



Basic Experimental Studies Involving Humans (BESH) Overview

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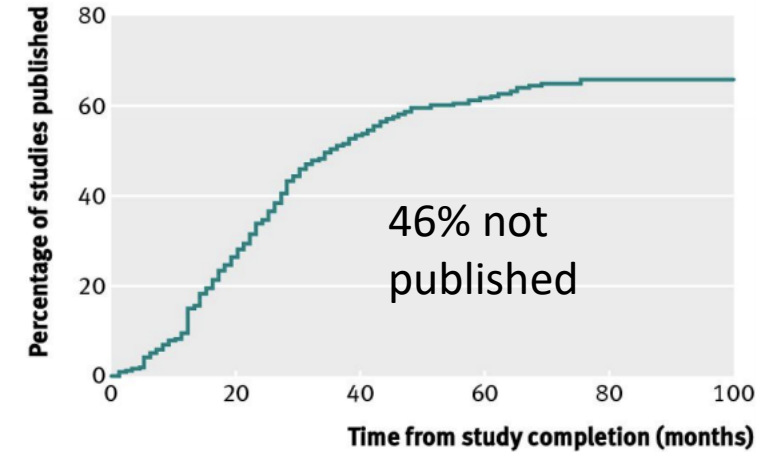
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Rationale for Clinical Trials Policies

- Common goal of enhancing research transparency
 - Reduce publication bias
 - Increase reporting of findings in a timely manner
- Commitment to research participants and taxpayers
 - GAO: NIH needs to be a better steward
<https://www.gao.gov/products/GAO-16-304>



No at risk

635	635	635	635	493	330	220	153	95	54	44
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Ross et al., BMJ, 2012

Problem extends beyond traditional clinical trials

- 39% observational studies not published (Baudart et al., 2016)
- 2.4% of all R01s/U01s have zero publications associated with the grant after 60 months (Riley, et al, submitted for publication)

Scientific Value of Centralized and Structured Registration and Reporting

- Minimize publication bias and encourage results reporting regardless of outcome
- Improve ability to synthesize studies (meta-analyses)
- Limit p-hacking and HARKing (hypotheses after results known)
- Identify research gaps and reduce duplication
- Facilitate study replication
- Aid study recruitment
- Encourage collaboration

Basic Experimental Studies with Humans (BESH)

- Basic experimental studies involving humans are subject to NIH clinical trials policies
- Differences in basic vs. applied research necessitated additional considerations for basic research under these policies
- BESH Parent Grant Applications
 - Meets NIH definition of a clinical trial AND
 - Meets the definition of basic research

Research Project Grant (Parent R01 Basic Experimental Studies with Humans Required)

R01 Research Project Grant

Reissue of PA-19-091

This Parent Funding Opportunity Announcement is for basic science experimental studies involving humans. These studies fall within the NIH definition of a clinical trial and also meet the definition of basic research. Types of studies that should submit under this FOA include studies that prospectively assign human participants to conditions (i.e., experimentally manipulate independent variables) and that assess biomedical or behavioral outcomes in humans for the purpose of understanding the fundamental aspects of phenomena without specific application towards processes or products in mind. Studies conducted with specific applications toward processes or products in mind should submit under the appropriate 'Clinical Trials Required' or 'Clinical Trial Optional' FOA.

Registration and Results Reporting Flexibility for BESH

- Delayed Enforcement and Short-Term Flexibilities for Some Requirements Affecting Prospective Basic Science Studies Involving Human Participants (NOT-OD-18-212)
 - Per 2018 Consolidated Appropriations Act, NIH delayed enforcement through 9/24/2019 (NOT-OD-16-149) to provide additional time to consult with the basic science community about the best reporting standards for fundamental research.
 - Registration and reporting for basic science studies involving human still required, but with additional flexibility to allow reporting on existing basic science portals.
- RFI on Reporting Standards for Prospective Basic Science Studies Involving Human Participants (NOT-OD-18-217) identified specific challenges of some BESH projects
- Extension of Certain Flexibilities for Prospective Basic Experimental Studies With Human Participants (NOT-OD-19-126) – through September 24, 2021
 - Allows NIH to engage further with the BESH community to gain a deeper understanding of the scientific and technical needs to best facilitate (in a least burdensome way) registration and reporting of BESH studies while ensuring this information is scientifically useful.



Connect with OBSSR

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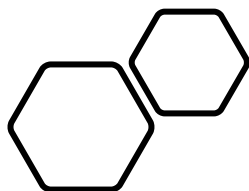
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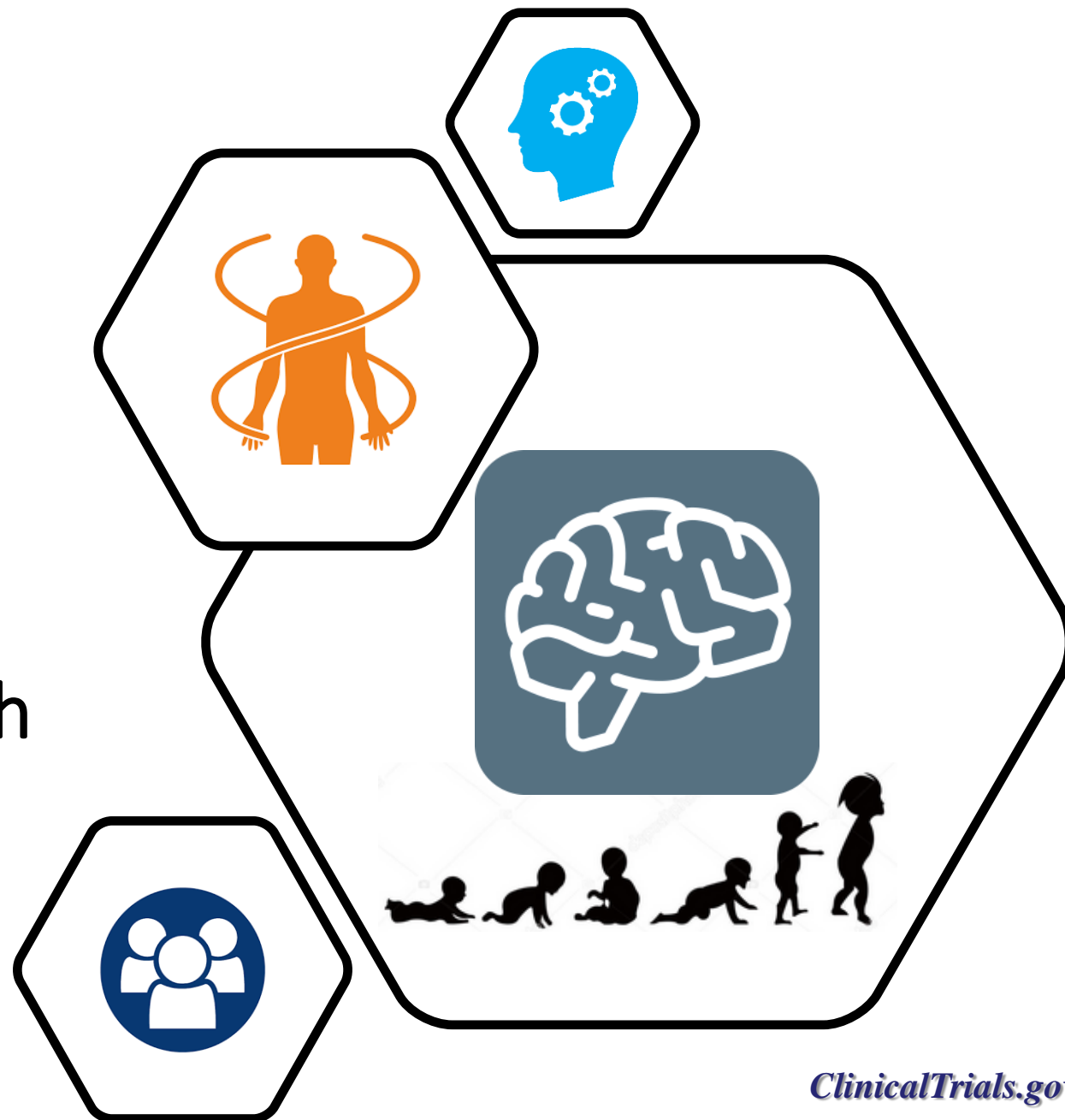
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NLM Findings from
Analysis of NIH Intramural and
Extramural Research Program Studies

August 26, 2020

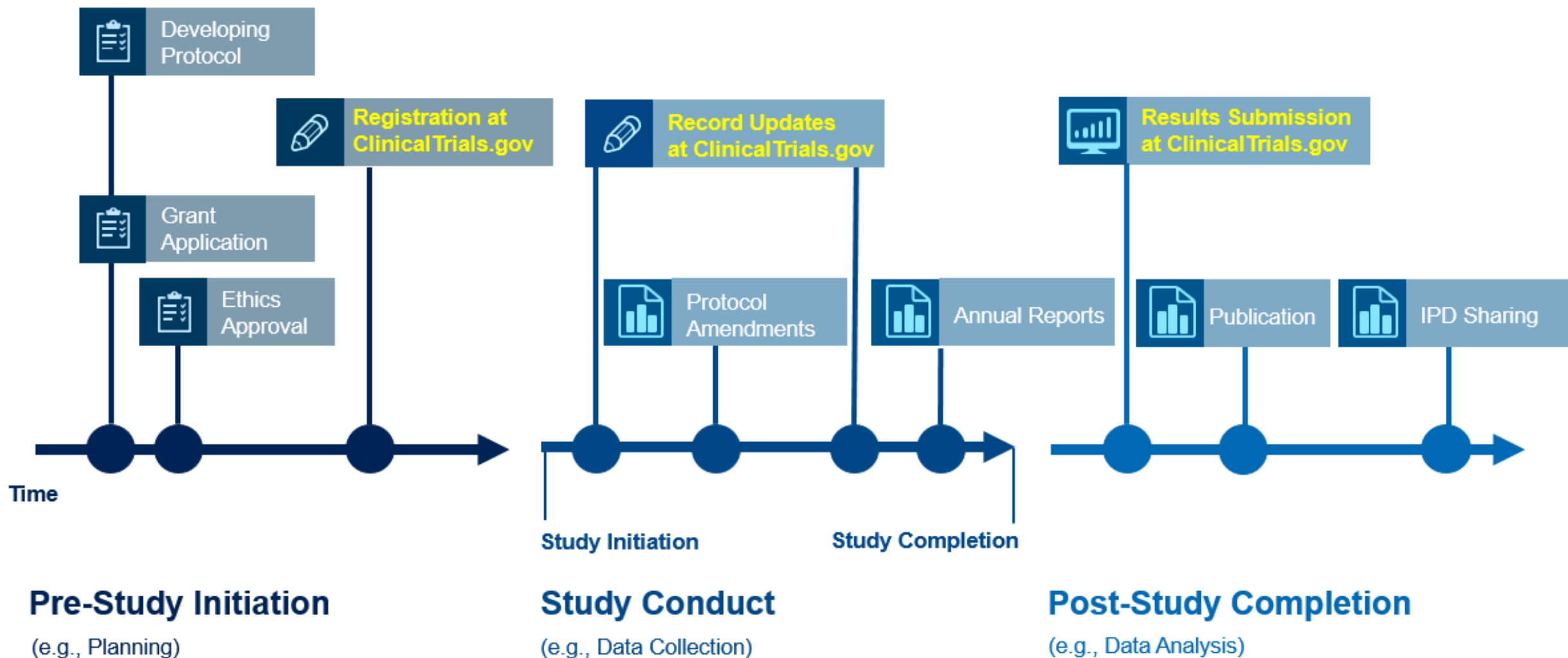
NIH-Funded Basic Experimental Studies with Humans (BESH): Registration and Results Reporting



ClinicalTrials.gov Model and NLM Analysis Project

Rebecca Williams, PharmD, MPH

NIH Policy Leverages Existing ClinicalTrials.gov Model



ClinicalTrials.gov Key Assumptions

General

- One protocol = one clinical trial = one study record
- Protocol = research plan with pre-specified approach to trial conduct
- Registration and results reporting timing based on protocol milestones (initiation and completion)

Registration (before study initiation)

- Description of study conduct based on pre-specified approach in protocol
 - Study design (including arms and interventions), eligibility criteria, etc.
 - Primary and secondary outcome measures

Results (after study completion)

- Aggregated, summary, tabular results information
 - No individual participant data
 - No figures, images, conclusions, or narrative text

Results: Outcome Measures

Publication

“At week 52, no difference was noted in major clinical responses or partial clinical responses between the placebo group (15.9% had a major clinical response ...) and the rituximab group (12.4% had a major clinical response ...)”

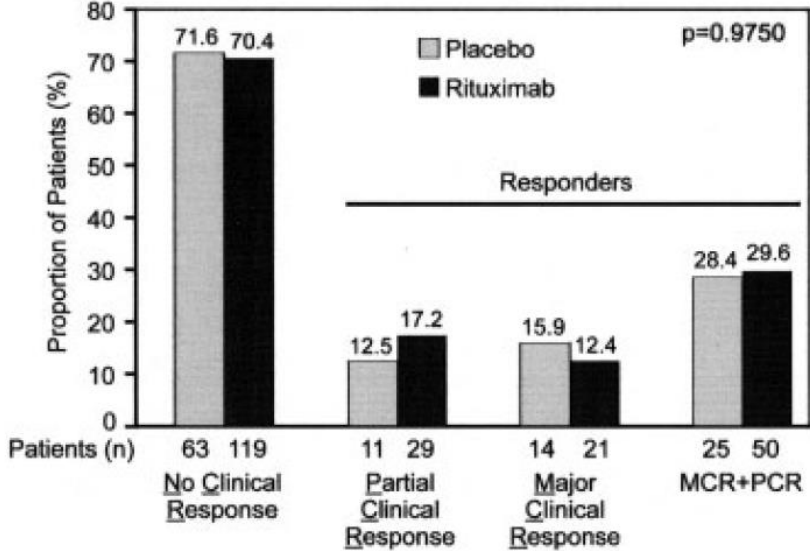


Figure 2A. Proportion of patients experiencing a major clinical response (MCR) ... at 52 weeks

ClinicalTrials.gov

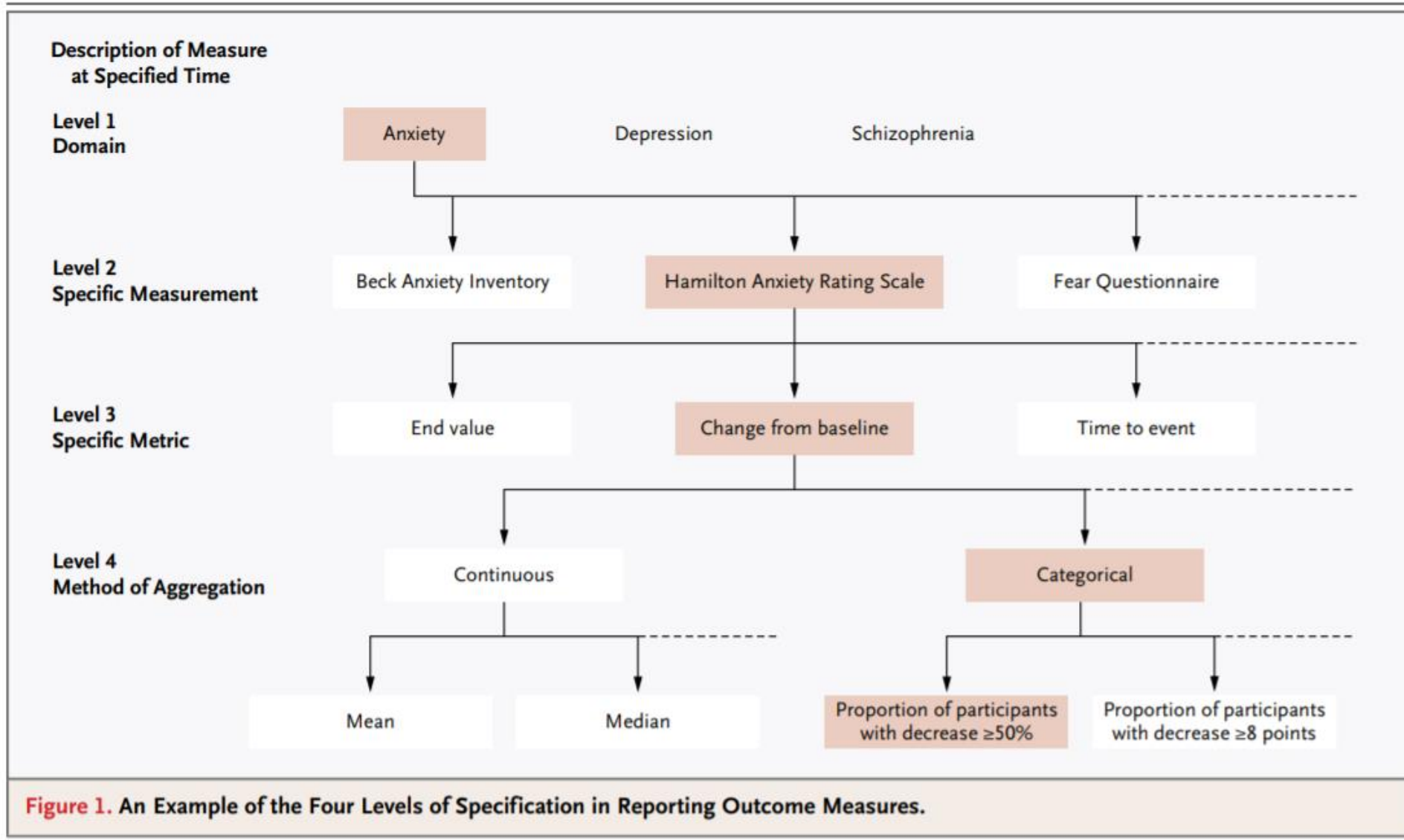
Primary Outcome

Measure Title	Participants Achieving Either a Major Clinical Response (MCR) or Partial Clinical Response (PCR) Defined by British Isles Lupus Assessment Group (BILAG) Scores Over the 52-week Treatment Period
Measure Description	The BILAG Index is used for measuring clinical disease activity in Systemic Lupus ...
Time Frame	Baseline to 52 weeks

Measured Values

	Placebo + Prednisone	Rituximab + Prednisone
Number of Participants Analyzed	88	169
[units: participants]		
MCR (excluding PCR)	14	21
PCR	11	29
Nonclinical Response	63	119

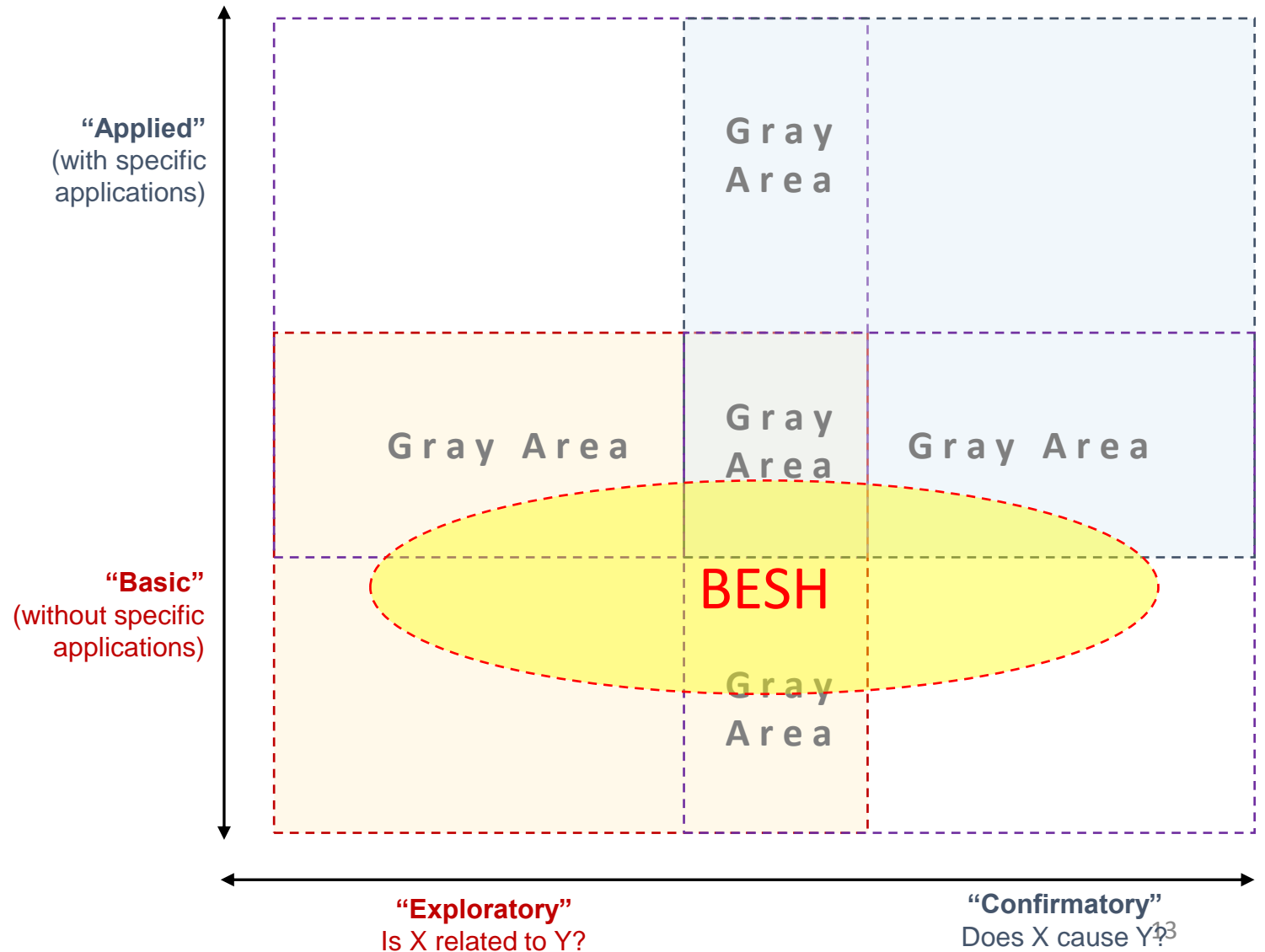
Outcomes Conceptual Framework



Range of Interventional Studies with Humans

Three Useful Definitional Categories to Consider

1. Interventional and observational
2. Basic and applied
3. Exploratory and confirmatory



Key Information Sources to Date

- Request for Information (RFI) – August 2018
 - Agreement on importance of registration and results reporting for transparency; ensuring research participant contributions advance science and health
 - Identified study types and aspects of ClinicalTrials.gov most challenging
 - Research domain: cognitive science, brain function, neurology
 - Study design: iterative, evolving, trial & error design; multiple related studies
 - Data elements: outcome measures, arms & interventions, disease or condition
- NLM Preliminary Analysis – January to April 2019
 - Evaluated issues raised by RFI commenters in registration and results reporting of BESH
 - Limitation: primarily relied on studies in the published literature
 - Summarized in Open Mike Blog in July 2019 (Wolinetz, Lauer, & Riley)
- NLM Extended Analysis – October 2019 to April 2020
 - Included evaluation of protocol documents and validation with researchers

Methods: NLM Extended Analysis

- 12 BESH Case Studies
 - 9 intramural principal investigators (PIs) recruited from 8 NIH ICs
 - NINDS [2], NICHD, NIMH, NCCIH, NIAID, NIDCD, NIAAA
 - 3 extramural PIs; recruiting support from Federation of Associations in Behavioral & Brain Sciences
 - With funding from NEI, NIDA, NICHD
- PIs completed a questionnaire re: experience with different platforms
- Materials
 - Intramural PIs provided protocols, resulting publications, and other documents
 - Extramural PIs did provide publications and other documents, but not protocols
- NLM staff reviewed documents to assess whether the ClinicalTrials.gov interventional study model could accommodate BESH
- Discussions with PIs about findings and issues in reporting BESH information

Researchers: NLM Extended Analysis

Intramural PIs (N = 9)

- **No** direct experience with PRS (NIH CC registers IRP studies)
- No results submission via PRS
- Few use ClinicalTrials.gov
- **Few** use other platforms
- Confusion about BESH dissemination and data sharing policies

Extramural PIs (N = 3)

- **2** had registered information via PRS
- No results submission via PRS
- Few use ClinicalTrials.gov
- **All** use other platforms (OSF)
- Confusion about BESH dissemination and data sharing policies

Summary of 12 Case Studies

1. Ancillary study exploring neural activity associated with **memory retrieval** as the research component of a treatment protocol
2. Research program exploring novel mutated genes associated with **hereditary hearing impairment** (*may be observational*)
3. Research program exploring neural correlates and processes underlying 7 aspects of **human cognition**
4. Research program exploring how the brain controls **motor function**
5. Two studies in a protocol studying complementary hypotheses involving neural correlates of **affective and discriminative aspects of touch**

Summary of 12 Case Studies (continued)

6. Research program exploring the genetic, cellular, biochemical, and other factors that contribute to **food allergy**
7. Research program exploring differences between **alcoholics** and non-alcoholic participants in terms of behavioral, structural imaging, and functional imaging data
8. Natural history study of **Juvenile Neuronal Ceroid Lipofuscinosis (Batten Disease, CLN3)** to obtain baseline and rate of progression data on clinical and biochemical markers and to establish a biorepository of samples (*may be observational*)
9. Hypothesis-driven study to explore the degree of mental simulation/behavior as a function of **drug-use history**

Summary of 12 Studies

10. Research program exploring the effects of prevalence in **visual search** to inform theoretical modeling and offer ways to resolve prevalence effects in real-world situations
11. Research program conducting longitudinal anatomical and functional **neuroimaging of children** from birth through age five
12. Research training program exploring the mechanisms underlying **inhibition induced devaluation** using behavioral and neuroimaging techniques

Overall Findings

- Validated preliminary analysis findings
- Provided deeper insights into the reasons for the challenges
- Emerging points to consider for registering and reporting results of exploratory BESH

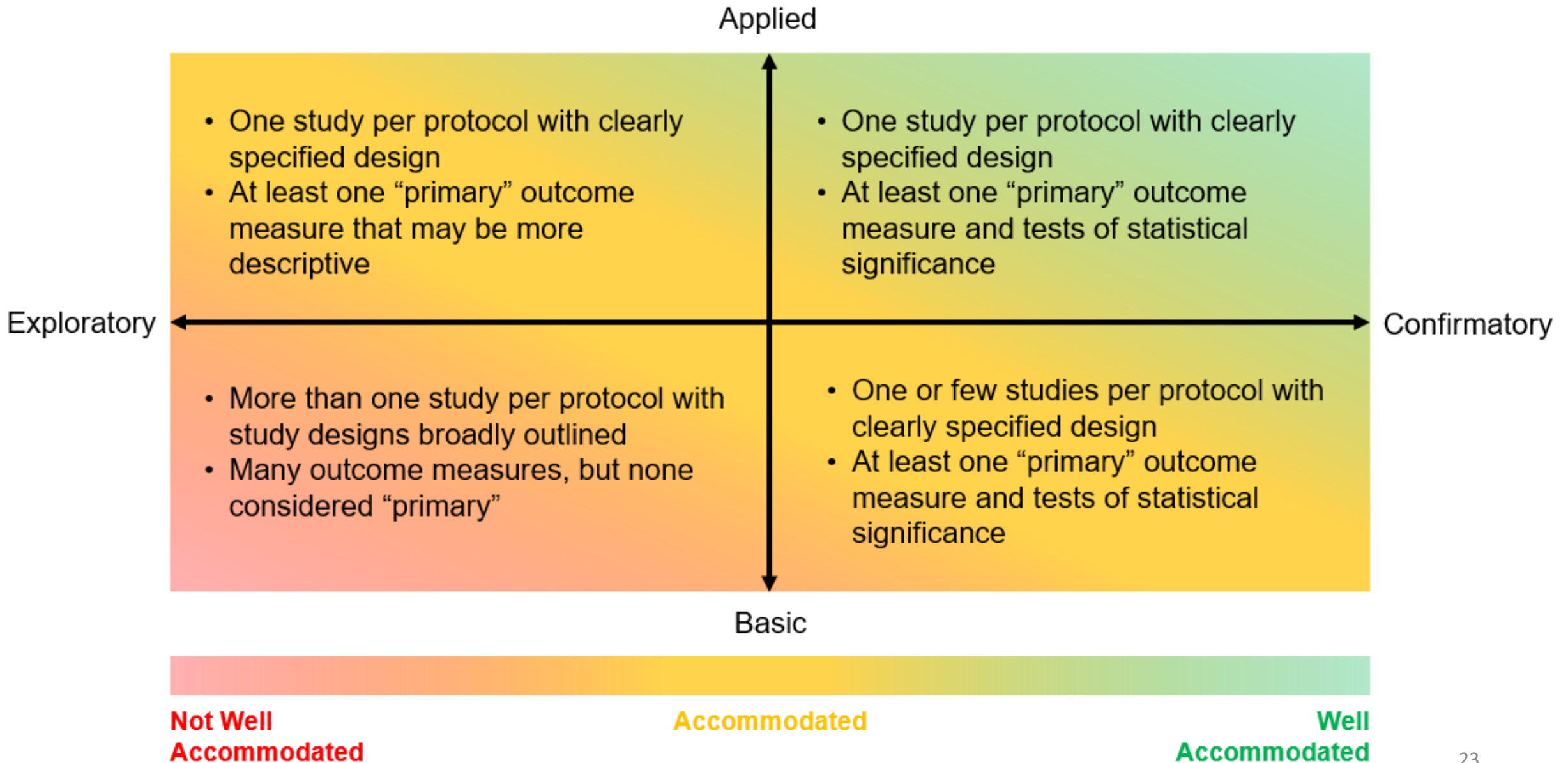
Overall Findings: Validated Challenges

- Multiple, inter-related experiments
 - BESH may involve or consist of many experiments that build on each other and are less scientifically meaningful and useful outside the context of other experiments
- Absence of detailed pre-specified primary outcome measures in protocol
 - BESH may explore many measures for purpose of formulating a model
 - Protocol documents described exploratory programs of research for IRB review
 - provided information on high-level research aims and
 - described the instruments and methods used for collecting measures and the interventions or manipulations assigned to participants
 - but did not specify experimental details
- Individual participant data (versus aggregate results)
 - Results for BESH may include individual-level participant data

Overall Findings: Validated Challenges (continued)

- Iterative exploratory studies
 - BESH may involve developing new methods of assessment or studies that develop or optimize procedures for use in same or future study
- Non-tabular formats
 - Analysis of collected data from BESH may involve graphical data, images (e.g., of brain), qualitative information, and statistical analyses without scientifically meaningful or useful summary-level data

Range of Interventional Studies with Humans



Findings: Challenges Using Examples from Case Studies

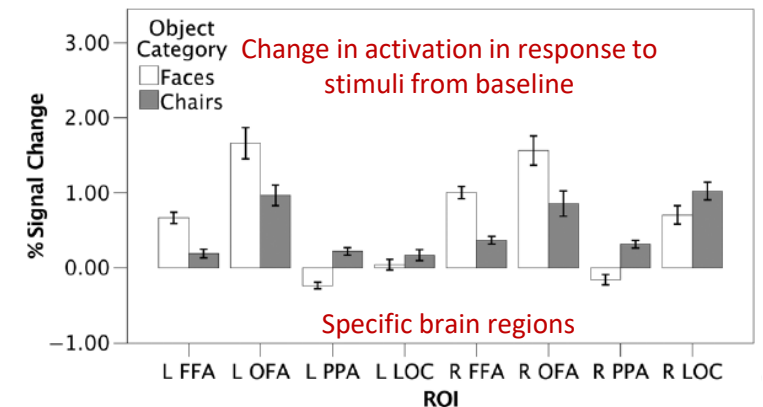
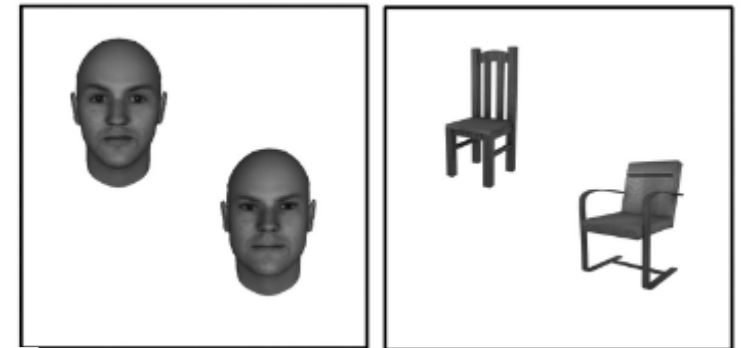
Elisa Golfinopoulos, PhD, NLM

Challenge: Multiple, Interrelated Small Experiments per Protocol (Case Study-3)

- Research Goals from Protocol
 - To study the functional organization of the brain and neural mechanisms underlying cognitive processes
 - To develop multivariate analysis approaches, labeling techniques, systematic calibration of fMRI signals, etc.
- Approach from Protocol
 - Cognitive tasks across 7 “themes” (e.g., attention and emotion processing)
 - Neuroimaging (e.g., fMRI, EEG, MEG)
 - 1 study protocol, 1 Principal Investigator, 69 Associate Investigators, high-level descriptions/overviews of many experiments across the 7 themes

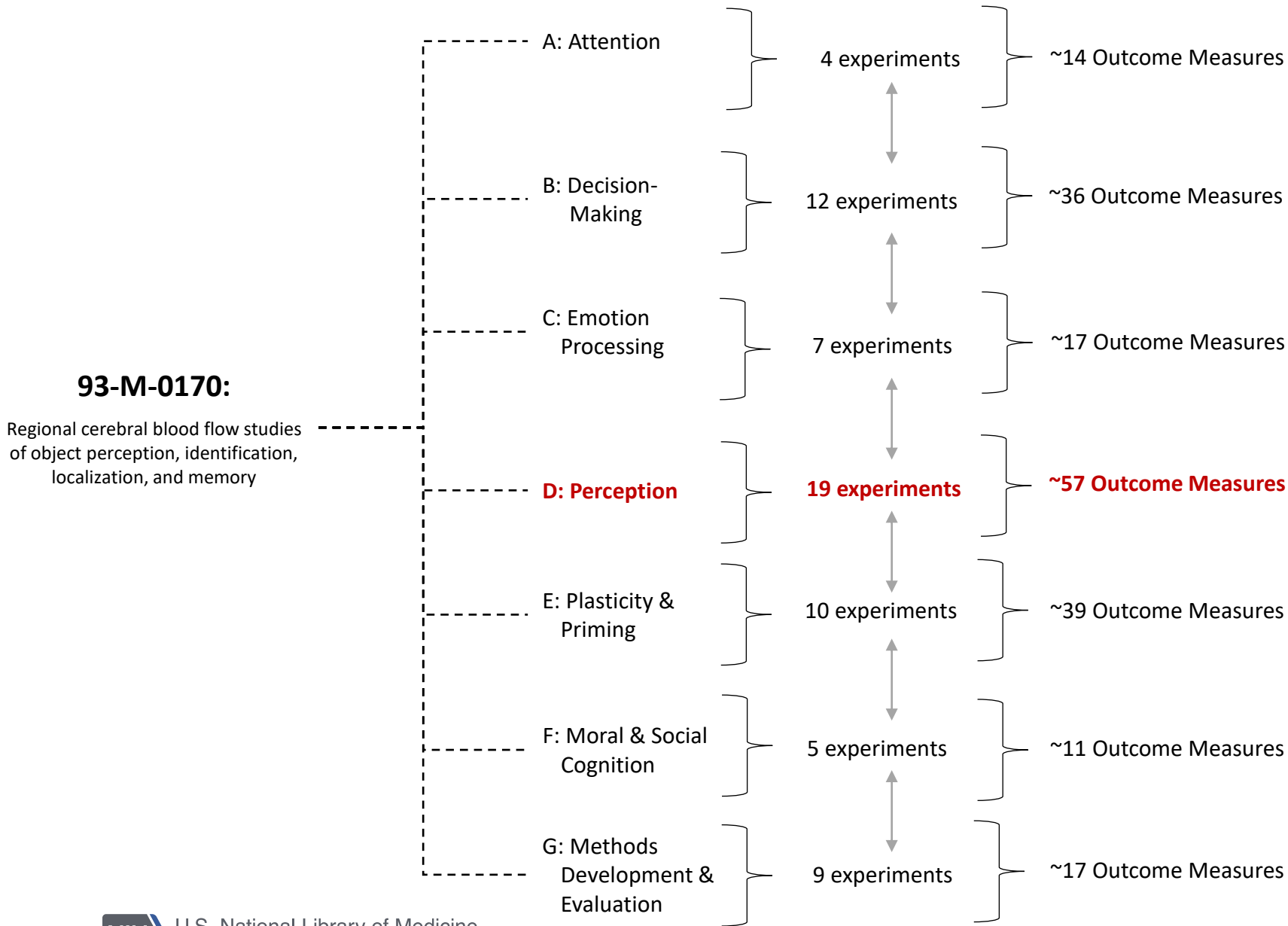
Experimental Details from CS-3 Publication

- Neural mechanisms of face versus object perception
 - Controlled reevaluation of the domain-general and domain-specific hypotheses of face perception
 - Can specific face perception neural mechanisms be generalized to perceive other non-face objects?
- Healthy participants in fMRI scanner
 - 3 Stimuli: faces, houses, chairs
 - 3 Tasks: localizer, same-different object, border detection
 - e.g., participants presented with 2 images and asked to press button when images are different (face vs. nonface)
- Measures
 - Change in neural activity in response to stimuli based on blood-oxygen-level dependent (BOLD) contrast



Source: Zachariou et al., 2018. *J Cogn Neurosci*, 30(10), 1499 – 1516.

1 Protocol → 7 Research Themes → 66 Experiments → ~ 190 OMs



Case Study 3 Overview

-  1 Principal Investigator & 69 Associate Investigators
-  4,100 Participants (anticipated)*
-  66 Listed Experiments (thus far)
-  ~ 190 Outcome Measures
-  26+ Years Duration
-  25+ Publications (linked to NCT00001360)

* Participants can participate in multiple experiments

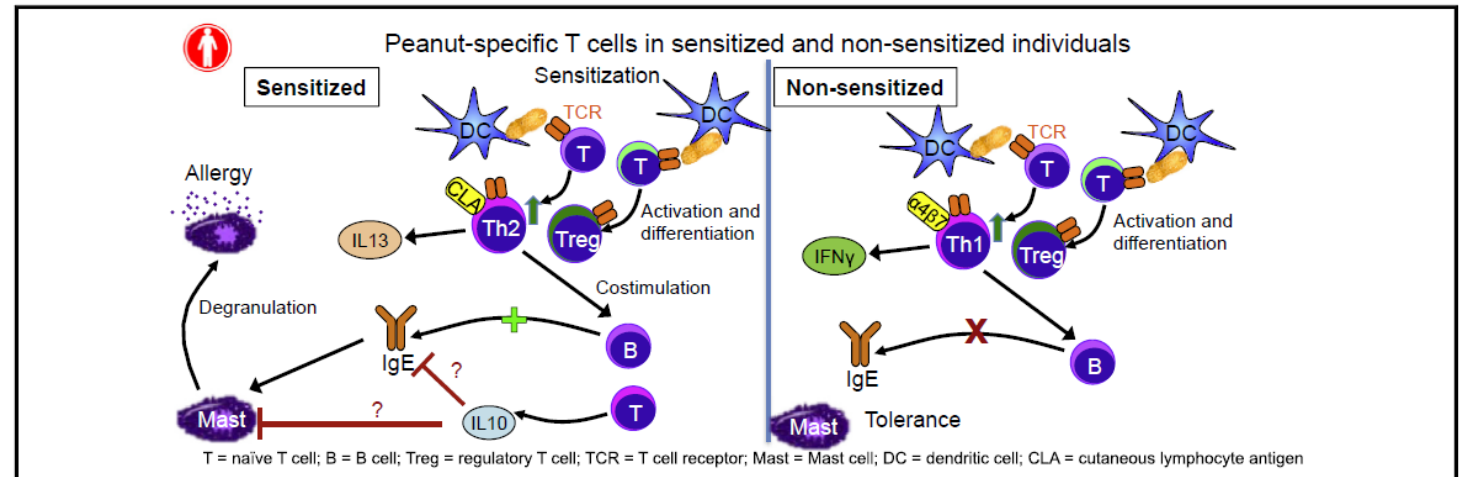
Challenge: Protocol Lists High-level Primary Objectives (Case Study-6)

- Research Goals from Protocol
 - “Objectives of this exploratory study are to:
 - (1) investigate the key genetic, cellular, immunologic, microbial, and biochemical pathways that lead to the development of food allergy, and
 - (2) identify biomarkers that predict the clinical course and natural history of patients with food allergy.”
- Research Approach from Protocol
 - Study Participants
 - Individuals with food allergy, food sensitization and/or a known or suspected genetic disorder
 - Unaffected relatives and unrelated healthy volunteers as controls
 - Data collected from blood, skin, saliva, stool, GI biopsy and other specimens to explore the immunologic, biochemical, microbial, and genetic basis of food allergy
 - Several measures: e.g.,
 - DEXA scans to assess bone mineral density (BMD) risk
 - Vaginal swabs to assess relationship of inflammation and abnormal bleeding
 - Serum for in vitro studies

Experimental Details from CS-6 Publication

- Characterize roles of immune cells involved in peanut allergy and tolerance
- Participants: Children with (1) peanut allergy, (2) sensitivity, (3) neither
- Methods
 - Oral food challenge stimulus with peanut extract
 - Peripheral blood draw
- Measures
 - Counts and phenotypes of T cells
 - Expression of other immune system components (e.g., cytokines)
 - Methylation of FOXP3 – a marker of T cell stability

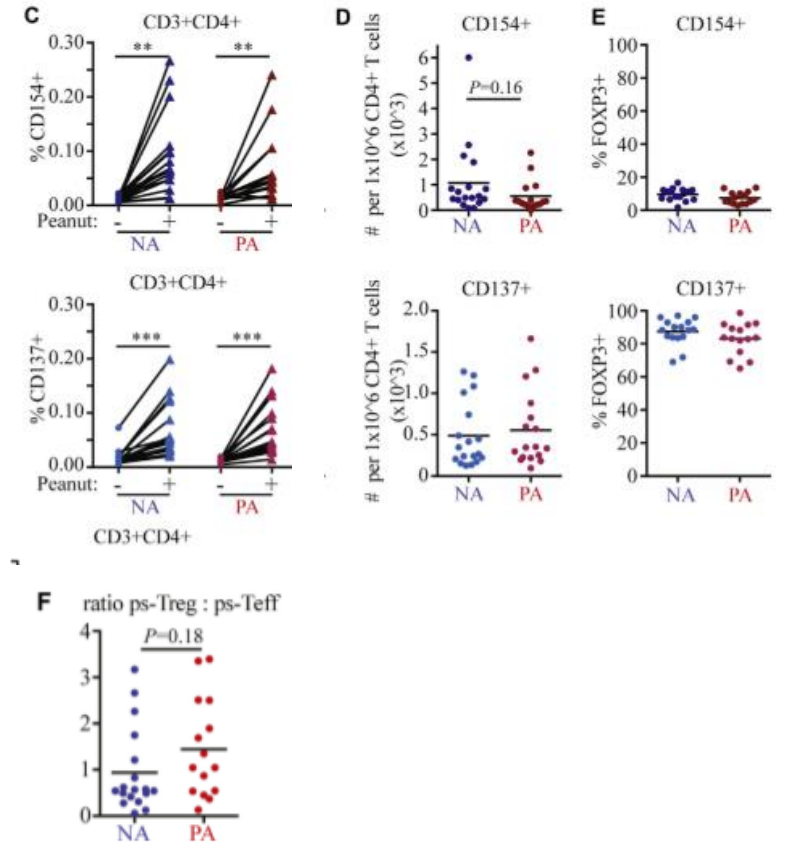
GRAPHICAL ABSTRACT



Selected Outcome Measures in CS-6 Publication

Detailed outcome measures specified during design of experiments and reported in publication

- Percentage of CD154+ ps-Teff and CD137+ ps-Treg cells expressing FOXP3 after stimulation with crude peanut extract (CPE) as a marker of cell stability in peanut allergic (PA) and nonallergic (NA) children
- Expression of IL-13, IL-10, IL-17, and IFN- γ in ps-Teff and ps-Treg cells after stimulation with CPE in PA and NA children
- Percent methylation of FOXP3 in CD137+ and CD154+ in PA and NA children

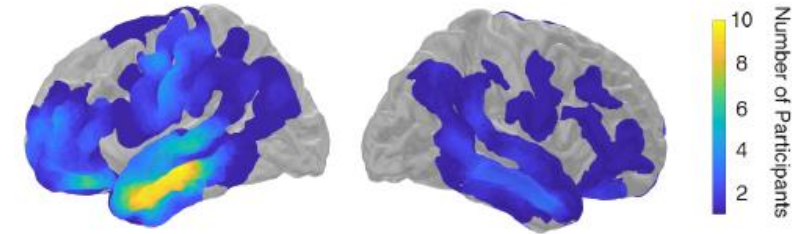


Challenge: Images for Reporting Results (Case Study-1)

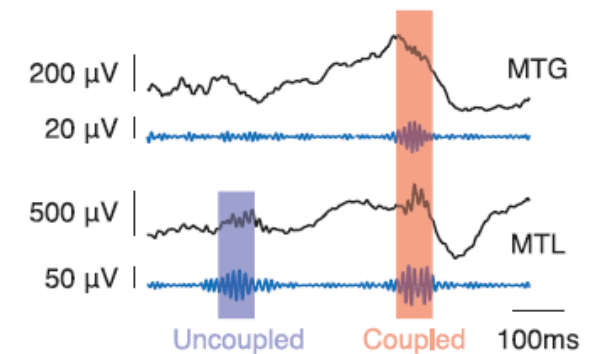
- Research Goals from Protocol
 - To provide standard care therapy for patients with drug-resistant epilepsy and collect prospective data on seizure outcomes following surgery
 - To investigate neurophysiological correlates of human cognitive function
- Research Approach from Protocol
 - Study Participants: Patients already undergoing diagnostic invasive monitoring with intracranial electrodes for seizure localization
 - Procedure: Continuous neurophysiological recordings from intracranial electrodes while performing cognitive tasks
 - Manipulation of visual displays on a computer (e.g., detection, recognition, and recall of visual stimuli)
 - Creation of cognitive models to account for behavior and relate model parameters to neural activity
 - 1 research protocol document, 300 participants anticipated, several small studies proposed
 - December 2010 and ongoing (9+ years)

Experimental Details from CS-1 Publication

- Role of fast oscillations in learning and memory retrieval
 - Hypothesis: Coupled ripples associated with correct retrieval
- Participants: 14 patients with drug-resistant epilepsy
- Methods: Intracranial electroencephalography while participants perform a verbal episodic memory task
- Measures
 - Mean oscillations (80- to 120-Hz) within medial temporal lobe (MTL) and other cortical areas at baseline & encoding/retrieval
 - Corrected number of coupled oscillations between MTL and other areas by number expected by chance during correct and incorrect memory retrieval
 - Cross-correlation of oscillations between MTL and other areas
 - Ratio of cross-correlation area to chance area during correct and incorrect memory retrieval as a measure of synchrony between MTL and neocortex during different trial types



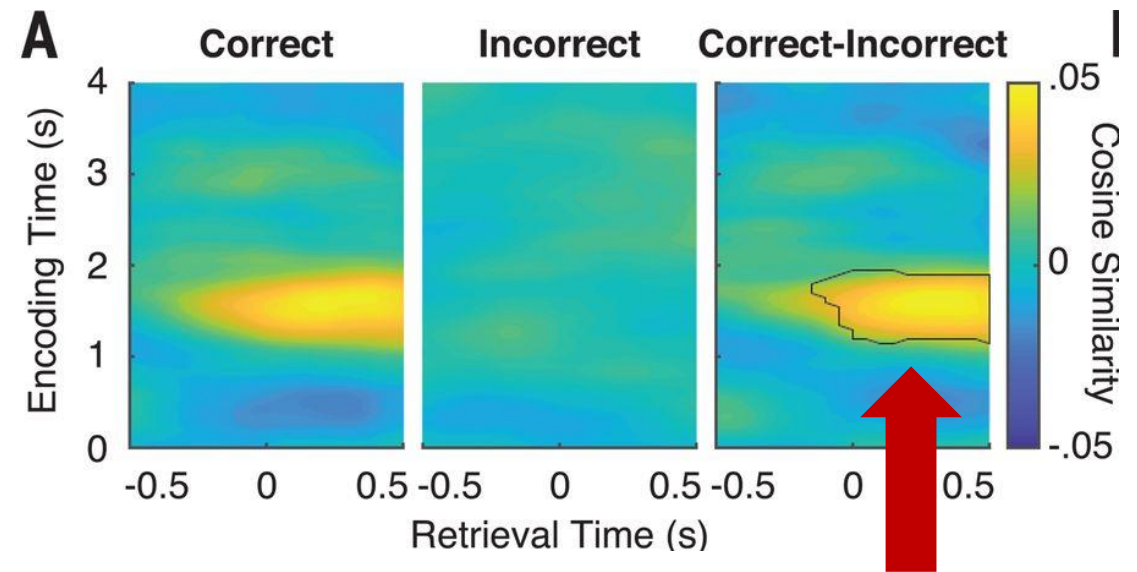
Distribution of electrodes across participants



Dynamic coupling of MTL and neocortex

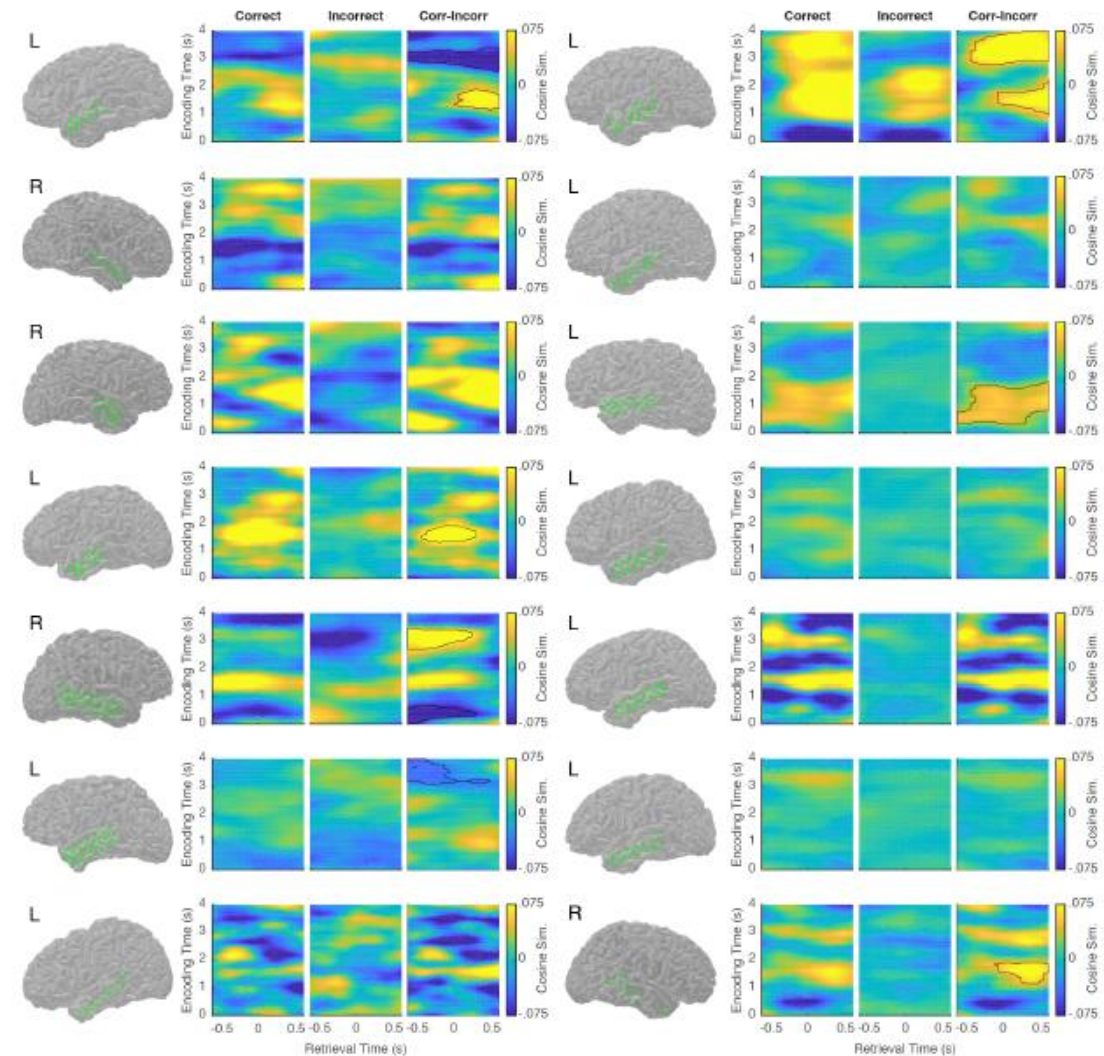
Use of Images from CS-1 Publication

- Encoding: Remembering novel associations between word pairs presented sequentially
- Retrieval: Saying the word paired with a presented word cue
- Hypothesis: Coupled ripples may reinstate neural representations of memory from encoding period
- Plot of reinstatement averaged across all participants triggered to occurrence of coupled ripple oscillations ($t = 0$) for
 - Correct retrieval trials
 - Incorrect retrieval trials
 - Difference in average reinstatement between correct and incorrect trials
- Temporal region of interest (black outline) constitutes all epochs that exhibited differences between correct and incorrect trials



Challenge: Individual Participant-level Data from CS-1 Publication

- Electrode locations and corresponding reinstatement plots for all 14 participants
 - The participant specific temporal region of interest constitutes all epochs that exhibited significant differences between correct and incorrect trials accounting for electrode placement and laterality



Challenge: Iterative Studies to Develop or Optimize Procedures (Case Study-4)

- Research Goals from Protocol
 - To explore the effects of brain stimulation on motor cortical function, oscillatory brain dynamics, eye movements, and fMRI activation
 - To optimize experimental protocols in healthy volunteers to inform patient-oriented hypothesis-driven protocols
- Approach
 - Use of TMS, tDCS, tACS, and C/PNS, alone or in combination, to stimulate volunteers during ≤ 20 sessions of ≤ 8 hours over a 20-year period
 - Stimulation applied before, after, or during physiological, neuroimaging, or behavioral measures
 - Test effects of stimulation on motor cortical excitability, cognitive and motor behavioral tasks, and brain state measures assessed with MRI, fMRI, MEG, EEG

Experimental Information from CS-4 Continuing Review Document

- Goal: To examine brain areas involved in modification of existing human motor memories through reconsolidation
- Participants: 26 healthy volunteers including 6 elderly
- Methods:
 - Behavioral stimulation
 - fMRI sessions
- Findings: Identification of brain regions ... that strengthen their functional connectivity with M1 following reconsolidation
 - Provided basic human pilot data to design a hypothesis-based experiment relevant to motor learning and rehabilitation in stroke patients

Issues to Consider for BESH Registration and Results Reporting

Rebecca Williams, PharmD, MPH

Overall Findings: Investigator Views

Benefits and Suggestions

Potential Benefits of Registering and Reporting Results for BESH

- Serves as an index/finding tool for BESH-related information
- Promotes research collaboration
- Mitigates duplication of effort
- Provides framework for tracking/monitoring program of research
- Facilitates management of portfolio of multiple inter-related experiments
- Promotes scientific rigor and transparency

Suggestions for Implementation

- Leverage existing documents (e.g., publications, annual reports (NIDB), RePORTER, IRB-approved consent forms)
- Narrative summaries with figures and images may be necessary to provide sufficient context to understand BESH
- Flexibility in reporting approach as research adapts to new findings
- Use of different or more inclusive platform than ClinicalTrials.gov (e.g., hypothetically HumanResearch.gov)

Overall Findings: Investigator Views Registration and Results Reporting Challenges

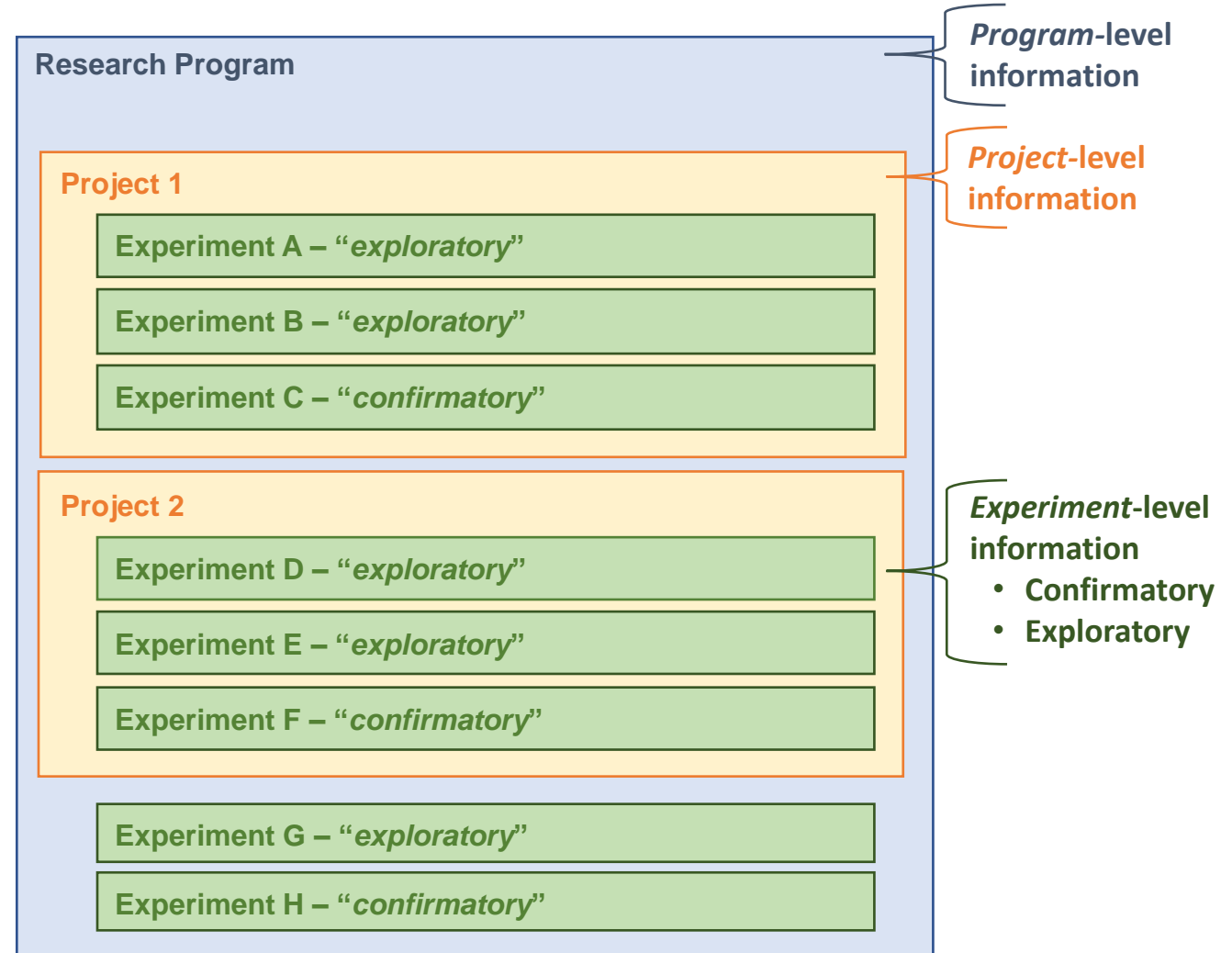
- Support transparency, but have overall concerns about policy implementation
- Challenges in dissemination of “exploratory” BESH using an “applied” trial model
 - Reporting exploratory studies based on applied trial model (e.g., “square pegs into round holes”)
 - Tabular results without context may be “non-meaningful”
 - Unvalidated exploratory findings may be misleading to public
 - Optimizing parameters specific to experimental context (“1-offs”) may not be generalizable/useful
- Current ClinicalTrials.gov model seems burdensome for limited utility: e.g., large numbers of experiments, large amounts of data, multiple assessments over long periods
 - Adds to existing reporting requirements (e.g., Annual Reports) – decreases limited resources
 - Reporting BESH results could be problematic (e.g., lack of standards for aggregating imaging data)
- Exploratory BESH distinct from applied clinical trials
 - “Intervention” as clinical application vs. stimulus, probe, or mechanistic interrogation in BESH
 - Hypothesis-driven requires more prespecification than exploratory BESH
 - Concern that reported BESH held to applied trial standards (e.g., changes perceived as “protocol violations”)

Key Factors to Consider for Implementing BESH Registration and Results Reporting

- “Unit” of Reporting
 - Timing/Due Dates for Registration and Results Reporting
 - Minimum Required Content
 - Content Format
 - Quality Control Review Process
- Definitions

Unit of Reporting

- Research Program
 - Largest unit described in protocol
 - May not list experiments
- Project – cluster of experiments
 - May be described in protocol
 - May not list experiments
 - Commonly reported in articles
- Experiment
 - Smallest unit
 - Reported in articles, but often clustered in projects
 - May be many small experiments



NLM BESH Analysis Team

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Stacey Arnold, PhD (results)

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Kafilat Osoba, MS (registration)

Heather Dobbins, PhD (results)

Tony Tse, PhD

Elisa Golfinopoulos, PhD (results)

Rebecca Williams, PharmD, MPH

Joslyn Johnson (registration)

Thank you

ClinicalTrials.gov Resources

- PRS Guided Tutorials – step-by-step instructions for submission
 - Informational page: <https://clinicaltrials.gov/ct2/manage-recs/resources#GuidedTuts>
 - Direct link: <https://prsinfo.clinicaltrials.gov/tutorial/content4/index.html#/>
- Questions? Contact us at: register@clinicaltrials.gov
 - 1-on-1 assistance is available to support you with submission
- Stay informed with email updates from *Hot off the PRS!*
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