The Challenge of developing clinically relevant long term trials

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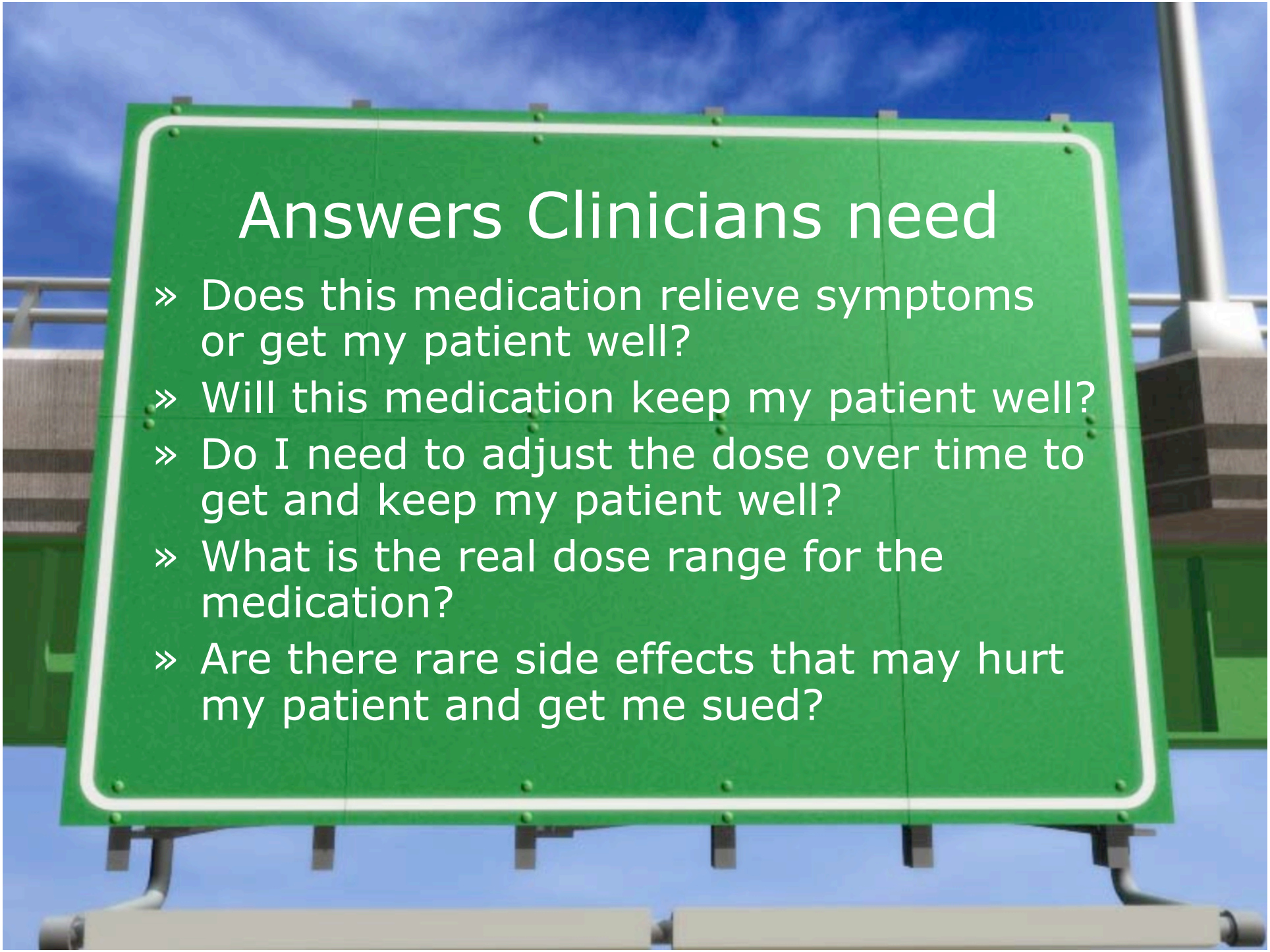
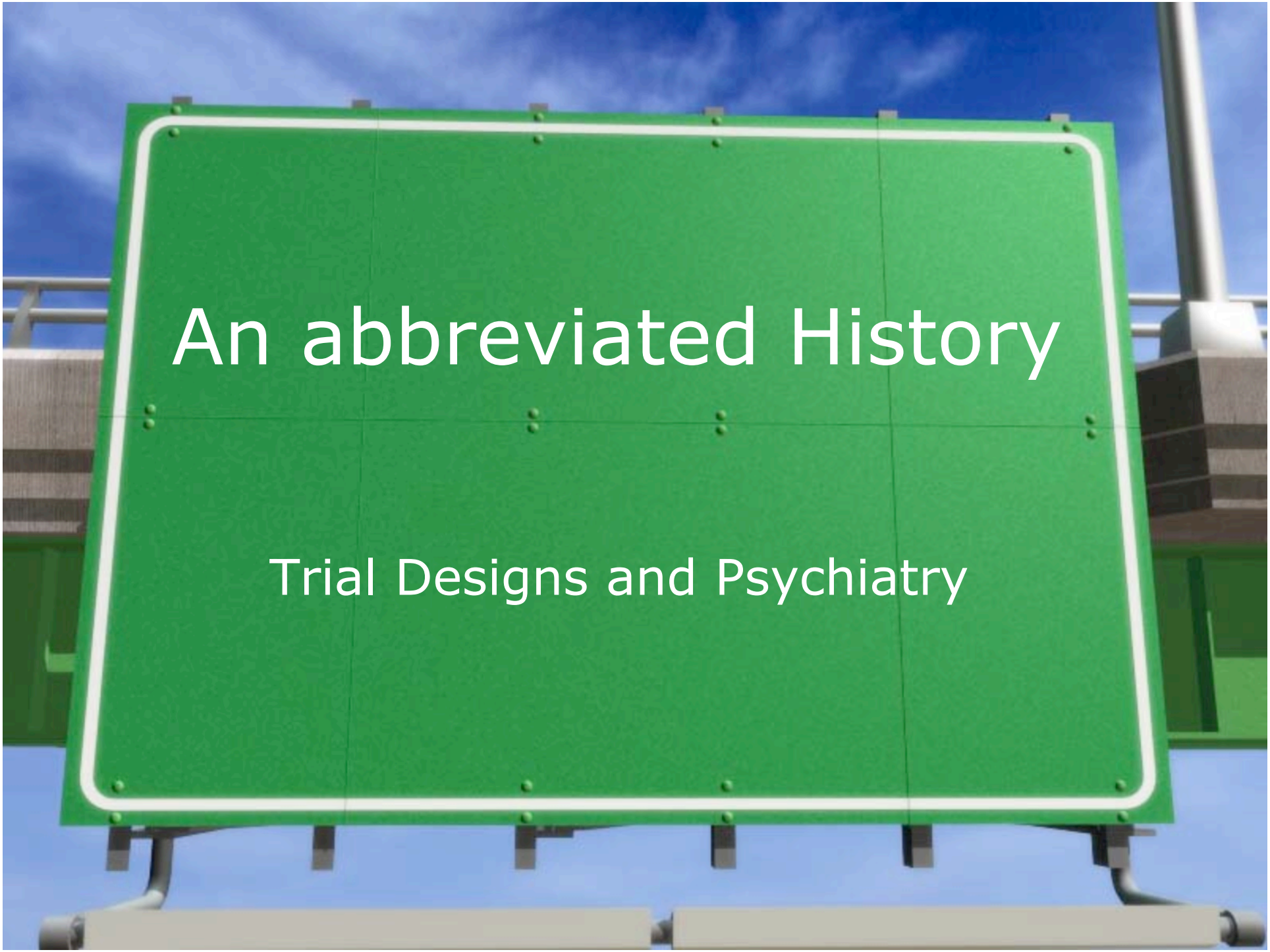
Long-term Clinical Trials
» Federally Sponsored
» Relatively few
» Relatively small sample sizes when compared with other fields
» Relatively short term
» Industry Sponsored
» Newer interest
» Inspired by regulatory guidelines
» Relatively short term (usually one year)


Motivation for Trial Designs
Maintenance of Efficacy
» Compared to placebo discontinuation
» Over time
Safety Data
» Do adverse effects initially reported resolve with longer term treatment
» Does the frequency of adverse events decrease over time?
» Do new adverse effects emerge?
Marketing Advantage


Answers Clinicians need
» Does this medication relieve symptoms or get my patient well?
» Will this medication keep my patient well?
» Do I need to adjust the dose over time to get and keep my patient well?
» What is the real dose range for the medication?
» Are there rare side effects that may hurt my patient and get me sued?


An abbreviated History
Trial Designs and Psychiatry


Older Federal Trial Mechanisms
» VA Collaborative Trial Network
» Academic- VA consortium
» Example Prien et al Lithium Maintenance
» NIMH Collaborative Trials
» Depression trials: Elkin et al
» Schizophrenia trials: Keith, Schooler
» ECDEU Sites
» Network to study innovative compound development: Jonathan Cole and his vision


Single site longitudinal studies
» Antipsychotic dosage and discontinuation trials
» Hogarty, Carpenter, Marder, and others
» Treatment Resistant Depression Trials
» Frank and Kupfer, Reynolds
» Longitudinal Trial of Bipolar Disorder
» Frank and Kupfer
» Panic Disorder Trials
» Mavissakalian


Newer Initiatives
» Federal
» STEP
» CATIE
» STAR*D
» NIDA CTN
» APA
» Practice Research Network


Industry Endeavors
» Multi-site Continuation Trials
» MDD
» Panic Disorder
» Social Anxiety Disorder
Bipolar Disorder
PTSD
Schizophrenia
» Multi-site Maintenance Trials
» Panic Disorder
PTSD
» Longitudinal "Acute" Trials
» InterSept


Questions to consider
As we embark on this exploration
of the design of longer term trials


How Long is Long?
» Many of our current conceptualizations of trial length have emerged out of the US Major Depression literature:
» Acute treatment 6-12 weeks
» Continuation treatment 3-6 months
» Maintenance treatment after 6 months
DOES ONE SIZE FIT ALL SYNDROMES?


How to address logistics for longer term trials
» Sample characteristics
» Attrition
» Quality control and the maintenance of vast amounts of data
» Cost


How to address other costs
» Delayed of academic productivity
» Delayed time to market

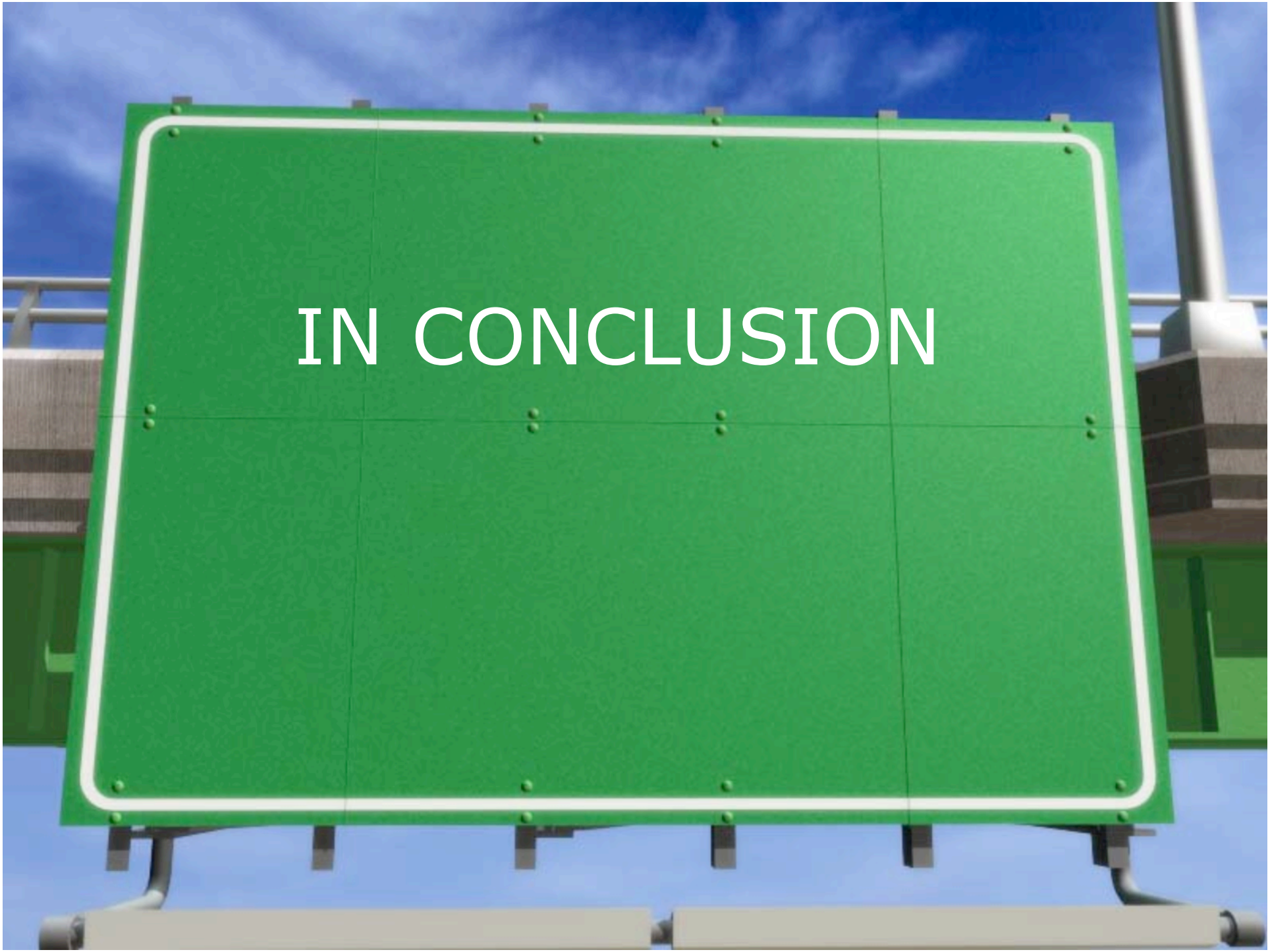

What should the endpoints be?
» Symptom control
» Exacerbation
» Health (achieved or maintained)
» Quality of Life
» Functioning and productivity
» Suicide or suicide attempts
» Death
» OR MULTIPLE ENDPOINTS SIMULATANEOUSLY


How to gather the data?
» Face-to Face
» Clinician interview, self-report, neuropsychology
» Paper and pencil, electronic
» Telephone-Video
» Clinician interview, computerized
» Computer
» Traditional self-report measures, traditional clinician measures, neuropsychology
» Systematic review of employment and health records


As we re-think trial design
» Statistical approaches:
» Can new or alternative approaches modify our choice of endpoints and data collection?
» Can different approaches help to decrease overall sample size and cost?
» Can we use these trials to help model and develop new statistical methodology?


As we re-think trial design
» Can we consider reconceptualizing:
» Dosing schedules (fixed versus flexible)
» Concomitant therapies of all types
» Placebo
» How visits are performed


As we rethink trial design:
» Do we need to reconsider the time point when a trial is specified as beginning?
» The time point when the trial is over? How long is long enough? When is it too long?


IN CONCLUSION

Do we need to consider designing different types of trials:

For different psychiatric disorders

For regulatory purposes

To answer different types of questions?