
Issues in Conducting Trials in Nonrestorative Sleep

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Conflict of Interest Disclosures

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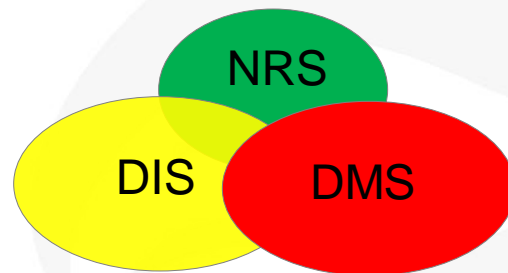
1. I do not have any potential conflicts of interest to disclose, **OR**

2. I wish to disclose the following potential conflicts of interest:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	
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Financial support	
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Treatment of Insomnia

- Difficulty Initiating Sleep (DIS)
- Difficulty maintaining sleep (DMS)
- Nonrestorative Sleep (NRS)



Insomnia Program Objective

- Develop a clinical plan to get an agent approved as a treatment for insomnia with demonstrated efficacy in:
 - Sleep onset – well precedented
 - Sleep maintenance – well precedented
 - Nonrestorative sleep – never been done

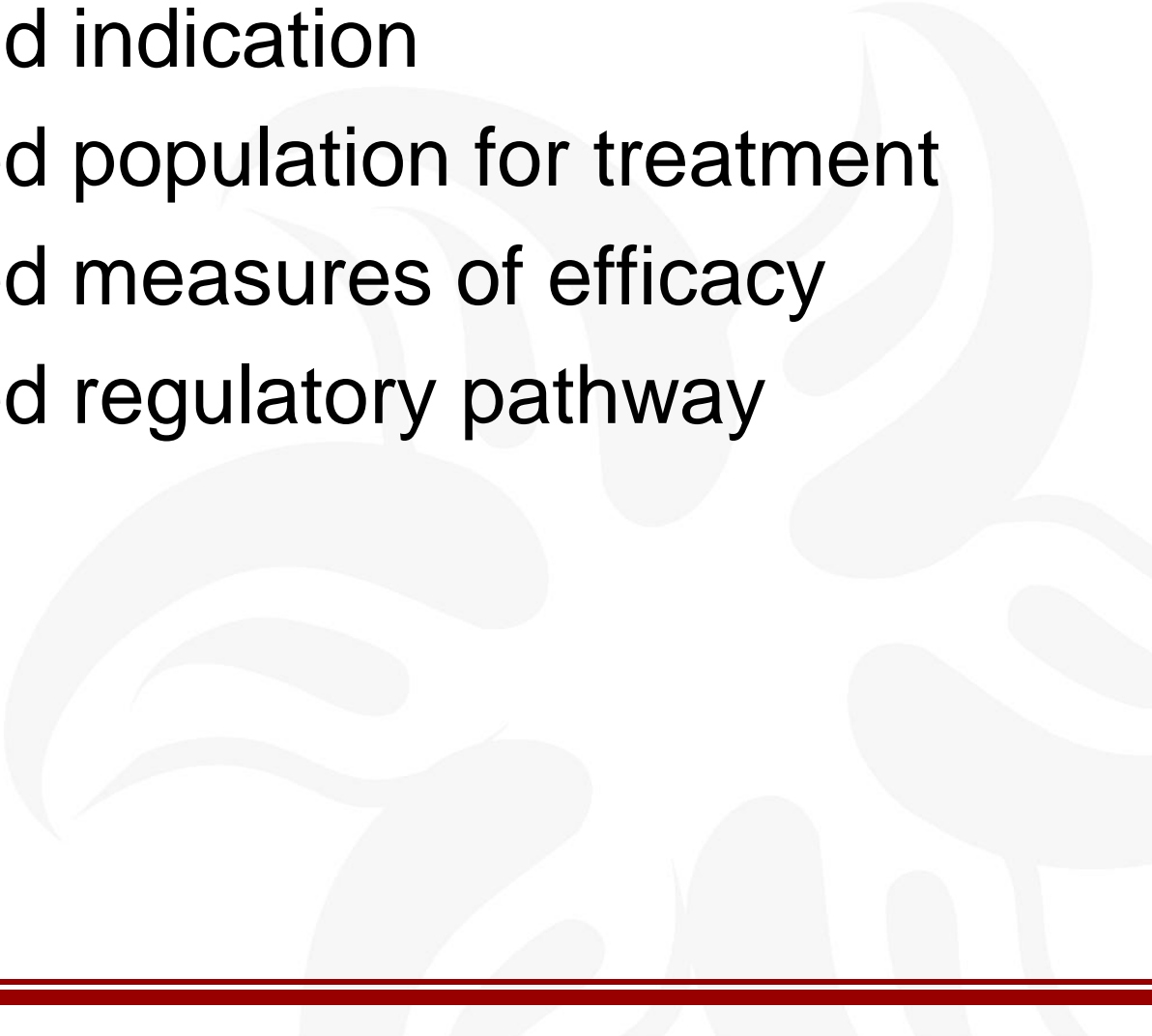
DSM-IV discusses NRS with Insomnia

- **DSM-IV Diagnostic Criteria: Primary Insomnia**
 - The predominant complaint is difficulty initiating or maintaining sleep, *or nonrestorative sleep*, for at least 1 month.
 - The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
 - The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium).
 - The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
- **DSM-IV Diagnostic Features: Primary Insomnia**
 - *...Less commonly, individuals with Primary Insomnia may complain only of nonrestorative sleep—that is, feeling that their sleep was restless, light, or of poor quality.*

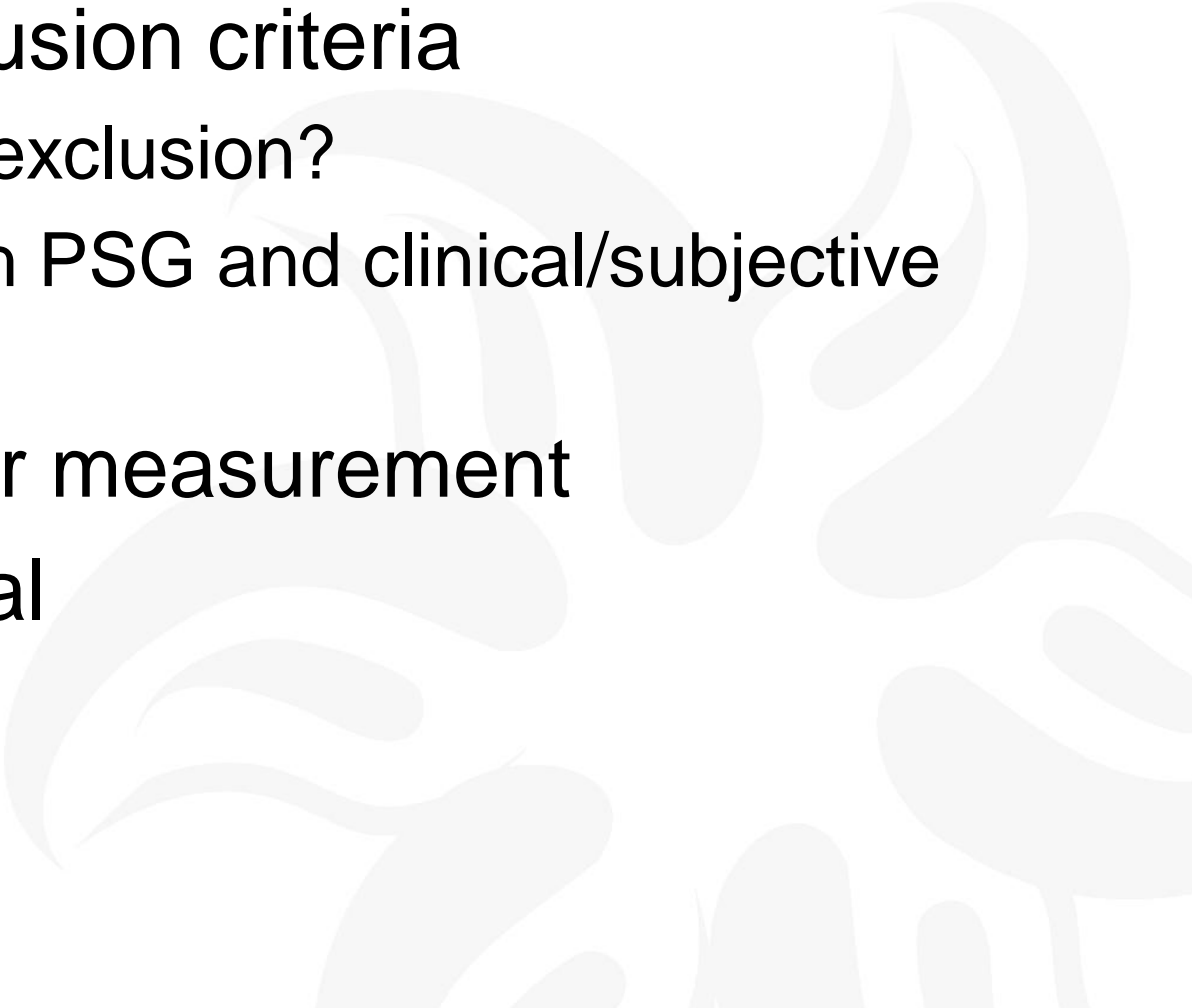
Investigating Insomnia and NRS

- Clinical programs for sleep onset/maintenance are well precedented
- Measurements exist to reflect patient subjective complaints of difficulty initiating and/or maintaining sleep, early morning awakening
 - Subjective – LSO, sWASO, sTST
 - Objective (PSG) correlates – LPS, WASO, TST
- Regulatory pathway is known for onset/maintenance claims
- Nonrestorative sleep is a subjective complaint without an objective correlate
- In the case of NRS, objective evidence that there is NO underlying sleep initiation/maintenance problem is required for diagnosis

Investigating Nonrestorative Sleep

- Unprecedented indication
 - Unprecedented population for treatment
 - Unprecedented measures of efficacy
 - Unprecedented regulatory pathway
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- A faint, light gray watermark of a stylized human figure is visible in the background, positioned behind the list of bullet points. The figure appears to be in a dynamic, possibly athletic or dancing pose, with arms and legs extended.

Design Issues to consider

- Inclusion/exclusion criteria
 - Diagnosis of exclusion?
 - Consider both PSG and clinical/subjective criteria
 - Endpoint(s) for measurement
 - Duration of trial
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Inclusion Criteria (1)

General Population Criteria

- **Subjects with NRS** and no problems either getting to sleep or staying asleep:
 - Awoke unrestored or unrefreshed, associated with significant distress or impairment in social, occupational, or other important areas of functioning during the daytime, for at least 3 nights per week for the past 3 months prior to screening Visit 1.
 - Aged 18-64 years
 - Maybe > 64 but do they exist?
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Inclusion Criteria (2)

Self Report Sleep Criteria at Screening

- Self report sWASO for < 45 minutes for the past 3 months prior to screening (Visit 1) except for isolated instances.
 - Self report LSO < 20 minutes for the past 3 months prior to screening (Visit 1) except for isolated instances.
 - Customary bedtime between 9 PM and midnight and rise between 4 and 9 in the morning.
 - Maintain a normal daytime-awake, nighttime-asleep schedule, including
 - between 6.5 and 9 hours each night in bed
 - less than 3 hours variation in night-to-night bedtime (including days off) for the past month prior to screening
 - must have had “normal” duration of sleep (individualized)
 - [adequate opportunity to sleep](#)
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Inclusion Criteria (3)

PSG Sleep Criteria (2 – 3 nights?)

- Neither screening night (PSG #2 or PSG #3) showing WASO ≥ 45 minutes.
 - Neither screening night (PSG #2 or PSG #3) showing LPS ≥ 20 minutes.
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Exclusion Criteria (1)

Psychiatric and Medical Disorders

- History or presence of any medical or neurological condition that could interfere with sleep (eg, Restless Legs Syndrome, Parkinson's disease, epilepsy, fibromyalgia or chronic pain syndromes) or pain symptoms that interfere with sleep.
 - Alcohol or substance abuse or dependence, unless in full remission for at least 1 year.
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Exclusion Criteria (2)

Sleep Disorders

- History or presence of any breathing-related sleep disorder, narcolepsy, or any other dysomnias; or any parasomnia; or restless legs syndrome (as defined by International Restless Leg Consortium criteria).
 - Multivariable Apnea risk index (MAP) ≥ 0.5 at Screening.
 - PSG findings consistent with any breathing-related sleep disorder, periodic limb movement disorder, narcolepsy, or any other dyssomnia or parasomnia, including:
 - An apnea-hypopnea index >10 per hour and/or;
 - A periodic limb movement with arousal index >10 per hour.
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Exclusion Criteria (3)

Concomitant Medications

- Current use of medications with known psychotropic effects (ie, drugs normally prescribed for depression, mania, anxiety, or psychosis) or known or suspected effects on sleep. This therefore includes the following CNS active medications:
 - Anxiolytics, antidepressants, anticonvulsants, antipsychotics, narcotic analgesics, lithium, barbiturates, systemic corticosteroids, theophylline, sedative-hypnotics.
 - Histamine-1 antagonists (except for loratadine and fexofenadine).
 - Over-the-counter and herbal medications with known or suspected psychotropic or sleep-enhancing properties.
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Exclusion Criteria (4)

Alcohol, Caffeine and Tobacco

- Use of alcohol as a sleep aid or more than 2 drinks consumed per day or more than 14 consumed per week, except for isolated instances.
 - Excessive caffeine use (>four 8-oz cups of caffeinated beverages/day, on average, or any use after 6 PM) for at least 3 months, except for isolated instances.
 - Excessive cigarette or cigar smoking (>1 pack of cigarettes/day or >1 cigar/day or use of either during normal bedtime hours) over the last 3 months.
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Exclusion Criteria (5)

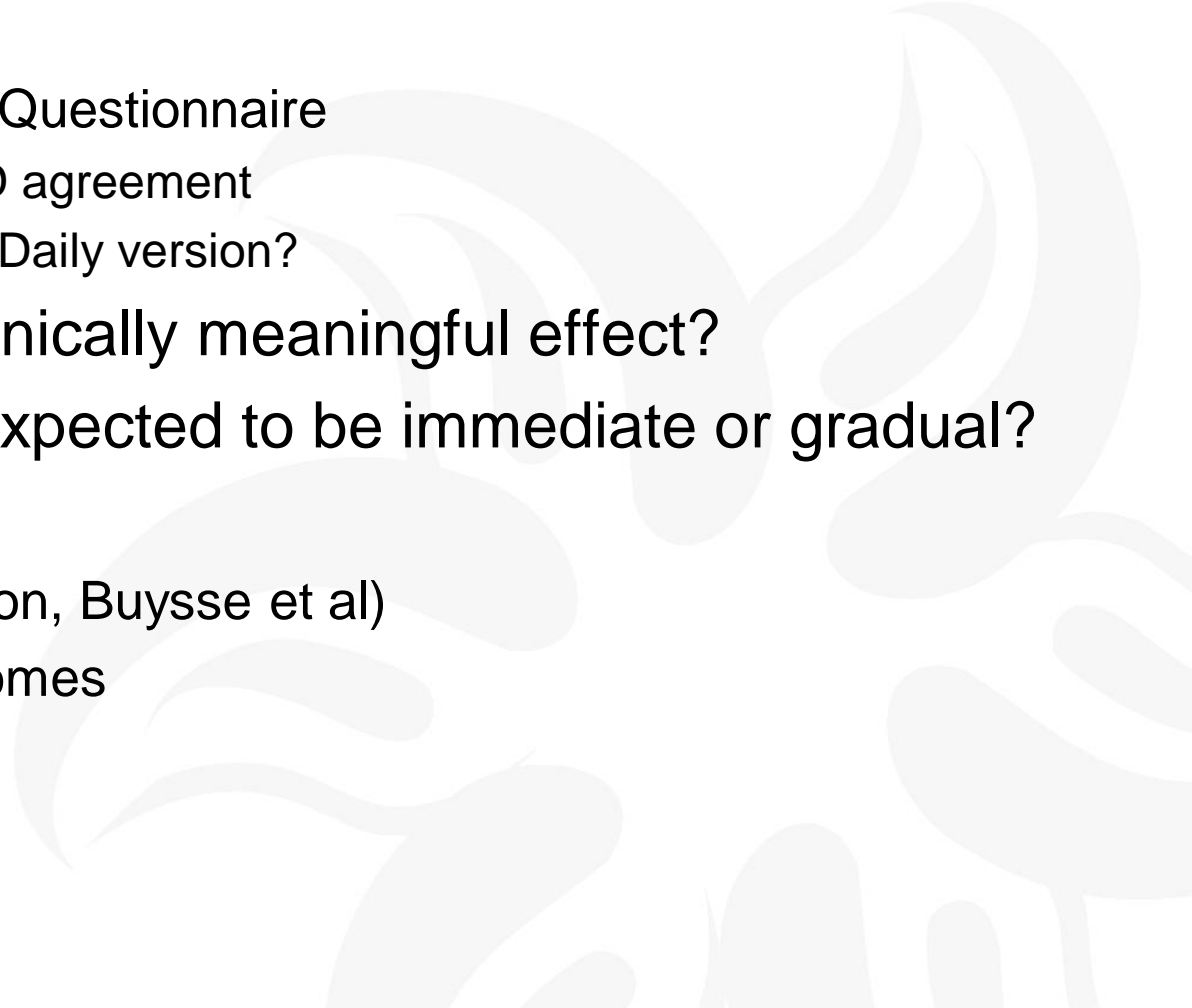
Sleep Pattern

- Regular napping (≥ 3 daytime naps/week) or any after 6 PM.
 - Initiated formal cognitive behavioral or medical therapy for sleep complaints within 1 month of beginning the study.
 - Currently on or planning to be involved in night or rotating shift work, or have traveled across more than three time zones in the 14 days prior to screening, or plan to travel across time zones during the study.
 - Other?
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Other factors to consider for Inclusion/Exclusion

- What else could influence awakening refreshed and restored?
 - Sleeping alone vs co-sleeping
 - Sleep surface
 - Location (home vs. away)
 - Environment (temperature, noise level, light)
- How can a study control for these factors?

Efficacy Measures – Primary Endpoint

- Primary measure
 - Restorative Sleep Questionnaire
 - Requires SEALD agreement
 - Weekly version, Daily version?
 - How to define a clinically meaningful effect?
 - Is onset of effect expected to be immediate or gradual?
 - Other measures?
 - Of NRS (see Vernon, Buysse et al)
 - Of functional outcomes
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Efficacy Measures: Secondary Endpoints

- Global Impression of change
 - PGIC
 - CGIC
- Next Day Functioning/QOL
 - Day Consequences of Sleep Questionnaire (DCSQ)
 - Sheehan Disability Scale (SDS)
 - SF-36
 - Multidimensional Assessment of Fatigue (MAF)
 - Endicott Work Productivity Scale (EPWS)
- Residual AM effects
 - Leeds Sleep Evaluation Questionnaire (LSEQ)
- Requires plan for multiplicity of testing

Duration of Trial

Proof of Concept

- What evidence would enable a decision for full development? (POC)
 - 4 – 6 week trial?
 - Parallel group vs. crossover?

Registration Trials

- 12 week studies required as per regulatory guidance
 - This requires a significant investment
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Other Considerations

- Global vs. “local”
 - Does NRS “translate”?
 - Are measures (RSQ) translated and valid
- Study Investigators/Centers
 - Does one need to be a sleep specialist to diagnose NRS?
 - Do studies need to be conducted only by sites with sleep laboratory?
- Patient considerations
 - Screen/rand ratio 5:1? Greater?
 - Other factors