Sleep for Stroke Management And Recovery Trial

NINDS U01NS099043

StrokeNet Meeting

October 16, 2018

Study Team

Key roles:

- **Project PIs:** Devin Brown, Ronald Chervin
- **UM Project Manager**: Kayla Gosselin
- **NCC**: Joseph Broderick, Joelle Sickler, Jamey Frasure, Diane Sparks, Mary Ann Harty, Emily Stinson
- **NDMC**: Valerie Durkalski, Reneé Martin, Jessica Griffin, Catherine Dillon, Faria Khattak, Ellen Underwood, Jocelyn Anderson
- **Event Adjudicators:** Darin Zahuranec, Deborah Levine
- **Telemedicine partner**: Jeff Durmer (FusionHealth, Chief Medical Officer), Helgi Helgason (Director of Clinical Operations)
- Lewis Morgenstern (Co-I)
- **Consultants**: Craig Anderson, Dawn Bravata
- **NINDS**: Claudia Moy, Joanna Vivalda, Scott Janis
- **Independent Medical Safety Monitors**: Kingman Strohl, Anna May

Study Organization

- NINDS
- Steering Committee
- Operations Committee
- NCC
  - Project management
  - Central IRB
  - Contracts management
- NDMC
- DSMB/Medical safety monitors
- Fusion Health

110 sites

- All RCCs

- Non-StrokeNet sites, VA sites – not currently included

Background

- Post-stroke/TIA sleep apnea prevalence ~75%
- Risk factor for incident and recurrent stroke, post-stroke deaths, and poor functional outcome after stroke
- Attractive target for intervention, especially given that its treatment is very low risk

Background

- Observational studies have shown much better outcomes for sleep apnea patients who use their CPAP
- Pilot trials and observational studies have shown safety of CPAP in acute stroke patients
- Multiple pilot trials including our own have laid the foundation for a definitive trial

AHA secondary prevention guidelines 2014

"Given these generally promising albeit mixed results across the randomized trials and the observational cohort studies, what is clearly needed is a randomized trial with adequate sample size to examine whether and the extent to which treatment of sleep apnea with CPAP improves outcomes such as stroke severity, functional status, and recurrent vascular events."

Study Overview

- Investigator-initiated, phase 3 multicenter, prospective randomized open-, blinded-endpoint (PROBE) controlled trial
- 110 sites nationwide – recruitment from acute or rehab hospitalization
- ~3,000 subjects randomized; 15,000 subjects screened
- Enrollment over 4 years

Objectives and Primary Endpoints

Objectives: Determine whether treatment of obstructive sleep apnea (OSA) with positive airway pressure started shortly after acute ischemic stroke or high risk TIA:

(1) reduces recurrent stroke, acute coronary syndrome, and all-cause mortality 6 months after the event, and

(2) improves stroke outcomes at 3 months in patients who experienced an ischemic stroke.

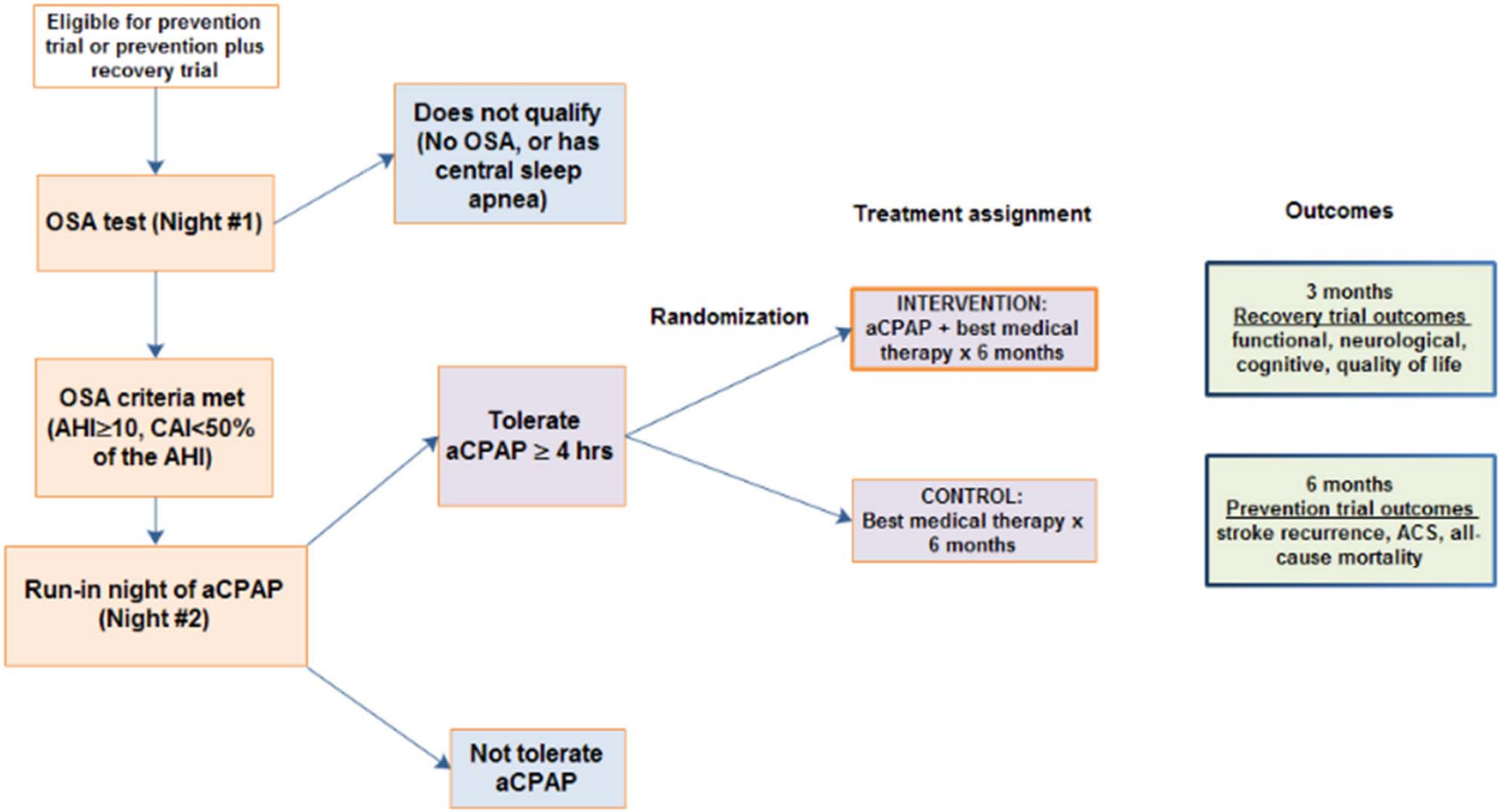
Primary Endpoints:

(1) Prevention endpoint: the composite outcome of recurrent ischemic stroke, acute coronary syndrome, or all-cause mortality at 6 months,

(2) Recovery endpoint: functional outcome at 3 months.

Secondary Endpoints: neurological, cognitive, and quality of life outcomes at 3 months.

Flow


Eligible for prevention trial or prevention plus recovery trial
OSA test (Night #1)
Does not qualify (No OSA, or has central sleep apnea)
OSA criteria met (AHI≥10, CAI<50% of the AHI)
Run-in night of aCPAP (Night #2)
Tolerate aCPAP ≥ 4 hrs
Not tolerate aCPAP
Randomization
Treatment assignment
INTERVENTION: aCPAP + best medical therapy x 6 months
CONTROL: Best medical therapy x 6 months
Outcomes
3 months
Recovery trial outcomes
functional, neurological, cognitive, quality of life
6 months
Prevention trial outcomes
stroke recurrence, ACS, all-cause mortality

Inclusion criteria

- Inpatient at an enrolling site
- ≥ 18 years old
- Ischemic stroke, or TIA with $ABCD^2 \geq 4$ within the prior 14 days

Exclusion Criteria

- Pre-event inability to perform all of own basic ADLs
- Unable to obtain informed consent
- Incarcerated
- Known pregnancy
- Current mechanical ventilation or tracheostomy
- Current or recent use of positive airway pressure
- Anatomical or dermatologic anomaly that precludes CPAP mask
- Severe bullous lung disease
- Current or prior spontaneous pneumothorax

Exclusion criteria (2)

- Hypotension requiring current treatment with pressors
- Other specific medical circumstances that suggest CPAP risk to Site PI
- Massive epistaxis or previous history of massive epistaxis
- Cranial surgery or head trauma, past 6 months, possible CSF leak
- Recent hemicraniectomy or suboccipital craniectomy, or any other recent bone removal procedure for relief of intracranial pressure
- Receipt of FiO_2 >50% (details pending)

Eligibility

- Determined to be eligible for consent if eligibility met at any time within the first 14 days of stroke symptom onset
  - Exclusions may resolve

Nox T3 results

- Provide to subject and study team only after subject completes Sleep SMART, e.g.:
  - After non-qualifying Nox T3 test
  - After failed run-in night
  - At time of withdrawal
  - After final (6-month) study visit

Who’s not eligible

- Venous infarction from DVST
- Primary ICH

Who is eligible

- Any amount of hemorrhagic conversion into ischemic infarction
- Prior diagnosis of OSA
- Supplemental O_2 (except >50% FiO_2)
- Those with aphasia, cognitive dysfunction, altered LOC

Patient approach

- Apply eligibility criteria
- Study team approach
- Use recruitment video to introduce study
- Informed consent process

Baseline information

- Obtain baseline information on all consented subjects
- Medical history (risk factors, etc), blood pressure
- Pre-stroke modified Rankin
- Pre-stroke depression, sleep apnea, sleep duration, sleepiness questions
- Informant based cognitive status assessment – from person who knows subject best

	Baseline with reference to pre-stroke period	**Baseline**
Stroke risk factors		X
Medical history (height, weight, etc)		X
Sleep duration/sleep apnea symptoms (STOP-BANG)	X	
Informant-based prestroke cognitive status (IQCODE)	X	
Pre-stroke modified Rankin Scale (mRS)	X	
Depression (Hospital Anxiety and Depression Scale (HADS-D))	X	
Blood pressure		X
Epworth Sleepiness Scale	X	

Night following consent (ideally)

- Screen for sleep apnea with Nox T3 device
- Apply device at night
- Collect in AM
- Upload to FusionHealth
- Data processed that day to determine eligibility
- Subject is eligible for run-in night, if:
  - AHI_{T3} ≥10 (some significant sleep apnea)
  - Central apnea index <50% of total AHI_{T3} (mostly obstructive)
- No sleep apnea or too much central sleep apnea: participation complete

Next night (ideally)

- Fit subject with appropriately sized mask - RT
- Have subject practice placement and removal of mask
- aCPAP run-in night
  - Apply aCPAP for one night to determine randomization eligibility
  - Have RT check on subject during night and troubleshoot any issues
- Randomization criteria:
  - Use aCPAP for ≥4 hours
  - aCPAP CAI <10
- Does not meet randomization criteria: participation complete

Repeat T3 or aCPAP?

- T3: up to 2 additional nights
  - If T3 technical issues; interrupted by clinical activity; subject denied sleeping ≥4 hours during the night of testing and test showed AHI_{T3} <10; or if the test was conducted while the subject used supplemental O_2 and showed AHI_{T3} <10
- aCPAP: up to 2 additional nights
  - If use <4 hours and interrupted/limited due to clinical activity

Randomization

- If run-in night qualifies
- Log into WebDCU, randomize subject
- Enter data into Fusion Health's KOEO system

Recruitment/retention

- Recruitment: ED, inpatient acute, rehab
- Recruitment video
- Study brochures
- Compensation
  - Baseline info + Nox T3: $25
  - Run-in night: $25
  - 3-month outcomes: $75
  - 6-month outcomes: $75
- aCPAP use monitored remotely; telemedicine-based care management
- Outcomes: By return visit, but also provision for home visits or as last resort telephone follow-up
- At baseline, obtain at least 3 phone numbers/contact info to aid in outcome scheduling

Study Intervention

Intervention: Automatically adjusting continuous positive airway pressure (aCPAP) delivered with the ResMed Airsense 10 autoset, plus usual care

Control: Usual care

aCPAP arm

- 6 months of aCPAP + guideline concordant care
- Assistance with aCPAP by RT during hospitalization
- Show subject and caregiver aCPAP training materials
- Telemedicine-based care management after discharge
  - Remote monitoring of use, residual AHI, mask leak
  - Proactive management and troubleshooting (including send new equipment directly to subject)
    - technology team
    - respiratory therapy team
    - sleep medicine physicians
- Possible escalation to bilevel PAP by Fusion Health
- Possible further escalation to sleep medicine clinical care (outside that provided by the trial) if these steps fail

Usual care arm

- 6 months of guideline concordant care
- No aCPAP (if clinical team orders this, it will just be a protocol violation, intention-to-treat analysis)

Both arms

- Site PI to assure guideline concordant care during hospitalization
- Site PI (or stroke provider) to send letter to PCP at discharge to provide recommendation about secondary prevention
- Subjects should be counseled about healthy lifestyle recommendations from AHA for secondary prevention

Outcomes

- 3 months, 6 months
  - In person, if not possible then home visit. If not possible, then by telephone as last resort. Less compensation to study sites for telephone outcomes.

	3 months	**6 months**
Depression (Hospital Anxiety and Depression Scale (HADS-D))	X	X
Blood pressure	X	X
Epworth Sleepiness Scale	X	X
Generic quality of life (Global PROMIS 10)	X	X
Medication Adherence	X	X
10-meter walk test	X	
Functional outcome (mRS)	**X**	X
Neurological outcome (NIHSS)	X	X
Cognitive outcome (short MoCA)	X	X
Stroke-specific quality of life (short SSQOL)	X	X
Assessment for recurrent stroke, ACS, death	X	**X**

After trial care

- Intervention subjects: may keep their aCPAP and equipment
- Suggest continued care under sleep medicine practitioner for those who continue use after the trial
- At trial end, offer to both arms a referral to sleep medicine clinician

Planning your team

- Site PI: typically stroke neurologist
- Sleep medicine physician: helpful if available, but not required
- Respiratory therapist(s)
- Coordinator
- Blinded outcome assessor

Central planning already accomplished

- Three years of planning to secure award (2014 – 2017)
- Operations Committee: weekly calls since Sept, 2017
- Site selection
- Contracts and agreements
- Initial cIRB approval
- Initial DSMB approval
- New project coordinators and NDMC staff hired
- WebDCU planning for Sleep SMART
- Planning for Investigator Meeting
- Development of recruitment video begun
- Elaboration of Protocol and MOP

Before subject enrollment starts

Logistics

- Talk with your biomedical engineering department about any local requirements to have equipment inspected and stickered
- Create a relationship with RT (there is $ for RT)
- Work out subject compensation methods
- Identify secure location to store equipment
- Educate inpatient nursing and RT staff about the trial
  - Try to generate enthusiasm

Regulatory

- Clinical trial agreement with UC
- Local IRB acknowledgment
- DUA and consignment agreement with Fusion Health

Future plans

- Investigator meeting:
  - Feb 22 (Feb 21 evening reception) – Detroit airport hotel
  - 2 individuals per site 110 enrollment sites
- Enrollment: thereafter

Thank you!