

# ISCTM Apathy Working Group Session

February 19, 2019

Washington, DC

Co-Chairs: Drs. Krista Lanctôt and  
David Miller

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# Attendees

Larry Adler

Ariana Anderson

Karen Anderson

Ross Baker

Monique Carter

Deidra Couch

Michael Davidson

Sanjay Dube

Anna Eramo

Larry Ereshefsky

Tiffany Farchione

Nahome Fisseha

Dan Gruener

Zahinoor Ismail

Jean Kim

Eva Kohegyi

Krista Lanctot

Alan Lipschitz

Didier Meulien

David Miller

Moyra Mortby

Stephane Pollentier

Jill Rasmussen

Michael Ropacki

Paul Rosenberg

Myuri Ruthirakuhan

Juliette Toure

Dawn Velligan

Mark Versavel

Kathleen Welsh-Bohmer

James Youakim

# Agenda

Time	Topic
4:25 - 4:30	Welcome and Introduction
4:30 – 4:35	Vision statement
4:35 – 4:50	Update on Diagnostic Criteria for Apathy in Neurocognitive Disorders: Survey results/update re: consensus meeting at AAIC 2019
4:50 – 5:00	Apathy using the RDoC construct
5:00 – 6:00	Issues in apathy research <ul style="list-style-type: none"><li>- Overview of existing outline</li><li>- Literature search completed</li><li>- Discussion</li></ul>

# Vision Statement

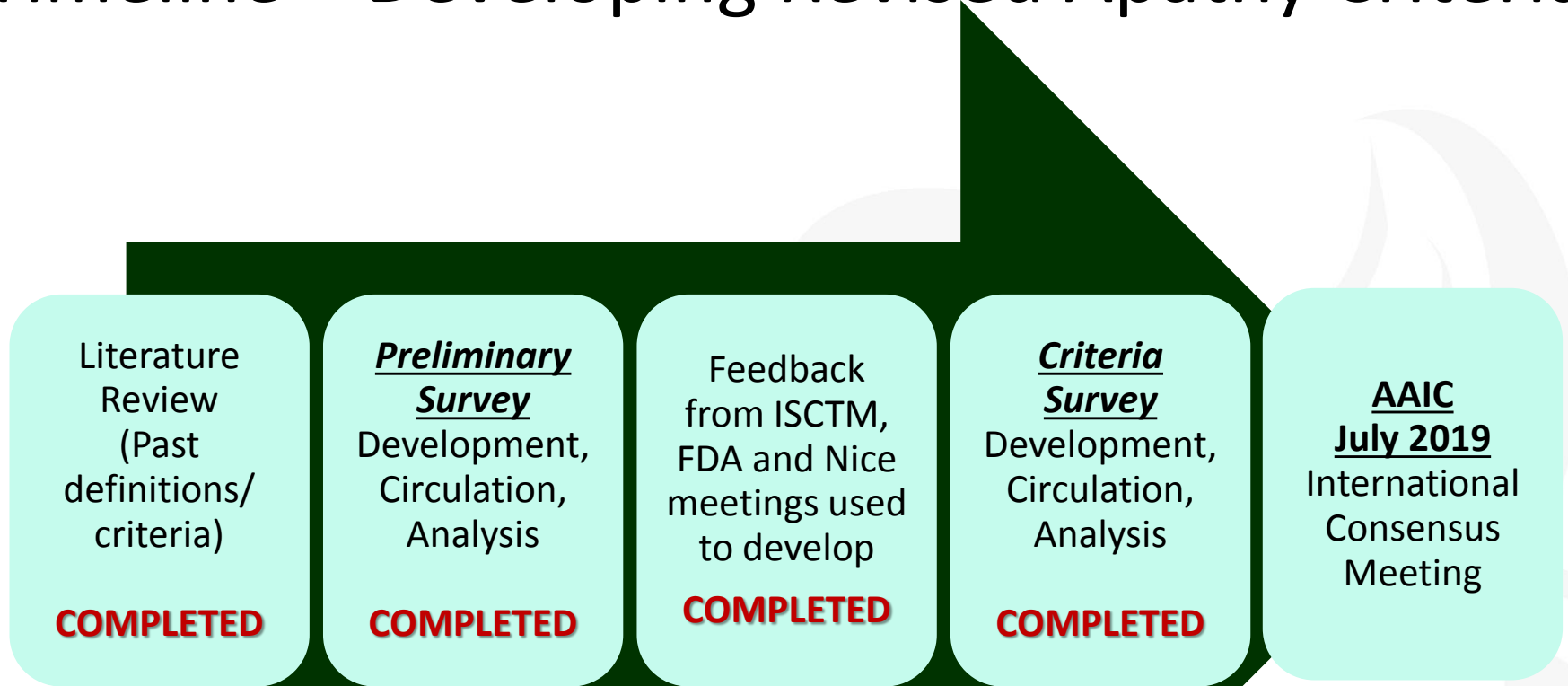
Apathy as a behavioural and psychological symptom in dementia (BPSD) has increasingly been the focus of research over the last 10 years. This interest has led to the publication of provisional diagnostic criteria and stimulated interest in this syndrome as a treatment target for both Alzheimer's disease and related dementias. Apathy can both precede and emerge concurrently with cognitive impairment and other BPSD. The Apathy Working Group brings together industry, academic and drug regulatory experts. This expertise will be used to define the relevance of apathy and to better understand, recognize and manage apathy within BPSD and provide a basis for further research.

Agenda Item 2

# **UPDATE ON DIAGNOSTIC CRITERIA FOR APATHY IN NEUROCOGNITIVE DISORDERS**

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# Timeline – Developing Revised Apathy Criteria

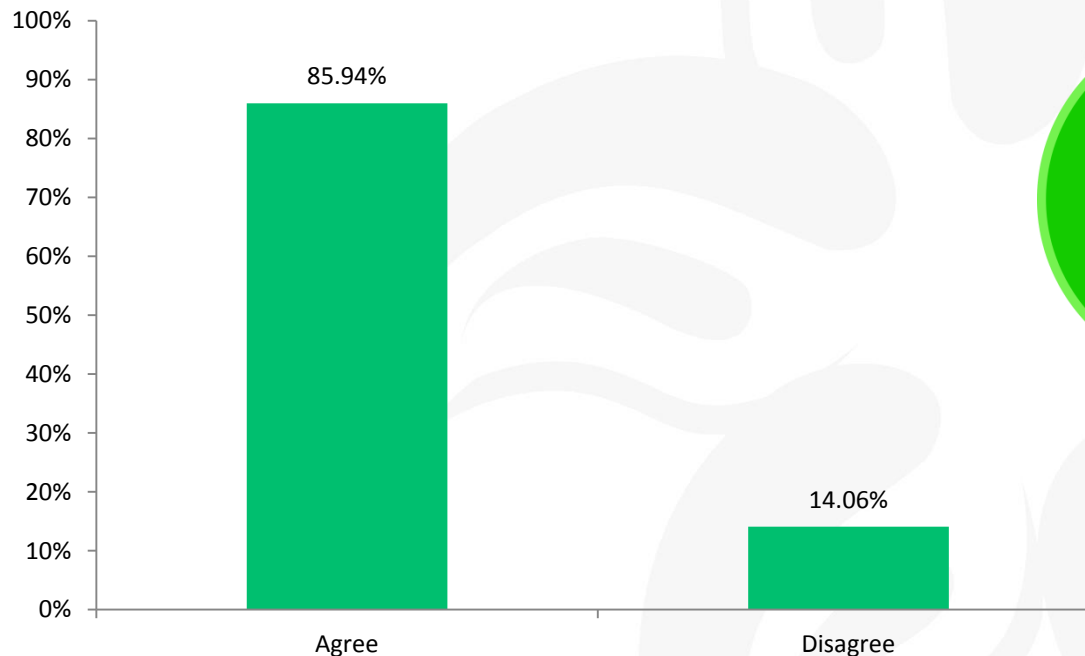


# Survey Results

- 145 respondents
  - 41 members of ISCTM
  - 47 members of IPA
  - 58 members of ISTAART NPS PIA

# Survey Results: Criterion A

The patient meets criteria for mild or major neurocognitive disorder (e.g.: AD, FTD, DLB, vascular dementia, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment, prodromal AD, subjective cognitive impairment, or other cognitive disorder).



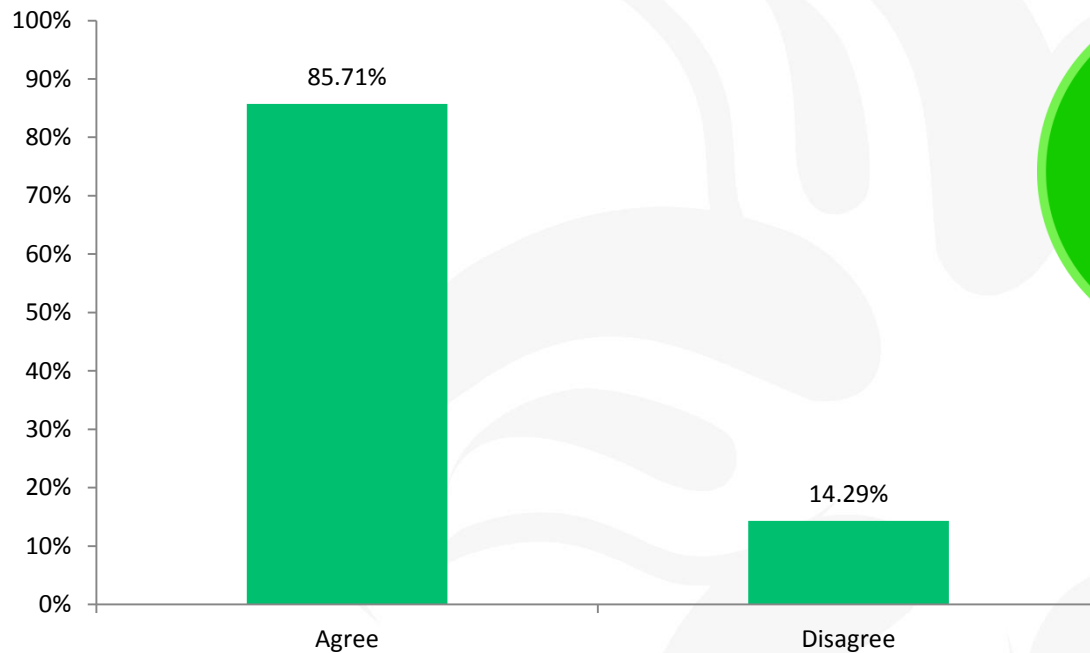


# Survey Results: Criterion B

The patient exhibits at least one symptom in at least three of the following four domains (B1 to B4). These symptoms have been persistent or frequently recurrent for a minimum of four weeks' and represent a change from the patient's usual behaviour. These changes may be reported by the patient themselves or by observation of others.

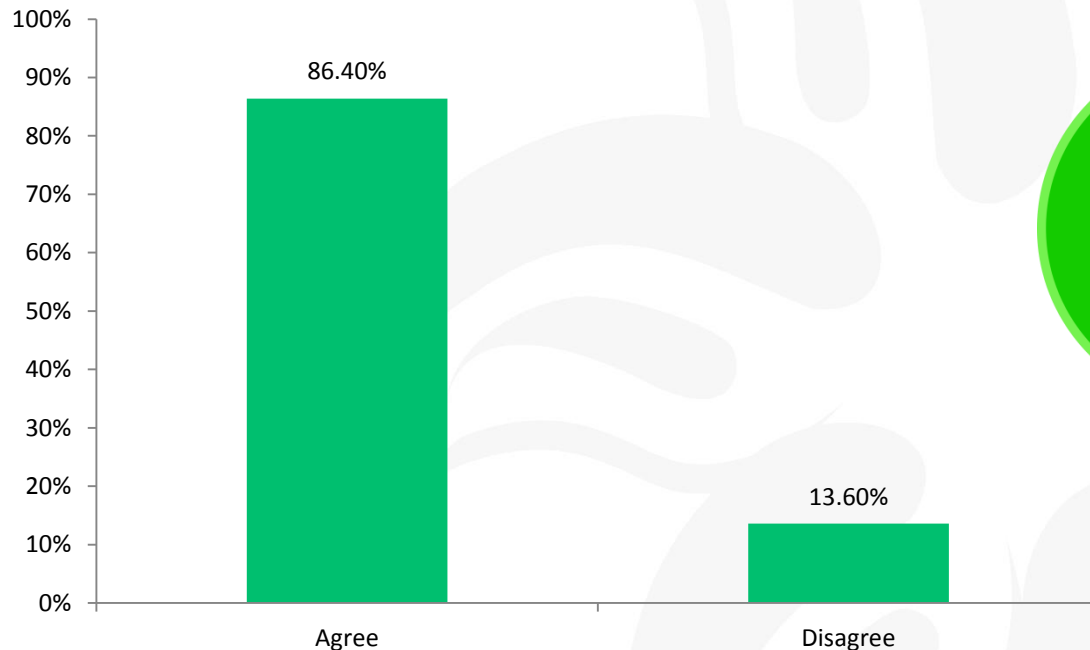
# Survey Results: Criterion B

B1: Loss of Initiative: Less spontaneous and/or active than usual self; contributes less to household chores



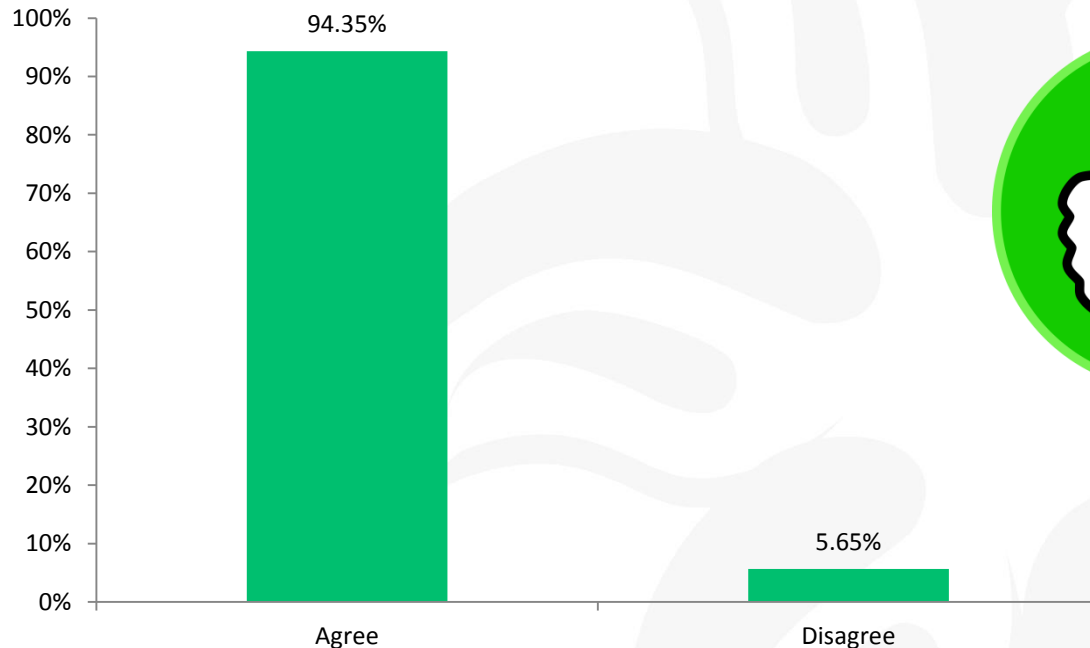
# Survey Results: Criterion B

B2: Loss of interest: Less enthusiastic about usual activities; less interested in, or less curious about routine or new events in their environment



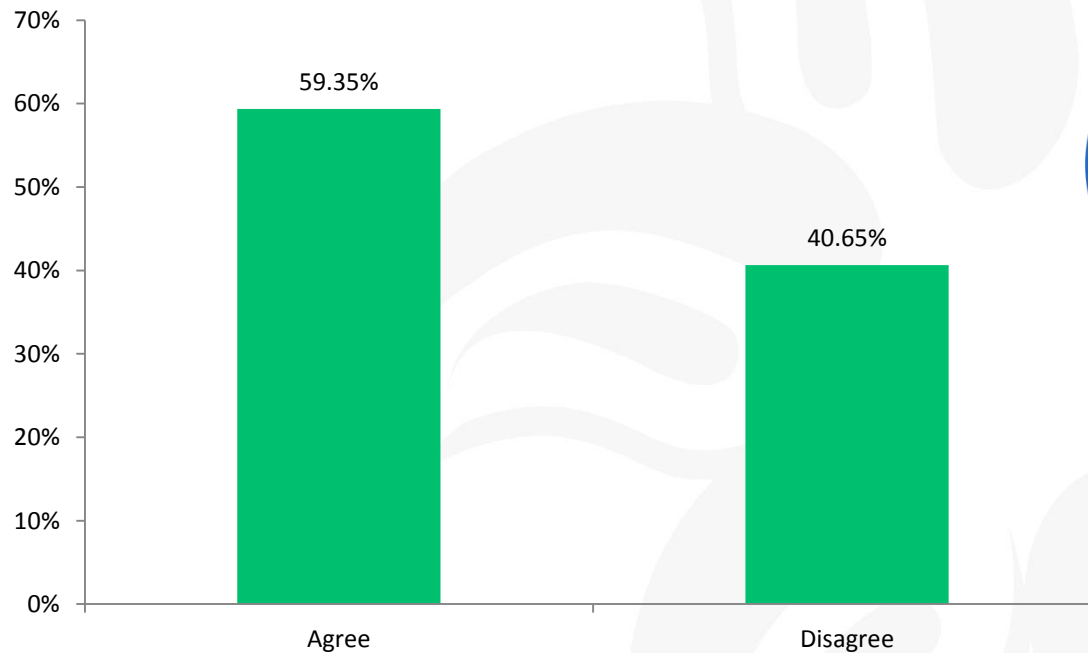
# Survey Results: Criterion B

B3: Emotional blunting: Less affectionate or lacking in emotions compared to their usual self; expresses less emotion in response to positive or negative events



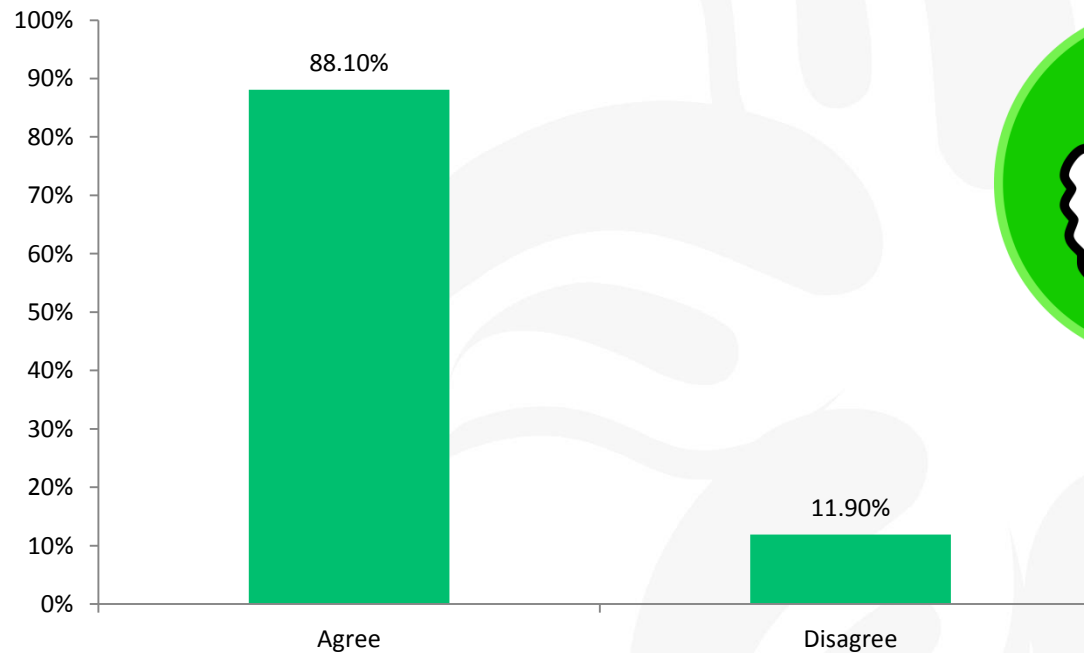
# Survey Results: Criterion B

B4: Loss of social activity: Less likely to initiate a conversation; less interested in activities and plans made by others; less interested in friends and family; reduced participation in social activities even when stimulated



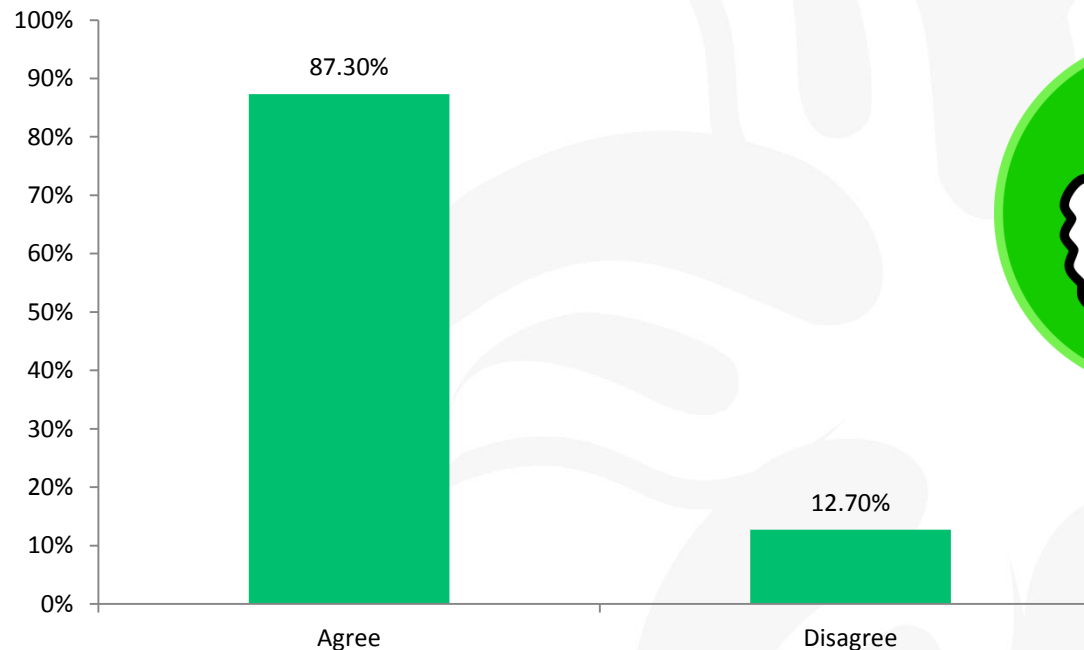
# Survey Results: Criterion C

These symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning.



# Survey Results: Criterion D

These symptoms are not exclusively explained by physical disabilities, motor disabilities, diminished level of consciousness, or the direct physiological effects of a substance?

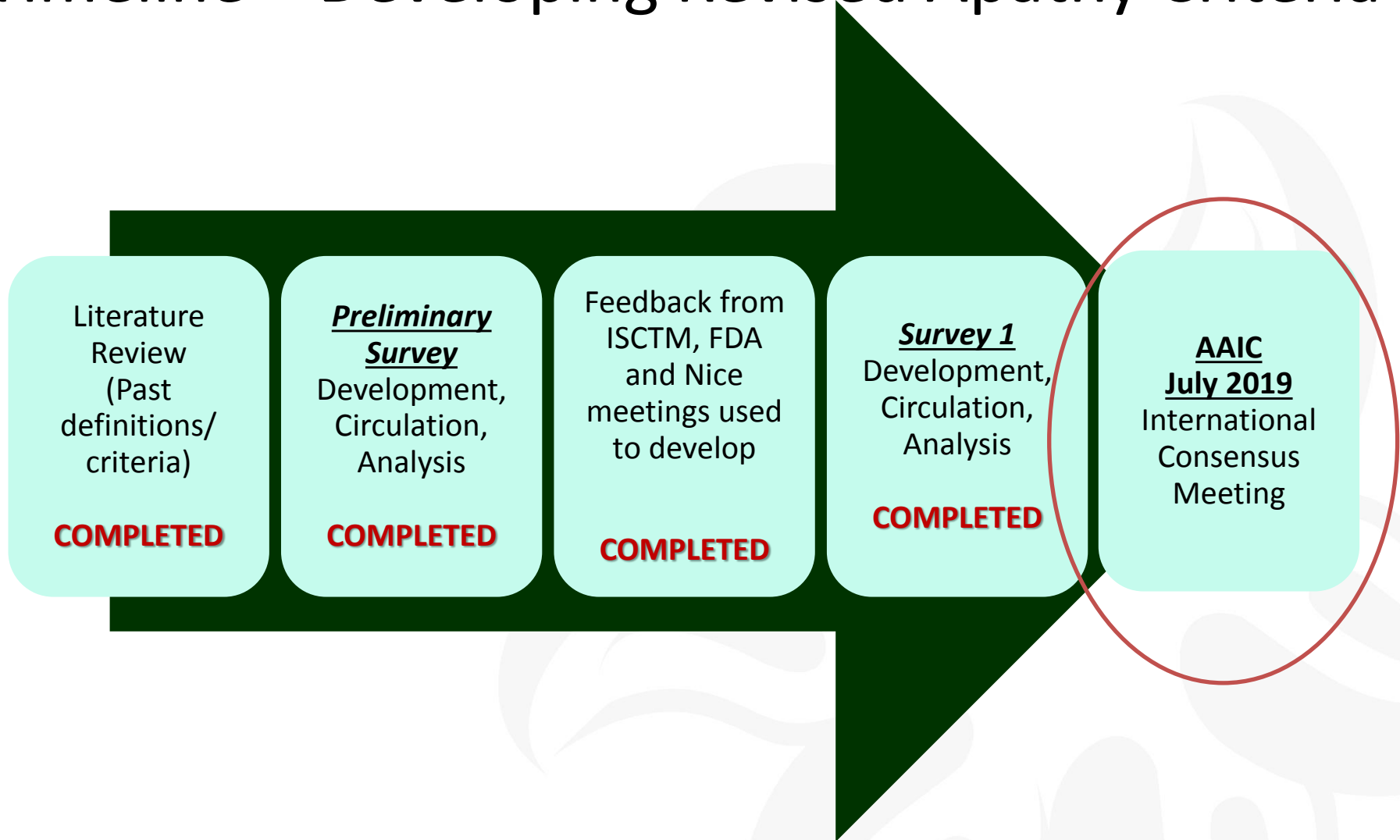


# Survey Results: Utility

- General agreement that diagnostic criteria are useful for clinical (93%) and research (90%) purposes
- General agreement that the criteria apply to all neurocognitive disorders (83% yes, 11% unsure, 6% no)



# Timeline – Developing Revised Apathy Criteria



# AAIC 2019

- Consensus meeting moved to AAIC 2019
- Saturday, July 13 (save the date!)
- Purpose:
  - Examine in-depth the results of the survey
  - Discuss the exact wording of the diagnostic criteria
  - Vote

Agenda Item 3

# **APATHY WITHIN THE RDOC FRAMEWORK**

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# Research Domain Criteria

- Focuses on 6 domains:
  - Negative valence – responses to aversive situations
  - Positive valence – responses to positive motivational contexts
  - Cognitive systems
  - Systems for social processes – responses to interpersonal settings, perception interpretation
  - Arousal/Modulatory systems – activate neuronal systems, maintain homeostatic regulation of systems including energy balance and sleep
  - Sensorimotor systems
- RDoC provides a way to evaluate behaviours and syndromal presentations, with the understanding that there will be interactivity and interdependence across the domains

# RDoC Matrix

- Apathy generally considered under the positive valence systems construct

Construct/Subconstruct		Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
<b>Positive Valence Systems</b>								
Reward Responsiveness	Reward Anticipation							
	Initial Response to Reward							
	Reward Satiation							
Reward Learning	Probabilistic and Reinforcement Learning							
	Reward Prediction Error							
	Habit - PVS							
Reward Valuation	Reward (probability)							
	Delay							
	Effort							

# Updating Apathy: Using Research Domain Criteria to Inform Clinical Assessment and Diagnosis of Disorders of Motivation

*Thida Thant, MD and Joel Yager, MD*

*(J Nerv Ment Dis 2018;00: 00–00)*

- Clinical apathy and associated dysfunctions can be addressed using constructs suggested by the RDoC domain of Positive Valence Systems
- Suggests the use of RDoC as a framework to suggest clinical questions and structure research studies

# How do our criteria fit with RDoC?

Apathy Domains	Revised Criteria	RDoC Domain	RDoC Construct
Initiative	Less spontaneous and/or active than usual self	Positive Valence System	Reward learning/ valuation/ responsiveness
	Contributes less than to household chores		
Interest	Less enthusiastic about usual activities		
	Less interested in, or less curious about routine or new events in their environment		
Emotion	Less affectionate or lacking in emotions compared to their usual self	Social Processes	Social communication
	Expresses less emotion in response to positive or negative events		
Social Activity	Less likely to initiate conversation	Social Processes	Social Communication Affiliation & Attachment Perception and Understanding of Self/Others
	Less interested in activities and plans made by others		
	Less interested in friends and family		
	Reduced participation in social activities even when stimulated		



**ISCTM APATHY WORKING GROUP  
PAPERS**

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# Recommendations for designing an clinical trial for apathy in Alzheimer's disease

## Progress so far

- Outline developed December 2017
- Literature search completed July 2018
- 8 trial design questions proposed

# Trial design paper sections

1. Current definitions of apathy
  - “motivation deficit syndrome”
2. Measuring apathy (how best to measure treatment effect?)
  - Scales: NPI-apathy, DAIR, AES, ADCS-CGIC
  - Discuss absence of “gold standard”, but there are recommendations
  - Self vs. informant reports
  - Recommendation of ideal caregiver?

# Trial design paper sections

## 3. Confounding comorbidities

- Depression – concerns with pseudo-specificity
- Cognition – should there be exclusion of patients with severe AD?
- Other NPS – agitation/aggression, psychosis have been shown to be confounders of apathy

# Trial design paper sections

4. What is the target population?
  - E.g. NPI-apathy subscale  $\geq 3$  – is this appropriate?
  - Should the study population consist only of subjects who have predominant apathetic symptoms? Alternatively, should subjects be included who have prominent apathy, even if these symptoms are not predominant? Should be clinically relevant for patient and / or carer.
  - What disease states should apathy be studied in? *AD, prodromal, etc. apathy in the presence of other BPSD that are NOT the main problem, apathy in other subtypes of dementia?*

# Trial design paper sections

## 5. Duration of clinical trials

- What would be considered the optimal treatment duration? Provide overview of past apathy trials and whether they were able to detect statistically significant improvements over their trial duration (e.g. ADMET found significance over 6 weeks)

# Trial design paper sections

6. Other outcome measures (secondary and exploratory)
  - Global
  - Caregiver burden
  - Function
  - Depression
  - Other NPS
  - Cognition

# Trial design paper sections

7. Other design considerations:
  - Concomitant medications (e.g. psychotropics, rescue meds)
  
8. Inclusion of biomarkers to further understanding of neurobiology?

# Trial design paper

Section	Volunteers
1. Current definitions of apathy	
2. Measuring apathy	Stephane Pollentier Jill Rasmussen
3. Confounding comorbidities	Judith Jaeger
4. Target population?	Ariana Anderson Craig Ritchie
5. Trial duration	David Miller Larry Ereshefsky
6. Other outcome measures	Michaela Defrancesco
7. Other design considerations	
8. Inclusion of biomarkers?	Larry Ereshefsky Krista Lanctôt



# **SUPPLEMENTAL SLIDES**



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