# NIH Definition of Clinical Trial Case Studies

In 2014, NIH began a multi-faceted effort to enhance the quality, relevance, feasibility, and transparency of NIH-funded clinical trials. A key element of these stewardship reforms was the development of a clearer, more comprehensive definition of clinical trial. The NIH clinical trial definition is:

> A research study[1] in which one or more human participants[2] are prospectively assigned[3] to one or more interventions[4] (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.[5]

The NIH definition may be broader than other clinical trial definitions because it reflects NIH's mission and considers all biomedical or behavioral outcomes to be health-related[6]. At the same time, not all clinical studies are clinical trials. Important features that distinguish a clinical trial from a clinical study are whether there is prospective assignment of an intervention, a study design that evaluates the effect of the intervention on the participants, and a health-related biomedical or behavioral outcome. If these features are present, the study is a clinical trial.

The simplified case studies provided below are designed to illustrate the differences between clinical trials and clinical studies using the following four questions:

- Does the study involve human participants?
- Are the participants prospectively assigned to an intervention?
- Is the study designed to evaluate the effect of the intervention on the participants?
- Is the effect being evaluated a health-related biomedical or behavioral outcome?

If the answer to all four questions is "yes," then the clinical study would be considered a clinical trial according to the NIH definition.

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

Studies that involve secondary research with biological specimens or health information, or studies that are intended solely to refine measures are not considered clinical trials.

[1] See Common Rule definition of "research" at 45 CFR 46.102(d).

[2] See Common Rule definition of "human subject" at 45 CFR 46.102(f).

[3] The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

[4] An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.

[5] A "health-related biomedical or behavioral outcome" is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

[6] The NIH definition is consistent with the clinical trial definition found in the final revised Common Rule: a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

## CASE STUDIES

Case #1: The study involves the recruitment of research participants who are randomized to receive one of two approved drugs. It is designed to compare the effects of the drugs on the blood level of a protein.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, one of two drugs.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the drugs on the level of the protein in the participants' blood.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, the level of a protein, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug; Mechanistic*

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Case #2: The study involves the recruitment of research participants with condition Y to receive a drug that has been approved for another indication. It is designed to measure the drug's effects on the level of a biomarker associated with the severity of condition Y.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, the approved drug.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the drug's effect on the level of the biomarker.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, the level of a biomarker, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug; Mechanistic*

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Case #3: The study involves the recruitment of research participants with condition X to receive investigational compound A. It is designed to assess the pharmacokinetic properties of compound A.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, compound A.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate how the body interacts with compound A
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, pharmacokinetic properties, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug; Mechanistic*

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Case #4a: The study involves the recruitment of research participants with disease X to receive an investigational drug. It is designed to assess safety and determine the maximum tolerated dose of the drug.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, the investigational drug.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to assess safety and determine the maximum tolerated dose of the investigational drug.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, safety and maximum tolerated dose, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug*

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Case #4b: The study involves the recruitment of research participants with disease X to receive a chronic disease management program. It is designed to assess usability and to determine the maximum tolerated dose of the chronic disease program (e.g., how many in-person and telemedicine visits with adequate adherence).

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, the chronic disease management program.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to determine the maximum tolerated dose of the program to obtain adequate adherence.

- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, tolerable intensity and adequate adherence of the intervention, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care*

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Case #5: The study involves the recruitment of research participants with disease X to receive either an investigational drug or a placebo. It is designed to evaluate the efficacy of the investigational drug to relieve disease symptoms.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, the investigational drug or placebo.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the investigational drug on the participants' symptoms.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, relief of symptoms, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug*

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Case #6: The study involves the recruitment of research participants with disease X to receive an investigational drug. It is designed to assess whether there is a change in disease progression compared to baseline. There is no concurrent control used in this study.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, the investigational drug.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the investigational drug on the subject's disease progression.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, disease progression, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug*

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Case #7a: The study involves the recruitment of research participants with disease X to test an investigational in vitro diagnostic device (IVD). It is designed to evaluate the ability of the device to measure the level of an antibody in blood.

- **Does the study involve human participants?** Yes, the study involves human participants.

**Are the participants prospectively assigned to an intervention?** No, in this context the IVD would not be considered an intervention. The IVD is being used to test its ability to measure antibody levels, but not to test its effects on any health-related biomedical or behavioral outcomes.

X **This study is not a clinical trial.**
*Keyword(s): Device*

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Case #7b: The study involves the recruitment of research participants with disease X to be evaluated with an investigational in vitro diagnostic device (IVD). The study is designed to evaluate how knowledge of certain antibody levels impacts clinical management of disease.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, measurement of an antibody level, with the idea that knowledge of that antibody level might affect clinical management.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate how knowledge of the level of an antibody might inform treatment.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being measured, how blood antibody levels inform treatment, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Device; Clinical Care*

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Case #8a: The study involves the recruitment of research participants with disease X. It is designed to compare the diagnostic performance of approved devices A and B, both of which are used in clinical practice, to measure disease markers. Device A will be used in half of the patients; device B will be used in the other half.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, in this context the diagnostic device would not be considered an intervention. The purpose of the study is to evaluate the diagnostic performance of two devices, but not to determine their effects on any health-related or behavioral outcomes.

X **This study is not a clinical trial.**
*Keyword(s): Device*

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Case #8b: The study involves the recruitment of research participants suspected to have disease X. It is designed to compare the ability of approved devices A and B to diagnose the disease and inform the clinical management of disease X. Device A will be used in half of the patients; device B will be

used in the other half.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, one of two diagnostic devices.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the ability of the two approved devices to inform the clinical management of disease X.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, diagnosis and clinical management of patients with disease X, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Device; Clinical Care*

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Case #8c: The study involves the recruitment of research participants suspected to have disease X. It is designed to compare the ability of commercial sensors A and B to improve diagnosis of the disease and inform the management of clinical outcomes. Device A will be used in half of the patients; device B will be used in the other half.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, one of two diagnostic devices.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the ability of the two commercially available devices to diagnose disease X, and in that way to inform diagnosis and clinical management.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, diagnosis and clinical management of patients with disease X, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Device; Clinical Care*

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Case #9: The study involves the recruitment of healthy volunteers who will be randomized to different durations of sleep deprivation (including no sleep deprivation as a control) and who will have stress hormone levels measured. It is designed to determine whether the levels of stress hormones in blood rise in response to different durations of sleep deprivation.

- **Does the study involve human participants?** Yes, the healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, different durations of sleep deprivation followed by a blood draw.

- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to measure the effect of different durations of sleep deprivation on stress hormone levels.
    - Given that this study uses an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind, this study can fall within the "Basic Experimental Studies with Humans" FOA designation.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, stress hormone levels, is a health-related biomedical outcome.

✓ **This is a basic experimental study involving humans**

** Basic Experimental Studies Involving Humans (BESH) use an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind. These studies are subject to NIH stewardship policies including Good Clinical Practice Training and the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. See here for more information.*

*Keyword(s): Behavioral; Mechanistic; Basic Experimental Study Involving Humans (BESH)*

** The details of Case #9 have been revised and updated as of January 7, 2019.*

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Case #10a: The study involves the analysis of de-identified, stored blood samples and de-identified medical records of patients with disease X who were treated with an approved drug. The study is designed to evaluate the level of a protein in the blood of patients that is associated with therapeutic effects of the drug.

- **Does the study involve human participants?** No, the study does not involve human participants because only de-identified samples and information are used.

X **This study is not a clinical trial.**
*Keyword(s): Drug; Biospecimens; Observational*

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Case #10b: The study involves the analysis of identifiable, stored blood samples and identified medical records of patients with disease X who were treated with an approved drug. The study is designed to evaluate the level of a protein in the blood of patients that is associated with therapeutic effects of the drug.

- **Does the study involve human participants?** Yes, patients are human participants because the blood and information are identifiable.
- **Are the participants prospectively assigned to an intervention?** No, secondary research with biospecimens or health information is not a clinical trial.

X **This study is not a clinical trial.**
*Keyword(s): Drug; Biospecimens, Observational*

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Case #11: The study involves the recruitment of a healthy volunteers whose blood is drawn for genomic analysis. It is designed to identify the prevalence of a genetic mutation in the cohort and evaluate potential association between the presence of the mutation and the risk of developing a genetic disorder.

- **Does the study involve human participants?** Yes, the healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** No, sample collection (blood draw) is not an intervention in this context.

X **This study is not a clinical trial.**
*Keyword(s): Observational*

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Case #12: Physicians report that some patients being treated with drug A for disease X are also experiencing some improvement in a second condition, condition Y. The study involves the recruitment of research participants who have disease X and condition Y and are being treated with drug A. The participants are surveyed to ascertain whether they are experiencing an improvement in condition Y.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, participants are not prospectively assigned to receive an intervention as they are receiving drugs as part of their clinical care. The surveys are being used for measurement, not to modify a biomedical or behavioral outcome.

X **This study is not a clinical trial.**
*Keyword(s): Drug; Observational*

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Case #13a: The study involves the recruitment of patients with disease X who are receiving one of three standard therapies as part of their clinical care. It is designed to assess the relative effectiveness of the three therapies by monitoring survival rates using medical records over a few years.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, there is no intervention. The therapies are prescribed as part of clinical care; they are not prospectively assigned for the purpose of the study. The study is observational.

X **This study is not a clinical trial.**
*Keyword(s): Clinical Care; Observational*

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Case #13b: The study involves the recruitment of research participants with disease X vs. healthy controls and comparing these participants on a range of health processes and outcomes including genomics, biomarkers, laboratory measures, etc. to explore differences that may be relevant to the development of disease X.

- **Does the study involve human participants?** Yes, the study involves human participants.

- **Are the participants prospectively assigned to an intervention?** No, the measures needed to assess the outcomes are not interventions in this context, as the study is not intended to determine whether the measures modify a health-related biomedical or behavioral outcome.

X **This study is not a clinical trial.**
*Keyword(s): Mechanistic; Observational*

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Case #14: The study involves the recruitment of healthy volunteers for a respiratory challenge study; participants are randomized to receive different combinations of allergens. The study evaluates the severity and mechanism of the immune response to different combinations of allergens introduced via inhalation.

- **Does the study involve human participants?** Yes, healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, healthy volunteers are prospectively assigned to randomly selected combinations of allergens.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is evaluating the effects of different combinations of allergens on the immune response in healthy individuals.
    - Given that this study uses an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind, this study can fall within the "Basic Experimental Studies with Humans" FOA designation.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the study evaluates the severity and mechanism of the immune reaction to allergens, which are health-related biomedical outcomes.

✓ **This is a basic experimental study involving humans**

** Basic Experimental Studies Involving Humans (BESH) use an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind. These studies are subject to NIH stewardship policies including Good Clinical Practice Training and the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. See here for more information.*

*Keyword(s): Mechanistic; Basic Experimental Study Involving Humans (BESH)*

** The details of Case #14 have been revised and updated as of January 7, 2019.*

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Case #15: The study involves the recruitment of research participants with Alzheimer's disease (AD) to evaluate the effects of an investigational drug on memory, and retention and recall of information.

- **Does the study involve human participants?** Yes, the study involves human participants.

- **Are the participants prospectively assigned to an intervention?** Yes, participants are prospectively assigned to receive the investigational drug.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is evaluating the effects of the drug on participants' memory.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the study evaluates memory, and retention and recall of information in the context of AD.

✓ **This study is a clinical trial.**
*Keyword(s): Drug; Behavioral*

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Case #16: The study involves the recruitment of individuals to receive a new behavioral intervention for sedentary behavior. It is designed to measure the effect of the intervention on hypothesized differential mediators of behavior change.

- **Does the study involve human participants?** Yes, the individuals are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive a behavioral intervention.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the intervention on mediators of behavior change.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, mediators of behavior change, are behavioral outcomes relevant to health.

✓ **This study is a clinical trial.**
*Keyword(s): Drug; Behavioral*

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Case #17a: The study involves the recruitment of patients with disease X to be evaluated with a new executive function task. It is designed to evaluate the ability of the new task to measure executive function.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, the executive function task.
- **Is the study designed to evaluate the effect of the intervention on the participants?** No, the study is designed to evaluate the ability of the executive function task to measure executive function (as measured by the current standard instrument), but not to modify it.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral*

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Case #18a: The study involves the recruitment of healthy adolescent volunteers followed over time to assess brain development and factors that influence brain development. Participants are administered a

battery of standard measures at each visit including blood draws, surveys, various cognitive performance measures (e.g., working memory tasks), and brain scans (e.g., fMRI) to assess the association of these measures over time.

- **Does the study involve human participants?** Yes, the healthy adolescent volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. The battery of standard measures and the brain scans are being used to describe patterns and associations over time, but not to modify them.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral; Observational; Mechanistic*

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Case #18b:

The study involves the recruitment of healthy volunteers and mild cognitive impairment patients who are administered a series of standard cognitive tasks while undergoing a brain scan or imaging procedure (e.g., fMRI). The purpose of administering these standard cognitive tasks (or behavioral tasks or presentation of stimuli) is to assess brain activity under standardized laboratory conditions and compare this activity between healthy individuals and mild cognitive impairment groups.

- **Does the study involve human participants?** Yes, the healthy volunteers and individuals with mild cognitive impairment are human participants.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. The standard cognitive tasks and the fMRI are being performed to measure and describe brain activity, but not to modify it.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral; Mechanistic*

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Case #18c:

The study involves patients with acute occipital stroke who are suspected of suffering visual field loss. They are randomized to a drug or to matching placebo. The investigators seek to determine whether the drug affects post-stroke changes in cortical visual representation as measured by fMRI.

- **Does the study involve human participants?** Yes, the participants are acute stroke patients.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned, by formal randomization, to receive a drug or placebo.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to determine whether the drug affects post-stroke changes in cortical visual representation.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, cortical visual representation is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral; Drug*

** The details of Case #18c have been revised and updated as of January 17, 2018.*

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Case #18d: The study involves healthy volunteers and compares temporal SNR obtained with a new fMRI pulse sequence with that from another sequence.

- **Does the study involve human participants?** Yes, the healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** No, in this context the different pulse sequences would not be considered an intervention. The pulse sequences are not being used to modify any biomedical or behavioral outcome; rather the investigator is comparing performance characteristics of the two pulse sequences.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral*

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Case #18e: The study involves the recruitment of patients prior to brain surgery. While an fMRI is performed, half of the volunteers will be randomly assigned to perform a language listening task, and half will be assigned to perform a language generation task. Brain function maps will be used by surgeons to identify language areas for surgical planning. The investigators will compare post-operative language function in the two groups.

- **Does the study involve human participants?** Yes, the participants are patients enrolled prior to brain surgery.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, a language listening task or a language generation task during pre-operative fMRI brain function mapping.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to compare the impact of different methods of brain function mapping on post-operative language function.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, post-surgery language function is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral; Clinical Care*

** The details of Case #18e have been revised and updated as of January 17, 2018.*

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Case #18f: Prior to a study of the effects of interference on working memory and brain function, an investigator wishes to test the study procedures and adjust the difficulty of the memory tasks for a range of individuals. To do so, the investigator runs a few healthy volunteers through the procedures and adjusts and finalizes the procedures prior to initiating the formal study

- **Does the study involve human participants?** Yes.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to different interference conditions.

- **Is the study designed to evaluate the effect of the intervention on the participants?** No, the purpose of these preliminary or practice runs is to evaluate and refine the study procedures, not the effect of the intervention on the participants.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral; Mechanistic*

** The details of Case #18f have been revised and updated as of January 17, 2018.*

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Case #19: The study involves the recruitment of research participants with CHF who were hospitalized before or after implementation of the Medicare incentives to reduce re-hospitalizations. Morbidity, mortality, and quality of life of these participants are evaluated to compare the effects of these Medicare incentives on these outcomes.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, the intervention (incentives to reduce re-hospitalization) were assigned by Medicare, not by the research study.

X **This study is not a clinical trial.**
*Keyword(s): Clinical Care; Observational*

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Case #20: The study involves the recruitment of healthcare providers to assess the extent to which being provided with genomic sequence information about their patients informs their treatment of those patients towards improved outcomes.

- **Does the study involve human participants?** Yes, both the physicians and the patients are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, physicians are prospectively assigned to receive genomic sequence information, which is the intervention.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of intervening with physicians, on the treatment they provide to their patients.
- **Is the effect being evaluated a health-related, biomedical, or behavioral outcome?** Yes, the effect being evaluated, the extent to which providing specific information to physicians informs the treatment of patients, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care*

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Case #21: The study involves the recruitment of research participants with a behavioral condition to receive either an investigational behavioral intervention or a behavioral intervention in clinical use. It is designed to evaluate the effectiveness of the investigational intervention compared to the

intervention in clinical use in reducing the severity of the obsessive compulsive disorder.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, either the investigational intervention or an intervention in clinical use.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate whether the investigational intervention is as effective as the standard intervention, at changing behavior.
- **Is the effect being evaluated a health-related, biomedical, or behavioral outcome?** Yes, the effect being evaluated, the interventions' effectiveness in reducing the severity of the condition, is a health-related behavioral outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral*

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Case #23:

The study involves the recruitment of physicians who will be randomly assigned to use a new app or an existing app, which cues directed interviewing techniques. The study is designed to determine whether the new app is better than the existing app at assisting physicians in identifying families in need of social service support. The number of community service referrals will be measured.

- **Does the study involve human participants?** Yes, both the physicians and the families are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, physicians are prospectively assigned to use one of two apps, which are the interventions.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of intervening with physicians, on social service support referral for families.
- **Is the effect being evaluated a health-related, biomedical, or behavioral outcome?** Yes, the effect being evaluated, the number of referrals, is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care*

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Case #27:

The study involves the recruitment of parents to participate in focus groups to discuss topics related to parental self-efficacy and positive parenting behaviors. It is designed to gather information needed to develop an intervention to promote parental self-efficacy and positive parenting behaviors.

- **Does the study involve human participants?** Yes, the parents are human participants.
- **Are the participants prospectively assigned to an intervention?** No, a focus group is not an intervention.

X **This study is not a clinical trial.**

*Keyword(s): Behavioral*

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Case #28: The study involves the recruitment of healthy volunteers to test a new behavioral intervention. It is designed to evaluate the effect of a meditation intervention on adherence to exercise regimens and quality of life to inform the design of a subsequent, fully-powered trial.

- **Does the study involve human participants?** Yes, study participants are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to a behavioral intervention.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the intervention on adherence, and quality of life.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, adherence and quality of life are health-related outcomes.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral*

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Case #29: The study involves the recruitment of healthy volunteers to test a new behavioral intervention. It is designed to evaluate the acceptability of the intervention. The outcome is acceptability, not efficacy, of the intervention to the target providers and their patients.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to a behavioral intervention.
- **Is the study designed to evaluate the effect of the intervention on the participants?** No, the study is not designed to evaluate the effect of the behavioral intervention on the participants. It is designed to assess user acceptability.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral*

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Case #30a: The study involves the recruitment of healthy family members of patients hospitalized for disease X to test two CPR training strategies. Participants will receive one of two training strategies. The outcome is improved CPR skills retention.

- **Does the study involve human participants?** Yes, family members of patients are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to one of two CPR educational strategies.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of educational strategies on CPR skills.

- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, retention of CPR skills is a health-related behavioral outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral*

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Case #30b: The study involves the recruitment of research participants in three different communities (clusters) to test three CPR training strategies. The rate of out-of- hospital cardiac arrest survival will be compared.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive one of three types of CPR training, which is the intervention.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of different CPR training strategies on patient survival rates post cardiac arrest.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, out-of-hospital cardiac arrest survival is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral*

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Case #31a: A study involves the recruitment of school children to evaluate two different tools for monitoring food intake. Food consumption behavior will be measured by asking children to activate a pocket camera during meals and to use a diary to record consumed food. The accuracy of the two food monitoring methods in measuring energy intake will be assessed.

- **Does the study involve human participants?** Yes, children are human participants.
- **Are the participants prospectively assigned to an intervention?** No, in this context the monitoring methods would not be considered an intervention. The study is designed to test the accuracy of two monitoring methods, but not to test the effect on any health-related biomedical or behavioral outcomes.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral*

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Case #31b: A study involves the recruitment of school children to evaluate two different tools for monitoring food intake. Food consumption behavior will be measured by asking children to activate a pocket camera during meals and to use a diary to record consumed food. Changes to eating behavior will be assessed.

- **Does the study involve human participants?** Yes, children are human participants.

- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to two food monitoring methods.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to determine whether using the monitoring methods changes eating behavior.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, eating behavior is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Behavioral*

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Case #32: A study involves the recruitment of children at two schools to monitor eating behavior. Children's food choices will be monitored using a remote food photography method. Food consumption and the accuracy of food monitoring methods will be assessed.

- **Does the study involve human participants?** Yes, the children participating in this study are human participants.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. The study involves observing and measuring eating behavior, but not modifying it. This is an observational study.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral; Observational*

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Case #33: A study involves the recruitment of children at two schools to evaluate their preferences for graphics and colors used in healthy food advertisements. Children will be presented multiple health advertisement and their preferences for graphics and colors will be assessed.

- **Does the study involve human participants?** Yes, children are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to see different advertisements.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the advertisements.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** No, preferences are not health-related biomedical or behavioral outcomes. There is no change to the participant as a result of expressing their preferences for graphics and colors.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral; Observational*

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Case #34: The study involves ambulatory patients who have new-onset stable angina and who are recruited from community practices. They are randomized to undergo CT angiography or an exercise stress test of the doctor's choice. To keep the trial pragmatic, the investigators do not prescribe a protocol

for how physicians should respond to test results. The study is designed to determine whether the initial test (CT angiography or stress test) affects long-term rates of premature death, stroke, or myocardial infarctions.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are randomized to undergo CT angiography or an exercise stress test.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to determine whether the initial test done affects long-term rates of certain clinical events.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, premature death, stroke, and myocardial infarction are health-related biomedical outcomes.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care*

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Case #35: The study involves patients who present with stable angina to community practices. As part of their routine care some of their physicians refer them for CT angiography, while others refer them for exercise stress tests. The study is designed to see whether or not there's an association between the type of test that is chosen and long-term risk of death, stroke, or myocardial infarction.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, the intervention is not prospectively assigned by the investigators. Rather, the intervention, in this case diagnostic study, occurs as part of routine clinical care.

X **This study is not a clinical trial.**
*Keyword(s): Clinical Care; Observational*

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Case #36a The investigators conduct a longitudinal study of patients with schizophrenia. Their physicians, as part of their standard clinical care, prescribe antipsychotic medication. The investigators conduct an imaging session before starting treatment; they repeat imaging 4-6 weeks later.

- **Does the study involve human participants?** Yes.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. Antipsychotic medications are given as part of clinical care, not as part of a prospective, approved research protocol.

X **This study is not a clinical trial.**
*Keyword(s): Clinical Care; Behavioral; Observational*

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Case #36b The investigators conduct a longitudinal study of patients with schizophrenia. Their physicians, as part of their standard clinical care, prescribe antipsychotic medication. As part of the research protocol, all participants will be prescribed the same dose of the antipsychotic medication. The investigators conduct an imaging session before starting treatment; they repeat imaging 4-6 weeks

later.

- **Does the study involve human participants?** Yes.
- **Are the participants prospectively assigned to an intervention?** Yes, although participants are all receiving antipsychotic medication as part of their standard medical care, the dose of the antipsychotic medication is determined by the research protocol, rather than individual clinical need.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of a dose of antipsychotic medication on brain function.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome**? Yes, brain function measured by imaging is a health-related outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care; Behavioral*

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Case #37 The study involves recruitment of healthy volunteers who will wear a thermal compression device around their legs. This pilot study is designed to examine preliminary performance and safety of a thermal compression device worn during surgery. Investigators will measure core temperature, comfort, and presence of skin injury in 15-minute intervals.

- **Does the study involve human participants?** Yes.
- **Are the participants prospectively assigned to an intervention?** Yes, participants are assigned to wear a thermal compression device.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of the thermal compression device on participant core temperature, comfort, and presence of skin injury.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome**? Yes, participant core temperature, comfort, and presence of skin injury are health-related biomedical outcomes.

✓ **This study is a clinical trial.**
*Keyword(s): Clinical Care*

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Case #38 The study involves collection of data on hospitalizations for various acute illnesses among people who live close to a border between two states that have recently implemented different laws related to public health (e.g. smoking regulations, soda taxes). The investigators want to take advantage of this "natural experiment" to assess the health impact of the laws.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** No, the interventions were assigned by state laws and state of residence, not by the research study.

X **This study is not a clinical trial.**
*Keyword(s): Clinical Care; Observational*

Case #39 Prior to a study of the effects of interference on working memory and brain function, an investigator wishes to test the study procedures and adjust the difficulty of the memory tasks for a range of individuals. To do so, the investigator runs a few healthy volunteers through the procedures and adjusts and finalizes the procedures prior to initiating the formal study.

- **Does the study involve human participants?** Yes.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to different interference conditions.
- **Is the study designed to evaluate the effect of the intervention on the participants?** No, the purpose of these preliminary or practice runs is to evaluate and refine the study procedures, not the effect of the intervention on the participants.

X **This study is not a clinical trial.**
*Keyword(s): Behavioral*

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Case #40 The study involves recruitment of healthy volunteers to engage in working memory tasks while undergoing transcranial magnetic stimulation (TMS) to induce competing local neuronal activity. The study is measuring task performance and neural oscillatory activity (using fMRI) to investigate the neural underpinnings of working memory storage and processing.

- **Does the study involve human participants?** Yes, healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, healthy volunteers are prospectively assigned to receive TMS stimulation protocols during a working memory task.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is evaluating the effects of local TMS stimulation on working memory performance and oscillatory brain activity in healthy individuals.
    - Given that this study uses an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind, this study can fall within the "Basic Experimental Studies with Humans" FOA designation.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the study evaluates working memory processes, which are health-related biomedical outcomes.

✓ **This is a basic experimental study involving humans**

** Basic Experimental Studies Involving Humans (BESH) use an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind. These studies are subject to NIH stewardship policies including Good Clinical Practice Training and the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. See here for more information.*

*Keyword(s): Mechanistic; Basic Experimental Study Involving Humans (BESH)*

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Case #41 The study involves recruitment of healthy volunteers to engage in a social valuation task while dopamine tone in the brain is manipulated using tolcapone, an FDA-approved medication. The study aims to understand the role of dopamine in social decision-making and to search for neural correlates of this valuation using fMRI.

- **Does the study involve human participants?** Yes, healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, healthy volunteers are prospectively assigned to receive tolcapone during a social valuation task.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is evaluating the effects of modulating dopamine tone on social decision-making. Although this study uses an FDA-approved drug to modulate dopamine tone, the goal of this intervention is to understand the role of dopamine in a fundamental phenomenon (social valuation), and not to study the mechanism of action of the drug or its clinical effects.
    - Given that this study uses an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind, this study can fall within the "Basic Experimental Studies with Humans" FOA designation.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the study evaluates working memory processes, which are health-related biomedical outcomes.

✓ **This is a basic experimental study involving humans**

** Basic Experimental Studies Involving Humans (BESH) use an intervention to understand fundamental aspects of a phenomena without specific application towards processes or products in mind. These studies are subject to NIH stewardship policies including Good Clinical Practice Training and the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. See here for more information.*

*Keyword(s): Mechanistic; Drug; Basic Experimental Study Involving Humans (BESH)*

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Case #42a The career development candidate proposes to independently lead a study to test a new drug A on patients with disease X. Patients will be randomized to a test and control group, with the test group receiving one dose of drug A per week for 12 months and controls receiving placebo. To assess presence, number, and type of any polyps, a colonoscopy will be performed. To assess biomarkers of precancerous lesions, colon mucosal biopsies will be collected. Complete blood count will be measured, and plasma will be stored for potential biomarker evaluation.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, drug A or placebo.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of drug A and placebo on the presence and type of polyps.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome**? Yes, the effect being evaluated, the presence and type of polyps, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug*

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Case #42b

*Ancillary Study to Case Study #42a*: Some types of drug A being evaluated in Case Study #42a have been reported to impact renal function. An internal medicine fellow performs an ancillary study where stored plasma from Case Study #42a will be evaluated for multiple biomarkers of renal function.

- **Does the study involve human participants?** Yes, patients are human participants because the plasma and information are identifiable.
- **Are the participants prospectively assigned to an intervention?** No, because the assignment of participants to an intervention occurs as part of an existing, separately funded clinical trial. This proposal would be considered an ancillary study that is not an independent clinical trial.

X **This study is not a clinical trial.**
*Keyword(s): Mechanistic*

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Case #42c

*Ancillary Study to Case Study #42a*: An internal medicine fellow designs an independent ancillary trial where a subset of patients from the parent trial in Case Study #42a will also receive drug B, based on the assumption that a two-drug combination will work significantly better than a single drug at both improving renal function and reducing polyps. The test subjects will be evaluated for renal function via plasma clearance rates at 6 and 12 months after initiation of drugs A and B.

- **Does the study involve human participants?** Yes, the study involves human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to receive an intervention, drugs A and B.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to evaluate the effect of drugs A and B on renal function.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, renal function, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**
*Keyword(s): Drug*

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