

Designing Clinical Trials in Perioperative Sleep Medicine A Rationale and Pragmatic Approach

Daniel J. Gottlieb, MD, MPH

Director, Sleep Disorders Center, VA Boston Healthcare System

Program in Sleep and Cardiovascular Medicine, Brigham & Women's Hospital

Division of Sleep and Circadian Disorders, Harvard Medical School



No financial conflicts
of interest.

**“Joe the Fat Boy,” from Dickens’
*Posthumous Papers of the Pickwick
Club, 1848***

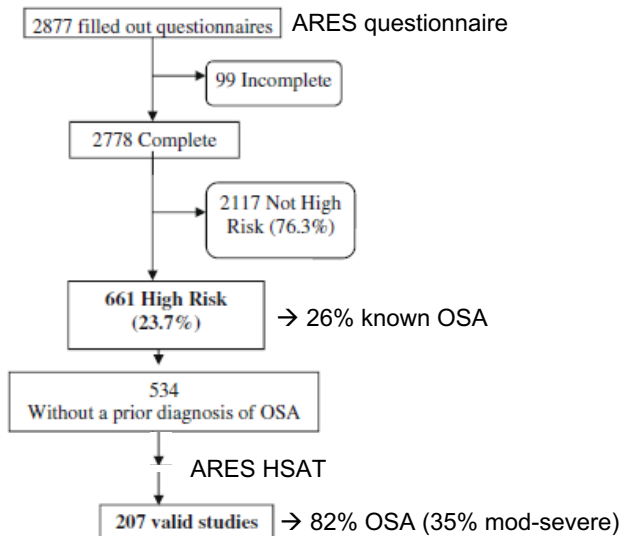
Prevalence of Obstructive Sleep Apnea

Wisconsin Sleep Cohort, 2007-2010

	Age	Prevalence in Men	Prevalence in Women
	30-70		
AHI \geq 5		34%	17%
AHI \geq 15		13%	6%
	50-70		
AHI \geq 5		43%	28%
AHI \geq 15		17%	9%

Prevalence of Obstructive Sleep Apnea in patients undergoing elective surgery

Washington University Study

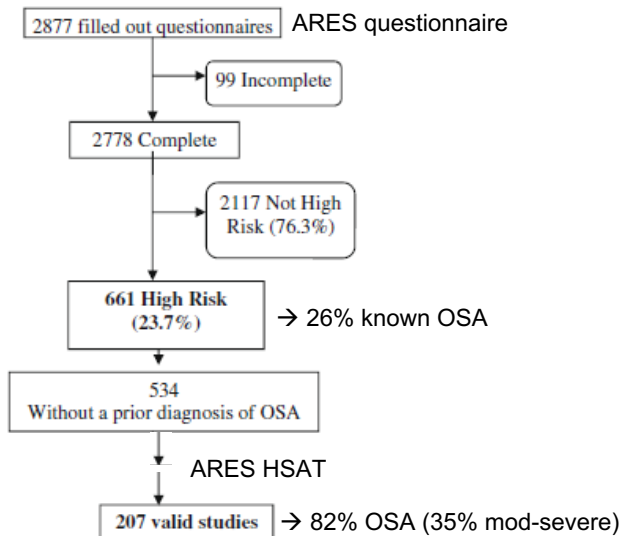


Minimum prevalence estimate: 22%

72% of OSA patients undiagnosed

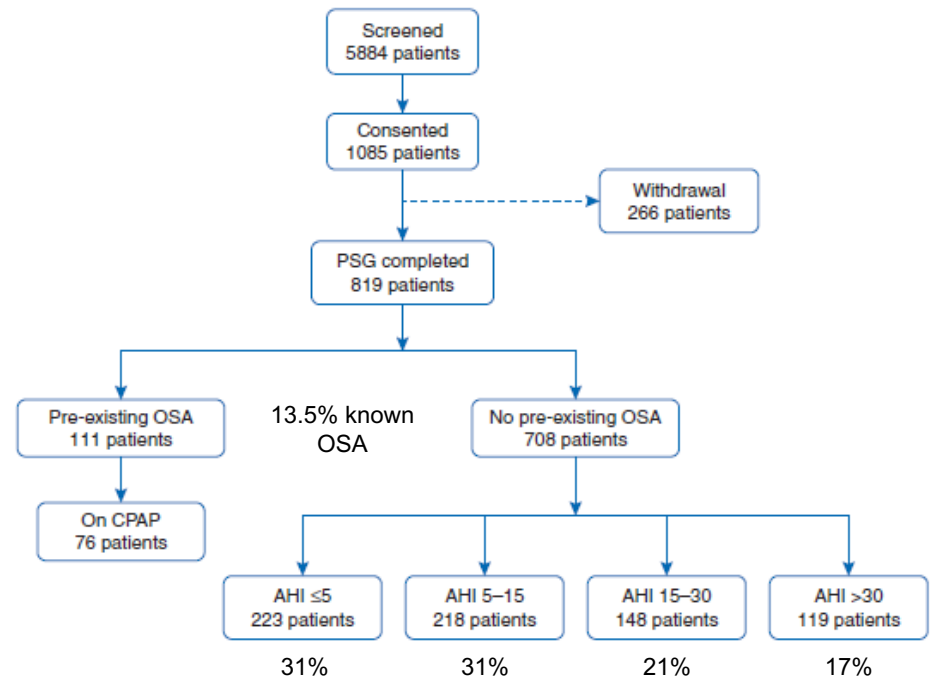
Prevalence of Obstructive Sleep Apnea in patients undergoing elective surgery

Washington University Study



Minimum prevalence estimate: 22%
72% of OSA patients undiagnosed

University of Toronto Study



Total prevalence estimate: 73%
81% of OSA patients undiagnosed

Does Obstructive Sleep Apnea Influence Perioperative Outcome? A Qualitative Systematic Review for the **Society of Anesthesia and Sleep Medicine** Task Force on Preoperative Preparation of Patients with Sleep-Disordered Breathing

Mathias Opperer, MD,*† Crispiana Cozowicz, MD,*† Dario Bugada, MD,‡ Babak Mokhlesi, MD, MSc,§
Roop Kaw, MD,|| Dennis Auckley, MD,¶ Frances Chung, MBBS, FRCPC,#
and Stavros G. Memtsoudis, MD, PhD, FCCP*†

50 studies of surgery with general or neuraxial anesthesia, including >400,000 OSA cases, >8M controls

- 11 ICD dx (~360,000 cases)
- 17 PSG/HSAT dx (~7000 cases, most retrospective)
- 15 screening questionnaire “high risk” (~5,000 cases)
- 7 diagnosis in chart/clinical diagnosis (~40,000 cases)

Does Obstructive Sleep Apnea Influence Perioperative Outcome? A Qualitative Systematic Review for the Society of Anesthesia and Sleep Medicine Task Force on Preoperative Preparation of Patients with Sleep-Disordered Breathing

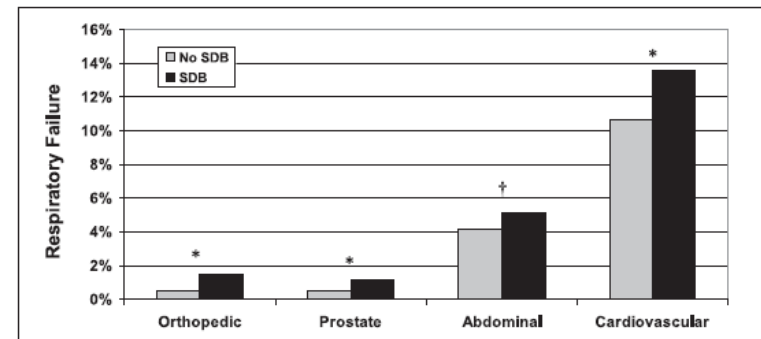
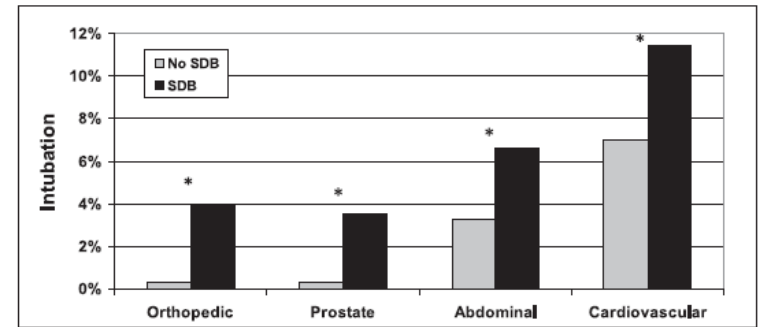
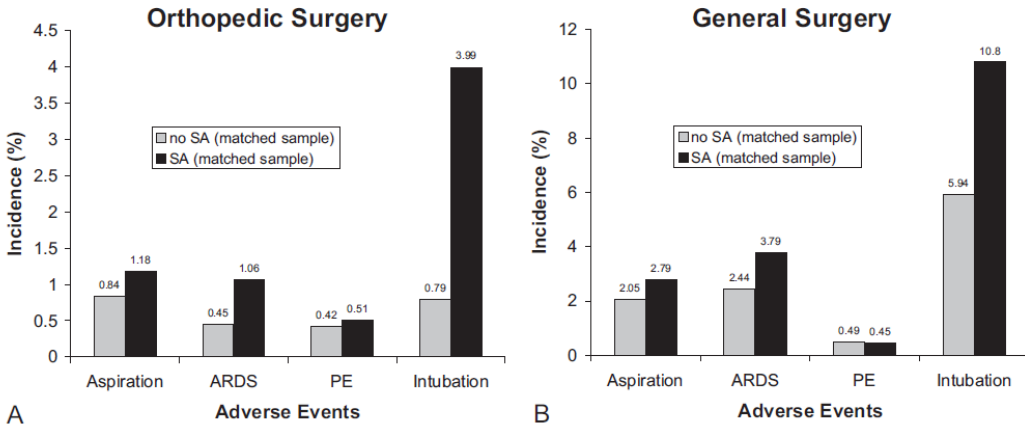
Mathias Opperer, MD,*† Crispiana Cozowicz, MD,*† Dario Bugada, MD,‡ Babak Mokhlesi, MD, MSc,§
 Roop Kaw, MD,|| Dennis Auckley, MD,¶ Frances Chung, MBBS, FRCPC,#
 and Stavros G. Memtsoudis, MD, PhD, FCCP*†

50 studies of surgery with general or neuraxial anesthesia, including >400,000 OSA cases, >8M controls

- 11 ICD dx (~360,000 cases)
- 17 PSG/HSAT dx (~7000 cases, most retrospective)
- 15 screening questionnaire “high risk” (~5,000 cases)
- 7 diagnosis in chart/clinical diagnosis (~40,000 cases)

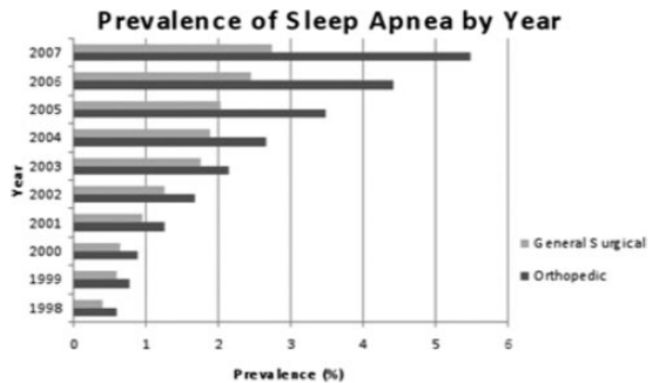
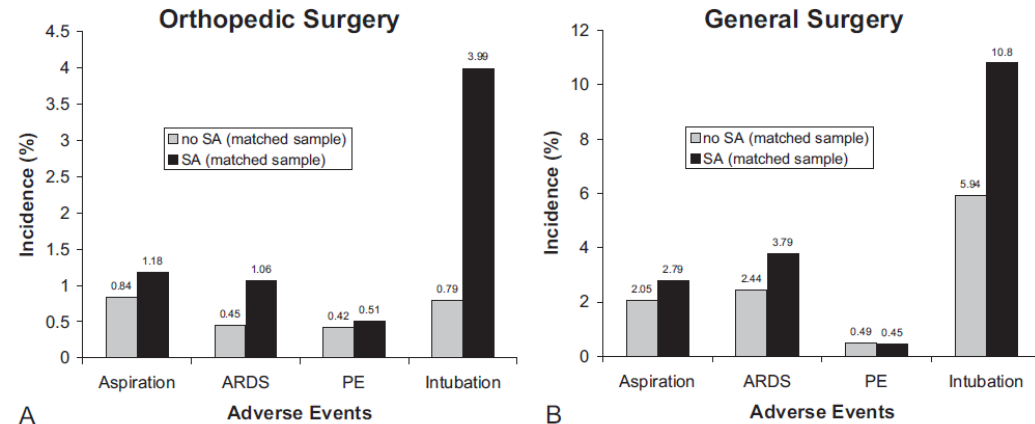
Table 1. Included Studies for Procedures Under General or Neuraxial Anesthesia			
Impact of OSA on outcomes	Detrimental Impact	Beneficial Impact	Not significant Impact
Pulmonary complications	9 studies ^{6,7,10,12-17}	0 studies	6 studies ^{9,18-22}
Desaturation	7 studies ^{14,23-28}	0 studies	5 studies ^{13,29-33}
Difficult intubation	4 studies ³⁴⁻³⁷	1 study ³⁸	1 study ³⁹
Cardiac complications	1 study ⁷	0 studies	9 studies ^{12-18,20,27}
Atrial fibrillation	5 studies ^{9,10,40-42}	0 studies	1 study ²⁷
Combined complications	8 studies ^{7,8,13-15,25,43,44}	0 studies	2 studies ^{21,45}
Resource utilization	11 studies ^{7,8,12-14,25,33,44,46-48}	2 studies ^{9,18}	6 studies ^{20,27,37,49-51}
Other outcomes	1 study ²⁹	2 studies ^{52,53}	1 study ⁵⁴
Mortality	1 study ¹²	3 studies ^{9,10,55}	9 studies ^{7,15,18-21,27,49,56}

AHRQ National Inpatient Sample Database



Approximately two-fold increased risk of major pulmonary complications

AHRQ National Inpatient Sample Database



Misclassification of OSA status may bias in either direction!

- Inclusion of OSA in the control group will bias toward a null result
- If diagnosis is influenced by severity of comorbid illness, could confound association of OSA with adverse outcomes

Questionnaire Screening for OSA Risk

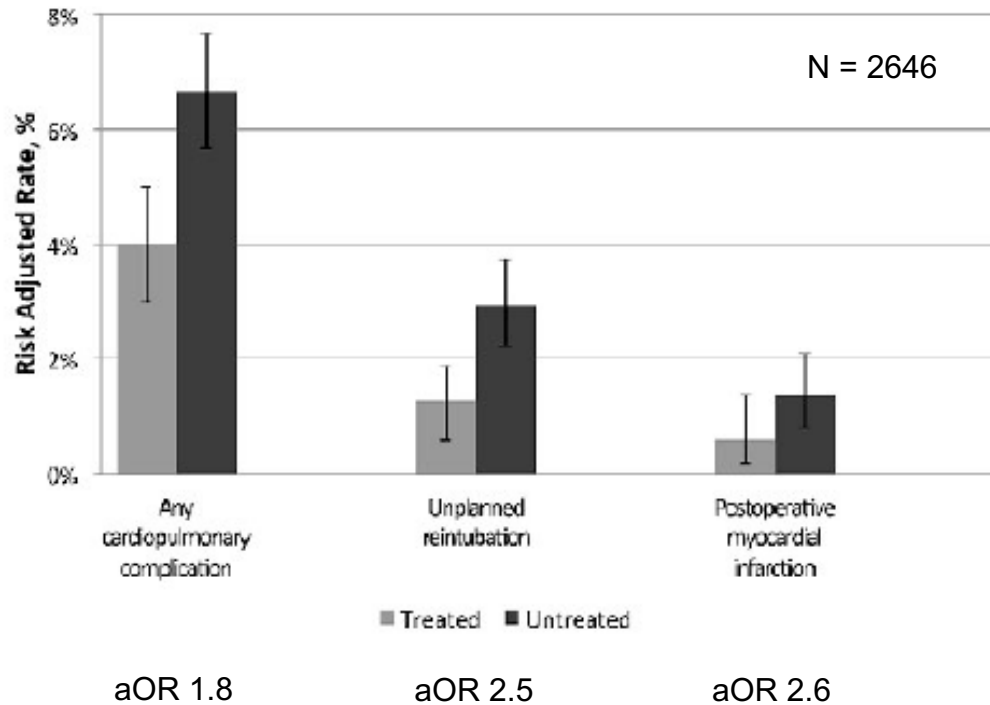
Practical and predictive of complications, but is it biased?

- STOP-Bang
 - Includes age, sex, BMI, HTN
- Perioperative Sleep Apnea Prediction (PSAP) Score
 - Includes age, sex, BMI, HTN, DM
- Score for Perioperative Prediction of OSA (SPOSA)
 - Includes age, sex, BMI, HTN, DM, ASA score, CAD, HF, AFib, HL, chronic lung disease, pulmonary HTN, liver ds, hemiplegia

Quasi-experimental Studies

Complication rates in 2646 patients with known or suspected OSA by CPAP treatment status:
Michigan Surgical Quality Collaborative

Risk-Adjusted Rates of Postoperative Cardiopulmonary Complications for Treated and Untreated Obstructive Sleep Apnea Patients



Strengths

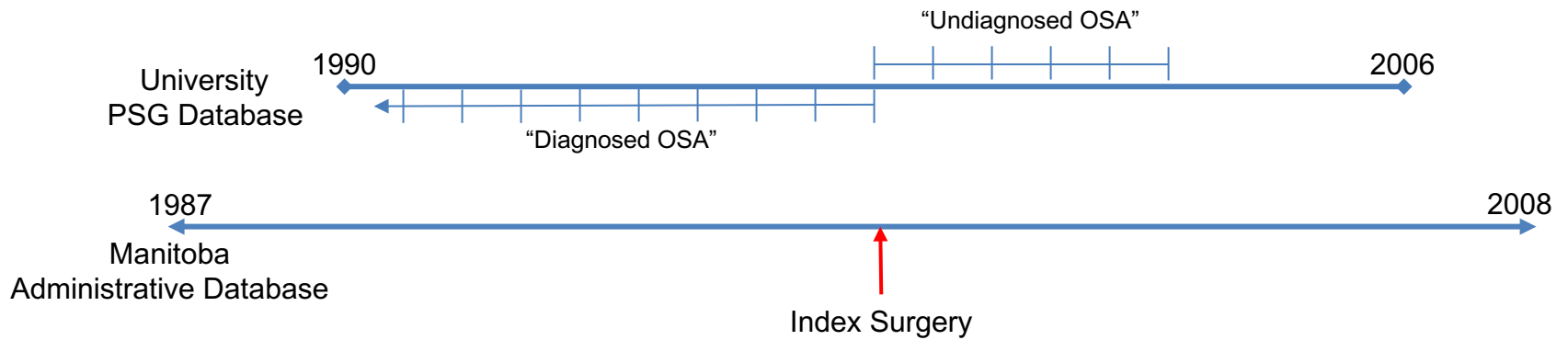
52 community and academic hospitals
Outcomes systematically assessed

Weaknesses

“Suspicion” of OSA not clearly defined
Self-report of CPAP use
Unknown if used post-op

Quasi-experimental Studies

Complication rates in 4211 patients with PSG-
documented OSA and matched controls



Outcomes

Cardiac arrest

ACS

Stroke

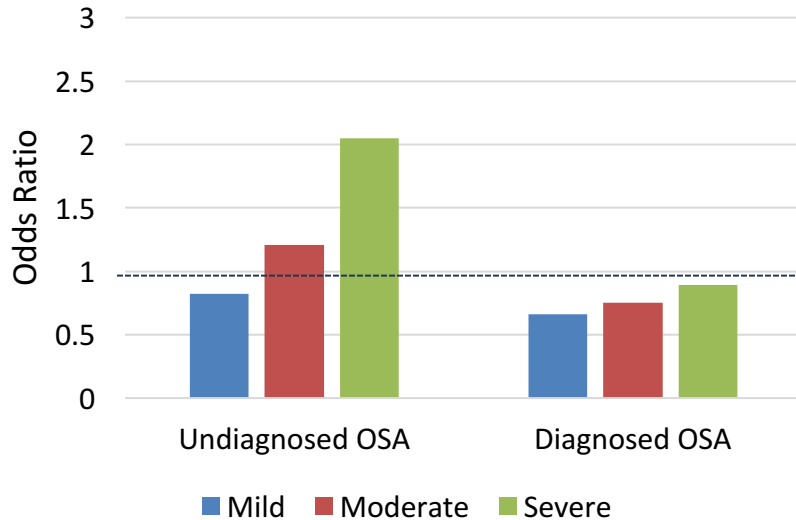
Atrial fib/flutter

ARDS

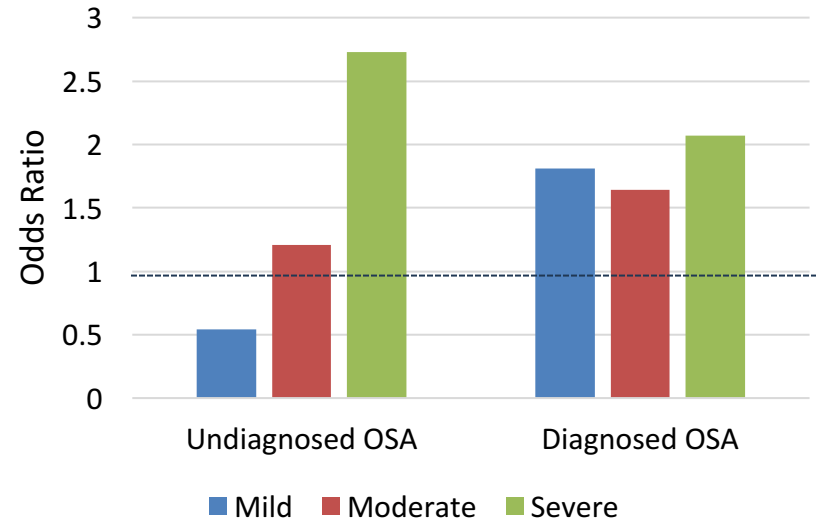
Respiratory failure

Pneumonia

Cardiovascular Complications



Respiratory Complications



Strengths

Definitive diagnosis of OSA

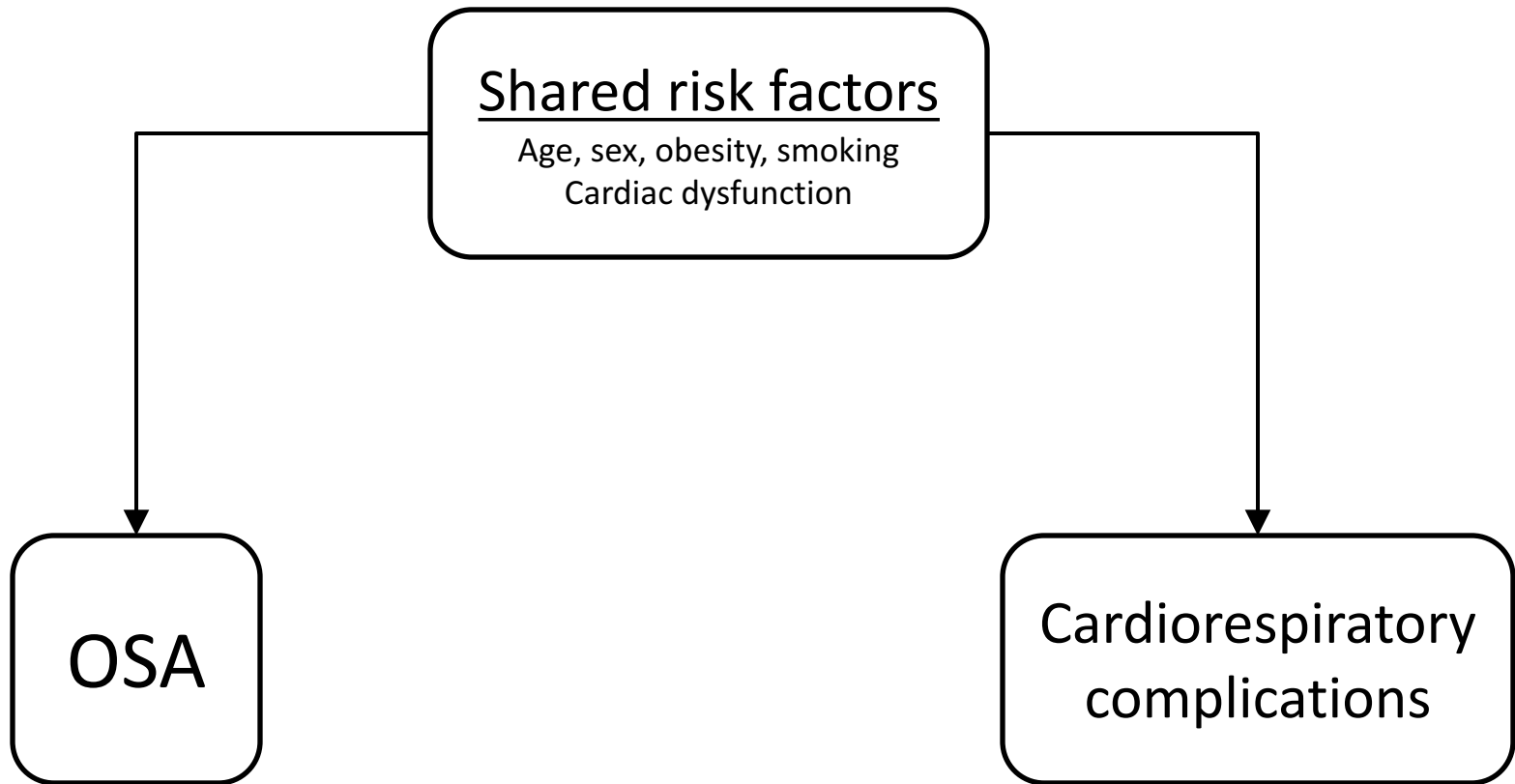
Weaknesses

Outcomes use ICD codes

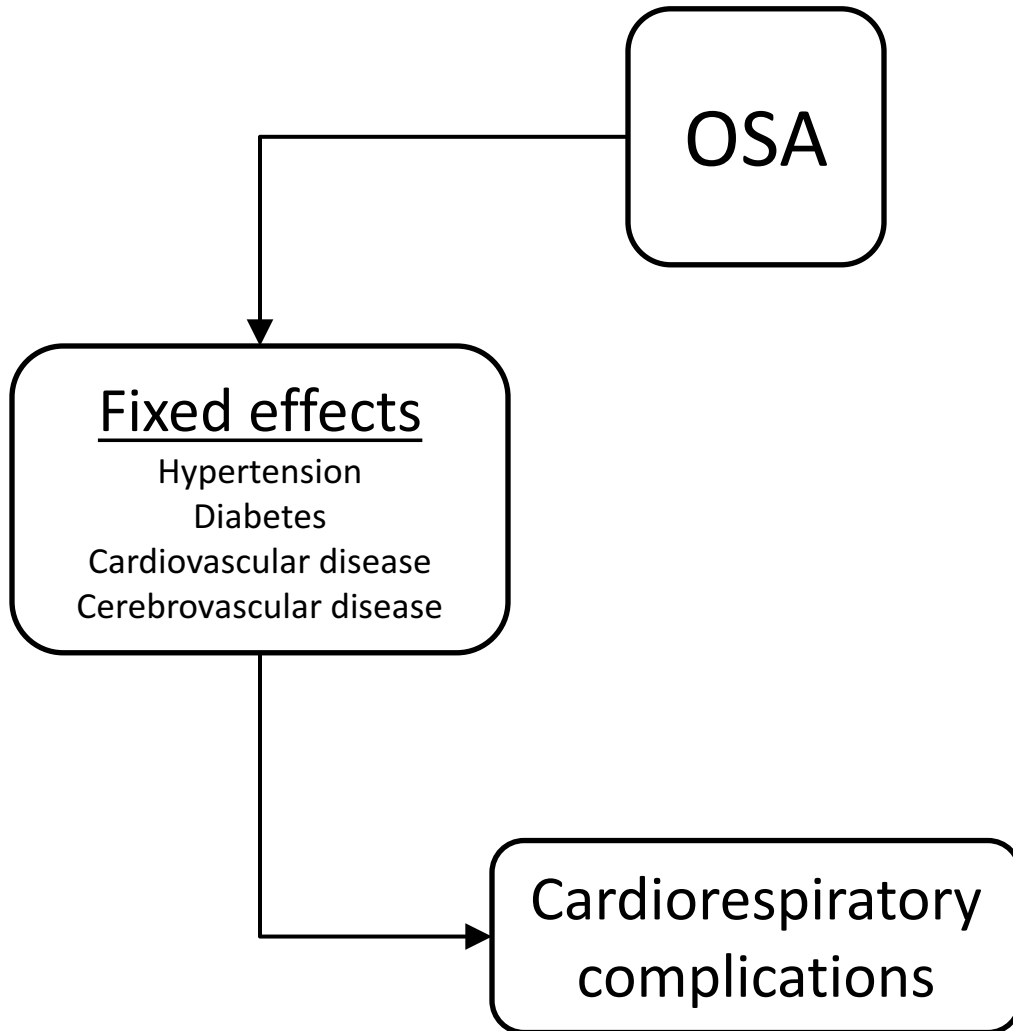
Diagnosis of OSA pre-surgery as a proxy for OSA treatment

Could referral for OSA evaluation be a result of perioperative complications?

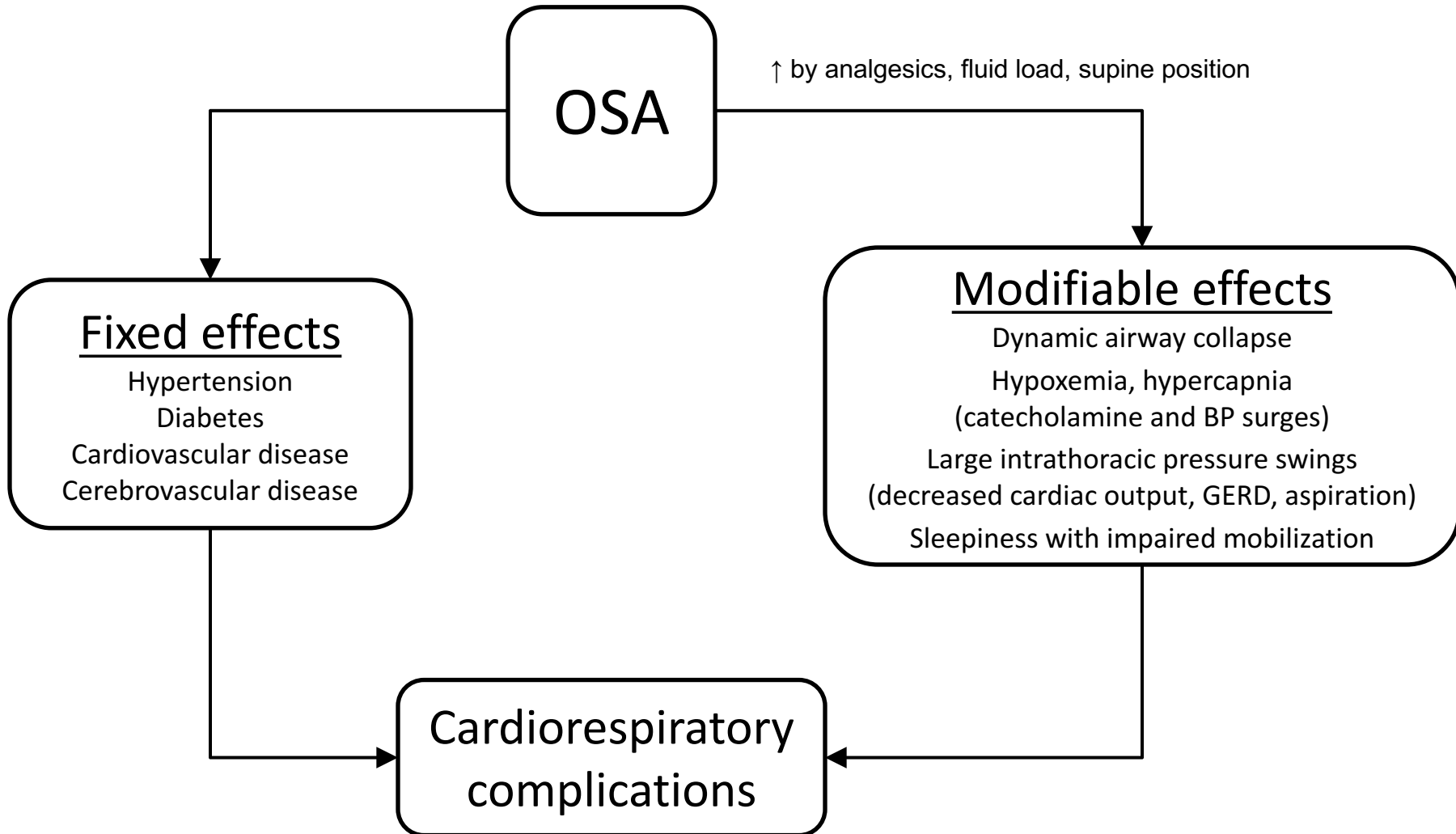
Does OSA cause the observed increase in perioperative complications?



Does OSA cause the observed increase in perioperative complications?



Does OSA cause the observed increase in perioperative complications?

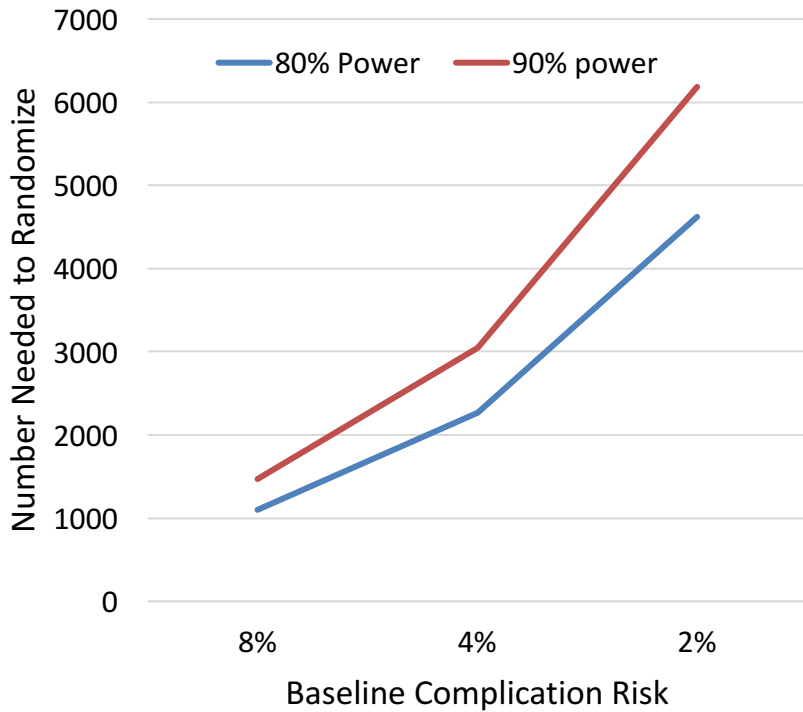


Rationale for a Clinical Trial in Perioperative Sleep Medicine

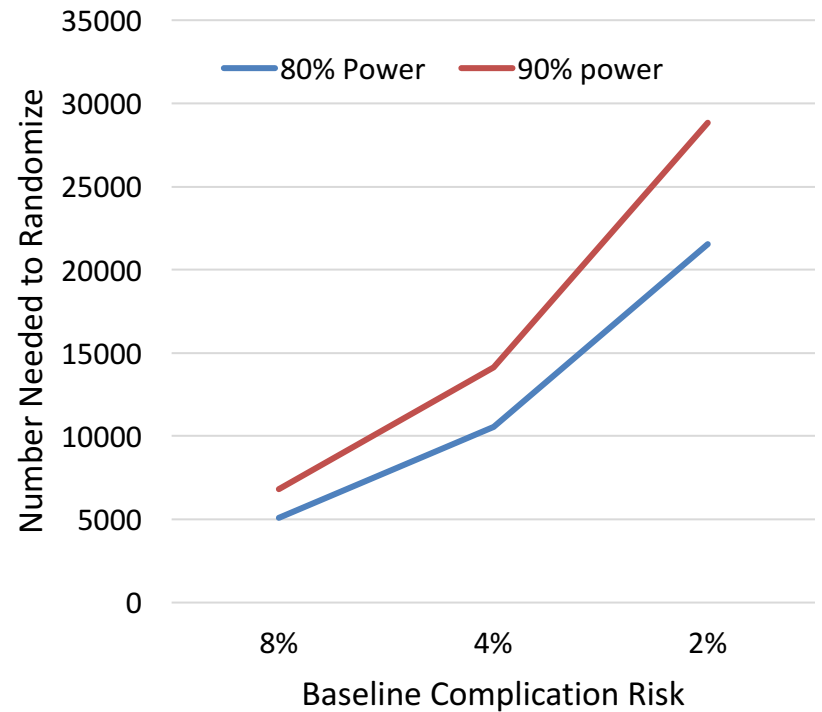
- OSA is associated with increased perioperative cardiopulmonary complications
- The population exposed to OSA in the perioperative period is very large
- We don't know whether OSA causes these complications or whether treatment of OSA reduces the risk of complications

Sample Size Estimates

50% reduced risk



25% reduced risk



Practical Barriers to RCT

- Short time frame from pre-op evaluation to surgery
 - Is recruitment feasible?
 - Are screening and diagnosis feasible?
 - Is treatment feasible?
- Disruption of surgical schedules
- Lack of patient interest

Ethical Barriers to RCT

- Effective OSA treatments are available: do all team members and patients have equipoise such that it is ethical to randomize to no treatment?

American Society of Anesthesiologists

Practice Guidelines for Perioperative Management of OSA

- Pre-op evaluation for possible OSA
- Consider CPAP pre-, intra- and post-operatively
- Consider use of local or regional anesthesia where feasible
- Extubation while awake for patients receiving general endotracheal anesthesia
- Non-supine positioning when possible
- Routine postoperative oxygen supplementation
- Minimize opioid analgesic use
- Increased intensity of postoperative monitoring

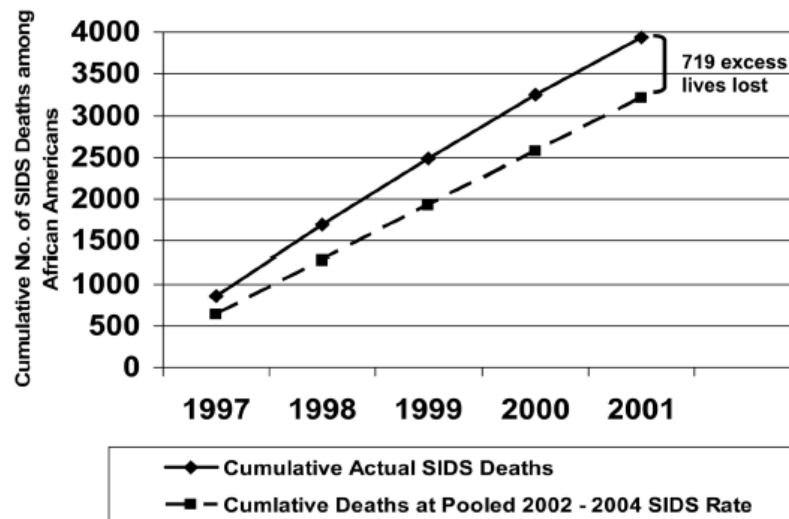
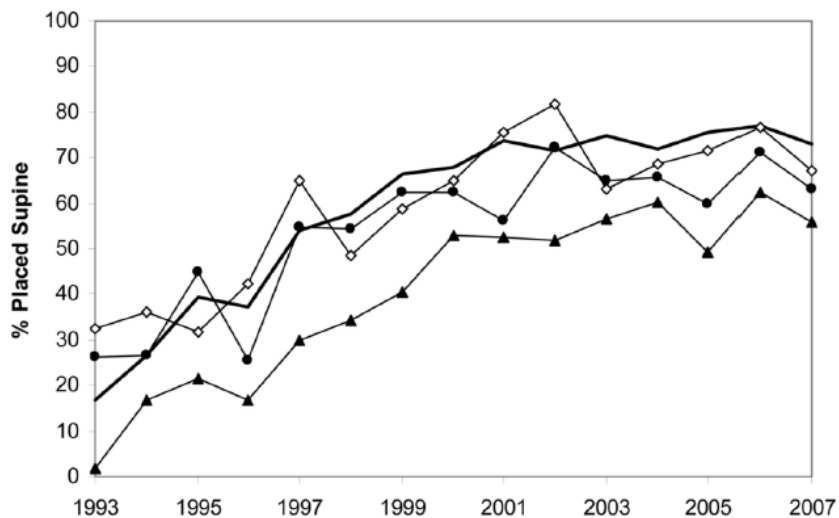
Clinical Implementation Study



American Academy of Pediatrics Guidelines (1992)

- Supine positioning
- No soft bedding
- No bed-sharing

DHHS Back to Sleep Campaign (1994)



Pragmatic (adjective):

Dealing with things sensibly and realistically...

(Oxford Dictionary)

What is a Pragmatic Clinical Trial?

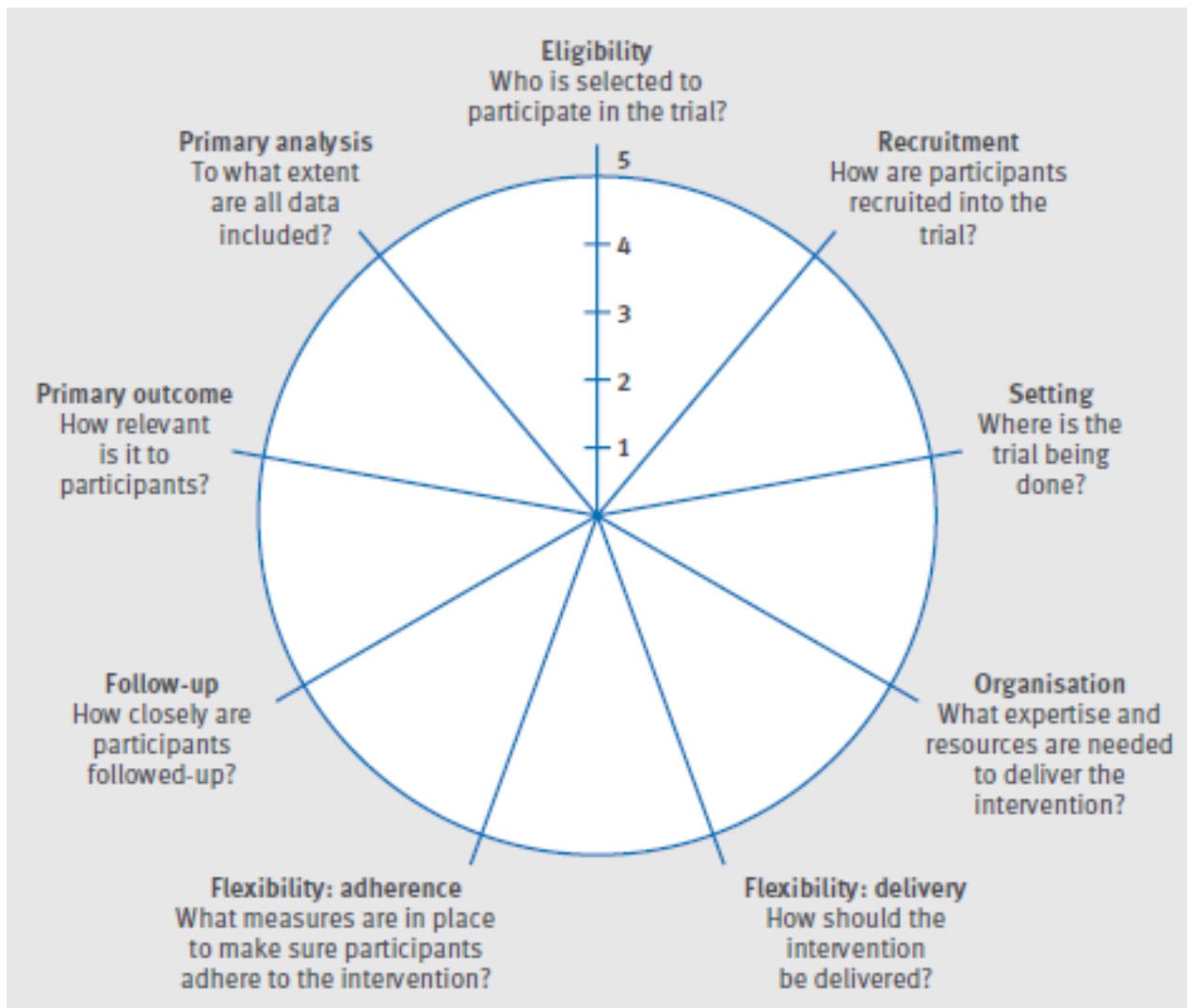
Explanatory

- Test efficacy
- Understand biology
 - Often placebo control
- Controlled conditions
 - Rigorous exclusion criteria
 - Protocolized intervention
 - Intensive adherence promotion
- Individual randomization

Pragmatic

- Test effectiveness
- Inform clinical care
 - Usual care control
- “Real-world” conditions
 - Include any patients who would be targeted in clinical practice
 - Flexibility in administration of intervention
 - Adherence as per usual care
- Cluster randomization common

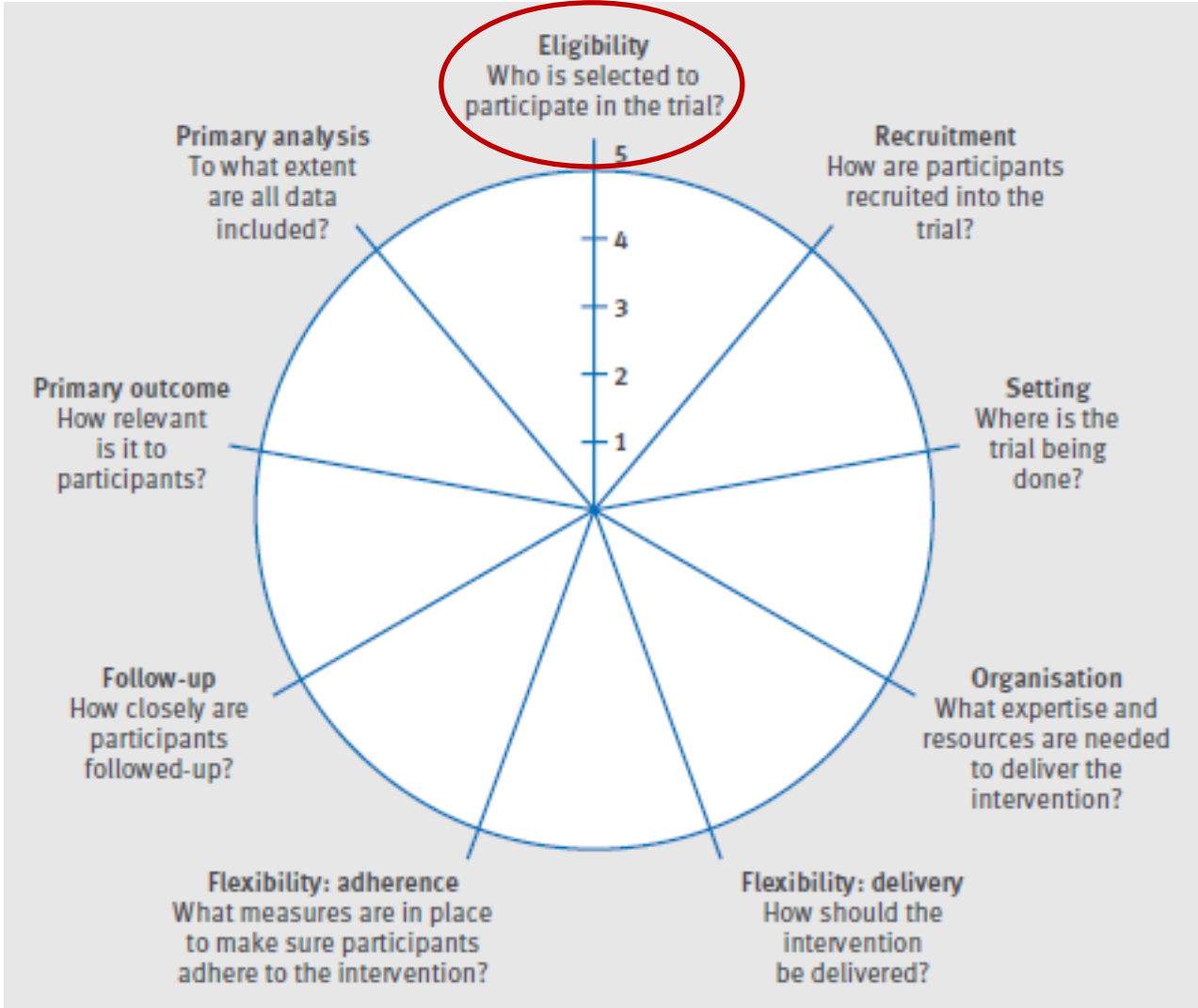
PRECIS-2 Tool



What is the intervention of interest?

- Provider awareness
- Intensive monitoring
- Non-specific interventions
 - Type of anesthesia, analgesia, positioning
- CPAP
 - In whom?
 - Pre-op? For how long?
 - Post-op? In hospital only or out of hospital?
- Hybrid: awareness for all, CPAP only for those at high risk of complications?

All patients undergoing surgery?
Specific surgery types?
Patients at very high risk of complications?

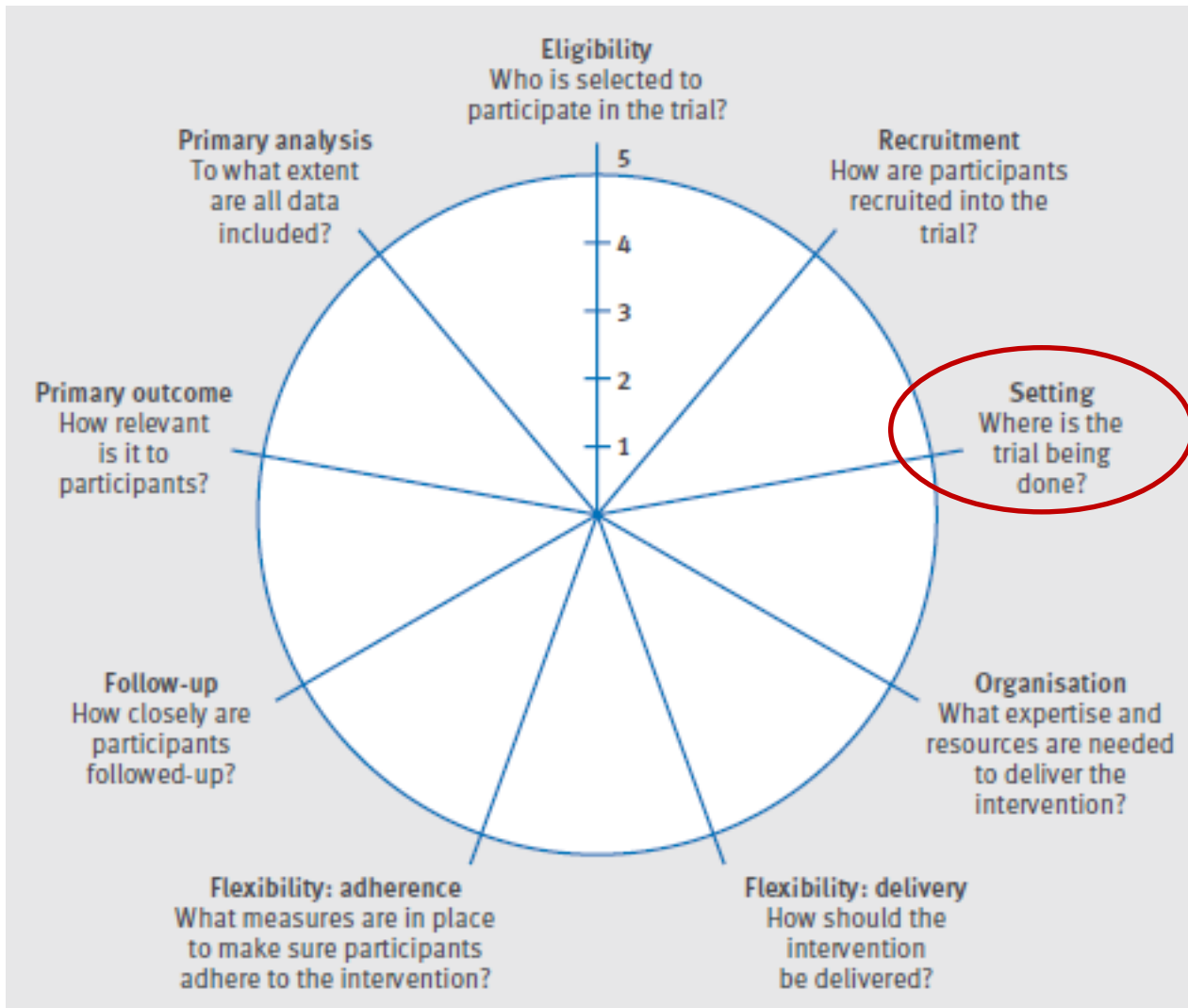


Hypercapnia May Identify a High Risk Group

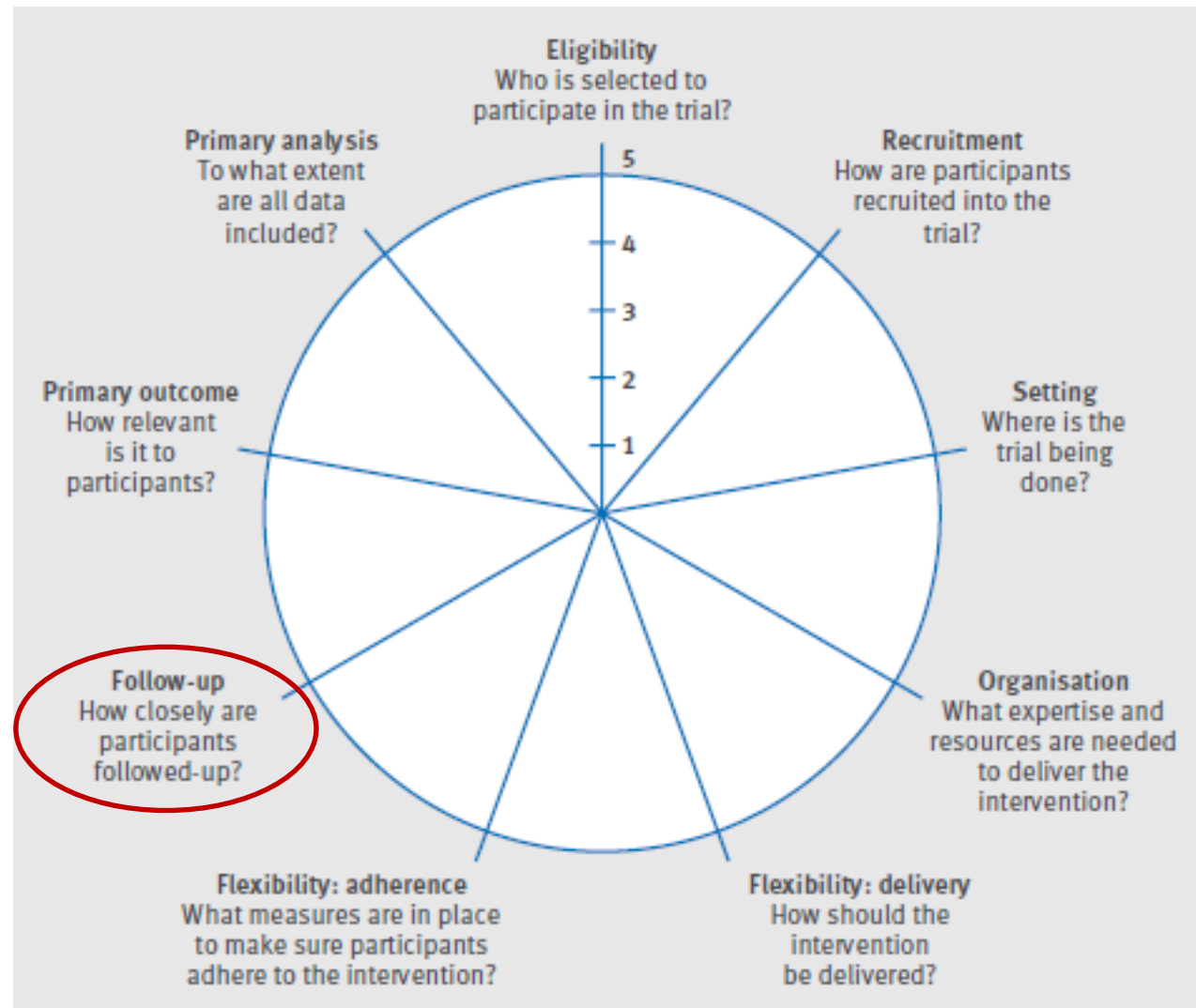
Adjusted Risk of Postoperative Outcomes in Patients With Definite OHS, Possible OHS, and Overlap Syndrome Versus Patients With OSA

Postoperative Outcome	Hypercapnic OSA (n = 194)	OSA (n = 325)	OR (95% CI)	P Value
Respiratory failure	39 (21)	8 (2)	10.9 (3.7-32.3)	< .0001
Heart failure	15 (8)	0	5.4 (1.9-15.7)	.002
Prolonged intubation	24 (13)	12 (4)	3.1 (0.6-15.3)	.2
Reintubation	12 (6)	5 (2)	1.7 (0.2-13.4)	.6
Tracheostomy	4 (2)	3 (1)	3.8 (1.7-8.6)	.002
ICU transfer	41 (21)	19 (6)	10.9 (3.7-32.3)	< .0001
Death at 30 d	2 (1)	0	... ^a	...
Death at 1 y	10 (5)	2 (0.6)	0.9 (0.1-7.5)	.9

Only 500 patients needed to detect a 50% decrease in respiratory failure with 90% power



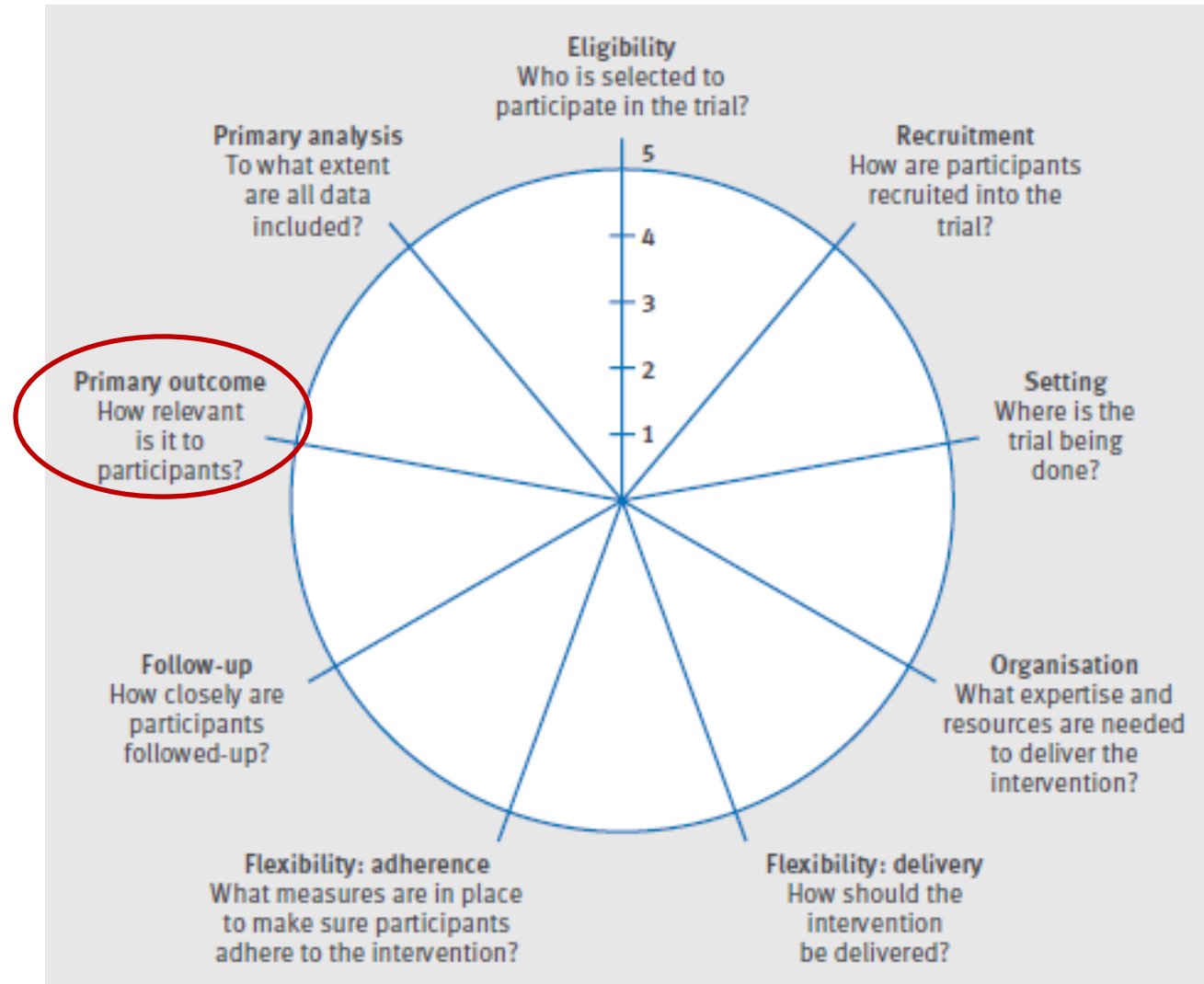
Multiple centers
Mix of community, academic,
public hospitals



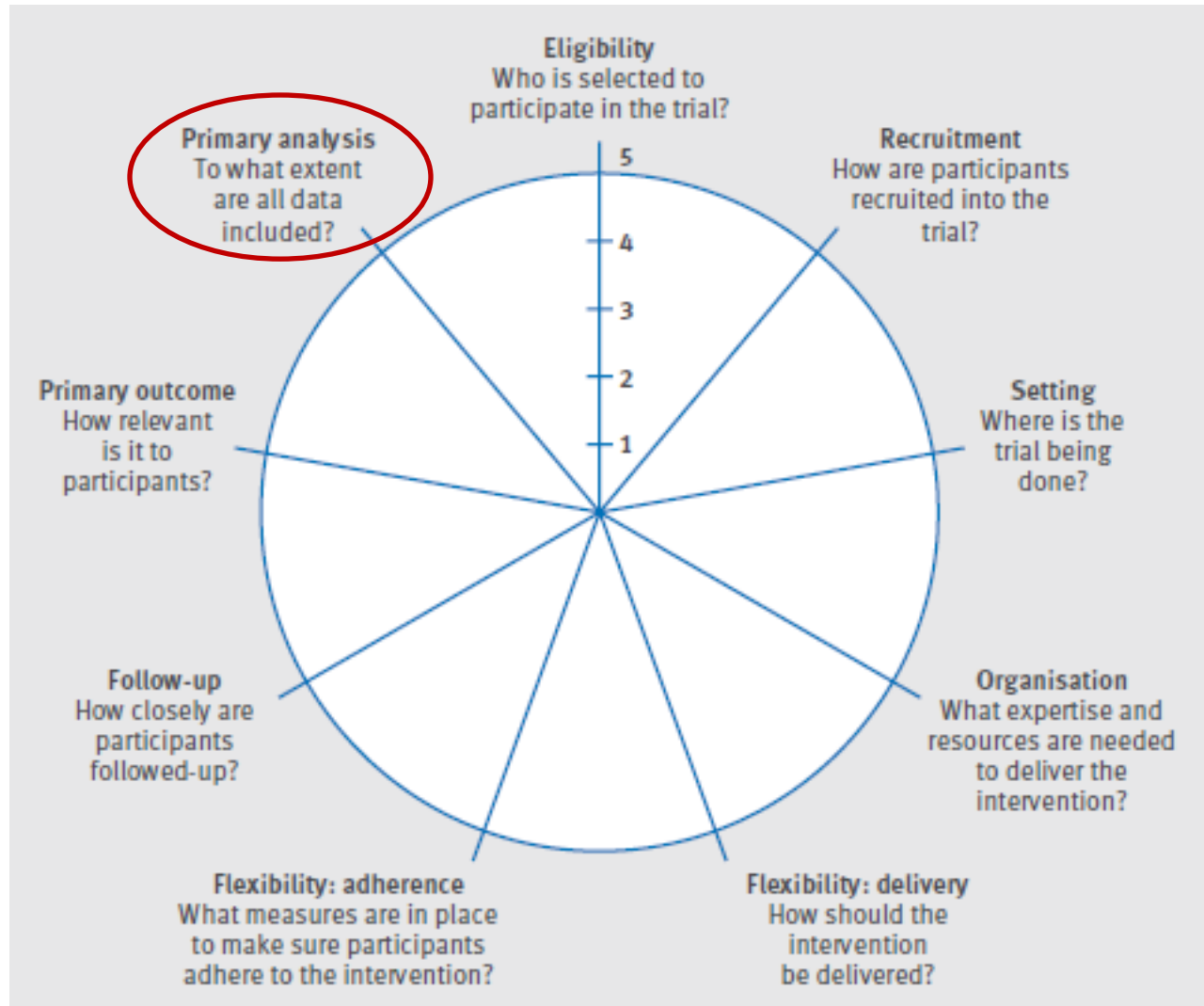
Standardized monitoring programs for perioperative complications (NSQIP, VASQIP) make this very pragmatic

Relevance to consumers:

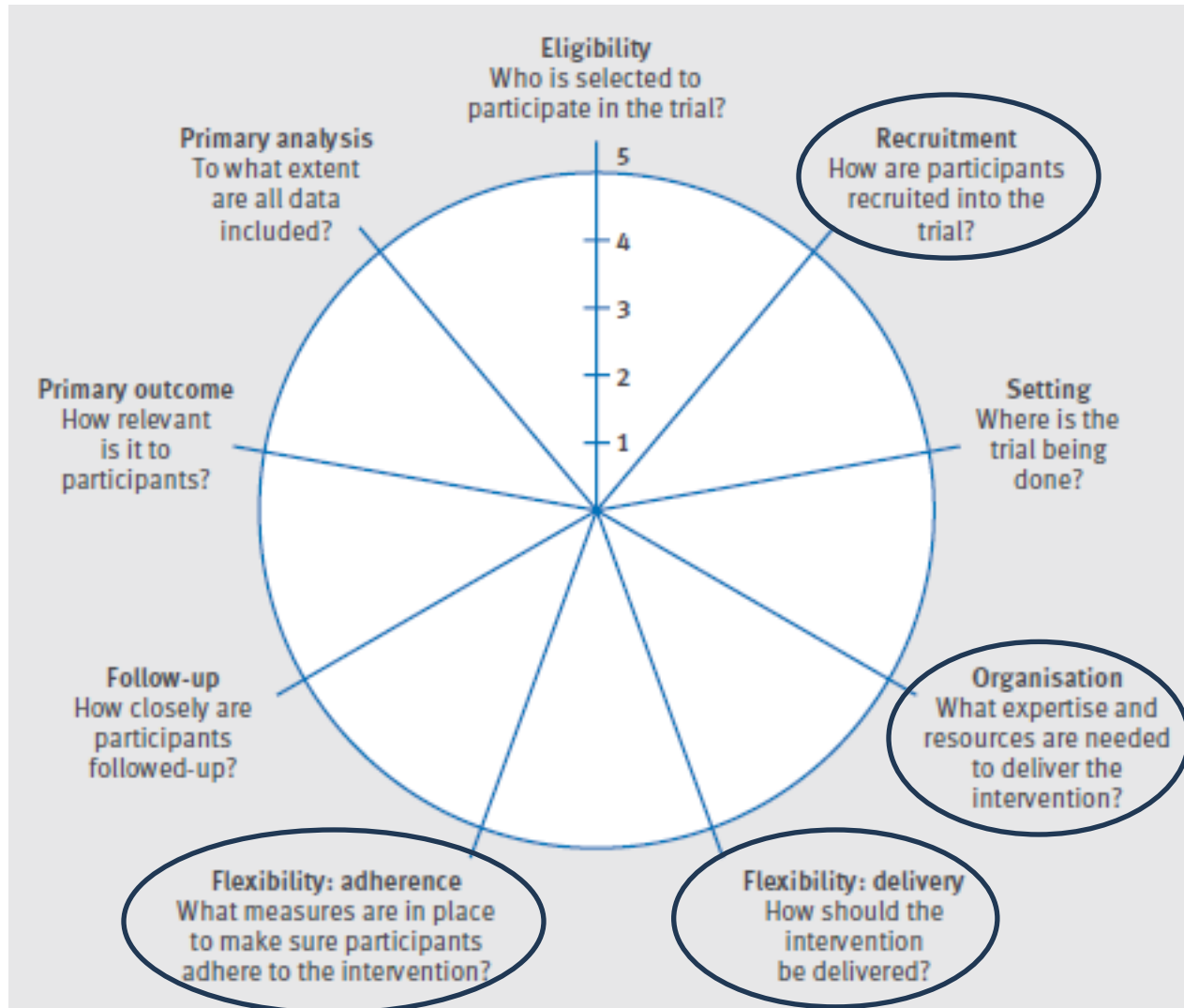
- Patients: death, respiratory failure, MI
- Policy makers: LOS, ICU days



Intent to treat!



Problem Domains for Pragmatic Trial in Perioperative Sleep Apnea Treatment

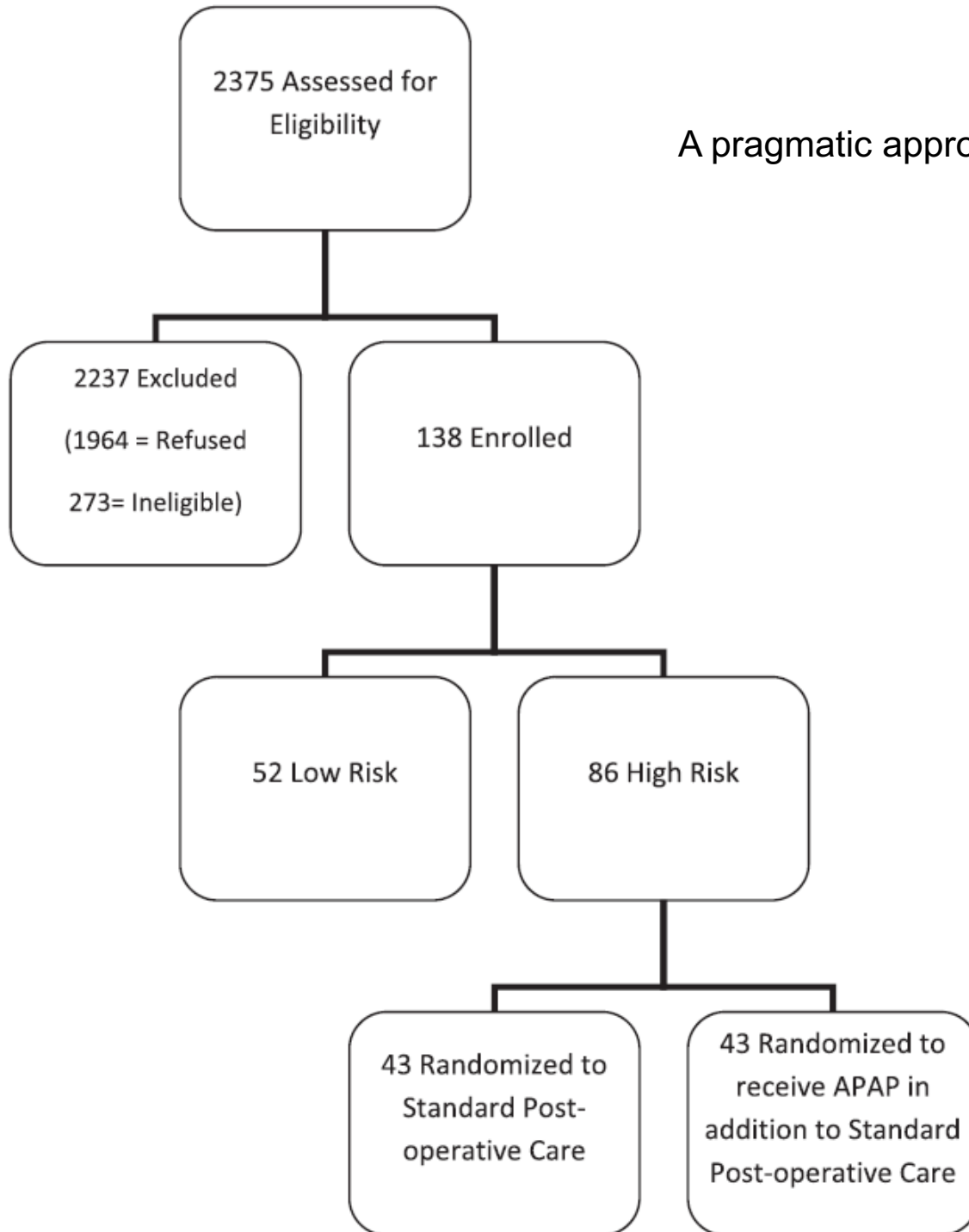


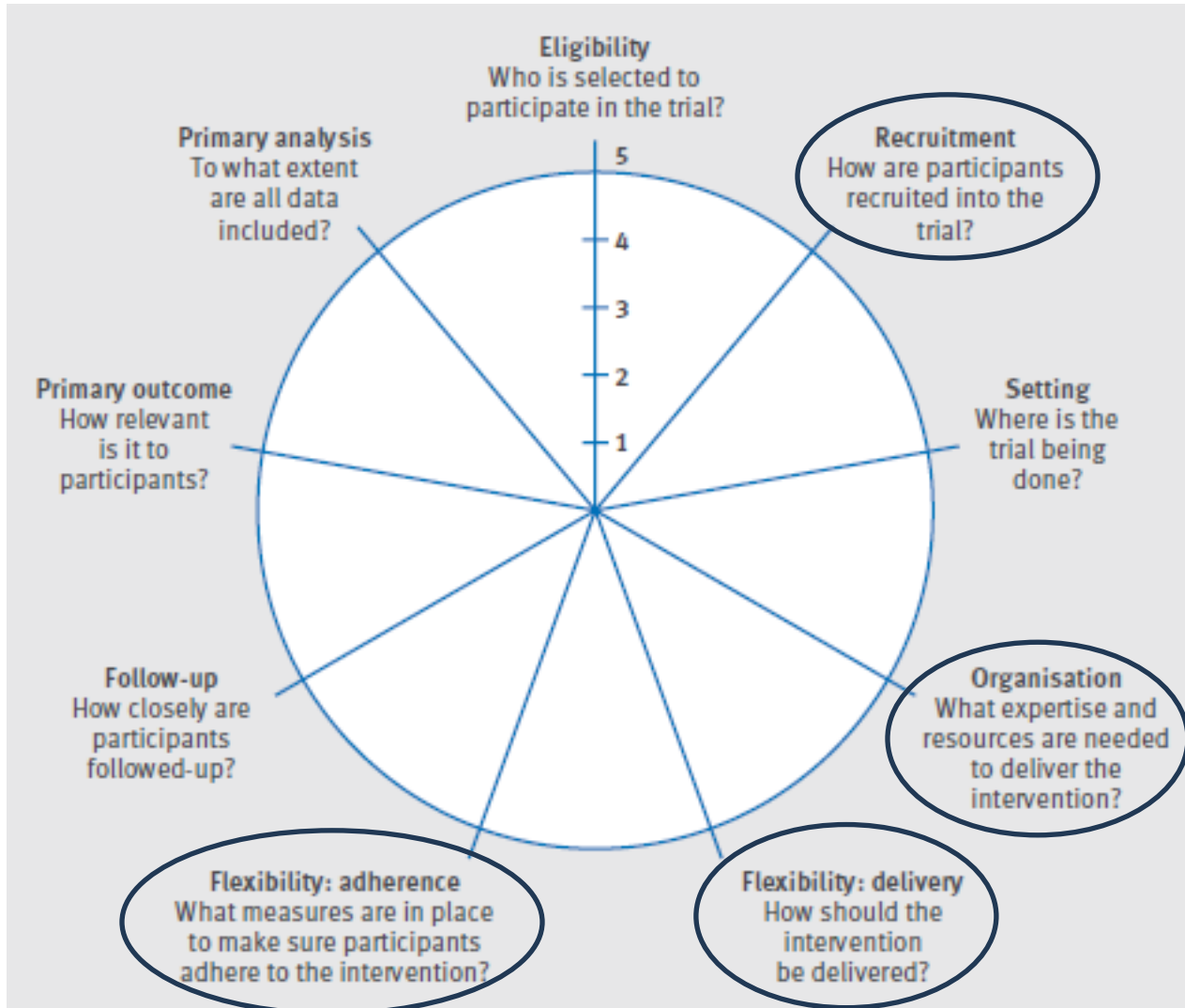
Recruitment

How are participants recruited into the trial?

- Recruit from usual patient care sites
 - pre-op evaluation clinic
- Recruitment by providers at those sites, rather than dedicated study personnel
- Recruitment as part of usual care, rather than a separate contact for recruitment
- Avoid advertisements, incentives, that would not be part of usual care

A pragmatic approach, but not a pragmatic result!

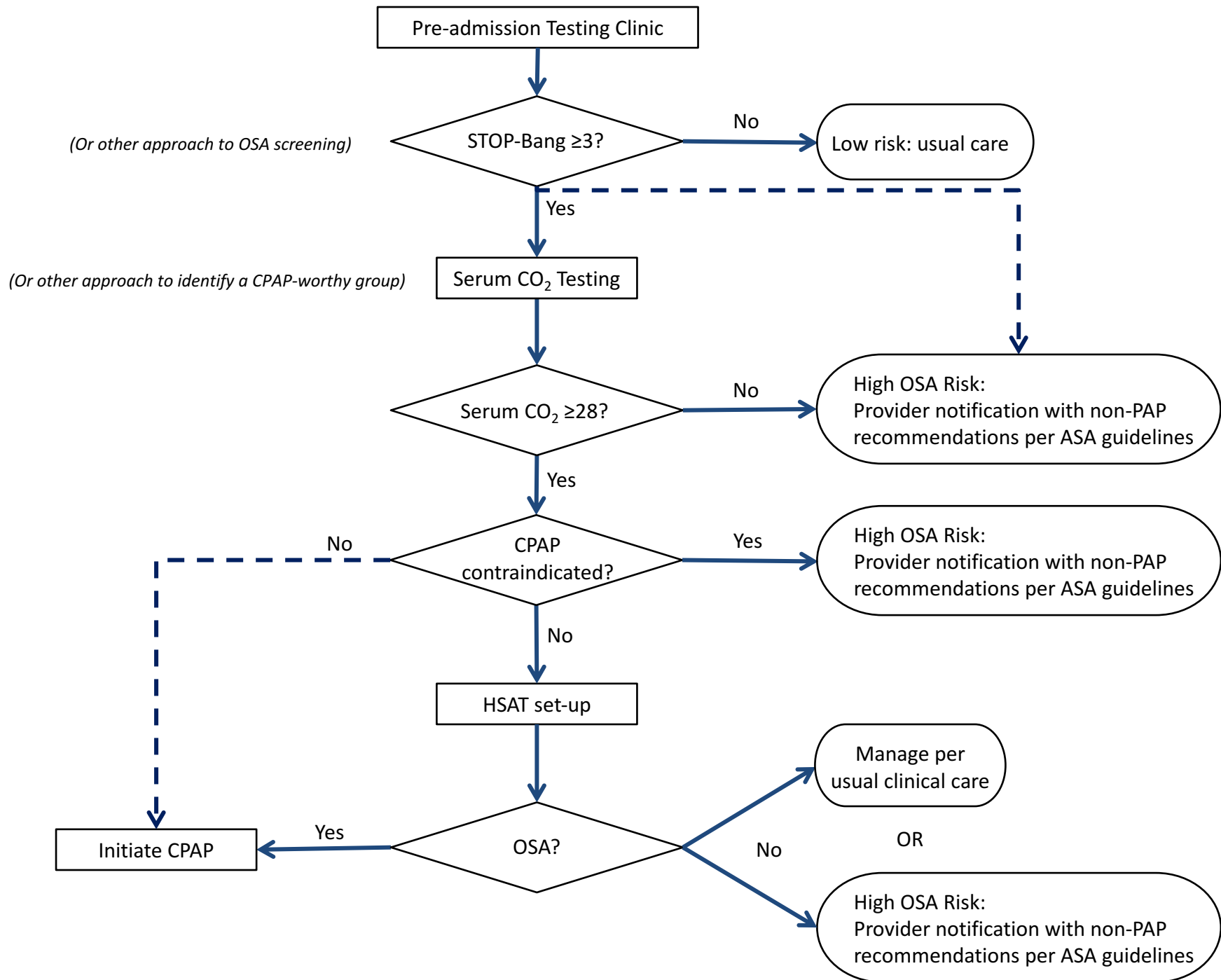




Possible solution: Treat organization of care as the intervention of interest

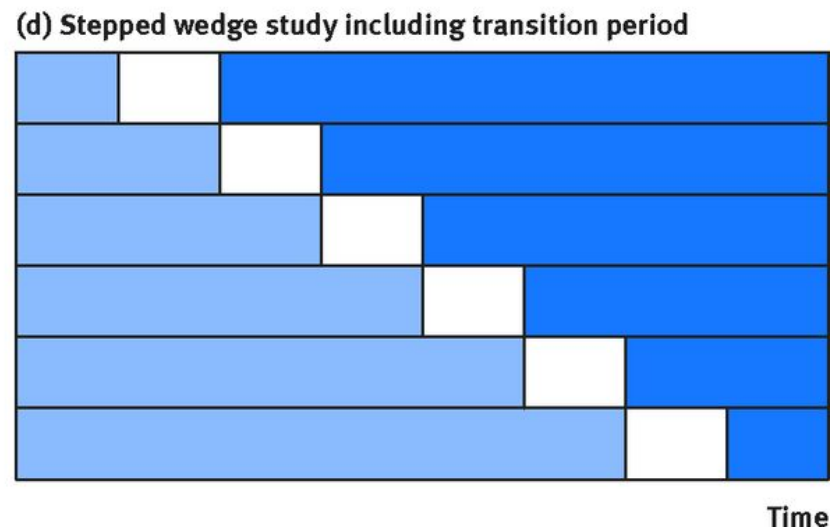
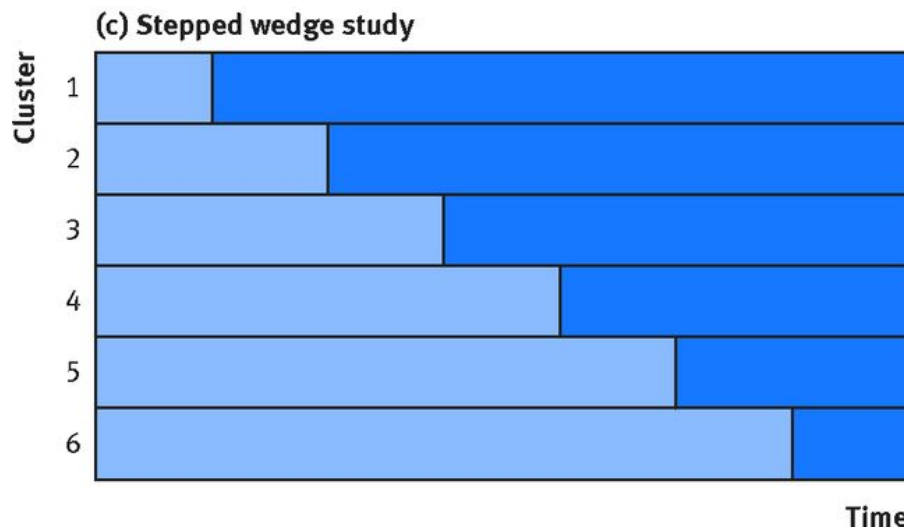
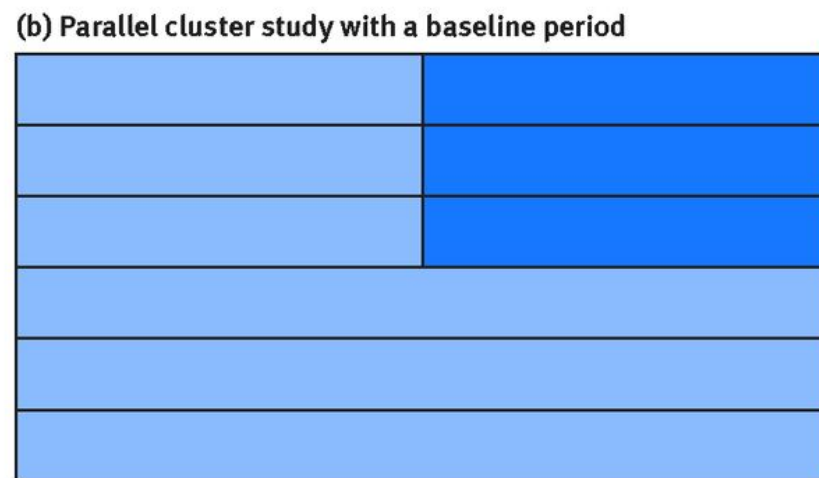
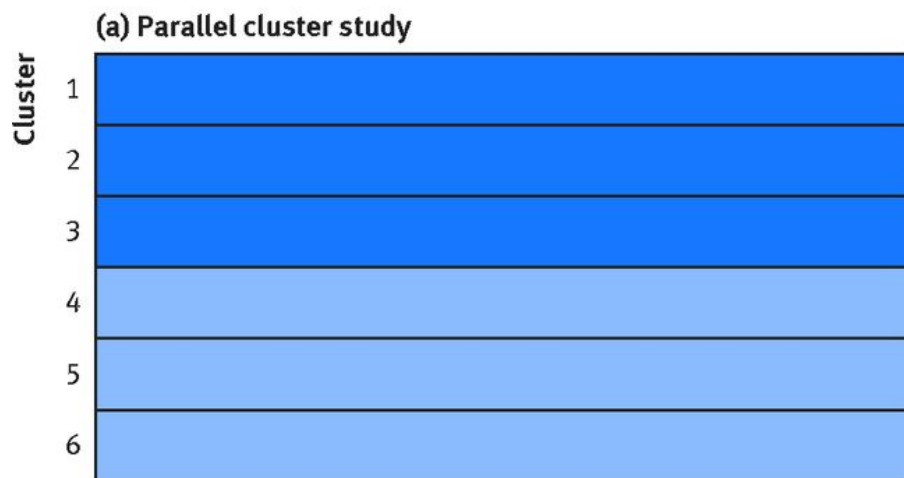
Hypothesis:

Implementation of ASA guidelines for perioperative assessment for and management of OSA will reduce the rate of perioperative complications



Cluster Randomization Designs

■ Cluster exposed to intervention ■ Cluster unexposed to intervention (control) □ Cluster in transition period

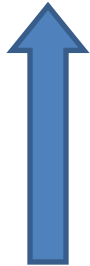


Design Benefits

- Organization: Incorporates intervention “into the usual organization of care for the condition of interest, using no more than the existing healthcare staff and resources in that setting.”
- Recruitment: All patients recruited as a matter of usual care, ensuring high “participation” rate
- Reduces risk of “contamination” of control condition
- Intervention and adherence: may be flexible, but whatever is done for the study will be the *de facto* local standard of care

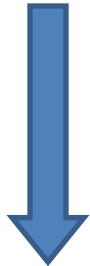
Flexibility in Intervention Delivery

More explanatory



- Protocolized CPAP administration
 - Technical training requirements of providers
 - Specified device, interface, titration
 - Uniform patient education
 - Specified time interval for initiation and use

More pragmatic



- General guidelines
 - Staff based on local training and availability
 - Variable timing

Important Design Issues

- What is the target population?
- What tool to screen for OSA? (Questionnaire, HSAT)
- Will CPAP be a part of the intervention?
 - Who gets CPAP? Based on AHI or other criteria?
 - Timing of CPAP? If pre-op, for how long?
 - Administered by whom?
- What non-PAP interventions?
 - Intraoperative: anesthetic technique, volume status
 - Postoperative: monitoring, oxygen, analgesia, positioning, fluid
- How will providers be made aware of OSA or OSA risk?
 - Surgeon, anesthesiologist, PACU staff, ward nurses, respiratory therapy
 - How will they be educated in best perioperative care of OSA patients?