TO: NIH Intramural Research Program (IRP) Clinical Directors (CDs) & Scientific Directors (SDs)

FROM: Leighton Chan, MD, MPH, Chief Scientific Officer for the NIH Clinical Center
Office of the Chief Scientific Officer (OCSO), NIH

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SUBJECT: Guidance on Basic Experimental Studies Involving Humans (**BESH**) Protocols in the IRP

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1. BACKGROUND

This memorandum provides guidance on implementing updated NIH policy (NOT-OD-26-032) for Basic Experimental Studies Involving Humans (**BESH**) within the NIH Intramural Research Program (**IRP**) and clarifies their relationship to ClinicalTrials.gov results reporting under the Food and Drug Administration Amendments Act (FDAAA) (42 CFR Part 11).

Under this policy, BESH studies are defined as *interventional research designed to understand fundamental biological, physiological, or behavioral mechanisms without intent to directly influence clinical care.* BESH studies are no longer classified as NIH **clinical trials**.

For the IRP, BESH studies will be registered but will not be subject to NIH clinical trial results reporting requirements in ClinicalTrials.gov.

Upon further review, some studies previously categorized as BESH were determined to meet the definition of an Applicable Clinical Trial, or ACT/pACT. These studies will remain classified as clinical trials and must submit results information in ClinicalTrials.gov in accordance with FDAAA requirements.

NIH IRP policy reminder: NIH IRP policy requires **ALL** NIH-funded clinical studies and trials, including BESH, to be registered in ClinicalTrials.gov. At this time, results reporting is required for all **interventional** clinical trials including studies that meet the definition of FDAAA ACT/pACT criteria. See below, section 3.

2. WHAT QUALIFIES AS A BESH STUDY (NIH POLICY)

Under NIH policy, a study is considered a BESH if it meets both of the following:

- Purpose: The study is designed to improve understanding of how biological, physiological, or behavioral processes work, rather than to test a treatment or evaluate a health outcome.
- Study Design: Participants are assigned by the investigator to a condition or activity (such as a task, stimulus, drug, or procedure) so researchers can examine its effect on a specific process in the body or behavior.

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Key components of a BESH study:

- Any intervention used in the study should **serve as a research tool to investigate underlying processes**, rather than to evaluate it as a treatment.
- The study focuses on **how systems function**, rather than whether an intervention improves health.
- The study is not intended to directly inform or change clinical care **within the next five years**.

This definition aligns with NIH guidance distinguishing BESH from clinical trials that evaluate the safety, efficacy, or effectiveness of interventions.

3. HOW THE UPDATED POLICY AFFECTS THE IRP

Studies REQUIRED to Report Results (when NIH is the Responsible Party):

- Interventional clinical trials
- Studies that meet all of the following FDAAA ACT/pACT criteria must report results:
  - Meet at least **one FDA jurisdiction** criterion:
    - Conducted under an IND or IDE, or
    - Have at least one U.S. study site, or
    - Involve a product manufactured in and exported from the United States

  AND

  - Involve an **FDA-regulated** drug, device, or biologic that is being studied as part of the research

  AND

  - For drug trials, have a Study Phase that is **not "Phase 1"** (for example Phase N/A, Phase 1/2, Phase 2-4 may have to report) or for device trials, have a Primary Purpose that is **not** "Device Feasibility"

Important Clarification: A drug or device is considered FDA-regulated only if it is being evaluated as part of the study. Products used solely for routine care (e.g., anesthesia, contrast agents, background therapy) and **not studied** as interventions do not qualify toward ACT determination.

Note: Use the *ACT Checklist* available on ClinicalTrials.gov to evaluate whether a study qualifies as an ACT: https://cdn.clinicaltrials.gov/documents/ACT_Checklist.pdf.

Studies NOT REQUIRED to Report Results:

- Observational studies
- Interventional studies that qualify as BESH **and** remain outside ACT/pACT scope, characterized by:
  - A focus on basic biological, physiological, or behavioral mechanisms
  - Use of tools (e.g., MRI) for measurement or observation only
  - No evaluation of a drug, device, or biologic as the intervention of interest
  - No FDA-regulated product under study
  - No assessment of health-related outcomes
  - A design not intended to directly inform or change clinical care **within the next 5 years (as a practical guideline**)

4. IMPACT ON EXISTING IRP PROTOCOLS

- Existing clinical trials in the IRP designated "basic science" have been reviewed to determine whether they meet BESH criteria and to assess their relationship to FDAAA.
- PIs of these studies have been/will be notified of their reporting status.
- To discuss categorization of a specific study, contact the OCSO at ccScientificReview@cc.nih.gov.

5. IMPACT ON FUTURE BESH PROTOCOLS

If you have a new protocol that you would like categorized as BESH, please contact ccScientificReview@cc.nih.gov. The required steps and approvals are outlined below.

BESH Qualification Requirements

- Must meet the NIH definition above (i.e., mechanism-focused, no intent to improve care)
- Must not evaluate or optimize tools, products, or interventions
- Expected BESH response pattern:

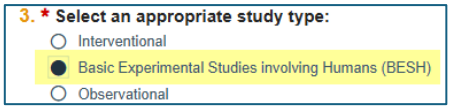
Human participants: **YES**	Prospectively assigned intervention: **YES**	Evaluation of effect: **YES**	Health-related outcome: **NO**

Required Approvals

- IC Scientific Director (SD) **OR** Clinical Director (CD)
- Include IC leadership concurrence with SR submission for CSO concurrence
  - See attached BESH Approval Form
  - A copy of this form will be posted in PROTECT under: *Scientific Review > Help Center > Library > "SRC: BESH Leadership Signature Form"*
- NIH Clinical Center Chief Scientific Officer (CSO)

PROTECT System (Effective June 01, 2026)

- Entering BESH studies in PROTECT:
  - Select **"BESH"** for the field Study Type in the Scientific Review (SR) Form



  - Submit the *BESH Approval Form* under "Documents" with an Initial Scientific Review (ISR).

ClinicalTrials.gov Registration via PQS

- Complete in collaboration with the OCSO to ensure accurate classification
- Pay particular attention to designating:
  - "U.S. FDA-regulated Drug or Device Product"
  - Study Phase
  - Intervention Type

Note: Incorrect entries (e.g., mislabeling FDA-regulated status or study phase) may trigger unintended ACT designation and reporting obligations.

Support is available for both ClinicalTrials.gov reporting and BESH classification:

- ClinicalTrials.gov reporting (BTRIS):
  - Email: BTRISSupport@nih.gov; Phone: 301-827-8270
- Points of Contact for FDAAA Compliance at ICs
  - IRP Sourcebook: https://oir.nih.gov/sourcebook/intramural-program-oversight/intramural-data-sharing/guide-fdaaa-reporting-research-results/assistance-available-help-results-reporting-0
- BESH classification and questions (OCSO):
  - Email: ccScientificReview@cc.nih.gov

6. APPENDIX

Definitions

- **Applicable Clinical Trial (ACT):** A study that meets the criteria defined under FDAAA (42 CFR Part 11) requiring registration and results reporting on ClinicalTrials.gov. Generally includes interventional studies of FDA-regulated drugs, devices, or biologics that meet jurisdictional criteria and are not exempt (e.g., exempted studies include Phase 1 drug trials or early feasibility device studies).
- **Basic Experimental Studies Involving Humans (BESH):** Studies in which human participants are prospectively assigned to an intervention to understand fundamental biological, physiological, or behavioral mechanisms. These studies are not intended to evaluate clinical outcomes or improve health directly and are not classified as NIH clinical trials under current policy.
- **BTRIS:** BTRIS (Biomedical Translational Research Information System) is the NIH Clinical Center's centralized data repository and support service for accessing, managing, and reporting clinical research data.
- **Clinical Trial (NIH Definition):** A research study in which one or more human participants are prospectively assigned to one or more interventions to evaluate the effects on health-related biomedical or behavioral outcomes.
- **Device Feasibility Study (Early Feasibility Study):** A limited clinical investigation of a device early in development, typically not subject to FDAAA reporting requirements.
- **FDA-Regulated Drug, Device, or Biologic:** A product subject to FDA oversight that is being studied as part of the research. A product is considered "FDA-regulated" only if it is the object of investigation, not when used solely for standard care or ancillary purposes.
- **FDAAA:** FDAAA stands for the **Food and Drug Administration Amendments Act** of 2007. In the ClinicalTrials.gov context, FDAAA established legal requirements for registration of certain applicable clinical trials (ACTs), submission of summary results information, compliance timelines, and potential penalties for noncompliance. It is the primary statutory framework governing trial registration and results reporting obligations in the United States.
- **Health-Related Outcome:** A pre-specified measure that reflects the effect of an intervention on participants' health status, including biomedical or behavioral outcomes (e.g., symptom improvement, disease progression, physiological endpoints linked to health).
- **Intervention**: A manipulation of the participant or the participant's environment for the purpose of modifying a biological, behavioral, or physiological process (e.g., drug administration, device use, cognitive task, imaging procedure).

- **Investigational Device Exemption (IDE):** An FDA authorization permitting the clinical study of an investigational medical device.
- **Investigational New Drug (IND):** An FDA authorization allowing the clinical investigation of a drug or biologic in humans.
- **Phase 1 Trial:** An early-stage clinical trial involving drugs or biologics, primarily designed to evaluate safety, dosage, and pharmacokinetics. These studies are excluded from ACT reporting requirements.
- **Primary Purpose (Basic Science):** A designation used in PQS indicating that a study's primary aim is to advance fundamental knowledge rather than evaluate clinical outcomes.
- **Probable Applicable Clinical Trial (pACT):** A study that likely meets ACT criteria based on available information but may lack full data to confirm regulatory status. These studies are typically treated as ACTs for compliance purposes unless otherwise determined.
- **Prospective Assignment:** A study design in which participants are assigned to interventions according to a pre-defined protocol.
- **Responsible Party:** The entity (e.g., NIH or designated investigator) responsible for registering a clinical trial and submitting results information to ClinicalTrials.gov.
- **Tool/Instrument Optimization Study:** A study designed to improve or validate a device, method, or measurement tool (e.g., MRI sequence optimization). These studies do not qualify as BESH if they evaluate or enhance the tool itself.

References

- NIH Notices
  - NIH. *NOT-OD-26-032: Updated NIH Definition of Basic Experimental Studies Involving Humans (BESH).* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-032.html
  - NIH. *NOT-OD-26-067: Implementation of Revised BESH Policy and Implications for Clinical Trial Classification.* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-067.html
- Federal Regulations
  - Food and Drug Administration Amendments Act (FDAAA), Section 801 https://www.congress.gov/110/plaws/publ85/PLAW-110publ85.pdf
  - 42 CFR Part 11 – *Clinical Trials Registration and Results Information Submission* https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11
- FDA Guidance (ACT Determination)
  - FDA. *Clinical Trials Registration and Results Information Submission; Final Rule (42 CFR Part 11) – Preamble to Final Rule* https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission
  - FDA. *FDAAA 801 and the Final Rule: Questions and Answers* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdaaa-801-and-final-rule-questions-and-answers
  - FDA. *Investigational New Drug Application (IND) Regulations (21 CFR Part 312)* https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312

  - FDA. *Investigational Device Exemptions (IDE) Regulations (21 CFR Part 812)* https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812
  - Notices of Noncompliance and Civil Money Penalty Actions https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions

- ClinicalTrials.gov
  - ClinicalTrials.gov (Protocol Registration and Results System - PRS) https://clinicaltrials.gov
  - ClinicalTrials.gov Protocol Registration Data Element Definitions https://clinicaltrials.gov/policy/protocol-definitions
  - Applicable Clinical Trial Checklist https://cdn.clinicaltrials.gov/documents/ACT_Checklist.pdf
  - The ClinicalTrials.gov FAQ, "Am I required to submit results information for my applicable clinical trial (ACT)?" https://clinicaltrials.gov/policy/faq#fr_6

- NIH Policy Guidance
  - NIH Clinical Trial Definition https://grants.nih.gov/policy/clinical-trials/definition.htm
  - NIH BESH Overview https://grants.nih.gov/policy/clinical-trials/besh.htm
  - NIH Policy Manual 3007 – Clinical Trial Registration and Results Information Reporting https://policymanual.nih.gov/3007

- NIH IRBO Website for BESH
  - https://irbo.nih.gov/ancillary-review/scientific-review/

- NIH Intramural Systems
  - Protrak Query System (PQS): https://clinweb.cc.nih.gov/pqs
  - PROTECT System: https://protect.cc.nih.gov/PROD-IRB
  - BTRIS: https://www.cc.nih.gov/btris