Operational complexities when managing PTSD trials

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Disclosures

- Disclosures for Kerrin Young – Kerrin is an employee of Aptinyx, Inc.

PTSD clinical studies can be particularly challenging to design and execute

- De-risking clinical development requires a fundamental understanding of two things:
  1. The disease pathology and clinical characterization
  2. The barriers (procedurally) that may reduce subjects' desire to participate in a study or present challenges to ensuring data integrity
- A thoughtful approach is particularly important for PTSD studies
  - The patient population is inherently heterogeneous with an array of comorbidities
  - Endpoint scales and assessments can introduce and exacerbate variability if administered inconsistently
- With this understanding, sponsors can "right-size" study design to **reduce variability**, **remove unnecessary operational complexities**, and **maximize the potential for robust, on-time, and on-budget execution**

Disciplined integration of discovery and early development knowledge increases the probability of clinical success

(Plenge et al., 2016, Merck Research Laboratories)

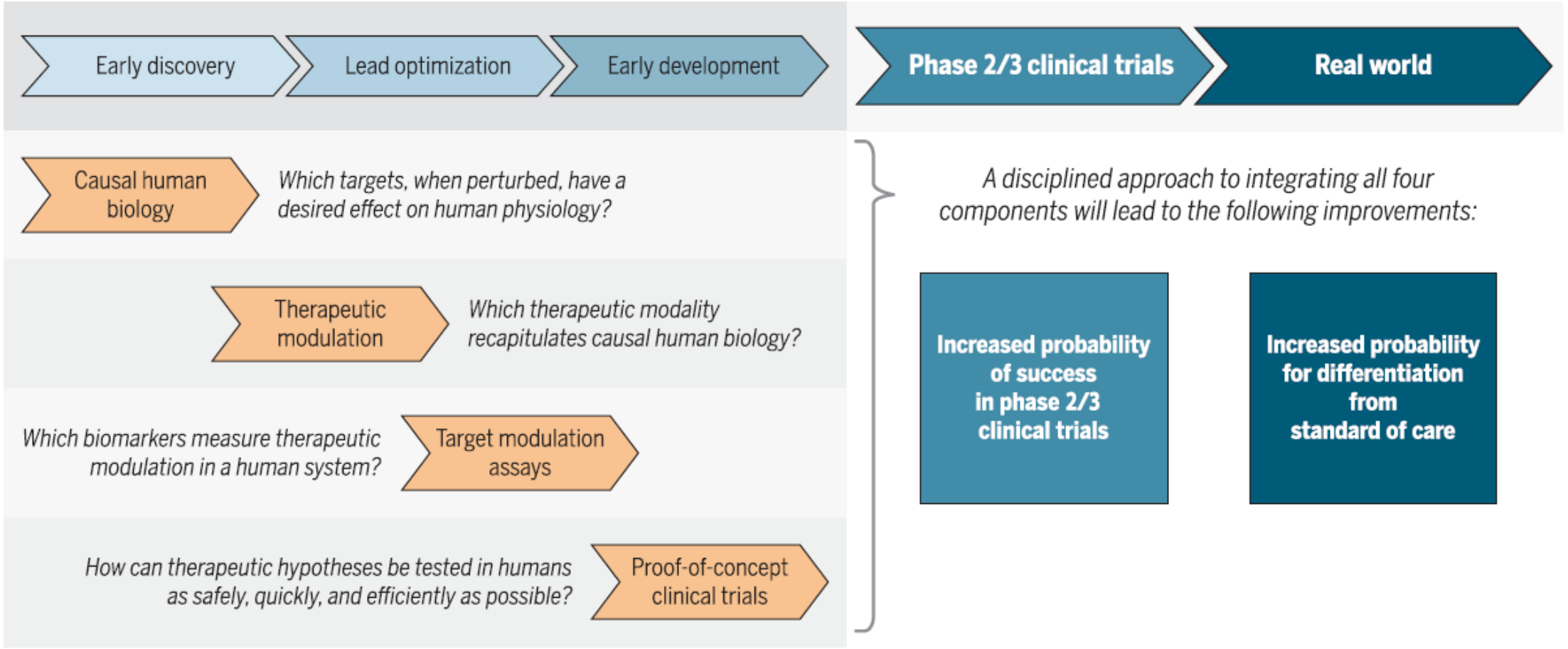
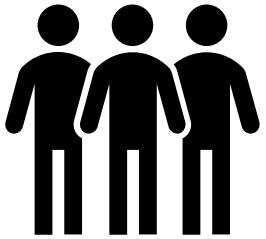
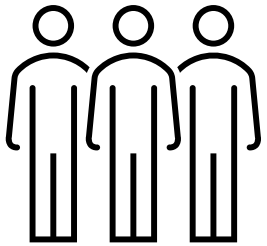


Fig. 1. A disciplined approach to identify drug targets and test therapeutic hypotheses. Four areas in translational medicine are causal human biology, therapeutic modalities that recapitulate human biology, biomarkers of target modulation, and next-generation clinical trial technologies. Connecting all four promises to improve the novelty, efficiency, and productivity of drug R&D.

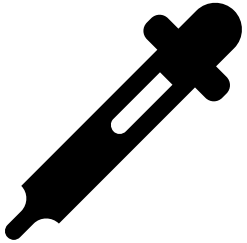
Getting inclusion and exclusion criteria right can have a direct impact on screen failure rate and data quality

- The PTSD patient population is inherently heterogeneous with a wide range of conditions and comorbidities
- The better a sponsor understands the biology of the disease and therapeutic mechanism of the drug, the more targeted the criteria can be
- The type and number of self- or clinical-administered assessment scales should be carefully considered so as not to:
  - Over-burden the patient selection process and demotivate subjects and sites
  - Inadvertently exclude viable subjects or include subjects that will inflate the variability
  - Unnecessarily increase screen failure rate and slow enrollment





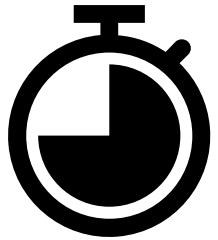
Collection of biomarker data can be useful but can also add operational complexity and patient and site burden



- May include periodic assessments of vital signs, including heart rate variability, neuroendocrine markets, and inflammation markers
- Carefully select and justify markers based on the value of the resulting data vs. the increased site and patient burden
- Balance “scientifically interesting” with alignment to primary study objectives
- Communicate to sites and subjects how these assessments contribute to the study outcome
- Seek vendor, investigator, and site input on how these assessment operationally impact the study execution

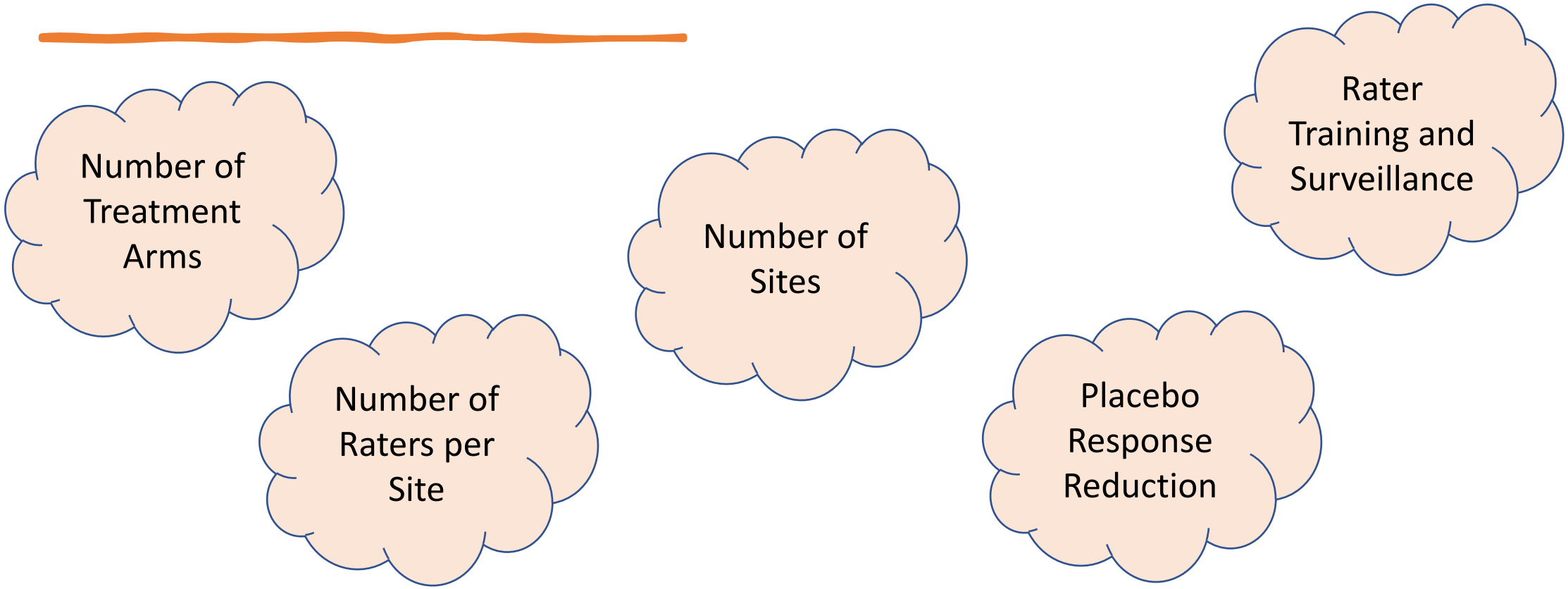
PTSD studies inherently rely on patient- and clinician- administered scales to assess baseline and improvement through treatment

- Some scales are required by regulators or professional guidance
  - SCID-5-CT
    - Borderline personality disorder module
    - Depression module
    - Anxiety module
  - CAPS-5
    - Sleep
    - Anxiety



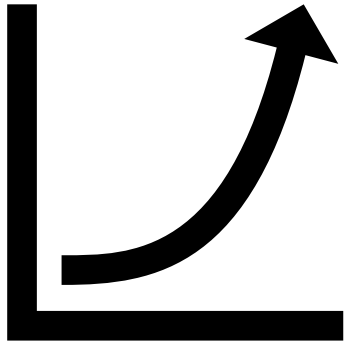
- Other scales are optional and can add specificity but also possibly more complexity, redundancy, time, and cost
  - PSQI Scale (sleep)
  - GAD-7 scale
  - HADS
    - Assessment of complex PTSD (not a DSM-5 diagnosis)

Several study design and operational steps can be taken to reduce variability and enhance data integrity



Other considerations applicable to any clinical study can make enrollment of PTSD studies more efficient and effective

- Simplify the protocol as much as possible
- Decrease the length of visits
- Employ a customized central recruitment campaign but also support locally-customized advertising at the site level
- Build a strong partnership with sites



Summary

- De-risking of the clinical development program is crucial for indications with clinical and biological heterogeneity
- Detailed clinical description and simple biomarker parameters can help to reduce variability through patient selection and stratification, if needed
- The design elements required for PTSD clinical studies can add operational complexity, but this complexity can be optimized and managed with thoughtful scientific and medical analysis, robust planning, and good communication to sites and patients