University of Pittsburgh Center for Sleep and Circadian Science

Inaugural Summer SWIM: Sleep and Circadian Workshop on Indispensable Methods

August 10-14, 2020

Meet the Expert:

Clinical Trials in Sleep and Circadian Medicine

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Clinical Trials in Sleep and Circadian Medicine

Objectives

1. Review key terms and definitions

2. Review types and elements of National Institutes of Health (NIH) clinical trial grant applications

3. Challenges for sleep and circadian trials

4. Mapping out success

Key terms and definitions

Clinical trial	A **research study** in which one or more **human subjects** are **prospectively assigned** to one or more **interventions** (which may include placebo or other control) to evaluate the effects of those interventions [illegible] **or behavioral outcomes**
Prospectively assigned	A pre-defined process that stipulates the assign[illegible] more arms of a clinical trial
Intervention	A manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
Health-related biomedical or behavioral outcomes	The pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.

Examples include: drugs; biologics; devices; procedures; delivery systems; strategies to change health-related behavior; treatment, prevention, and diagnostic strategies.

https://grants.nih.gov/policy/clinical-trials.htm

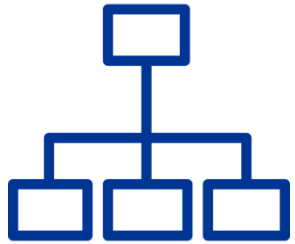
Types of clinical trials

Efficacy (explanatory) trials	Determine whether an intervention produces the expected result under ideal circumstances. ▪ Phase I: "First in human" studies to define safety, dose range ▪ Phase II: Small test of treatment efficacy, doses ▪ Phase III: Large clinical trial for efficacy, safety vs. standard treatment
Effectiveness (pragmatic) trials	Determine the impact of an intervention with demonstrated efficacy when it is delivered under "real-world" conditions.
Dissemination research	Systematic study of processes and factors that lead to widespread use of an evidence-based intervention by the target population. Its focus is to identify the best methods that enhance the uptake and utilization of the intervention
Implementation research	Study of the processes and factors that are associated with successful integration of evidence-based interventions within a particular setting

Rabin et al., A Glossary for Dissemination and Implementation Research in Health. *Journal of Public Health Management and Practice* 2008; 14: 117-123

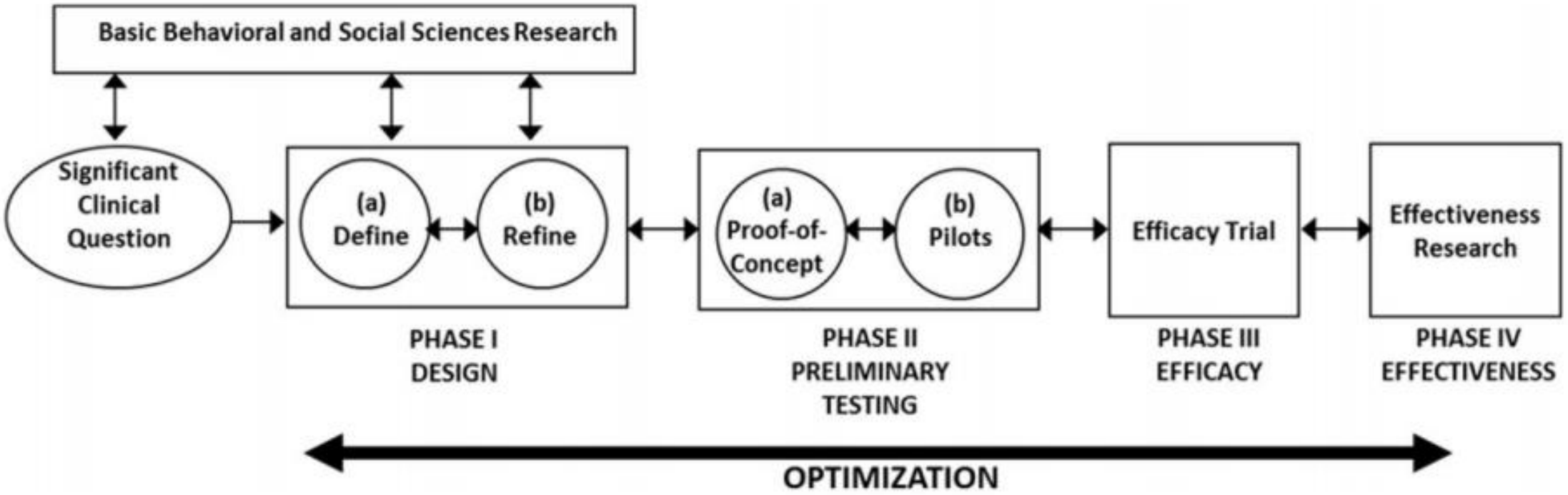
NIH Stage Model for Behavioral Intervention Development

Stage 0	Basic science, research on mechanisms of change
Stage I	Creating a new intervention; Intervention generation, refinement, modification, and adaptation (Ia) and pilot testing (Ib)
Stage II	Traditional efficacy testing in research settings with research providers
Stage III	Hybrid efficacy-effectiveness; efficacy testing with real-world providers, real-world settings, maximizing internal validity
Stage IV	Effectiveness research; community settings and providers, maximizing external validity
Stage V	Dissemination and implementation research; strategies of implementation and adoption of empirically supported interventions in community settings



[1]Onken, Blaine, Battjes. Behavioral therapy research: A conceptualization of a process. In S.W. Henngler & R. Amentos (Eds.), *Innovative approaches from difficult to treat populations* (pp. 477-485), Washington, DC: American Psychiatric Press. [2]Rousaville, Carroll, Onken. 2001; *Clin Psychol Sci Prac* 8: 133-142

ORBIT model for developing behavioral treatments for chronic diseases



Czajkowski, 2015. *Health Psychol* 34: 971-982

ORBIT model for developing behavioral treatments for chronic diseases

Model of pathway by which a behavioral treatment is hypothesized to improve a clinical outcome. CSΔ = Clinically Significant Change

Czajkowski, 2015. *Health Psychol* 34: 971-982

Clinical trial designs

Randomized, parallel group controlled trial (RCT)

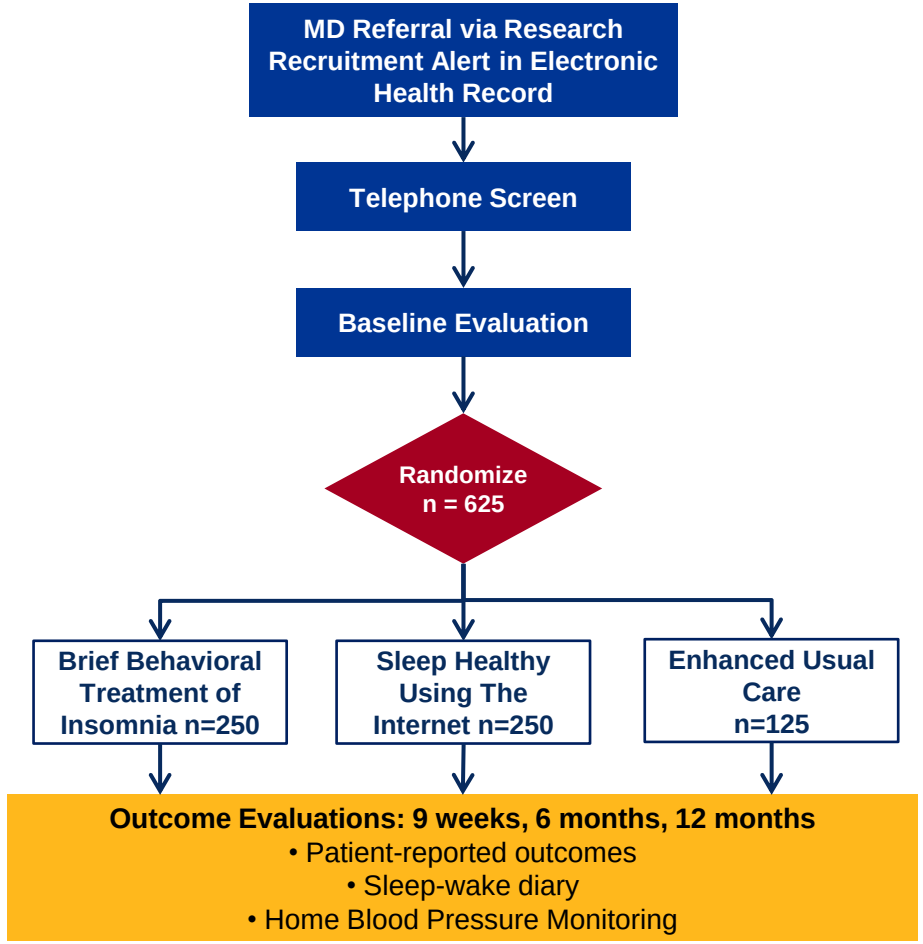
Randomized cross-over trial

Factorial trial

Cluster randomized trial

Stepped wedge randomized trial

Sequential Multiple Assignment Randomization Trial (SMART)



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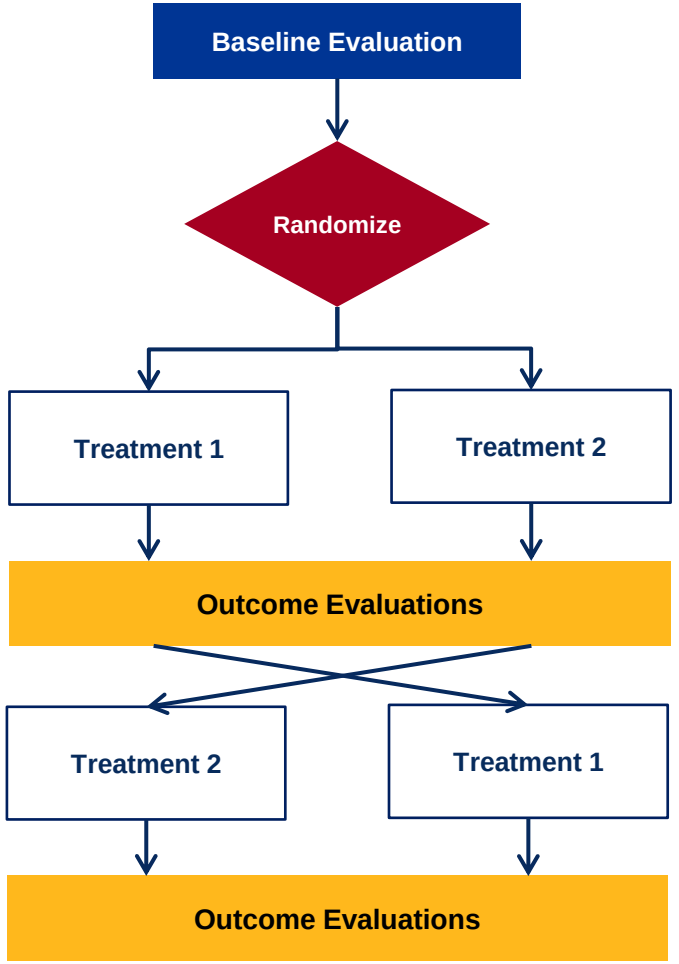

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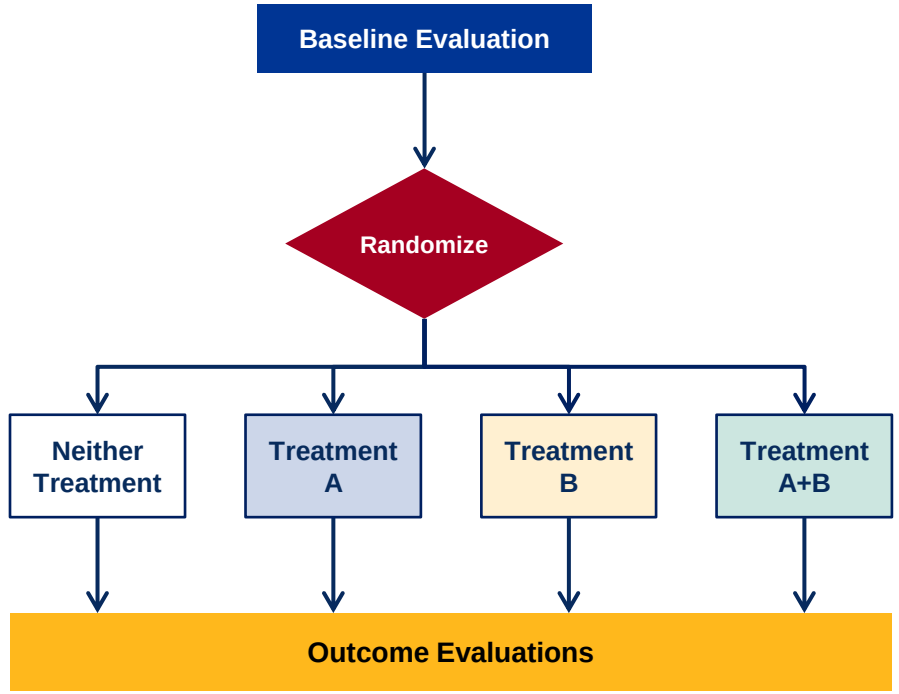

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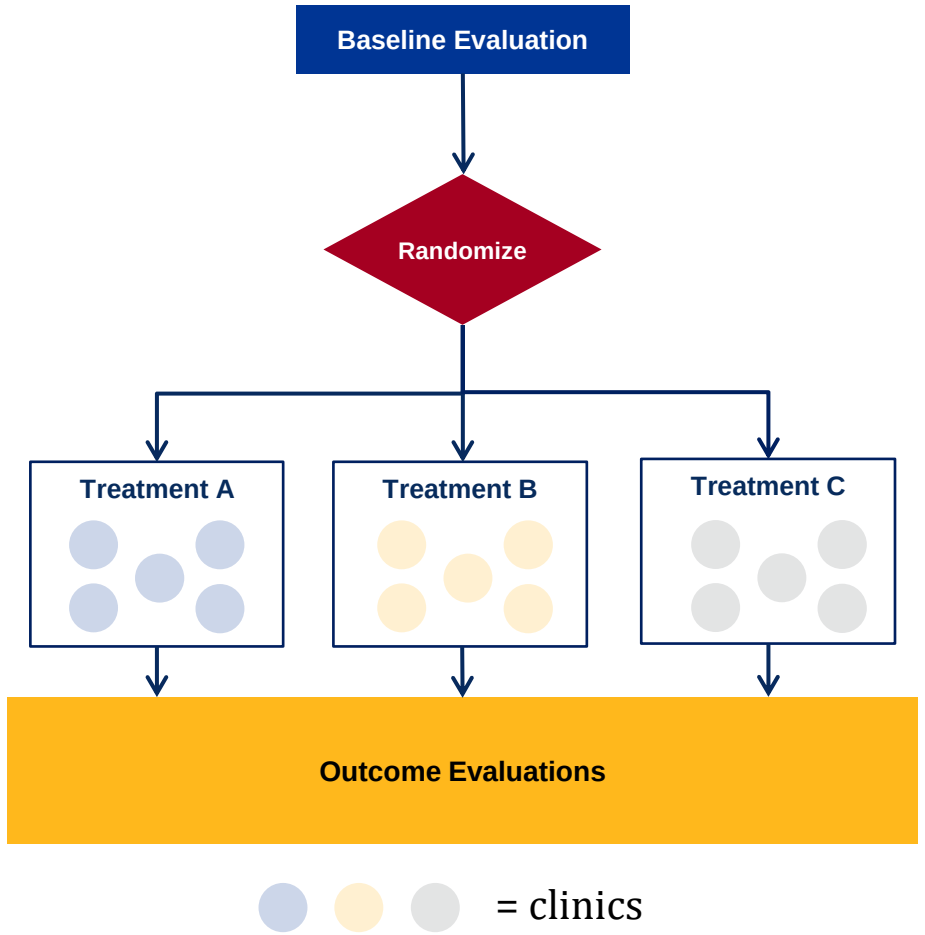

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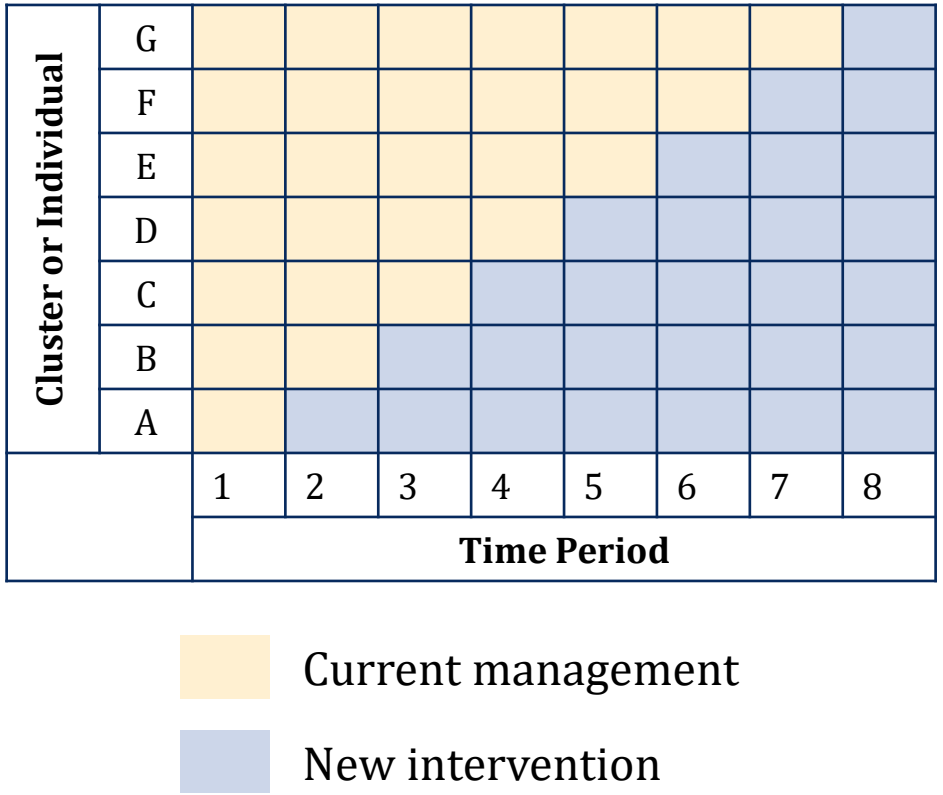

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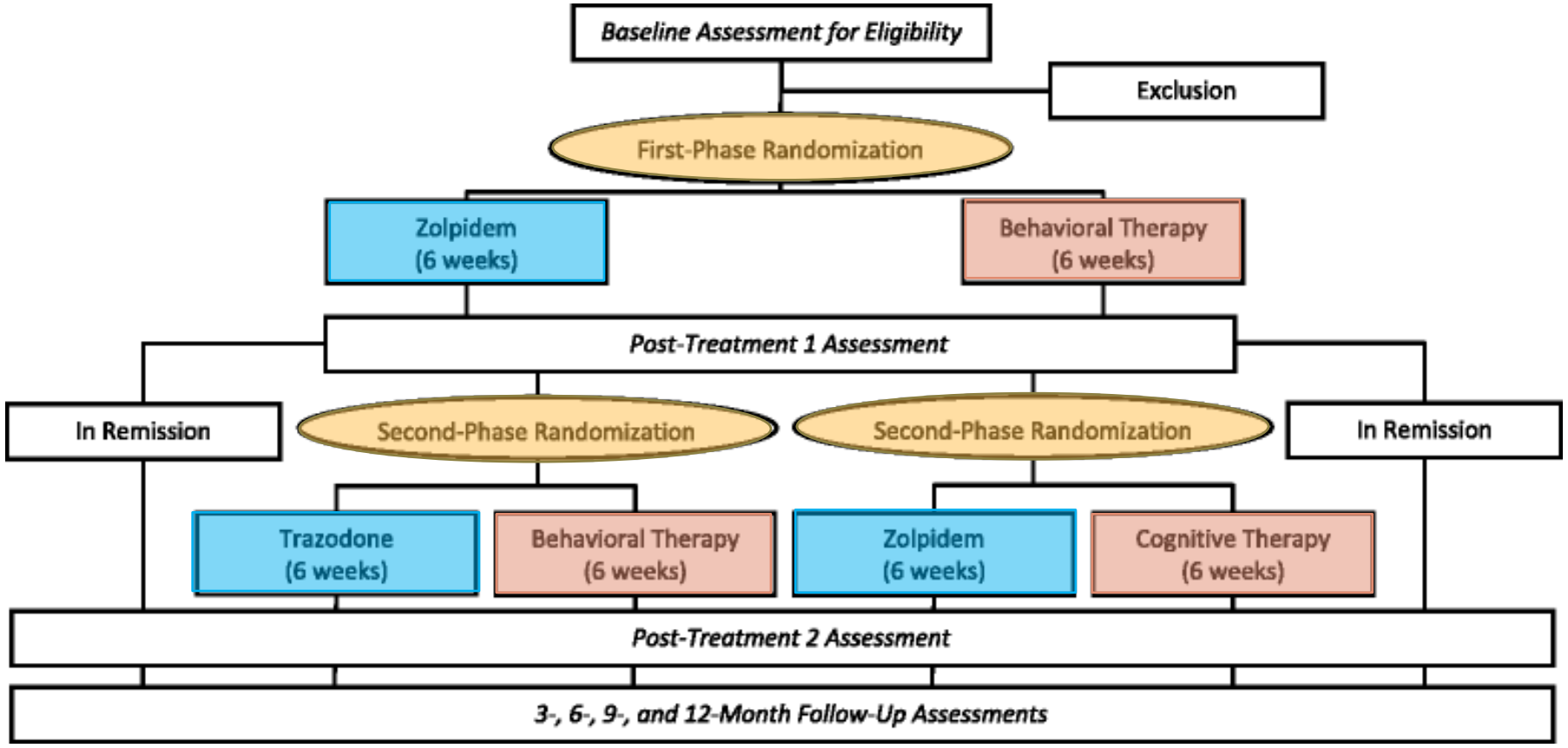
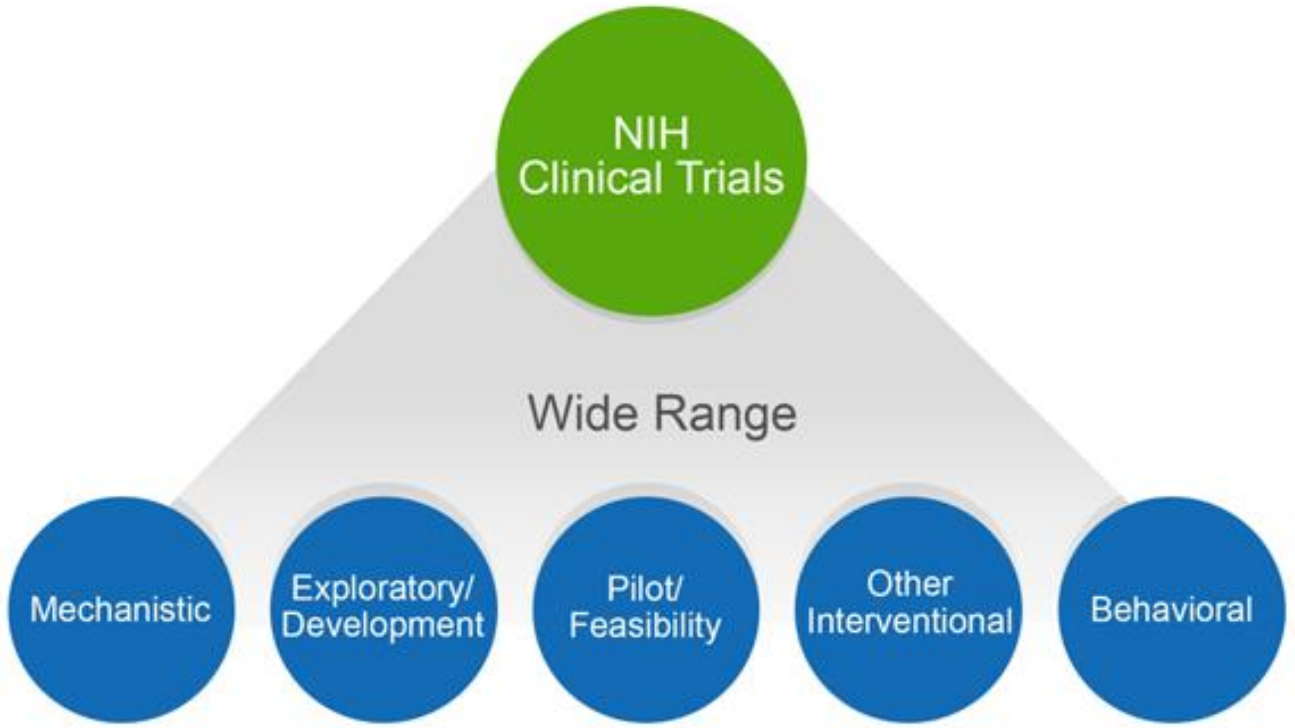


Morin, *Trials* 2016; **17**:118 **DOI:** 10.1186/s13063-016-1242-3. Morin, *JAMA Psychiatry* 2020; oi:10.1001/jamapsychiatry.2020.1767. Published online July 8

Types of NIH applications



Clinical trials can be conducted under a number of different NIH funding mechanisms. Some examples:

- K23, K01: Career Development Awards
- R34: Research Project Planning Grant
- R21: Exploratory/Developmental Research Grant
- R01: Research Project Grant
- R61/R33: Phased Exploratory/ Developmental Grant
- UG3/UH3 Multi-Site Clinical Trials

Elements of an NIH clinical trials application

- Research Plan
  - Specific Aims (1 page)
  - Research Strategy: Significance, Innovation, Approach: 12 pages (6 for R21)
- Other Attachments
  - Trial Management Plan (5 pages)
  - (Network Description)
- Human Subjects and Clinical Trials Information
  - Section 2: Study Population Characteristics
    - Conditions or focus of the study
    - Eligibility criteria
    - Recruitment and Retention Plan
    - Study timeline
  - Section 3: Protection and Monitoring Plans
    - Single IRB plan
    - Data and Safety Monitoring Plan
    - Overall structure of the study team
  - Section 4: Protocol Synopsis
    - Narrative study description
    - Interventions description
    - Statistical design and power
    - Dissemination Plan
  - Section 5: Other Clinical-Trial Related Attachments
    - Clinical Trial Research Experience (3 pages)

Challenges for sleep and circadian clinical trials

Sleep: Behavior, process, state

Perception of sleep and CR

Time is *definitely* not on your side

- Understanding of time
- Quantities, durations, events

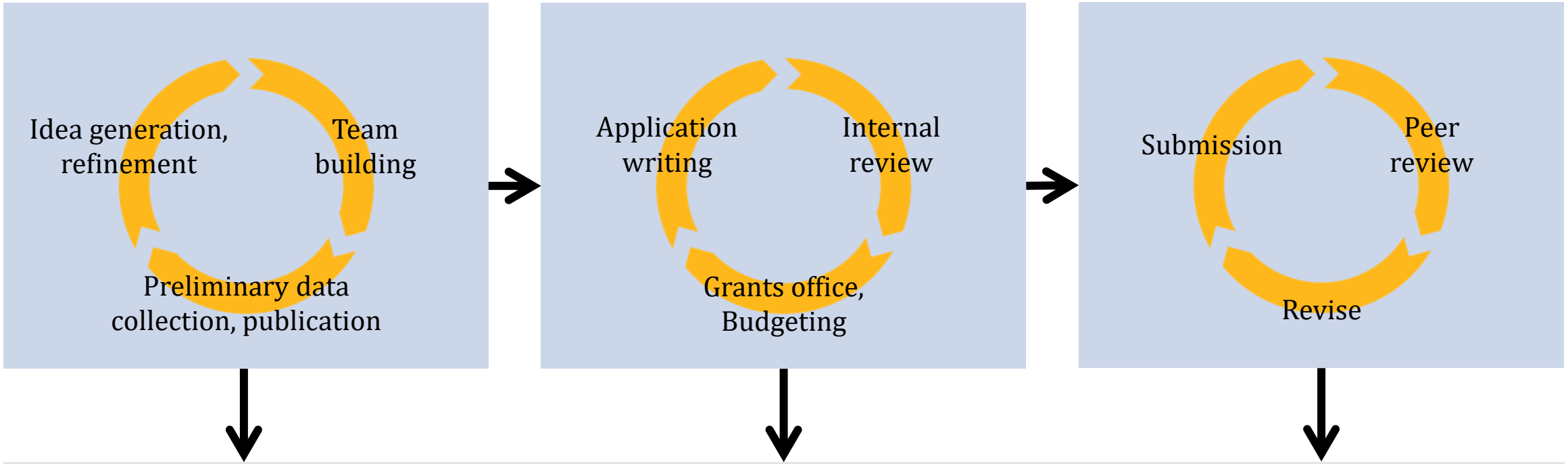
Sleep and CR typically observed once per day

Sleep and CR are multidimensional

Many important outcomes are downstream of sleep/CR

Multiple treatment modalities: Challenges for comparisons and control conditions

Mapping out success



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