ, however, since for the study in altitude certainty in the evidence was already downgraded 1 for indirectness it was not downgraded for inconsistency as well.
d. Minus 2 for imprecision due to the very limited number of patients.

Table e18: PICO 7

QUESTION

Should positional therapy or CPAP be used for adult patients with position-dependent obstructive sleep apnoea?	
POPULATION:	Adult patients with position-dependent obstructive sleep apnoea.
INTERVENTION:	Positional therapy (prevent supine).
COMPARISON:	CPAP.
MAIN OUTCOMES:	Apnoea-hypopnoea index; Sleep efficiency; Sleepiness; Health-related quality of life; Energy level scores; Compliance time (h/night); Adverse events (overall).
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In case of supine-related obstructive slepp apnoea (positional OSA), positional therapy to prevent the supine position is discussed to be an effective first or second line therapy. Therefore, a formal European recommendation is urgently required.	It is of interest not only to focus on AHI, but also on other outcome parameters, including quality of life, comorbidities, and oxygenation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1.*	CPAP was slightly more effective than positional therapy, but compliance was lower. The mean sleep efficiency did not significantly differ between therapy modalities. Sleepiness as measured by ESS showed no clinically relevant difference and HRQoL was also very similar.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1.*	Side effects were rare and mild with both therapy options, but two out of three studies found significantly less side effects with positional therapy. They comprise skin irritation (CPAP and positional therapy), xerostomia (CPAP) and shoulder/neck pain (positional therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	*See Appendix 2.*	There is a lack of long-term RCTs with higher number of patients, including different levels of OSA severity, various comorbidities and weight categories.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability		There is probably a high degree of agreement regarding the value of the above outcome parameters for assessing treatment efficacy. There are differences in the recognition and acceptance of the various side effects.

○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	With clear definition of the population to treat, there is no substantial difference in therapy outcome, considering somewhat less treatment efficacy in positional therapy, while therapy compliance is lower in CPAP.	Therapy preferences might differ between individuals. A general favorisation of one or the other treatment modality can not be expressed, considering the comparable effect on sleepiness and HRQoL.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not look for studies on cost-effectiveness.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for studies on health equity	The availability of positional therapy might differ between countries due to different healthcare systems. However, given the fact that no elaborate training is required to implement positional therapy, availability seems only limited by device costs.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not look for studies assessing acceptability	The intervention is usually acceptable for clinicians, patients and health insurers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility	No elaborate training is required to implement positional therapy. Limited reimbursement, however, might impair the actual clinical application.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We suggest either PT using vibratory devices or CPAP among adult patients with mild or moderate position-dependent OSA as defined by a supine AHI at least twice as high as the non-supine AHI and no relevant non-supine AHI (<15/h) (Conditional recommendation for either the intervention or CPAP, very low certainty of evidence).

Justification

Based on five RCTs the panel determined that in patients with position-dependent OSA CPAP showed a slightly better effectiveness over PT, while the compliance on CPAP is somewhat lower. Clinically relevant differences in symptomatic relief (ESS) and HrQoL were not observed. The recommendation was restricted to the PT based on vibratory stimulation due to the limitation of adherence with other options.

Subgroup considerations

It is difficult to compare the cost within Europe and its coverage varies across patients/ countries. Local differences of reimbursement still need to be investigated.

Implementation considerations

Availability differs due to different healthcare systems.

Monitoring and evaluation

Regular at least yearly follow-up with evaluation of adherence, symptoms, quality of life, efficacy (AHI, oxygenation), contraindications, side effects.

Research priorities

More RCT in OSA patients are warranted with different degrees of sleep apnoea, including patients with higher degree of disease severity.

PICO 7 APPENDICES

PICO 7 Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with positional therapy (prevent supine)				
Apnoea-hypopnoea index (AHI) assessed with: polysomnography or portable device Scale from: 0 (best) to higher (worst)	The mean apnoea-hypopnoea index was **4.2** events/h	mean **6.33 events/h more** (3.02 more to 9.65 more)	-	71 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b]	Additionally Permut: intervention: decreased from median 11 events/h (9-15, 6-26) to median 2 (1-4, 0-8); control: decreased from median 11 events/hour (9-15, 6-26) to median 0 (0-2, 0-7); p < 0.001
Sleep efficiency assessed with: PSG Scale from: 0 (worst) to 100 (best)	The mean sleep efficiency was **84** %	mean **2 % lower** (0 to 0)	-	71 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b]	Additionally: Skinner 2 (2008): "No significant differences in sleep efficiency observed between treatments" - - - Permut: "There was no change in sleep efficiency noted with either treatment, from a baseline of 89% (79%-93%, 38%-97%) to 88% (82%-94%, 48%-98%) and 85% (72%-92%, 46%- 98%), with the PD and CPAP therapy, respectively (p = 0.17)."
Sleepiness assessed with: Epworth Sleepiness Scale Scale from: 0 (best) to 24 (worst)	The mean sleepiness was **10.4** points	mean **1.2 points higher** (3.9 lower to 4.5 higher)	-	58 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	Additionally Jokic: "Epworth Sleepiness Scale scores..., but were not significantly different between positional treatment (median, 10; range 1 to 19) and CPAP (median, 9; range, 2 to 17; median difference, 21.5; 95% CI, 22.9 to 0.8; p 5 0.2)."
Health-related quality of life assessed with: Short Form 36 Physical Score Scale from: 0 (worst) to 100 (best)	The mean health-related quality of life was **44.6** points	mean **0.1 points higher** (2.6 lower to 2.9 higher)	-	20 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPAP	Risk with positional therapy (prevent supine)				
Compliance time (h/night) assessed with: diary-reported Scale from: 0 (worst) to higher (better)	The mean compliance time (h/night) was **4.9** h/night	mean **2.5 h/night more** (1.3 more to 4.6 more)	-	71 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b]	Additionally Jokic: "Four patients preferred positional treatment, seven patients preferred CPAP treatment, and two had no preference." - - - Permut: Based on the questionnaire responses, 50% of patients preferred the PD, 34% preferred CPAP therapy, and 16% had no preference.
Adverse events (overall) Assessed with: scores from responses to 19 self-report questions undertaken at the end of the period with each device (score 0, no effect; 1, mild effect but did not disturb sleep; 2, sleep disturbed; 3, could not use device). Scale from: 0 (best) to higher (worst)	The mean adverse events (overall) was **8.4** points	mean **3.6 points fewer** (3.4 fewer to 5.8 fewer)	-	20 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	
Energy level scores assessed with: Nottingham Health profile	"Slightly better with CPAP than with positional therapy (p = 0.04)"		-	13 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	

a. Downgraded one for study limitations: more than 2 domains high risk of bias.
b. Downgraded two for imprecision: only 71 patients included, data not feasible to be analysed quantitatively.
c. Downgraded two for imprecision: 95% CI suggest the possibility of both benefit and harm; only 71 patients included, data not feasible to be analysed quantitatively.

PICO 7 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index assessed with: polysomnography or portable device Scale from: 0 (best) to higher (worst)	CRITICAL	⨁⨁◯◯ LOW[a]
Sleep efficiency assessed with: PSG Scale from: 0 (worst) to 100 (best)	CRITICAL	⨁⨁◯◯ LOW[a]
Sleepiness assessed with: Epworth Sleepiness Scale Scale from: 0 (best) to 24 (worst)	CRITICAL	⨁◯◯◯ VERY LOW[b,c]
Health-related quality of life assessed with: Short Form 36 Physical Score Scale from: 0 (worst) to 100 (best)	CRITICAL	⨁◯◯◯ VERY LOW[b,c]
Energy level scores assessed with: Nottingham Health profile	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Compliance time (h/night) assessed with: diary-reported Scale from: 0 (worst) to higher (better)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Adverse events (overall) assessed with: scores from responses to 19 self-report questions undertaken at the end of the period with each device (score 0, no effect; 1, mild effect but did not disturb sleep; 2, sleep disturbed; 3, could not use device). Scale from: 0 (best) to higher (worst)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

a. Downgraded two for imprecision: only 71 patients included, data not feasible to be analysed quantitavely.
b. Downgraded one for study limitations: more than 2 domains high risk of bias.
c. Downgraded two for imprecision: 95% CI suggest the possibility of both benefit and harm; only 71 patients included, data not feasible to be analysed quantitatively.

Table e19: PICO 8

QUESTION

Should positional therapy (intervention) or custom made dual-block mandibular advancement devices (control) be used for adult patients with position-dependent obstructive sleep apnoea?	
POPULATION:	Adult patients with position-dependent obstructive sleep apnoea.
INTERVENTION:	Positional therapy (intervention).
COMPARISON:	Custom made dual-block mandibular advancement devices (control).
MAIN OUTCOMES:	Apnoea-hypopnoea index (events/h); Sleep efficiency %; 4% oxygen desaturation index (events/h); Sleepiness ESS; Arterial hypertension; Adherence; Adverse events; Quality of life.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Due to a high prevalence of CPAP non-adherence, there is a high demand for alternative therapies. Both mandibular advancement devices (MADs) and techniques to treat supine position - related obstructive sleep apnoea (positional OSA have n to have a potential to be an effective first or second line therapy. Therefore, a formal European recommendation is urgently required.	It is of interest not only to focus on AHI, but also on other outcome parameters, including quality of life, comorbidities, and oxygenation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1.*	Similar effectiveness documented for noth therapies. Target population restricted to patients with positional OSA in those receiving positional therapy whereas all patient groups with OSA were considered for MADs.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Side effects were rare and mild for both therapies. *See Appendix 1.*	Side effects were slightly dominating for MAD. MAD related effects including salivation ans changes in bite, craniofacial changes and temporomandibular problems. Positional therapy related to lower back/shoulder pain related to a fixed sleep position.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of evidence was very low. *See Appendix 2.*	There is a proportional lack of long term RCTs including various phenotypes of OSA.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability		Varies depending on the patient. Specifically these

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		differences relate to dominating symptom and existing comorbidities.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Selection of target group for treatment will influence desirable effects. Undesirable effects unrelated to target group.	Overall efficacy variable and there are few, if any, predictors or biomarkers other than body position and its relation to OSA that may be used to predict efficacy. Determination of desirable effects should beside conventional measures of OSA, include also sleepiness and HRQoL.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not look for studies on resources.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioeconomic aspects can be given.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not look for studies on cost-effectiveness.	There are huge differences between health care systems throughout Europe. There are unique reimbursement strategies. Therefore, no general statements on socioecoionomic aspects can be given.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for studies on health equity.	Different reimbursement policies apply depending on the country.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	We did not look for studies assessing acceptability.	Different reimbursement policies apply depending on the country.

○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not look for studies assessing feasibility.	Different reimbursement policies apply depending on the country.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies

	JUDGEMENT						
OF REQUIRED RESOURCES							
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

In patients with mild positional OSA, we suggest using either vibrational positional therapy or MAD (conditional recommendation for either the intervention or control, very low certainty of evidence).

Justification

Based on only one RCT, the panel determined that in patients with mild positional OSA vibrational positional therapy and MAD show similar effectiveness. However, more side effects with MAD were found and adherence with the MAD was lower. For positional therapy, given different techniques and weak long-term adherence have to be taken into account. Patients´ values and preferences may vary individually and may influence choosing for one or the other therapy.

Subgroup considerations

Physical limitations (discomfort or pain at the level of the shoulders or back) for positional therapy users, bite and craniofacial changes as well as intermittent temporomandibular dysfunction precluding use of the MAD need to be taken into account when long-term treatment is established.

Implementation considerations

Only applicable in patients with position dependent OSA patients.

There is evidence from comparative studies that vibration positional therapy may be effective in more severe cases.

Monitoring and evaluation

Regular at least yearly follow-up with evaluation of adherence, symptoms, quality of life, efficacy (AHI, oxygenation), contraindications, side effects. Weight changes and age effects could alter position-dependency.

Research priorities

Further RCTs are warranted in OSA patients with different degrees of sleep apnoea, including those with more severe disease. The definition of POSA has to be taken into account when comparing future studies.

PICO 8 APPENDICES

PICO 8 Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with custom made dual-block mandibular advancement devices (control)	Risk with positional therapy (intervention)				
Apnoea-hypopnoea index (events/h) (AHI) assessed with: PSG at 12 months follow-up; ITT Scale from: 0 (best) to higher (worst)	see comment	see comment	-	99 (1 RCT)	⨁⨁◯◯ LOW[a]	Positional therapy: decrease from median 13.0 (IQR 9.7, 18.5) to median 8.0 (IQR 5.1, 12.9), p < 0.001 - - - - - CPAP: decrease from median 11.7 (IQR 9.0, 16.2) to median 8.5 (IQR 4.8, 11.7), p < 0.001 - - - - - between groups: not stat. sign. difference, no p-value given
Sleep efficiency % assessed with: PSG at 12 months follow-up; ITT Scale from: 0 (worst) to 100 (best)	see comment	see comment	-	99 (1 RCT)	⨁⨁◯◯ LOW[a]	Positional therapy: decrease from baseline median 92.0 (IQR 84.0, 95.5) to median 91.0 (IQR 86.0,95.0), not stat. sign. - - - - - - CPAP: increase from baseline median 92.0 (IQR 86.0,95.0) to median 93.0 (IQR 87.0,96.0), not stat. sign. - - - - - between group differences: not stat. sign., no numbers given
4% oxygen desaturation index (events/h) (ODI) assessed with: PSG at 12 months follow-up; ITT	see comment	see comment	-	99 (1 RCT)	⨁⨁◯◯ LOW[a]	Positional therapy: decrease from baseline median 10.5 (IQR 7.0,15.8) to median 7.0 (IQR 4.0,13.0), p < 0.001 - - - - - CPAP: decrease from baseline median 9.0 (IQR 6.0,14.0) to median 7.0 (IQR 4.0,11.0), not stat. sign. - - - - - between group difference: not stat. sign., no p-value given
Sleepiness ESS assessed with: Epworth Sleepiness Scale at 12 months follow-up; ITT Scale from: 1 (best) to 24 (worst)	see comment	see comment	-	99 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	Positional therapy: decrease from baseline median 7.5 (IQR 4.0,12.0) to median 6.0 (IQR 3.8,10.0), not stat. sign. - - - - - CPAP: decrease from baseline median 8.0 (IQR 4.0,13.0) to median 8.0 (IQR 3.0,12.5), not stat. sign. - - - - - between group difference: not stat. sign., no p-value given

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with custom made dual-block mandibular advancement devices (control)	Risk with positional therapy (intervention)				
Arterial hypertension assessed at 12 months follow-up; ITT; systolic above 140mmHg and diastolic above 90mmHg	see comment	see comment	-	99 (1 RCT)	⨁⨁◯◯ LOW[a]	Systolic: positional: decrease from median 133.5 (IQR 125.0,150.0) to 130.0 (IQR 120.0,150.0), not stat. sign. - CPAP: decrease from median 130.0 (IQR 120.0,140.0) to 128.0 (IQR 120.0,138.0), not stat. sign. - between group difference: not stat. sign., no p-value given - diastolic: positional: decrease from median 90.0 (IQR 80.0,97.5) to median 82.5 (IQR 80.0,97.3), p<0.05 - CPAP: decrease from median 85.0 (IQR 80.0,90.0) to median 80.0 (IQR 80.0,86.0), not stat. sign. - no gr-d
Adherence assessed with: temperature measuring chip, objectively, at 12 months follow-up; defined as device usage ≥ 4 h/night on at least 5 days/week; ITT	see comment	see comment	-	99 (1 RCT)	⨁⨁◯◯ LOW[a]	Positional therapy: mean 68.9 ± 37.7 % patients - - - - - CPAP: mean 54.5 ± 44.5 % patients - - - - - between group difference: not stat. sign. p-value: 0.086
Adverse events assessed with: self-reported until 12 months of follow-up; data from pts not dropped out (per protocol): 29 in each arm	see comment	see comment	-	58 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	Reporting at least one AE: positional: 20 patients (69 %) - CPAP: 28 patients (96.6 %) - positional therapy specific AEs: woken up by vibration: 4 patients (10.8 %); no reaction to vibration: 4 patients (10.8 %) - CPAP specific AEs: tooth pain: 21 (27.3 %); temporomandibular dysfunction: 9 (11.7 %); open bite: 7 (9.1 %); dry mouth 4 (5.2 %); hypersalivation: 1 (1.3 %); dental fracture: 1 (1.3 %); oral lesions: 1 (1.3 %) - both groups: persistent snoring, tiredness, comfort problems,
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire (FOSQ-30) at 12 months follow-up; ITT Scale from: 5 (worse) to 20 (better functioning)	see comment	see comment	-	99 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	Positional therapy: increase from baseline median 19.0 (IQR 17.3,19.7) to median 19.3 (IQR 17.2,19.7), not stat. sign. - - - - - CPAP: decrease from baseline median 18.4 (IQR 16.2,19.7) to median 18.3 (IQR 16.3,19.6), not stat. sign. - - - - - between group difference: not sign., no p-value given

a. Minus two for imprecision for limited number of patients and unclear direction of result (benefit or harm included possibilities).
b. Minus one for study limitations: patients not blinded, subjective outcome.

PICO 8 Appendix 2

Outcomes	Importance	Certainty of the evidence (GRADE)
Apnoea-hypopnoea index (events/h) assessed with: PSG at 12 months follow-up; ITT Scale from: 0 (best) to higher (worst)	CRITICAL	⨁⨁◯◯ LOW[a]
Sleep efficiency % assessed with: PSG at 12 months follow-up; ITT Scale from: 0 (worst) to 100 (best)	CRITICAL	⨁⨁◯◯ LOW[a]
4% oxygen desaturation index (events/h) assessed with: PSG at 12 months follow-up; ITT	CRITICAL	⨁⨁◯◯ LOW[a]
Sleepiness ESS assessed with: Epworth Sleepiness Scale at 12 months follow-up; ITT Scale from: 1 (best) to 24 (worst)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Arterial hypertension assessed with: PSG at 12 months follow-up; ITT; systolic above 140mmHg and diastolic above 90mmHg	CRITICAL	⨁⨁◯◯ LOW[a]
Adherence assessed with: temperature measuring chip, objectively, at 12 months follow-up; definded as device usage ≥ 4 h/night on at least 5 days/week; ITT	CRITICAL	⨁⨁◯◯ LOW[a]
Adverse events assessed with: self-reported until 12 months of follow-up; data from pts not dropped out (per protocol): 29 in each arm	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Quality of life assessed with: Functional Outcomes of Sleep Questionnaire (FOSQ-30) at 12 months follow-up; ITT Scale from: 5 (worse) to 20 (better functioning)	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

a. Minus two for imprecision for limited number of patients and unclear direction of result (benefit or harm included possibilities).
b. Minus one for study limitations: patients not blinded, subjective outcome.

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