20th Anniversary Session

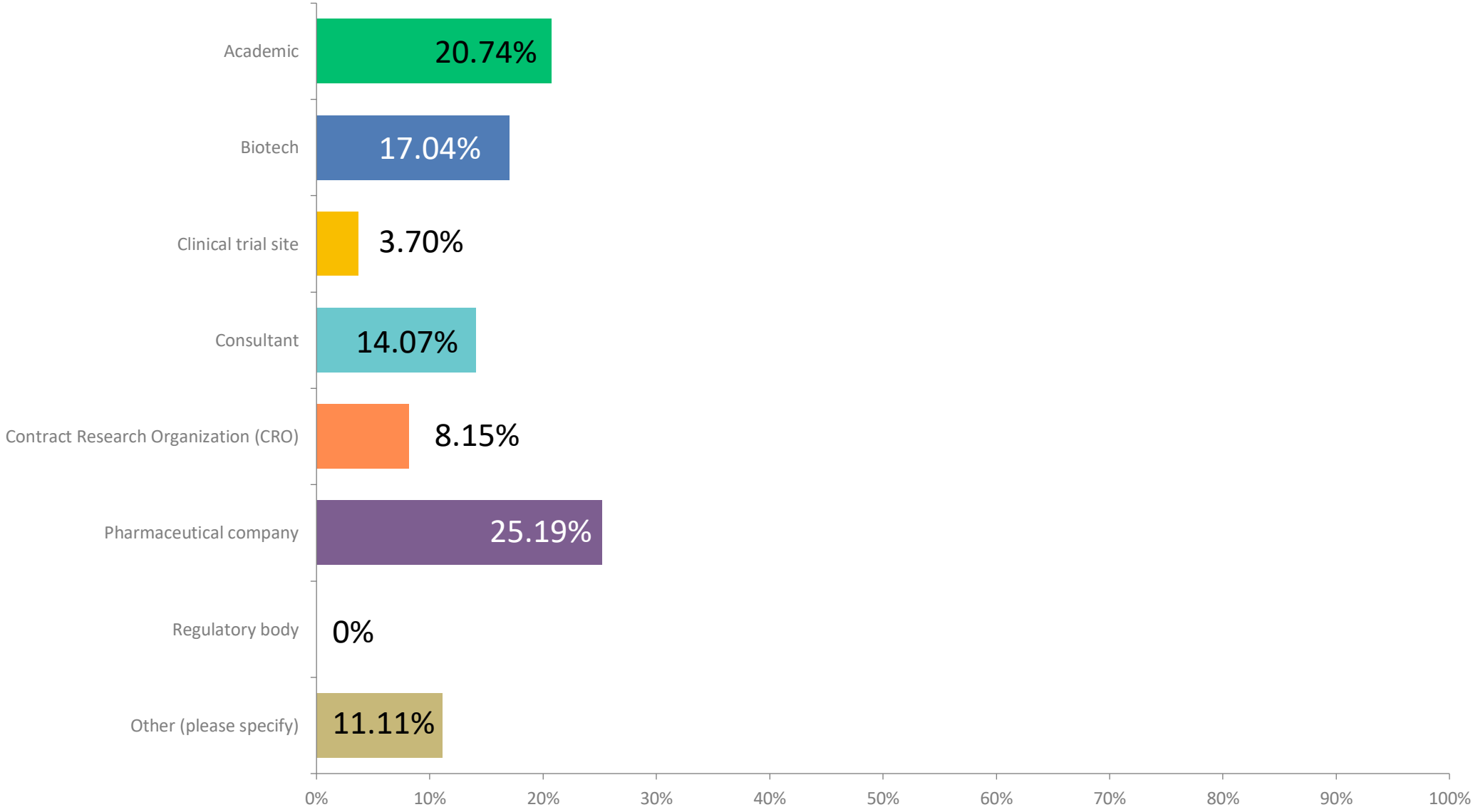
Overview of Methodological Advancements & What We Can Do Better in the Future – 'Survey Says'

Michael T. Ropacki, PhD

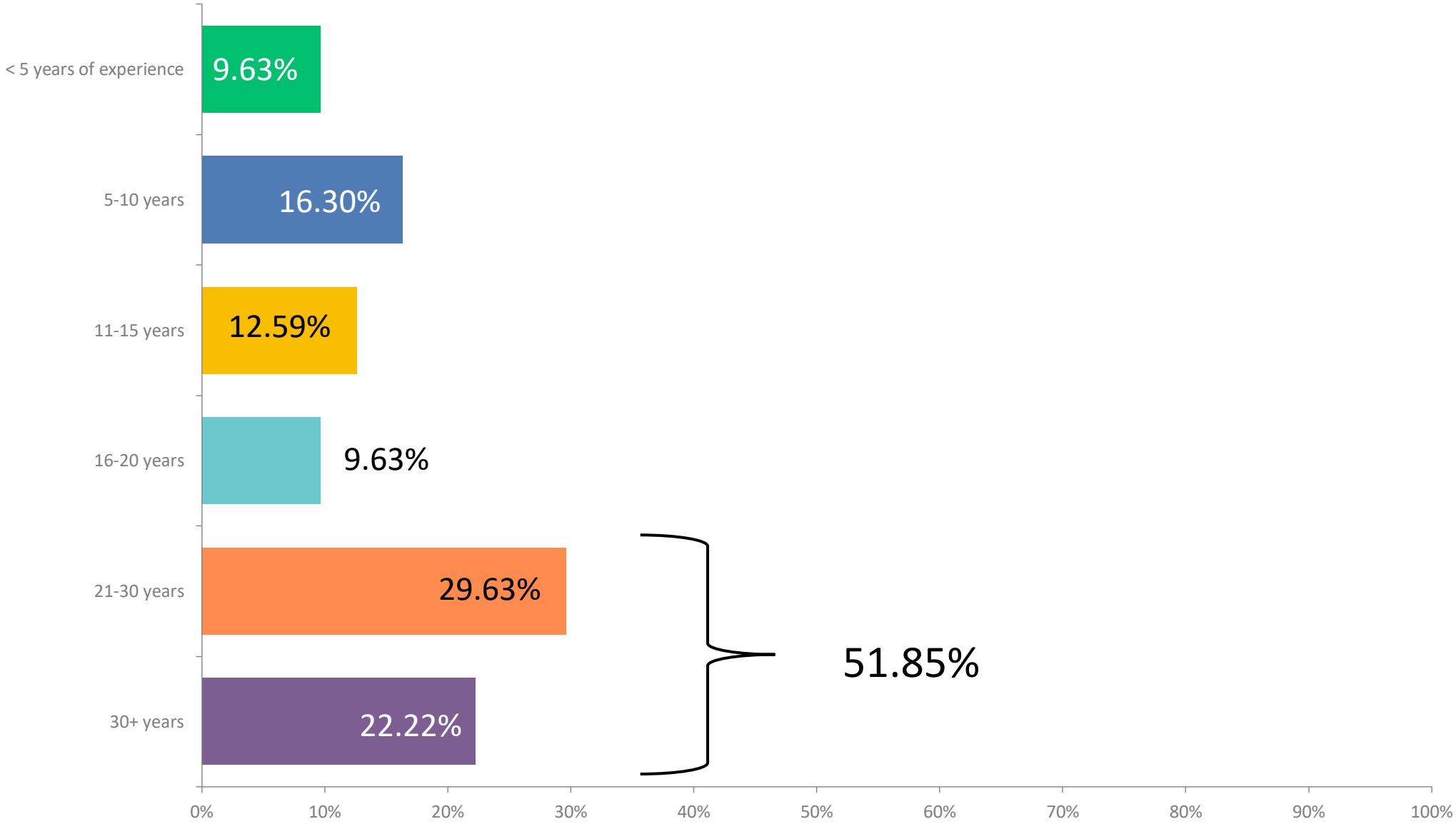
Disclosures

- Strategic Global Research & Development – Owner
- Oryzon – Employee
- Scientific Advisory Board Member
  - Novoic – Chair, Scientific Advisory Board
  - Kannalife Sciences – Scientific Advisory Board
  - ‘Stealth Mode’ Biopharma – Scientific Advisory Board

Overview of ISCMT ‘Survey Says’ – Respondents (N = 135)



Overview of ISCMT ‘Survey Says’ – Years of Experience



Novel clinical endpoints (COAs) and their psychometric validation

High Priority	**63.20%**
Medium Priority	**32.80%**
Total	**96.00%**

Advancements:

- ‘Newer’ (but now aging) clinical endpoints with better psychometric properties have begun to be used in clinical trials.

ELSEVIER CrossMark

Alzheimer's & Dementia 13 (2017) 186-195

Perspective

Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project

Karen Ritchie[a,b,j,l,*], Michael Ropacki[c,l], Bruce Albala[d], John Harrison[e,f], Jeffrey Kaye[g], Joel Kramer[h], Christopher Randolph[i], Craig W. Ritchie[j]

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ELSEVIER

Schizophrenia Research

Volume 72, Issue 1, 15 December 2004, Pages 1-3

Editorial Introduction

The MATRICS initiative: developing a consensus cognitive battery for clinical trials

Michael F. Green [a b], Keith H. Nuechterlein [a c]

ELSEVIER

Schizophrenia Research

Volume 68, Issues 2–3, 1 June 2004, Pages 283-297

The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery

Richard S.E Keefe [a], Terry E Goldberg [b], Philip D Harvey [c], James M Gold [d], Margaret P Poe [a], Leigh Coughenour [a]

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REVIEW OPEN ACCESS

Meaningful Clinical Changes in Alzheimer Disease Measured With the iADRS and Illustrated Using the Donanemab TRAILBLAZER-ALZ Study Findings

Alette M. Wessels, PhD, Ellen B. Dennehy, PhD, Sherie A. Dowsett, PhD, Samuel P. Dickson, PhD, and Suzanne B. Hendrix, PhD

Correspondence
Dr. Wessels
wessels_alette_maria@lilly.com

Neurology: Clinical Practice 2023;13:e200127. doi:10.1212/CPJ.0000000000200127

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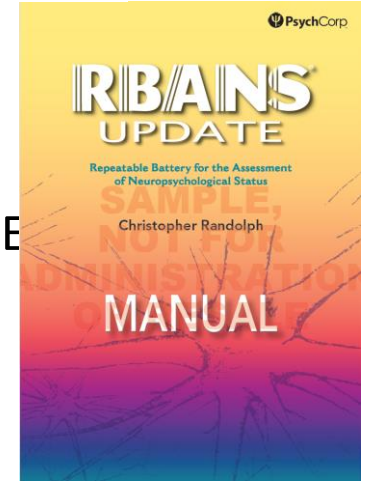

Novel clinical endpoints (COAs) and their psychometric validation

Room for improvement:

- Majority of COAs used in CNS clinical trials are ancient
  - See Poster - Clinical Outcome Assessments in clinical trials: when is the gold standard just the old standard
- Most commonly used COAs do not have good psychometric properties
  - ADAS-Cog, MMSE, & NPI
- Novel Composite Endpoints have issues as well:
  - Derivation: Theoretically (PACC) versus statistically derived (ADCOMS) composites
  - Overweighting (e.g., PACC)
  - Psychometric limitations of component scales (e.g., ADCOMS, PACC)
- Consensus batteries use in clinical trials is limited
  - EPAD – NE
  - MATRICS
- Improved validation methods versus solely traditional psychometric validation
- Need for novel clinical endpoints that are less intrusive and more ecologically valid

High Priority	**71.20%**
Medium Priority	**22.40%**
Total	**93.60%**

Placebo Response Mitigation

Advancements:

- Companies with training to address placebo response - various
  - Placebo Response Mitigation Training
- Trainings
- Publications

Clinical Trial Acceleration | Therapeutic Excellence

WEBINAR: Placebo Response Mitigation Strategies & Tools for Optimizing Clinical Trials

www.nature.com/npp

Neuropsychopharmacology

ARTICLE OPEN

Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders

Elan A. Cohen[1], Howard H. Hassman[1], Larry Ereshefsky[1,2], David P. Walling[2], Vera M. Grindell[2], Richard S. E. Keefe[3,4], Katarzyna Wyka[5] and William P. Horan[3,6]

Placebo Response Mitigation

Room for improvement:

- Sponsor adoption of methodology to actually reduce placebo response
  - Leveraging run-in periods to extinguish placebo response
    - Upside: Increased power to determine a true drug effect
    - Downsides:
      - Costs – Additional study visits and time
      - Complexity – Need to blind the protocol, longer trials
      - Dropouts – Longer trials and those with PBO first few weeks could increase withdrawals
- Additional empirical data and evidence supporting trainings and placebo response mitigation techniques

Real-World Data

(e.g., reg ta/EHR)

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  - T IS/PMCs
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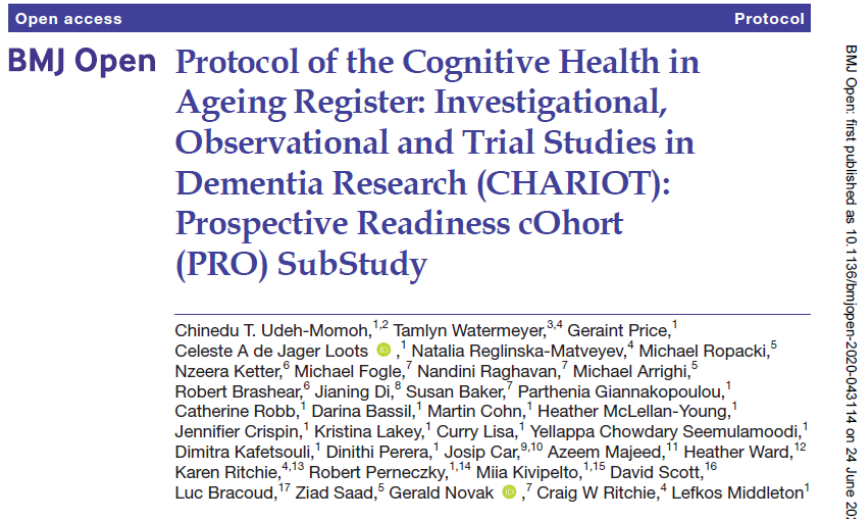
- Seve ents
- Data coming from prospective readiness cohorts



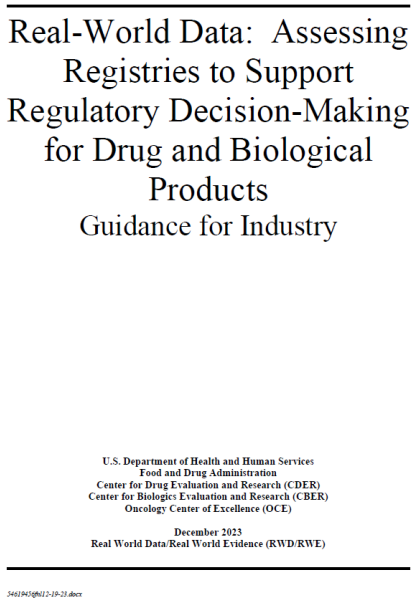
Open access Protocol

BMJ Open

Protocol of the Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy

Chinedu T. Udeh-Momoh,[1,2] Tamlyn Watermeyer,[3,4] Geraint Price,[1] Celeste A de Jager Loots ,[1] Natalia Reglinska-Matveyev,[4] Michael Ropacki,[5] Nzeera Ketter,[6] Michael Fogle,[7] Nandini Raghavan,[7] Michael Arrighi,[5] Robert Brashear,[6] Jianing Di,[8] Susan Baker,[7] Parthenia Giannakopoulou,[1] Catherine Robb,[1] Darina Bassil,[1] Martin Cohn,[1] Heather McLellan-Young,[1] Jennifer Crispin,[1] Kristina Lakey,[1] Curry Lisa,[1] Yellappa Chowdary Seemulamoodi,[1] Dimitra Kafetsouli,[1] Dinithi Perera,[1] Josip Car,[9,10] Azeem Majeed,[11] Heather Ward,[12] Karen Ritchie,[4,13] Robert Perneczky,[1,14] Miia Kivipelto,[1,15] David Scott,[16] Luc Bracoud,[17] Ziad Saad,[5] Gerald Novak ,[7] Craig W Ritchie,[4] Lefkos Middleton[1]

BMJ Open: first published as 10.1136/bmjopen-2020-043114 on 24 June 202

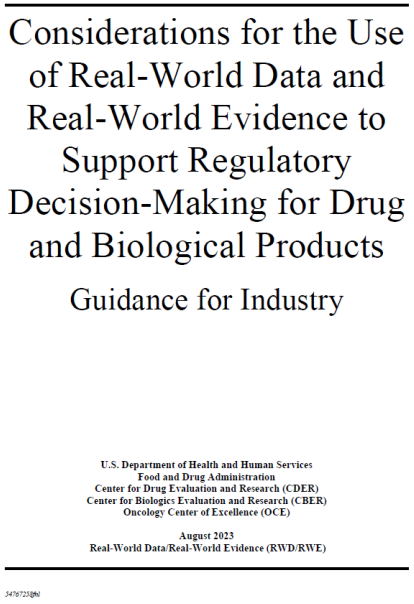


Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

December 2023
Real World Data/Real World Evidence (RWD/RWE)

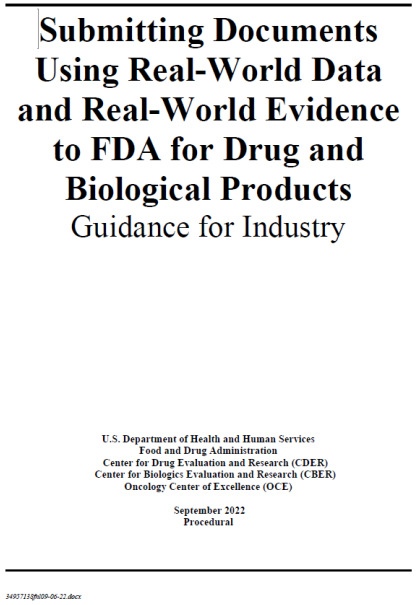


Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

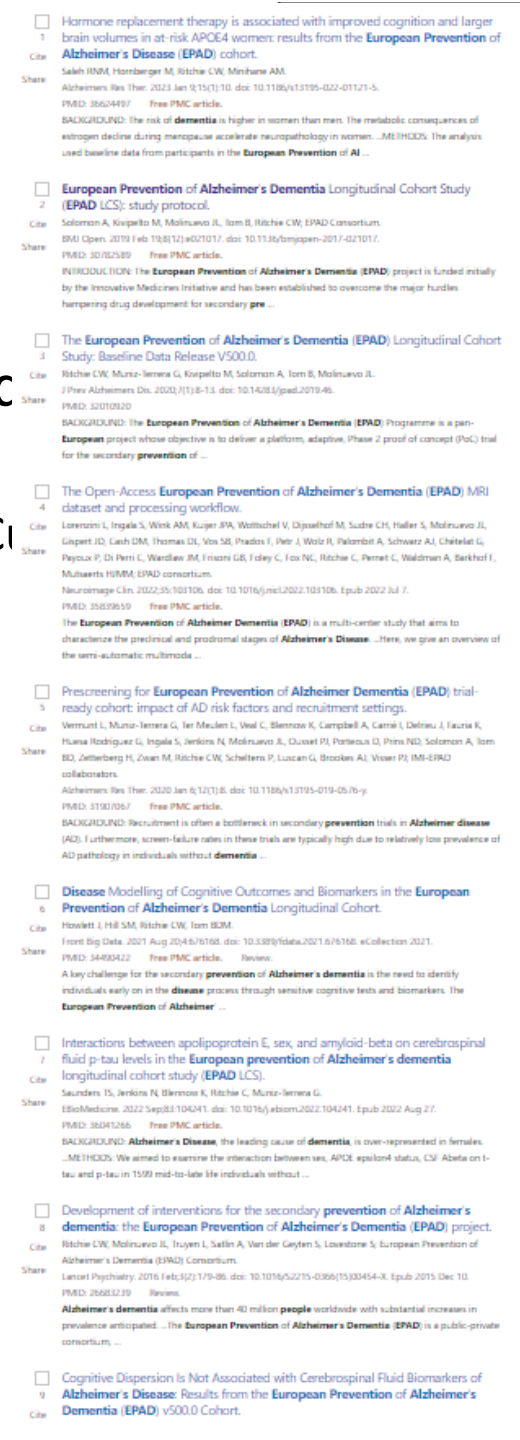


Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2022
Procedural



1 Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort.

2 European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol.

3 The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0.

4 The Open-Access European Prevention of Alzheimer's Dementia (EPAD) MRI dataset and processing workflow.

5 Prescreening for European Prevention of Alzheimer Dementia (EPAD) trial-ready cohort: impact of AD risk factors and recruitment settings.

6 Disease Modelling of Cognitive Outcomes and Biomarkers in the European Prevention of Alzheimer's Dementia Longitudinal Cohort.

7 Interactions between apolipoprotein E, sex, and amyloid-beta on cerebrospinal fluid p-tau levels in the European prevention of Alzheimer's dementia longitudinal cohort study (EPAD LCS).

8 Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project.

9 Cognitive Dispersion Is Not Associated with Cerebrospinal Fluid Biomarkers of Alzheimer's Disease: Results from the European Prevention of Alzheimer's Dementia (EPAD) v500.0 Cohort.

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ster: Investigational, earch (CHARIOT): Prospective

isk of Alzheimer's disease-related

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ng Older Adults: Associations cing Factors.

Related Factors in Elderly at Risk dinal Cohort Study.

dults: A Feasibility Study of an

althy Older Adults and

	33.60%
	48.00%
	81.60%

Real-World Data (e.g., registries, prospective readiness cohorts, claims data/EHR)

Room for improvement:

- Continued methodological and technological improvements
  - Alignment with newer Guidance to help ensure regulatory acceptance
- Additional approved drugs leveraging RWE in the approval process
  - Example: Prograf (tacrolimus) with other immunosuppressants to prevent organ rejection in pediatric and adults receiving lung transplants (16Jul2021).

Real-World Evidence and Its Role in Regulatory Decisions

As demonstrated by the Prograf approval for the indication of preventing organ rejection in adult and pediatric patients receiving lung transplants, real-world evidence (RWE) can play a significant role in regulatory decision-making when appropriate. According to FDA's definition, RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of RWD.

FDA defines RWD as data about a patient's health status and/or the delivery of health care routinely collected from a variety of sources, including health care provider records, medical and pharmacy claims, and disease registries. RWD can also be collected outside the health care setting — for instance, data from mobile technologies that gather biometric information.

REVIEW

The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A. Purpura[1], Elizabeth M. Garry[1], Nicholaas Honig[1], Abigail Case[1] and Jeremy A. Rassen[1,*]

The US Food and Drug Administration (FDA) is open to accepting real-world evidence (RWE) to support its assessment of medical products. However, RWE stakeholders lack a shared understanding of FDA's evidentiary expectations for the use of RWE in applications for new drugs and biologics. We conducted a systematic review of publicly available FDA approval documents from January 2019 to June 2021. We sought to quantify, by year, how many approvals incorporated RWE in any form, and the intended use of RWE in those applications. Among approvals with RWE intended to support safety and/or effectiveness, we classified whether and how those studies impacted FDA's benefit-risk considerations, whether those studies were incorporated into the product label, and the therapeutic area of the medical product. Finally, we qualified FDA's documented feedback where available. We found that 116 approvals incorporated RWE in any form, with the proportion of approvals incorporating RWE increasing each year. Of these approvals, 88 included an RWE study intended to provide evidence of safety or effectiveness. Among these 88 approvals, 65 of the studies influenced FDA's final decision and 38 were included in product labels. The 88 approvals spanned 18 therapeutic areas. FDA's feedback on RWE study quality included methodological issues, sample size concerns, omission of patient level data, and other limitations. Based on these findings, we would anticipate that future guidance on FDA's evidentiary expectations of RWE use will incorporate fit-for-purpose real-world data selection and careful attention to study design and analysis.

REVIEW

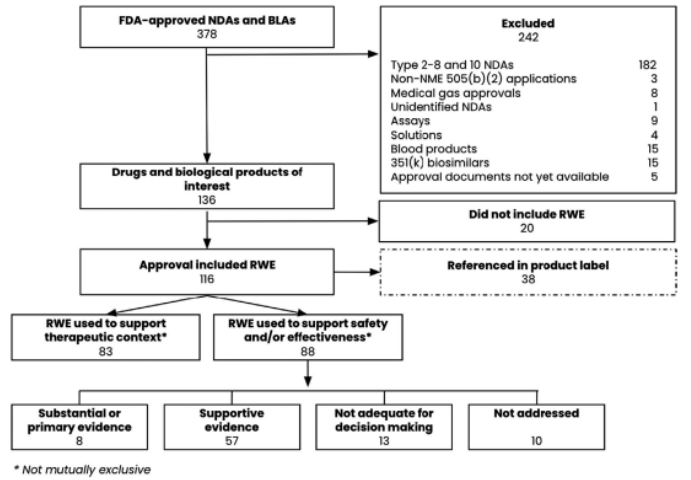


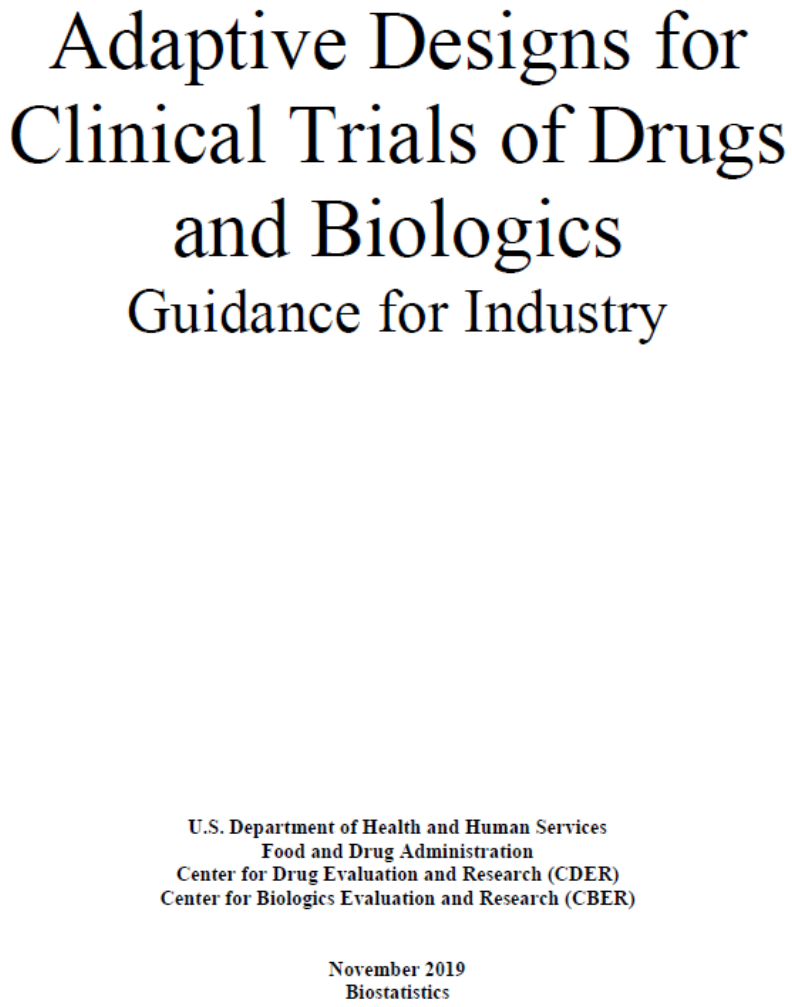
Figure 1 Inclusion of FDA-approved NDAs and BLAs between January 2019 and June 2021. BLA, biologics license application; FDA, US Food and Drug Administration; NDA, new drug application; NME, new molecular entity; RWE, real-world evidence.

High Priority	**31.20%**
Medium Priority	**54.40%**
Total	**85.60%**

Adaptive Trial Designs

Advancements:

- Adoption of adaptive trial designs is an area where there has been increased uptake and use in CNS clinical trials.
  - Unknown/high placebo rates
  - Noisy measures
  - Non-compliant populations
- Facilitating this adoption has been Guidance documents from our regulatory colleagues.



Adaptive Trial Designs

Room for improvement:

- Increased adoption by pharmaceutical companies that are ‘stuck’
- Improved knowledge and understanding of adaptive trials
  - Clinical Development & Clinical Operations
- Buy-in from in-house biostatistics colleagues
- Acceptance and approval of senior leadership
- Regulatory acceptance regarding the data analyses
  - Making Sponsors jump through hoops before getting onboard
    - Mathematical Proofs
    - Promising Zone Simulations
    - Provision of Code to Agency

Summary

- **The highest priority issues from the ISCTM survey included (total% = high + medium priority)*:**
  - Novel Clinical Endpoints – 96.00%
  - Placebo Response Mitigation – 93.60%
- **There have been many methodological advancements the last 20-years.**
- **There remains significant room for improvements.**
  - Development and validation of novel COAs, new non-DB*, and DB
    - Digital measures (i.e., not digitized paper-and-pencil measures)
    - Non-invasive and ecologically valid measures
  - Implementation of techniques in clinical trials to reduce placebo response
    - Run-in periods
  - Empirical evidence supporting trainings and placebo response mitigation techniques
  - Increased knowledge and understanding of adaptive designs
  - Improved adoption of adaptive trials by pharmaceutical companies that are ‘stuck’

*Digital Biomarkers