SUPPLEMENTARY MATERIAL

A Systematic Review and Meta-analysis of the Safety of the Apnea Test in Adults and the Case for Maintaining Positive Airway Pressure

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Table S1. Outcome definitions reported by each included study

SDC ref	Study	Data source	Outcome	Events/n	Matched prespecified definition	Verbatim wording reported by the study
S1	Al Jumah M 1992	Abstract	E1 — Test aborted	1/24	Yes	Not reported verbatim (data extracted from the abstract)
S1	Al Jumah M 1992	Abstract	E3 — Hypotension	1/24	Yes	Not reported verbatim (data extracted from the abstract)
S2	Arslan K 2024	Full text	E1 — Test aborted	4/44	Yes	In 9% of the cases (n=4), the apnea test could not be completed despite two attempts.
S2	Arslan K 2024	Full text	E3 — Hypotension	4/44	Yes	Not reported verbatim (data extracted from the abstract)
S3	Atik B 2019	Full text	E1 — Test aborted	17/151	Yes	Not reported verbatim (data extracted from the abstract)
S4	Aviram D 2025	Full text	E1 — Test aborted	5/70	Yes	In five patients, DNC was not concluded because of AT abortion: three of five aborted tests were due to hypoxemia... and the other two tests were aborted due to hemodynamic instability. These five patients were included in our analysis.
S4	Aviram D 2025	Full text	E3 — Hypoxemia	3/70	Yes	Not reported verbatim (data extracted from the abstract)
S4	Aviram D 2025	Full text	E3 — Hemodynamic instability	2/70	Yes	Not reported verbatim (data extracted from the abstract)
S5	Balkaya AN 2022	Abstract	E2b — Test not performed (any reason)	10/37	No	Not reported verbatim (data extracted from the abstract)
S6	Barrier D 2025	Full text	E1 — Test aborted	0/15	Yes	The first apnea test was consistent with brain death diagnosis in all cases. Consequently, all patients underwent the second apnea test under HFO, which was also consistent in all cases.
S6	Barrier D 2025	Full text	E3 — Pneumothorax	0/15	Yes	There were no occurrences of pneumothorax or pneumomediastinum during apnea test under HFO
S7	Belsh JM 1986	Abstract	E3 — Severe composite	0/33	Yes	Not reported verbatim (data extracted from the abstract)
S8	Cakin O 2017	Abstract	E2a — Not tested for safety reasons	14/211	Yes	Not reported verbatim (data extracted from the abstract)
S9	Chen Z 2021	Full text (derived)	E1 — Test aborted	754/2185	Yes	0.345*2185 determinaciones)
S9	Chen Z 2021	Full text (derived)	E2b — Test not performed (any reason)	266/2185	Yes	Not reported verbatim (data extracted from the abstract)
S32	Merchant RA 2024	Full text	E1 — Test aborted	3/92	Yes	Apnea tests could not be completed successfully in 3 of 92 (3%) patients—two patients undergoing the oxygen insufflation technique (one hypoxemia and one hypotension) and one patient on mechanical ventilation (aborted for hemodynamic instability).
S32	Merchant RA 2024	Full text	E3 — Hypotension	7/90	Yes	Hypotension occurred during 3 of 58 (5%) tests with mechanical ventilation and 4 of 32 (12.5%) tests [with oxygen insufflation].
S32	Merchant RA 2024	Full text	E3 — Hypoxemia	0/58	Yes	Oxygen desaturation to SpO2<90% did not occur during any apnea tests performed on mechanical ventilation
S32	Merchant RA 2024	Full text	E3 — Severe composite	0/92	Yes	No patient suffered pneumothorax, arrhythmia, or cardiac arrest during apnea testing
S10	Cuninghame S 2026	Full text	E1 — Test aborted	9/361	Yes	of an apnea test, 352 (97%) safely completed the apnea test, with nine apnea tests aborted. Of these nine, seven were due to an adverse event that arose during the test, and two were [other].
S10	Cuninghame S 2026	Full text	E1 — Test aborted for an adverse event	7/361	Yes	Complications during apnea test leading to test discontinuation: 7 (3)
S10	Cuninghame S 2026	Full text	E3 — Hypoxemia	5/361	Yes	The adverse events noted were hypoxemia (5/7) and hemodynamic instability (2/7)
S10	Cuninghame S 2026	Full text	E3 — Hemodynamic instability	2/361	Yes	Not reported verbatim (data extracted from the abstract)
S10	Cuninghame S 2026	Full text	E3 — Cardiac arrest	0/361	Yes	No cardiac arrests occurred during any apnea tests during the study period
S10	Cuninghame S 2026	Full text	E2b — Test not attempted	7/368	No	a total of 368 BD/DNC assessments were performed. Of these, 361 (98%) had an apnea test attempted.
S11	Datar S 2014	Full text	E1 — Test aborted	1/63	Yes	Not reported verbatim (data extracted from the abstract)
S11	Datar S 2014	Full text	E3 — Hypoxemia	1/63	Yes	Not reported verbatim (data extracted from the abstract)
S11	Datar S 2014	Full text	E3 — Hypotension	11/63	Yes	Mild hypotension occurred in 11 patients (17.4%)... There were no instances of major cardiac arrhythmias.
S11	Datar S 2014	Full text	E3 — Arrhythmia	0/63	Yes	Mild hypotension occurred in 11 patients (17.4%)... There were no instances of major cardiac arrhythmias.
S12	Ding ZY 2015	Full text	E1 — Test aborted	5/25	Yes	tests were suspended because they became unstable or desaturases.
S12	Ding ZY 2015	Full text	E2a — Not tested for safety reasons	8/33	No	Although 33 patients needed to do apnea tests, only 25 patients did the tests because others could not provide normocarbia and hyperoxia.

S13	Eminoglu S 2019	Full text	E2b — Test not performed (any reason)	63/151	No	Not reported verbatim (data extracted from the abstract)
S14	Fan L 2024	Full text	E1 — Test aborted	7/55	Yes	Not reported verbatim (data extracted from the abstract)
S15	Farooq S 2022	Full text	E3 — Severe composite	0/102	Yes	No cardiac arrhythmias or any other major complications were noted
S17	Goudreau JL 2000	Full text (derived)	E3 — Hypotension	35/145	Yes	Not reported verbatim (data extracted from the abstract)
S17	Goudreau JL 2000	Full text (derived)	E3 — Arrhythmia	1/145	Yes	Not reported verbatim (data extracted from the abstract)
S17	Goudreau JL 2000	Full text (derived)	E3 — Any complication	22/145	Yes	Not reported verbatim (data extracted from the abstract)
S18	Hirsinger B 2026	Abstract	E2a — Not tested for safety reasons	52/371	Yes	52 (14%) did not undergo apnea testing, mainly because of respiratory or hemodynamic instability.
S18	Hirsinger B 2026	Abstract	E1 — Test aborted	34/319	Yes	The test was aborted in 34 (11%) patients due to adverse events, of which the most common was hypoxemia; five other severe adverse events were recorded.
S19	Hubbard JL 2016	Abstract	E3 — Severe composite	0/67	No	There were no reported complications arising from CPAP use
S20	Jeret JS 1994	Abstract	E1 — Test aborted	14/70	Yes	Not reported verbatim (data extracted from the abstract)
S20	Jeret JS 1994	Abstract	E3 — Marked hypotension	23/70	Yes	Not reported verbatim (data extracted from the abstract)
S21	Karasu D 2015	Abstract	E1 — Test aborted	4/79	Yes	Not reported verbatim (data extracted from the abstract)
S22	Kashefi P 2024	Full text	E1 — Test aborted	1/30	Yes	Not reported verbatim (data extracted from the abstract)
S22	Kashefi P 2024	Full text	E3 — Hypoxemia	3/30	Yes	Not reported verbatim (data extracted from the abstract)
S22	Kashefi P 2024	Full text	E3 — Arrhythmia	2/30	Yes	Not reported verbatim (data extracted from the abstract)
S22	Kashefi P 2024	Full text	E3 — Cardiac arrest	0/30	Yes	Not reported verbatim (data extracted from the abstract)
S22	Kashefi P 2024	Full text	E3 — Pneumothorax	0/30	Yes	Other complications (pneumothorax)
S23	Kim HY 2014	Full text	E2a — Not tested for safety reasons	4/61	Yes	Three (9.7%) patients in the N-group were excluded due to uncorrected hypotension (SBP<90 mmHg) before the apnea test, and one patient (3.3%) in the C-group was excluded due to hypoxemia (SpO2<90%) before the apnea test.
S23	Kim HY 2014	Full text	E3 — Hypoxemia	12/114	Yes	The ratio of SpO2 under 90% during the apnea test for the first test (N-group 3/28, C-group 1/29) and second test (N-group 4/28, C-group 4/29).
S24	Kim JJ 2019	Full text	E1 — Test aborted	28/512	Yes	Not reported verbatim (data extracted from the abstract)
S25	Kotanoglu MS 2020	Full text	E2b — Test not performed (any reason)	27/102	No	Not reported verbatim (data extracted from the abstract)
S26	Kramer AH 2017	Full text	E1 — Test aborted	2/86	Yes	Not reported verbatim (data extracted from the abstract)
S26	Kramer AH 2017	Full text	E1 — Test aborted (O2 catheter arm)	1/36	Yes	Not reported verbatim (data extracted from the abstract)
S26	Kramer AH 2017	Full text	E1 — Test aborted (CPAP arm)	1/50	Yes	Not reported verbatim (data extracted from the abstract)
S27	Lambeck J 2024	Full text	E1 — Test aborted	0/139	Yes	It was not necessary to either interrupt or abort the mAT in any of the 139 patients
S27	Lambeck J 2024	Full text	E2a — Not tested for safety reasons	1/140	Yes	only 1 (0.007%) of the 140 patients tested was considered too unstable to undergo the mAT
S27	Lambeck J 2024	Full text	E3 — Hypoxemia	0/139	Yes	There was no case in which PaO2 was <=60 mmHg in the post-mAT phase
S27	Lambeck J 2024	Full text	E3 — Hypotension	12/139	Yes	Mean arterial pressure (MAP) transiently dropped below 60 mm Hg in 12 patients
S27	Lambeck J 2024	Full text	E3 — Severe composite	0/139	Yes	No other severe complications during the AT were observed
S28	Lang CJG 1997	Abstract	E1 — Test aborted	0/55	Yes	Not reported verbatim (data extracted from the abstract)
S28	Lang CJG 1997	Abstract	E3 — Severe composite	0/55	Yes	All apnoea tests were without serious adverse effects (hypoxia, newly induced cardiac arrhythmia, cardiac asystole)
S28	Lang CJG 1997	Abstract	E3 — Hypotension	1/55	Yes	Not reported verbatim (data extracted from the abstract)
S29	Levesque S 2006	Full text	E1 — Test aborted	5/57	Yes	Unit = test (19 patients x 3 techniques = 57 tests). In three patients, some of the tests were stopped prematurely according to the predefined criteria. In patient no. 2, the apnea tests were stopped at 9 mins both with the T-piece and with the CPAP because systolic arterial pressure fell below 90 mmHg; in patients no. 8 and 10, the tests were stopped with the oxygen catheter and the T-piece because of desaturation (Results, full text).
S29	Levesque S 2006	Full text	E1 — Test aborted (O2 catheter arm)	2/19	Yes	In three patients, some of the tests were stopped prematurely according to the predefined criteria. In patient no. 2, the apnea tests were stopped at 9 mins both with the T-piece and with the CPAP because systolic arterial pressure fell below 90 mmHg; in patients no. 8 and 10, the tests were stopped with the oxygen catheter and the T-piece because of desaturation (Results, full text).
S29	Levesque S 2006	Full text	E1 — Test aborted (T-piece arm)	2/19	Yes	In three patients, some of the tests were stopped prematurely according to the predefined criteria. In patient no. 2, the apnea tests were stopped at 9 mins both with the T-piece and with the CPAP

						because systolic arterial pressure fell below 90 mmHg; in patients no. 8 and 10, the tests were stopped with the oxygen catheter and the T-piece because of desaturation (Results, full text).
S29	Levesque S 2006	Full text	E1 — Test aborted (CPAP arm)	1/19	Yes	In three patients, some of the tests were stopped prematurely according to the predefined criteria. In patient no. 2, the apnea tests were stopped at 9 mins both with the T-piece and with the CPAP because systolic arterial pressure fell below 90 mmHg; in patients no. 8 and 10, the tests were stopped with the oxygen catheter and the T-piece because of desaturation (Results, full text).
S30	Madden M 2020	Abstract	E1 — Test aborted	0/5	Yes	Not reported verbatim (data extracted from the abstract)
S31	Marks SJ 1990	Abstract	E3 — Severe hypoxemia at end of test	0/9	No	Not reported verbatim (data extracted from the abstract)
S33	Migdady I 2021	Full text	E1 — Test aborted	4/98	Yes	inability to complete the AT due to hemodynamic complications in 4 patients (4% of all ATs)... inconclusive results due to unknown reason in 1 patient (1%).
S33	Migdady I 2021	Full text	E3 — Composite (hypoxemia/hypotension/arrhythmia)	9/98	Yes	Collectively, complications of the AT due to hypoxia, hypotension, or arrhythmia occurred in 9 patients (9%), 4 of which [precluded completion].
S34	Migdady I 2022	Full text	E2a — Not tested for safety reasons	4/8	Yes	Not reported verbatim (data extracted from the abstract)
S35	Orliaguet GA 1994	Abstract	E1 — Test aborted	1/20	Yes	Not reported verbatim (data extracted from the abstract)
S35	Orliaguet GA 1994	Abstract	E3 — Hypoxemia	1/20	Yes	Not reported verbatim (data extracted from the abstract)
S36	Park J 2019	Full text	E1 — Test aborted	1/126	Yes	Unit = test, both techniques pooled (49 CAT instances in 25 patients, 1 not completed for unstable vital signs, brain SPECT substituted; 77 MAT instances in 39 patients, no failures). Arm-level counts in Table S4.
S37	Rudolf J 1998	Full text	E3 — Hypoxemia	0/36	Yes	No relevant hypoxia (paO2<80 torr) was observed in either group
S38	Saposnik G 2004	Abstract	E3 — Hypotension	15/129	Yes	Not reported verbatim (data extracted from the abstract)
S38	Saposnik G 2004	Abstract	E3 — Hypoxemia	30/129	Yes	Not reported verbatim (data extracted from the abstract)
S38	Saposnik G 2004	Abstract	E3 — Severe composite	4/129	Yes	Not reported verbatim (data extracted from the abstract)
S39	Sayan HE 2020	Full text	E2a — Not tested for safety reasons	65/169	Yes	the apnea test was performed on 104 (61.5%) patients and was not or could not be performed on 65 (38.5%) patients.
S39	Sayan HE 2020	Full text	E2a — Not tested (hemodynamic instability)	51/169	Yes	Not reported verbatim (data extracted from the abstract)
S40	Shappell CN 2013	Full text	E2b — Test not completed	60/226	No	One hundred sixty-six (73.5%) had completed apnea testing. Of the 60 without completed apnea testing, 56 (93.3%) had ancillary tests consistent with BD.
S41	Sharpe MD 2004	Full text	E3 — Severe composite	0/60	Yes	clinically insignificant reduction in arterial blood pressure during testing, but no other complications occurred
S42	Sołek-Pastuszka J 2019	Full text	E1 — Test aborted	3/76	Yes	In three cases, classic I-AT was aborted due to rapid desaturation defined as a drop in O2 saturation below 90%, after 1.5 min... 4 min... and 5 min.
S42	Sołek-Pastuszka J 2019	Full text	E3 — Hypoxemia	3/76	Yes	Not reported verbatim (data extracted from the abstract)
S42	Sołek-Pastuszka J 2019	Full text	E3 — Severe composite	0/60	Yes	I-AT and CPAP-AT were completed in 60 patients without serious complications such as severe desaturation, cardiac arrhythmia, or pneumothorax.
S16	Giani M 2016	Abstract	E1 — Test aborted	0/169	Yes	Not reported verbatim (data extracted from the abstract)
S16	Giani M 2016	Abstract	E3 — Severe composite	0/169	Yes	Not reported verbatim (data extracted from the abstract)
S16	Giani M 2016	Abstract	E3 — Severe hypoxemia	11/342	Yes	Not reported verbatim (data extracted from the abstract)
S43	Su YY 2008	Abstract	E2b — Test not completed	33/46	No	Not reported verbatim (data extracted from the abstract)
S44	Wu XL 2008	Abstract	E3 — Any complication	37/179	Yes	Not reported verbatim (data extracted from the abstract)
S44	Wu XL 2008	Abstract	E3 — Hypotension	30/179	Yes	Not reported verbatim (data extracted from the abstract)
S44	Wu XL 2008	Abstract	E3 — Hypoxemia	10/179	Yes	Not reported verbatim (data extracted from the abstract)
S44	Wu XL 2008	Abstract	E3 — Arrhythmia	0/179	Yes	serious cardiac arrhythmia did not occur in all patients
S45	Yee AH 2010	Abstract	E1 — Test aborted	10/207	Yes	Not reported verbatim (data extracted from the abstract)
S46	Zhao DX 2024	Full text	E1 — Test aborted	0/6	Yes	flow was performed safely and successfully in six of the eight of the patients with confirmed DNC... and was never aborted
S46	Zhao DX 2024	Full text	E2a — Not tested for safety reasons	2/8	Yes	A significant proportion of ECMO patients with neurological exam consistent with DNC did not have an AT due to safety concerns

E1, apnea test aborted because of an adverse event; E2a/E2b, patients not tested for safety reasons / for any reason; E3, specific adverse events. 'Matched prespecified definition' indicates whether the study's definition matched the protocol definition.

Table S2. Study-by-study characteristics of the 46 included studies

Ref	Study	Country	Design (as reported)	Design class	n	Technique	Risk of bias	Data source	Contributes to
S1	Al Jumah M 1992	Arabia Saudi	Serie casos	Retrospective	24	Insufflation	Moderate	Abstract only	E1, Hypotension
S2	Arslan K 2024	Turquia	Retrospectivo	Retrospective	44	Mixed	Low	Full text	E1, Hypotension
S3	Atik B 2019	Turquia	Retrospectivo	Retrospective	151	Insufflation	Low	Full text	E1
S4	Aviram D 2025	Israel	Retrospectivo	Retrospective	70	Positive pressure	Low	Full text	E1, Hypoxemia
S5	Balkaya AN 2022	Turquia	Retrospectivo	Retrospective	37	Insufflation	High	Abstract only	E2b
S6	Barrier D 2025	Francia	Prospectivo	Prospective	15	HFO	Low	Full text	E1
S7	Belsh JM 1986	EE.UU.	Prospectivo	Prospective	33	Insufflation	Moderate	Abstract only	Severe composite
S8	Cakin O 2017	Turquia	Retrospectivo	Retrospective	211	Insufflation	Moderate	Abstract only	E2a
S9	Chen Z 2021	China	Retrospectivo	Retrospective	2185	mixta (ECMO)	Moderate	derivado	None (described qualitatively)
S10	Cuninghame S 2026	Multicentrico	Prosp. multic.	Prospective	368	Mixed	Low	Full text	E1, E2b, Hypoxemia, Technique comparison
S11	Datar S 2014	EE.UU.	Retrospectivo	Retrospective	63	Insufflation	Low	Full text	E1, Hypoxemia, Hypotension, Arrhythmia
S12	Ding ZY 2015	China	Prospectivo	Prospective	33	Insufflation	Low	Full text	E1, E2a
S13	Eminoglu S 2019	Turquia	Retrospectivo	Retrospective	151	Insufflation	Moderate	Full text	E2b
S14	Fan L 2024	China	Prosp. multic.	Prospective	55	Insufflation	Low	Full text	E1
S15	Farooq S 2022	EE.UU.	Retrospectivo	Retrospective	102	CO2/mixta	Low	Full text	Severe composite
S16	Giani M 2016	Italia	Retrospectivo	Retrospective	342	Positive pressure	Moderate	Abstract only	None (described qualitatively)
S17	Goudreau JL 2000	EE.UU.	Retrospectivo	Retrospective	145	Insufflation	Moderate	derivado	None (described qualitatively)
S18	Hirsinger B 2026	Francia	Retrospectivo	Retrospective	371	Mixed	Moderate	Abstract only	E1, E2a
S19	Hubbard JL 2016	EE.UU.	Retrospectivo	Retrospective	67	Mixed	High	Abstract only	None (described qualitatively)
S20	Jeret JS 1994	EE.UU.	Prospectivo	Prospective	70	Insufflation	Moderate	Abstract only	E1, Hypotension
S21	Karasu D 2015	Turquia	Retrospectivo	Retrospective	79	Insufflation	Moderate	Abstract only	E1
S22	Kashefi P 2024	Iran	Transversal	Retrospective	30	Insufflation	Low	Full text	E1, Hypoxemia, Arrhythmia
S23	Kim HY 2014	Corea del Sur	Retrospectivo	Retrospective	114	Insufflation	Low	Full text	E2a, Hypoxemia
S24	Kim JJ 2019	Corea del Sur	Retrospectivo	Retrospective	512	Insufflation	Low	Full text	E1
S25	Kotanoglu MS 2020	Turquia	Retrospectivo	Retrospective	102	Insufflation	Moderate	Full text	E2b
S26	Kramer AH 2017	Canada	Retrosp. multic.	Retrospective	86	Mixed	Low	Full text	E1, Technique comparison
S27	Lambeck J 2024	Alemania	Prospectivo	Prospective	140	Positive pressure	Low	Full text	E1, E2a, Hypoxemia, Hypotension, Severe composite
S28	Lang CJG 1997	Alemania	Prospectivo	Prospective	55	Exogenous CO_2	Moderate	Abstract only	E1, Hypotension, Severe composite
S29	Levesque S 2006	Canada	Ensayo/crossover	Prospective	57	Mixed	Moderate	Full text	E1, Technique comparison
S30	Madden M 2020	EE.UU.	Serie casos	Retrospective	5	CO2 (ECMO)	High	Abstract only	None (described qualitatively)
S31	Marks SJ 1990	EE.UU.	rct	Retrospective	9	Insufflation	High	Abstract only	None (described qualitatively)
S32	Merchant RA 2024	EE.UU.	Retrospectivo	Retrospective	92	Mixed	Low	Full text	E1, Hypotension, Severe composite, Technique comparison
S33	Migdady I 2021	EE.UU.	Retrospectivo	Retrospective	98	Insufflation	Low	Full text	E1
S34	Migdady I 2022	EE.UU.	Retrospectivo	Retrospective	8	insuflación (ECMO)	Low	Full text	None (described qualitatively)
S35	Orliaguet GA 1994	Francia	Prospectivo	Prospective	20	Insufflation	Moderate	Abstract only	E1, Hypoxemia
S36	Park J 2019	Corea del Sur	Retrospectivo	Retrospective	126	Mixed	Low	Full text	E1, Technique comparison
S37	Rudolf J 1998	Alemania	Prospectivo	Prospective	36	Insufflation	Low	Full text	Hypoxemia
S38	Saposnik G 2004	Argentina	Retrospectivo	Retrospective	129	Insufflation	Moderate	Abstract only	Severe composite
S39	Sayan HE 2020	Turquia	Retrospectivo	Retrospective	169	Insufflation	Low	Full text	E2a
S40	Shappell CN 2013	EE.UU.	Retrospectivo	Retrospective	226	Mixed	Low	Full text	E2b
S41	Sharpe MD 2004	Canada	Prospectivo	Prospective	60	Exogenous CO_2	Low	Full text	Severe composite
S42	Sołek-Pastuszka J 2019	Polonia	Retrosp. (datos prosp.)	Retrospective	76	Insufflation	Low	Full text	E1, Hypoxemia, Severe composite, Technique comparison
S43	Su YY 2008	China	Prospectivo	Prospective	46	Insufflation	High	Abstract only	E2b
S44	Wu XL 2008	China	Retrospectivo	Retrospective	179	Insufflation	Moderate	Abstract only	Hypoxemia, Hypotension, Arrhythmia
S45	Yee AH 2010	EE.UU.	Retrospectivo	Retrospective	207	Insufflation	Moderate	Abstract only	E1
S46	Zhao DX 2024	EE.UU.	Retrospectivo	Retrospective	8	insuflación (ECMO)	Low	Full text	None (described qualitatively)

Ref numbers correspond to Supplementary References S1–S46. Design class is the coding used for the post hoc subset analysis (Amendment 2): the randomized crossover is prospective; cohorts based on retrospective record review are retrospective. Risk of bias by the Joanna Briggs Institute checklist, cross-checked with the Hoy tool. Data source indicates whether extraction and risk-of-bias assessment were made from the full text or from the abstract/conference record (17 studies); for two studies a count was derived from a percentage reported in the full text. 'Contributes to' lists the pooled syntheses to which the study supplied a numerator and denominator; 13 studies contribute to none and are part of the evidence base described qualitatively.

Table S3. Sensitivity and subset analyses for the primary outcome (E1)

Analysis	k	Events/tests	Pooled proportion (95% CI)	95% PI	Comment
Primary analysis (GLMM, logit, profile-likelihood CI)	24	157/2774	4.56% (2.85–6.71)	0.8–22.5%	Prediction interval is the headline heterogeneity measure; I^2 = 69% (DerSimonian–Laird cross-check)
Leave-one-out (range of pooled estimates)	23	—	4.27%–5.11%	—	No single study drives the estimate
Freeman–Tukey double-arcsine model	24	157/2774	4.72%	—	Prespecified cross-check
DerSimonian–Laird logit model	24	157/2774	5.86% (4.22–8.06)	—	Prespecified cross-check
Broad definition of E1 (all aborted tests, including two stopped for observed respiratory effort)	24	159/2774	4.65% (2.93–6.77)	0.8–22.0%	Sensitivity analysis; the primary analysis applies the protocol definition
Low risk of bias	16	88/1943	3.87% (2.10–6.34)	0.6–21.9%	Prespecified sensitivity analysis
Excluding studies extracted from abstracts only	17	93/2000	4.10% (2.33–6.51)	0.7–21.4%	Prespecified sensitivity analysis (7 abstract-only studies in E1)
Prospective design (post hoc, Amendment 2)	9	39/797	3.71% (0.63–11.15)	0.1–68.5%	Randomized crossover classified as prospective
Retrospective design (post hoc, Amendment 2)	15	118/1977	4.92% (3.22–6.77)	1.7–13.7%	
Cohorts ≥100 tests (post hoc, Amendment 2)	7	97/1815	3.41% (0.97–8.33)	0.2–44.1%	
Cohorts <100 tests (post hoc, Amendment 2)	17	60/959	5.34% (3.14–8.07)	1.1–21.5%	
Technique subgroup: insufflation	13	96/1410	6.69% (4.15–9.87)	1.8–22.0%	Prespecified subgroup (ecological); between-group difference P = 0.37 (mixed-effects meta-regression); see Table S3 continued for the within-study comparison
Technique subgroup: mixed protocols	7	56/1085	3.96% (1.70–7.97)	0.4–27.9%	
Technique subgroup: positive pressure (incl. one high-flow series)	3	5/224	2.23% (0.73–5.13)	—	Exact Clopper–Pearson (GLMM did not converge with k = 3); one exogenous-CO_2 series (0/55) not classifiable

Table S3 (continued). Sensitivity analyses of the within-study technique comparison (test aborted for an adverse event)

Analysis	k	Positive pressure	Insufflation	Peto OR (95% CI)	P
Primary (all within-study comparisons)	6	3/389	16/448	0.26 (0.10–0.66)	0.0045
Mantel–Haenszel OR, continuity correction 0.5	6	3/389	16/448	0.25	—
Risk difference (fixed effect)	6	3/389	16/448	−2.9% (−4.5 to −1.2)	—
Leave-one-out, range	5	—	—	0.23–0.29	0.0034–0.036
Excluding Lévesque (paired arms)	5	2/370	14/429	0.23 (0.08–0.63)	0.0044
Excluding Sołek-Pastuszka (sequential design)	5	3/329	13/372	0.28 (0.10–0.79)	0.016
Excluding both	4	2/310	11/353	0.25 (0.08–0.77)	0.016
Excluding Cuninghame (largest)	5	3/264	9/212	0.29 (0.09–0.92)	0.036
Hypoxemia by arm	4	0/262	14/363	0.13 (0.04–0.38)	0.0002

I^2 = 0% in all analyses. CI, confidence interval; OR, odds ratio.

Table S4. Arm-level counts for the within-study technique comparison and the source of each count

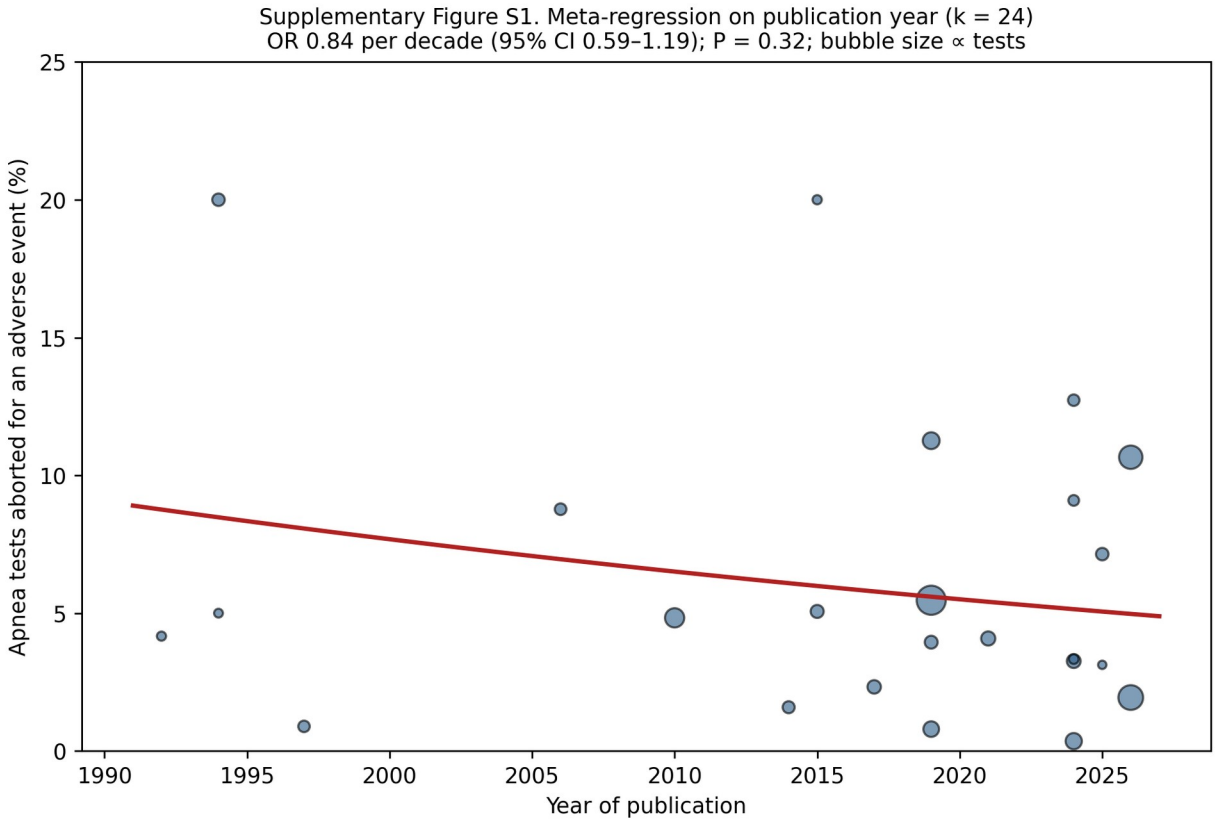
Study	Design	Positive pressure: aborted/n	Insufflation: aborted/n	Hypoxemia by arm (PP vs INS)	Source

Lévesque 2006	Randomized crossover; 19 patients analysed (patient 17 withdrawn before the protocol), three methods each	1/19 (CPAP 10 cmH2O)	2/19 (O2 catheter); T-piece 2/19, same patients	0/19 vs 2/19	Results: three patients had tests stopped prematurely. Patient 2 stopped at 9 min with both T-piece and CPAP for systolic pressure below 90 mmHg; patients 8 and 10 stopped at 7 min with the O2 catheter, and patient 10 also at 8 min with the T-piece, for desaturation below 90%.
Kramer 2017	Multicentre cohort, 14 ICUs in two cities; technique by city protocol; tests identified retrospectively from a provincial clinical information system	1/50 (CPAP valve)	1/36 (O2 catheter)	Not reported by arm	Results: one test in each group was discontinued for physiological instability. Two further tests in the CPAP city were terminated before pH criteria were met, with no overt instability and for reasons the authors could not establish; these are not counted as adverse events. Cohort includes 7 patients under 18 among 77.
Park 2019	Before–after retrospective cohort; unit is the test, not the patient	0/77 (Ambu bag with PEEP valve)	1/49 (O2 catheter 15 L/min)	Not reported as counts	Results: 49 instances of the conventional test in 25 patients, of which one was not completed because of unstable vital signs and brain SPECT was substituted; 77 instances of the modified test in 39 patients, with no failures. One patient in the modified-test group died during the observation period after the first test from abrupt deterioration; not counted as an aborted test.
Sołek-Pastuszka 2019	Sequential within-patient; CPAP test about 1.5 h after the insufflation test, after brain death had been confirmed	0/60 (ventilator CPAP 10 cmH2O)	3/76 (O2 catheter 6 L/min)	0/60 vs 3/76	Methods: the insufflation test was aborted in three cases for rapid desaturation below 90%, after 1.5, 4 and 5 min. Of the 76, sixteen did not contribute a CPAP test: three aborted insufflation tests, eight in whom apnea backup ventilation could not be suspended in CPAP mode, three with incomplete documentation and two with 12 h between tests. None of these exclusions depends on the outcome of the test.
Merchant 2024	Retrospective cohort; technique at clinician discretion	1/58 (ventilator, pressure support 0, PEEP kept, apnea backup off)	2/32 (O2 insufflation 4–6 L/min)	0/58 vs 4/32; hypotension 3/58 vs 4/32	Results: three of 92 attempted tests could not be completed because of patient instability, two with oxygen insufflation (one hypoxemia, one hypotension) and one on mechanical ventilation. Two tests with undocumented technique excluded.
Cuninghame 2026	Prospective multicentre cohort, 74 ICUs	0/125 (O2+PEEP 0/103; O2+PEEP+CO2 0/22)	7/236 (passive oxygenation)	0/125 vs 5/236	Results: of 361 tests, nine were aborted; seven were due to an adverse event and two to observed respiratory effort. All seven adverse events occurred with passive oxygenation. Of the nine

					aborted, eight were without PEEP and one with PEEP.

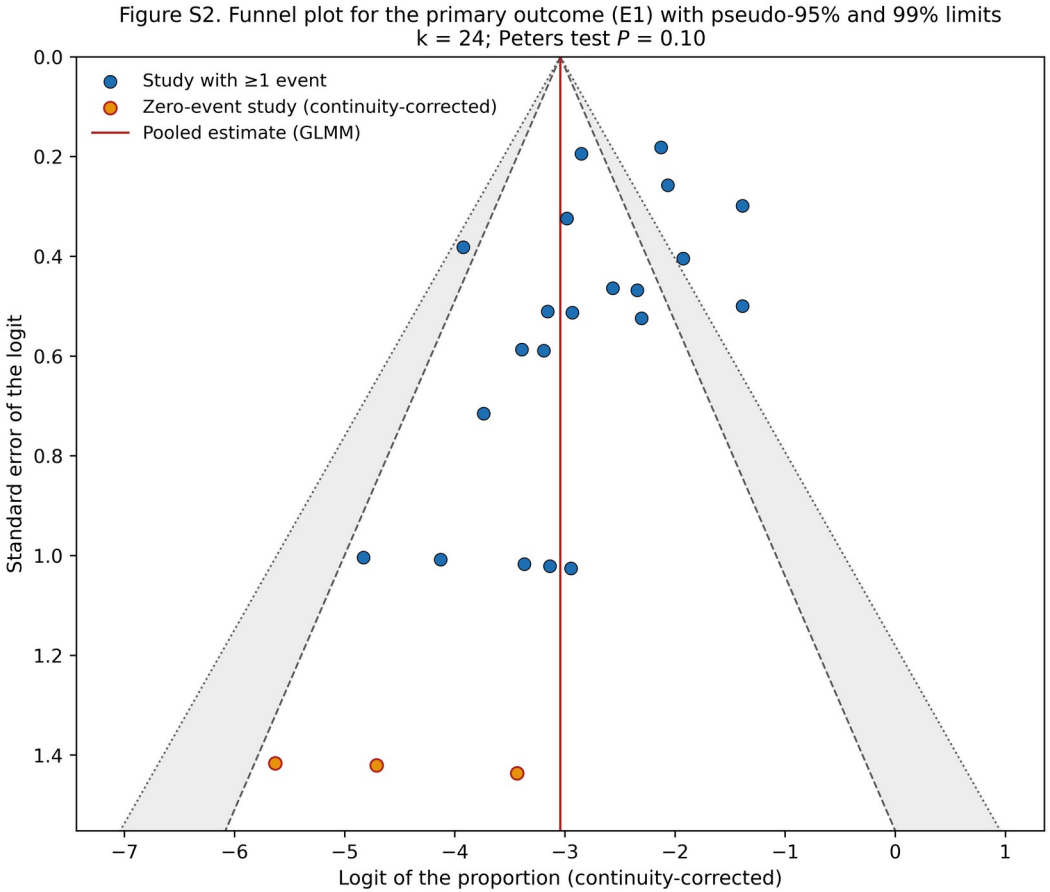
CPAP, continuous positive airway pressure; INS, insufflation; PEEP, positive end-expiratory pressure; PP, positive pressure. Excluded from the comparison: Hubbard 2016 (CPAP 67 vs non-CPAP 78; saturations and aborted tests not recorded), Kim 2019 and Yee 2010 (single technique), Hirsinger 2026 (technique breakdown not available). Counts were extracted independently by two authors and re-verified against the full text of each study on 25 August 2026; the earlier version of this table took the Lévesque counts from the conference abstract and the Park denominators from patients rather than tests, and both were corrected at that verification.

Figure S1. Meta-regression of the proportion of aborted apnea tests on year of publication (k = 24)



Mixed-effects meta-regression of the logit proportion on publication year with a moment estimate of residual between-study variance: OR 0.84 per decade (95% CI 0.59–1.19; P = 0.32). Because all positive-pressure series are recent, year and technique are confounded. Bubble size is proportional to the number of tests.

Figure S2. Funnel plot for the primary outcome (E1) with pseudo-95% and 99% confidence limits



Zero-event studies are shown continuity-corrected; their position on the logit scale is an artefact of the correction. Peters test P = 0.10. Larger and prospective series gave lower estimates than smaller and retrospective ones, a pattern compatible with a modest small-study effect.

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PRISMA-S checklist (reporting of literature searches)

Section	Item	Checklist item	Location where reported
INFORMATION SOURCES AND METHODS	1	Database name. Name each individual database searched, stating the platform for each.	Methods: MEDLINE via PubMed; Embase via embase.com; Scopus; Web of Science Core Collection; Cochrane CENTRAL via Wiley
	2	Multi-database searching. If databases were searched simultaneously on a single platform, state the name of the platform, identifying the databases searched.	Methods: each database searched separately on its own platform; no multi-database interface used
	3	Study registries. List any study registries searched.	Methods: none searched; stated explicitly as a limitation
	4	Online resources and browsing. Describe any online or print source purposefully searched or browsed.	Methods: reference lists of included studies and of relevant reviews were screened
	5	Citation searching. Indicate whether cited or citing references were examined, and describe any methods used.	Methods: backward citation searching of included studies and reviews; no formal forward citation tracking
	6	Contacts. Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers or others.	Methods: authors were not contacted; several full texts were obtained directly by the authors
	7	Other methods. Describe any additional information sources or search methods used.	Methods: no preprint server, trial registry or other grey-literature source was interrogated
SEARCH STRATEGIES	8	Full search strategies. Include the search strategies for each database and information source, copied and pasted exactly as run.	Full search strategies for all five databases, exactly as run, are appended at the end of this Supplement and deposited with the OSF registration (https://doi.org/10.17605/OSF.IO/6JUMD)
	9	Limits and restrictions. Specify that no limits were used, or describe any limits or restrictions applied and provide justification.	Methods: no language restriction; searched from inception to July 2026; no design filter applied
	10	Search filters. Indicate whether published search filters were used, and if so, describe the filter and cite the source.	Methods: no published search filter was used; a two-concept strategy was applied
	11	Prior work. Indicate when search strategies from other reviews were adapted or reused.	Methods: strategy developed de novo; calibrated to retrieve known key references
	12	Updates. Report the methods used to update the search(es).	Methods: searches run in July 2026; no subsequent update before submission
	13	Dates of searches. For each search strategy, provide the date when the last search occurred.	Methods: all databases last searched in July 2026
PEER REVIEW	14	Peer review. Describe any search peer review process.	No formal PRESS peer review of the search was undertaken; stated as a limitation
MANAGING RECORDS	15	Total records. Document the total number of records identified from each database and other information sources.	Results and Figure 1: 2056 records identified across 5 databases
	16	Deduplication. Describe the processes and any software used to deduplicate records.	Methods; searches run July 2026 (all databases from inception); date of each search in the appended search documentation

The PRISMA 2020 checklist is appended to the main manuscript.

Search strategy — full documentation

Safety of the Apnea Test in the Determination of Brain Death/Death by Neurologic Criteria in Adults: A Systematic Review and Meta-analysis

Reported according to PRISMA-S (Rethlefsen 2021), item 8: full search strategies for each database. Two-concept strategy: brain death AND apnea test. Safety outcomes captured at screening, not in the search string, because harms are inconsistently indexed. Coverage from database inception to the search date. No language restriction. No study-design filter. No published search filter.

1. Execution summary

All five databases searched on 18 July 2026, through the Universitat de València institutional session.

Database	Platform / interface	Proximity syntax	Records	Export format
MEDLINE	PubMed	[tiab:~3] + exact phrases	401	.nbib (Citation manager, all results)
Embase	embase.com (Elsevier) — not Ovid	/exp + NEAR/3 :ti,ab,kw	677	RIS with abstract + Medline PMID
Scopus	Elsevier	W/3 TITLE-ABS-KEY	509	RIS (Zotero), all fields
Web of Science Core Collection	Clarivate	TS= NEAR/3	454	RIS Full Record with abstract
Cochrane CENTRAL	Wiley Search Manager	NEAR/3 :ti,ab,kw	15	RIS (Reference Manager) with abstract
Total			2056	before deduplication

401 + 677 + 509 + 454 + 15 = 2056, the figure reported in the manuscript and in Figure 1. After deduplication: 1219 duplicates removed, 837 records screened.

Anchor-reference check: Busl 2021 (PMID 32524528) retrieved. ✔️

2. Status of each string

PRISMA-S asks for strings "copied and pasted exactly as run". Four of five meet that standard directly; MEDLINE does not, and this is stated openly below.

Database	Status
Scopus	Verbatim — run exactly as written in §3.3
Web of Science	Verbatim — run exactly as written in §3.4
Cochrane CENTRAL	Verbatim — run exactly as written in §3.5
MEDLINE	Split execution, and neither the literal query text nor the retrieved result set was preserved. The logic below was run as two separate queries and combined, because the interface limited the number of operators per query. The PubMed search history had expired before the documentation was compiled and no export of the result set survived, so the 401 PMIDs retrieved on 18 July 2026 cannot be recovered. See §3.1 and §4.
Embase	Verbatim, reconstructed and verified. The literal embase.com string was not saved at the time of the original search. It was reconstructed from the pre-specified logic and re-executed on embase.com on 24 August 2026, returning 682 records against the 677 of 18 July 2026 — a difference consistent with five weeks of new indexing. The verified string is given in §3.2.

3. Search strings

3.1 MEDLINE (PubMed) — 18 July 2026 — 401 records

Set #1 (brain death):

```
("Brain Death"[Mesh] OR "brain death"[tiab] OR "brain-dead"[tiab] OR "brainstem death"[tiab]
OR "brain stem death"[tiab] OR "cerebral death"[tiab] OR "death by neurologic criteria"[tiab]
OR "death by neurological criteria"[tiab] OR "neurologic determination of death"[tiab]
OR "neurological determination of death"[tiab] OR "determination of brain death"[tiab])
```

Set #2 (apnea test):

```
("apnea test"[tiab:~3] OR "apnoea test"[tiab:~3] OR "apnea testing"[tiab] OR "apnoea
testing"[tiab]
OR "apnea tests"[tiab] OR "apnoea tests"[tiab] OR "apneic test"[tiab] OR "apnoeic test"[tiab]
OR "apnea challenge"[tiab] OR "apnoea challenge"[tiab] OR "apneic oxygenation"[tiab]
OR "apnoeic oxygenation"[tiab])
```

Combined: #1 AND #2

Execution note. Run as two queries whose results were combined and deduplicated: a core query restricted to exact phrases (test / testing / tests / challenge) returned 390 records, and a supplementary query adding the proximity operator and the apneic-oxygenation terms returned 276, of which 11 were new. Deduplicated union = 401.

The complete list of the 401 PMIDs retrieved on 18 July 2026 was not preserved. The PubMed search history expires after a short interval and had lapsed before this documentation was compiled, and no export of the result set survived. MEDLINE retrieval is therefore reproducible in its logic but not verifiable against the original result set; the search was not re-executed, because a list generated now would reflect subsequent indexing and would not be a record of what the July search retrieved.

A calibration run on 17 July 2026 with exact phrases only returned 389; the difference from 390 reflects same-day database updating.

3.2 Embase (embase.com, Elsevier) — 18 July 2026 — 677 records

String as executed on embase.com Advanced Search, entered as a single query. Verified by re-execution on 24 August 2026.

```
('brain death'/exp OR 'brain death' OR 'brain death':ti,ab,kw OR 'brain-dead':ti,ab,kw
OR 'brainstem death':ti,ab,kw OR 'brain stem death':ti,ab,kw OR 'cerebral death':ti,ab,kw
OR 'death by neurologic criteria':ti,ab,kw OR 'death by neurological criteria':ti,ab,kw
OR 'neurologic determination of death':ti,ab,kw OR 'neurological determination of death':ti,ab,kw
OR 'determination of brain death':ti,ab,kw)
AND
((((apnea OR apnoea OR apneic OR apnoeic) NEAR/3 (test OR testing OR tests OR
challenge*)):ti,ab,kw)
OR 'apneic oxygenation':ti,ab,kw OR 'apnoeic oxygenation':ti,ab,kw)
```

Mapping options left at platform default: map to preferred term in Emtree, search also as free text in all fields, explode using narrower Emtree terms, search as broadly as possible.

Execution note. The platform normalises the query by appending an unfielded 'brain death' after the exploded Emtree term, so the brain-death concept is retrieved through Emtree and free text simultaneously. This matches the note recorded at the time of the original search and explains why Embase gave the largest single yield; it also includes conference proceedings.

Verification. The original run on 18 July 2026 returned 677 records. Re-executing the string above on 24 August 2026 returned 682, a difference of five records consistent with five weeks of new indexing. The count used throughout the review is the 677 of the original search date.

An Ovid-syntax version of the same logic was drafted before execution but was not the version run and is not deposited.

3.3 Scopus — 18 July 2026 — 509 records

```
( TITLE-ABS-KEY ( "brain death" OR "brain-dead" OR "brainstem death" OR "brain stem death"
OR "cerebral death" OR "death by neurologic* criteria" OR "neurologic* determination of death"
OR "determination of brain death" )
AND
( TITLE-ABS-KEY ( ( apnea OR apnoea OR apneic OR apnoeic ) W/3
( test OR testing OR tests OR challenge* ) )
OR TITLE-ABS-KEY ( "apneic oxygenation" OR "apnoeic oxygenation" ) ) )
```

3.4 Web of Science Core Collection — 18 July 2026 — 454 records

```
TS=( ( "brain death" OR "brain-dead" OR "brainstem death" OR "brain stem death"
OR "cerebral death" OR "death by neurologic* criteria"
OR "neurologic* determination of death" OR "determination of brain death" )
AND
( ( (apnea OR apnoea OR apneic OR apnoeic) NEAR/3 (test OR testing OR tests OR challeng*) )
OR "apneic oxygenation" OR "apnoeic oxygenation" ) )
```

Exported as records 1–454, Full Record with abstract.

3.5 Cochrane CENTRAL (Wiley Search Manager) — 18 July 2026 — 15 records

```
#1 MeSH descriptor: [Brain Death] explode all trees
#2 ("brain death" OR "brain-dead" OR "brainstem death" OR "brain stem death"
    OR "cerebral death" OR "death by neurologic* criteria"
    OR "neurologic* determination of death" OR "determination of brain death"):ti,ab,kw
#3 #1 OR #2
#4 ((apnea OR apnoea OR apneic OR apnoeic) NEAR/3
    (test OR testing OR tests OR challeng*)):ti,ab,kw
#5 ("apneic oxygenation" OR "apnoeic oxygenation"):ti,ab,kw
#6 #4 OR #5
#7 #3 AND #6
```

Restricted to Trials (CENTRAL). Platform warning noted: a wildcard inside a quoted phrase may undercount rare variants of "neurologic* criteria".

4. Limitations of this documentation

Stated explicitly so that the record is honest rather than tidy.

Embase. The literal string was not captured at the time of the original search. It has since been reconstructed and verified by re-execution (§3.2), which returned a record count within five of the original. The reconstruction is therefore documented as verified rather than as a claim, but readers should note that it was recovered after the fact rather than logged at the time.

MEDLINE. This is the weakest link in the documentation. Neither the literal text of the two executed queries nor the list of 401 retrieved PMIDs was preserved, so retrieval from MEDLINE cannot be verified against the original search. What is documented is the logic, the two-query execution and the yield of each; what is not is the exact query text or the retrieved set. MEDLINE contributed 401 of the 2056 records before deduplication. This is stated rather than smoothed over.

No PRESS peer review of the strings was performed.

No grey literature. medRxiv, Europe PMC preprints and trial registries were not searched. Draft strings for those sources were prepared but not executed, and this restriction is reported as a limitation in the manuscript.

5. Supplementary search methods

- Backward citation searching: reference lists of all included studies and of Busl 2021.
- Forward citation searching: not performed formally.
- Author contact: not undertaken.
- Deduplication: in the reference manager with manual verification, 1219 duplicates removed. An independent in-house deduplication of the same exports left 850 records; the 13 additional entries were title variants of already-retained records lacking a DOI, none a distinct study. The 837 figure is used throughout.

6. Protocol amendment

The protocol specified a three-concept search (brain death AND apnea test AND safety). A two-concept strategy was adopted because adverse events and test abortions are inconsistently indexed: a cohort reporting a hypoxaemia-related abortion in a results table is frequently not tagged with any harm term in title, abstract or subject headings, so a mandatory safety block would have dropped exactly the studies the review depends on. This follows the standard guidance for reviews of harms (Cochrane Handbook, adverse-effects chapter): search on population and intervention, screen for the outcome. The two-concept yield was small enough to screen exhaustively, so no precision argument favoured narrowing it.

This deviation is reported as a protocol amendment in the manuscript and in the registration (amendment 1).