

Lessons Learned from Cognitive Dysfunction in Schizophrenia – That Might Apply to Cognition in Depression

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Disclosures

Consultant

AbbVie, DSP, Forum, Mnemosyne (scientific board), Roche

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Officer in non-profit

MATRICS Assessment, Inc. – but receive no financial compensation for the role, or from the sale of the MCCB.

Outline of Presentation

- Background and rationale for MATRICS
- The first challenge – pseudospecificity
- The consensus process
- Evaluating and selecting domains and tests for a standard assessment battery
- Unforeseen consequences: co-primary measures, foreign languages, co-norms
- What we did right and what we missed.

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

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NIMH Division Director: Ellen Stover, PhD



MATRICS:

Background and Rationale

- Increasing evidence that cognitive deficits are core features of schizophrenia
- Increasing support for relationships between cognition and functional outcome in schizophrenia
- Increasing research focus on the basic studies of neuropharmacology of cognition

Targeting Cognition in Schizophrenia: Why was there a Bottleneck?

- Lack of consensus regarding cognitive targets.
- No widely accepted endpoint.
- Ambiguity regarding optimal clinical trial design.
- Unclear path to FDA approval and labeling.

From the FDA point of view: Targeting Cognition in Schizophrenia:

- FDA registration targets DSM disorders
- “No fundamental objection to syndrome-based clinical targets (fever, pain, agitation)”
- “We will not accept a new clinical endpoint for the convenience of any drug company”
- NIMH can use its convening authority as independent scientific entity to define new and valid clinical endpoints

NIMH – MATRICS

Goals and Products

- Create Standardized Measure for use in Clinical Trials
- Define Optimal Experimental Designs
- Establish path to FDA Approval
- Attract large pharmaceutical companies to focus efforts on this important clinical target
- Success required involvement of: NIMH, FDA, pharmaceutical industry, and academia

The First Challenge of MATRICS: *Pseudospecificity*

Presents two types of challenges:

- Affects the rationale for the effort
- Affects the types of study designs
- A claim of a drug effect that is considered to be artificially narrow
- Serves only promotional purpose
- Implied advantage over other drugs in class regarding subgroup/symptom
- Misleading (since no evidence to support)

FDA Position is that a claim is pseudospecific until proven otherwise.

Examples of pseudospecificity and how it relates to cognition in schizophrenia

- Subgroup of recognized syndrome (e.g., major depression in women)
- Symptom of recognized syndrome (e.g., hallucinations in schizophrenia)
- Claiming specific benefit in single disease model for recognized nonspecific symptom (e.g., dental pain)

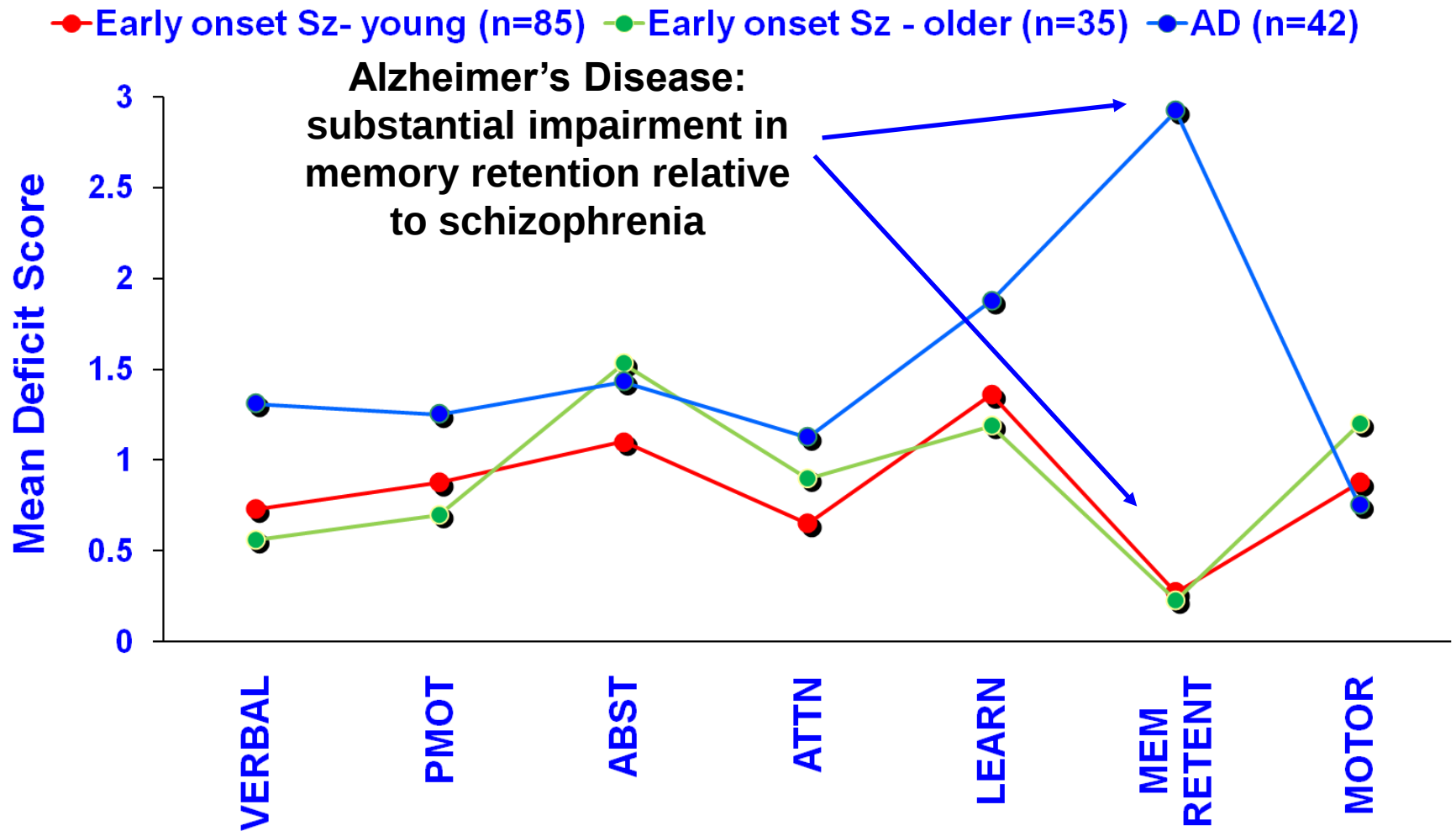
Cognition in schizophrenia would be pseudospecific if:

- 1) Cognitive impairment results from other illness features (e.g., psychosis)

OR

- 1) Cognitive impairment was general and no pattern of cognitive deficit is characteristic of schizophrenia

Alzheimer's Dementia compared with Schizophrenia Neuropsychological Deficit Scores



From Heaton et al. (1994)

The consequence of potential *Pseudospecificity* for study design

What design approaches should be used to isolate change in neurocognitive domains from changes in other symptom domains?

To isolate change in cognitive function from change in symptoms and other clinical features, include subjects who have been clinically stable and in the residual (nonacute) phase of their illness for a specified period of time ...

Statistical approaches cannot be used to rule out pseudospecificity ... Pseudospecificity is best dealt with by restricting symptom severity prior to randomization.

Buchanan et al. 2005; From April 2004 FDA-NIMH-MATRICES Workshop on Clinical Trial Designs for Neurocognitive Drugs for Schizophrenia

MATRICS Consensus Meetings

Principles for Developing Consensus

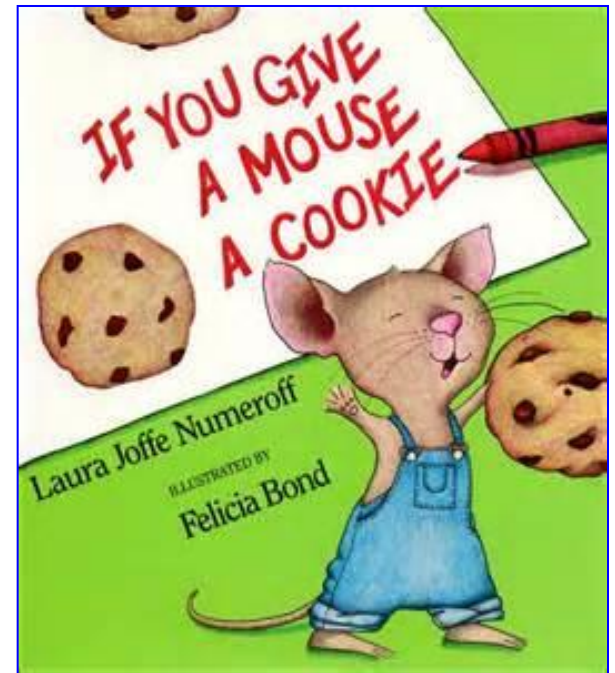
- Consensus should be as broad as possible
- Transparency of process
- Inclusion of academia, NIMH, industry, FDA, consumer representatives
- *A priori* development of a path to consensus (e.g., RAND Panel Method, a modified Delphi process)
- Management of conflicts of interest (both pharma and test developers)

Consensus did *not* mean everyone would agree on the final product --

The goal was to have everyone agree on the process.

The Next Series of Challenges: Arriving at a Consensus Endpoint ... and unexpected consequences

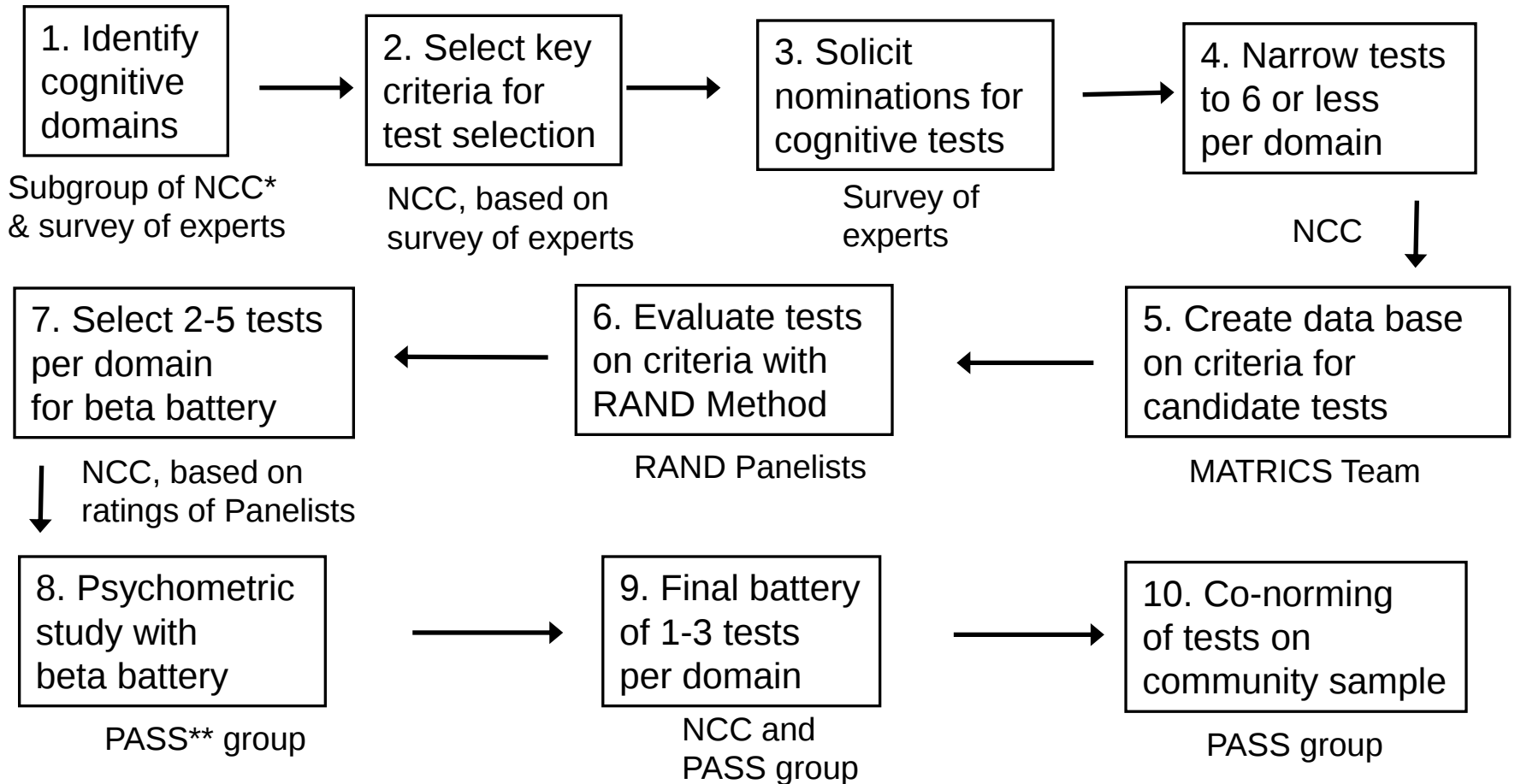
Start by selecting the relevant
cognitive domains, among many
possible...
then start a large multi-site data
collection to evaluate tests...
start a new non-profit company ...
then translate into over 20 foreign
languages...
then collect co-norms around the
world ...
then 10 years go by...



Neurocognition Committee for MATRICS-NIMH

- Keith Nuechterlein (UCLA) - Co-Chair
- Michael Green (UCLA) - Co-Chair
- Deanna Barch (Washington University)
- Jonathan Cohen (Princeton University)
- Susan Essock (Mt. Sinai School of Medicine)
- Wayne Fenton (NIMH)
- Fred Frese (Summit County Recovery Project)
- Jim Gold (Maryland Psychiatric Research Center)
- Terry Goldberg (NIMH)
- Robert Heaton (UCSD)
- Richard Keefe (Duke University)
- Helena Kraemer (Stanford University)
- Daniel Weinberger (NIMH)
- Steve Zalzman (NIMH)

Steps to MATRICS Consensus Cognitive Battery



*NCC: MATRICS Neurocognition Committee

**PASS: MATRICS Psychometric and Standardization Study



Essential Criteria for Consensus Cognitive Battery for Clinical Trials in Schizophrenia

Battery:

- Inclusion of the seven cognitive domains
- Valid assessment of cognition at the level of all individual major cognitive domains

Individual Tests:

- High test-retest reliability
- High utility as a repeated measure
- Demonstrated relationship to functional outcome
- Demonstrated tolerability and practicality

Criteria for MATRICS Consensus Cognitive Battery ... and the resulting balancing act

The tests need to have enough existing data to evaluate them for:

- Test-retest reliability
- Utility as a repeated measure
- Relationship to functional outcome
- Tolerability and practicality (?)

The need for existing psychometric data for evaluation makes it more difficult to select novel, or recently-developed, tests (though two specialized tests were selected for the MCCB).

CNTRICS was a response to this trade-off.

MATRICS Consensus Cognitive Battery

Speed of Processing

- Category Fluency
- BACS Symbol Coding
- Trial Making A

Attention / Vigilance

- Continuous Performance Test
- Identical Pairs version

Working Memory

- Maryland Letter Number Span
- WMS Spatial Span

Verbal Learning

- Hopkins Verbal Learning Test

Visual Learning

- Brief Visuospatial Memory Test

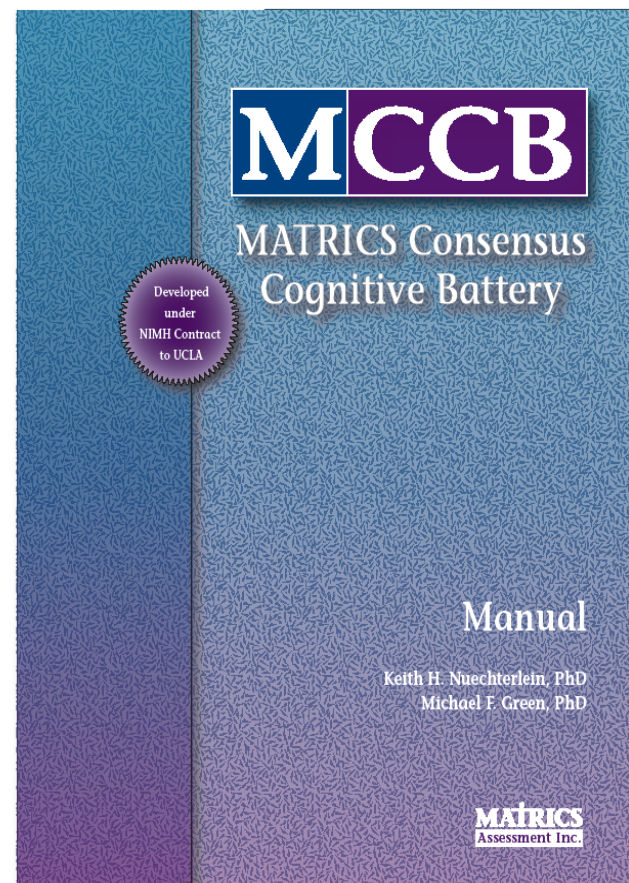
Reasoning and Problem Solving

- NAB Mazes

Social Cognition

- MSCEIT Managing Emotions

MATRICS Consensus Cognitive Battery (MCCB)



Distributed by:

- Multi-Health Systems (MHS)
- Psychological Assessment Resources (PAR)
- Pearson - Harcourt Assessment, Inc

MATRICES
Assessment Inc.

An Unexpected Requirement: A Co-primary Measure in Addition to Cognitive Performance

“The current position of the FDA is that concurrent change on a co-primary measure of functional outcome will be required for approval of a neurocognitive drug for schizophrenia.”

Buchanan et al. *Schizophrenia bulletin* 2005

Reasons for the FDA position:

- Increase face validity for consumers and clinicians
- Increase acceptance by consumers and clinicians
- The ultimate goal is better community functioning

This requirement generated:

- a surge of interest in defining and developing new co-primary measures (performance and interview-based)
- concern in the pharmaceutical industry about what to do in the absence of a specific recommendation
- launch of a new initiative (MATRICS-CT)

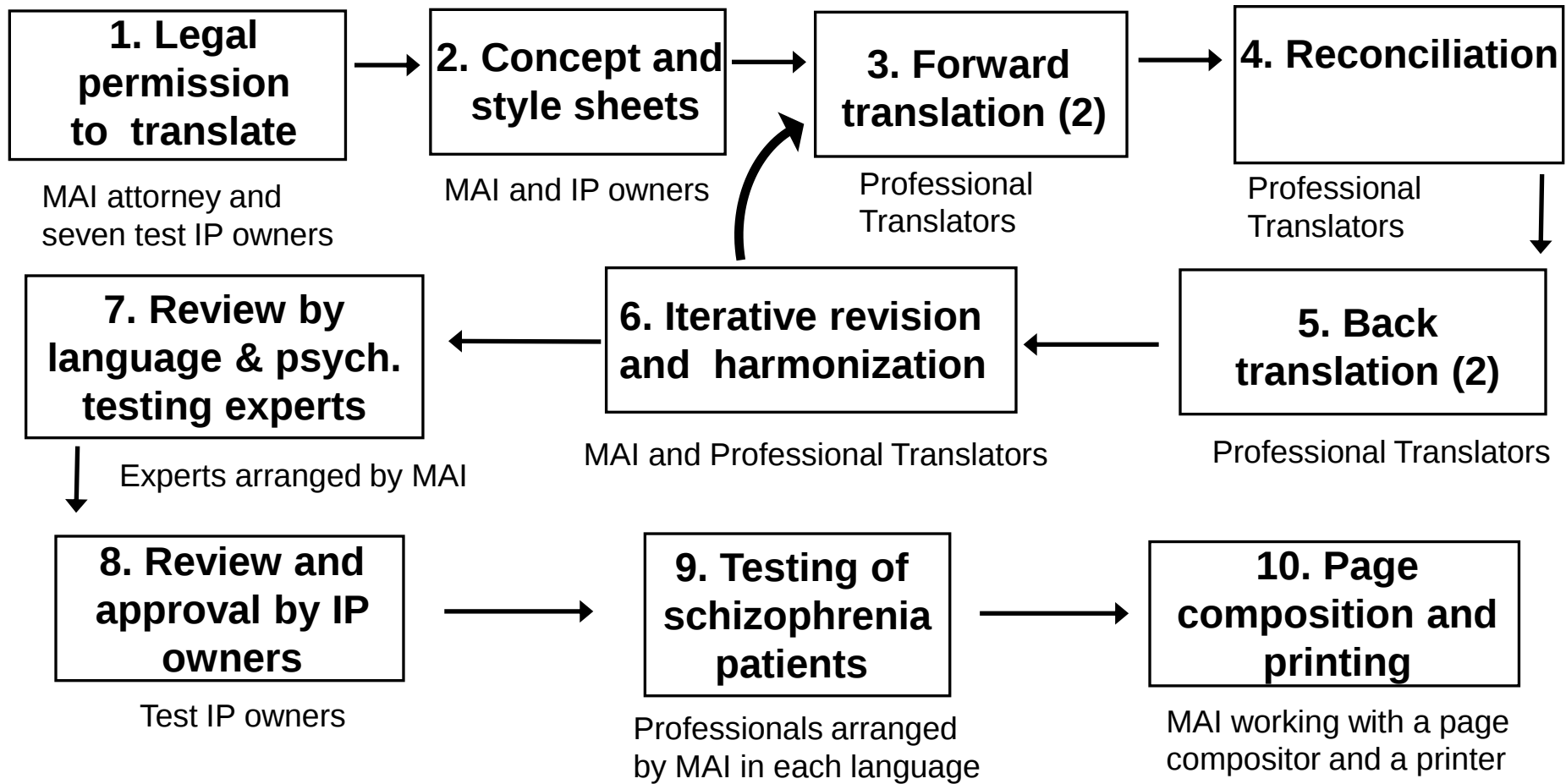
Importance of norms for trials of cognition enhancing drugs

- Norms (co-norms) should be obtained on representative community samples (stratified by age, gender, education)
- Improves ability to detect “signal” in clinical trials because it reduces error variance
- Norming accounts for variance due to age / gender
- Norming allows for more valid composite scores:
 - combining tests into domain scores
 - domain scores into a composite score
- Norming detects and adjusts for unexpected differences in difficulty level of tests among international translations so they can be combined
- Enables valid comparisons between cognitive domains

Follow up NIMH Initiatives to MATRICS to Help Address Subsequent Tasks

- 1) **CNTRICS: Initiative for cognitive neuroscience measures in clinical trials**
- 2) **MATRICES-CT: Co-primary and Translation: NIMH / Industry / Academic Consortium**
 - Translation and co-norming of MCCB into other languages for international trials
 - Psychometric evaluation of co-primary measures, and creation of a cross-culturally valid combination of co-primary subtests (Brief International Functional Capacity Assessment)
- 3) **Negative Symptoms Initiative**
 - New negative symptom scales (BNSS and CAINS)

Steps in Translation and Cultural Adaptation of the MATRICS Consensus Cognitive Battery



Commercial Translations of the MATRICS Consensus Cognitive Battery (MCCB)

English

- Chinese (Simplified and Traditional)
- Croatian
- Dutch
- German
- Hebrew
- Hindi
- Italian
- Japanese
- Kannada
- Marathi
- Polish
- Brazilian Portuguese
- Romanian
- Russian
- Serbian
- Spanish – Central and South American
- Spanish – Spain
- Tamil
- Telugu
- Ukrainian



What we did not anticipate in MATRICS?

MATRICS successfully met its goals, and provided its deliverables. Consensus process was viewed very favorably. Clinicaltrials.gov shows 48 open studies using the battery (psychopharm and other approaches)

But there are some things we did not anticipate:

- Balancing need for existing reliability data on potential tests with including novel tests (from cognitive neuroscience)
- Intellectual property (and related publishing and distribution issues) for tests selected for MCCB
- Need for co-primary measures
- Importance of co-norms
- Need for translations for international uses