The PCORI Methodology Standards Academic Curriculum

TEACHING GUIDE

Contents

Introduction

As mandated under its authorizing legislation, the Patient-Centered Outcomes Research Institute (PCORI) prepares methodology standards for patient-centered outcomes research (PCOR). The broader dissemination of and adherence to such standards serve to generate higher-quality and more-relevant research that allows patients to make informed clinical decisions. Further, the adoption and adherence to standards also improve transparency in research.

Published in November 2012, the PCORI Methodology Standards include 47 standards in 11 categories for PCOR, which are particularly relevant to comparative clinical effectiveness research.[1] This curriculum was developed to help researchers with varied expertise and experience gain knowledge and skills to apply these standards to research in progress and the design of new studies. While the primary audience is researchers in academic settings, the instructional materials are also appropriate for staff in funding agencies and patient advocacy organizations, masters- and doctoral-level students, research personnel, and other interested persons.

For each category of standard, there are 6 to 10 lectures, available in video format, audio-only, and printable handout. Additional instructional materials include four audio interviews and this teaching guide, which includes learning objectives, an outline of topics covered, a self-assessment test, and answer key for each category. The total running time of the lectures is approximately 22 hours. These resources are available at PCORI.org.

This teaching guide and all the instructional materials for the PCORI Methodology Standards were prepared by faculty at Johns Hopkins University's Bloomberg School of Public Health and School of Medicine through a PCORI contract and under the direction of PCORI's Methodology Committee.

[1] PCORI's Methodology Committee is leading an ongoing assessment of the currency of the methodology standards published in 2012. Additions and revisions to the standards are expected in 2016.

Category 1: Standards for Formulating Research Questions

This category contains nine modules. The learning objectives for this category are

Cognitive

- Name specific populations that may be affected by research
- Describe health decisions that may be affected by research
- Define participant subgroups
- Evaluate a gaps analysis

Attitudinal

- Value of applying a patient-centered approach

Skills

- Identify outcomes that people representing the population of interest (and subgroups) notice and care about
- Write a research question
- Find relevant systematic reviews (or, if not feasible, narrative reviews) and evaluate their quality and content
- Select appropriate interventions and comparators
- Develop a formal study protocol

The contents of this category include

Module 1	**Introduction** • Importance of patient-centered research questions • Rationale for the standards • Standards for formulating research questions

Module 2	**Review of Objectives (Skills)** • Review of skills • Identify outcomes that people representing the population of interest (and subgroups) may notice and care about • Write a research question • Find and evaluate the quality and content of a relevant review • Select appropriate interventions and comparators • Develop a formal study protocol • Other objectives
Module 3	**Overview** • Why is determining research questions essential to good research, and how does including the patient change how research questions are determined? • Ways to formulate questions • Different approaches to framing research • Determining needs for a new study, including identifying evidence gaps and ensuring that the question is not redundant or already answered; identifying preexisting reviews • Use of analytic frameworks • Identifying the population, intervention, comparison, outcome, time, setting (PICOTS) domains • Example of a detailed protocol with specified PICOTS (refer to Standard 11)
Module 4	**Identifying Research Questions That Are Relevant to Patients** • Research questions to inform decision making in health care • Population • Interventions • Comparators • Outcomes
Module 5	**Identifying Research Gaps** • Methodology for determining research gaps: options including scoping review • Robinson et al. PICOTS-based approach (2013) • Evaluating research gaps • Characterizing the reason for research gaps • Examples of research gaps

Module 6	**Identifying Previous Reviews** • Identifying systematic reviews relevant to your research question • Identifying previous reviews • Types of reviews • Assessing quality of reviews and relevance to research gaps and questions • Generalizing research findings to dissimilar outcomes, populations, and comparators
Module 7	**Creating Formal Research Protocols** • Connecting research questions to methodology • Research protocols • Specific plans for carrying out research • Common barriers • Connecting research questions to practical research techniques • Examples of excerpted protocols
Module 8	**Identifying PICOTS Elements (Population, Intervention, Comparator, Outcome, Time, and Setting)** • Example of writing a question with PICOTS • Defining a diverse/representative population while ensuring generalizability and feasibility • Comparisons and outcomes • Time and setting considerations
Module 9	**Case Study and Key Points** • Suggested template for formulating research questions • Drafting the research question • Identify gaps in evidence • Effects of bariatric surgery versus medical therapy on cardiometabolic risk in patients with type 2 diabetes • Specify PICOTS domains • Create a formal study protocol • Key take-home points

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Self-Assessment for Category 1: Standards for Formulating Research Questions

1. Patient-centeredness applies to which of the following categories? *(Select all that are correct.)*
    a. Recruiting participants and obtaining their consent
    b. Specifying outcomes of interest
    c. Identifying feasible interventions
    d. Selecting appropriate statistical methods

2. The following statements describe differences between research questions, hypotheses, and research aims. Which statements are true? *(Select all that are correct.)*
    a. Research questions, hypotheses, and research aims cannot be used for the same research endeavor.
    b. Hypotheses are statements based on data used as a starting point for future investigation.
    c. A research question should be answered by the study in question.
    d. Research aims are specific goals that the study is meant to accomplish.

3. Which of the following are components of a well-specified systematic review question? *(Select the single best answer.)*
    a. Population, intervention and exposure, confounding, outcomes
    b. Participation rate, study design, comparison, outcomes, timing
    c. Population, comparison, outcomes, biases, setting
    d. Population, intervention and exposure, comparison, outcomes, timing, setting

4. Which of the following statements do not accurately characterize the best way to formulate a research question? *(Select all that are correct.)*
    a. A question can be formulated with an emphasis on risk, prognosis, diagnosis, or treatment.
    b. There are different ways to formulate a research question depending on the issue.
    c. There is only one way to formulate a research question for any given study.
    d. Most feasible research questions have already been addressed.

5. Which of the following is a characteristic intrinsic to a study? *(Select the single best answer.)*
    a. Ethical considerations
    b. Internal validity (bias)
    c. External validity
    d. Heterogeneity
    e. None of the above

6. A diverse patient population is important to formulating research questions because it may impact which of the following? *(Select the single best answer.)*
    a. Understanding of research gaps and outcome definitions
    b. Patient-centeredness of outcome
    c. Feasibility of conducting the study
    d. All of the above

7. Which of the following accurately describes the role of systematic reviews in assessing research gaps? *(Select all that are correct.)*
    a. Systematic reviews are essential; if no review has been done, research gaps cannot be assessed.
    b. Systematic reviews should be abandoned in favor of well-reasoned guidelines on the part of professional organizations.
    c. Systematic reviews are important, but there are many areas in which they are unfeasible to conduct—for example, in areas of new or rapidly changing research.
    d. Research gaps can be assessed without systematic reviews, if such reviews are unfeasible.

8. Which of the following is a potential resource for searching for previous systematic reviews? *(Select the single best answer.)*
    a. Google Scholar
    b. PubMed
    c. Cochrane Reviews
    d. All of the above

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Answer Key for Category 1: Standards for Formulating Research Questions

1. a, b, c
2. b, c, d
3. d
4. c, d
5. e
6. d
7. c, d
8. d

Category 2: Standards Associated with Patient-Centeredness

This category contains seven modules. The learning objectives for this category are

Cognitive

- Explain how engaging patients and other relevant stakeholders can enhance the usefulness of a research study
- Describe the elements necessary to include representative participants in a research study
- Define the steps necessary to develop and test important properties of a new patient-reported outcome (PRO) measure

Attitudinal

- Value patient input in study design
- Recognize PROs as important in improving healthcare decision making
- Commit to implementing and disseminating PCOR findings

Skills

- Formulate a plan to ensure the representativeness of study participants
- Prepare a strategy to identify, select, recruit, and retain study participants
- Prepare an internal reliability consistency coefficient for a multi-item PRO measurement scale
- Engage relevant stakeholders in designing a study about the comparative effectiveness of two alternative treatment strategies for a chronic condition in adults, and in disseminating the study results
- Collect data in a thorough and systematic manner

The contents of this category include

Module 1	**Introduction** • Patient-centeredness standards • Patient-centeredness standards: settings • Intention of the standards

Module 2	**Objectives** • Patient-centeredness standards • Attitudinal objectives • Cognitive objectives • Skills objectives
Module 3	**Overview** • What is meant by patient (person)–centered outcomes research? • Why do we need patient-centeredness standards? • Rationale for patient-centeredness in research • Rationale for patient-centeredness standards • PCORI merit review criteria • Patient-centeredness standards-1 o What is a stakeholder? o What are examples of stakeholders? o What is engagement? o Stakeholder Involvement in phases of research o The PCORI Engagement Rubric o The PCORI Engagement Principles • Patient-centeredness standards-2
Module 4	**Patient and Stakeholder Selection and Engagement** • Objectives • Rationale for a stakeholder and engagement standard • Definition and classification of stakeholders • What do we mean by *engagement*? • Where in the process can stakeholders be engaged? • The PCORI Engagement Rubric • The PCORI Engagement Principles • Considerations in stakeholder selection • Levels of patient engagement • Communication in stakeholder engagement • PCORI's engagement activity inventory • Additional considerations in stakeholder engagement
Module 5	**Ensuring Representativeness** • Why is it important for the sample to be representative? • Which groups need to be included?

	• Sampling strategies to ensure generalizability of findings • Recruitment and retention of study participants • Other considerations in recruitment and retention • Decreasing selection bias
Module 6	**Patient Reported Outcomes (PROs)**
Module 6a	**Introduction, Objectives, and a Case Example** • Rationale for using PROs • Methodology standard for PROs • Relevant categories of research • Selection of PRO instruments • Case example: a woman with fibromyalgia • Objectives for PROs
Module 6b	**Overview** • Importance and definitions • Models and key challenges
Module 6c	**Measurement and Measure Development** • Measurement concepts/Health-related quality of life • Measure development/Conceptual models
Module 6d	**Reliability, Validity, and Responsiveness** • COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) checklist • Estimating reliability • Internal consistency • Types of validity • Responsiveness
Module 6e	**Analysis and Interpretation** • Methods and examples of analytic methods; statistical versus clinical significance

Module 6f	**Using PROs in Research, Clinical Practice, and Quality Improvement** • Examples of selection and use of PRO measures in research, clinical practice, quality improvement/quality measurement
Module 6g	**Summary and References** • Key points review • Where to go for additional learning (references)
Module 7	**Dissemination and Implementation** • Objectives • What is meant by dissemination? • Planning research dissemination and implementation • Stakeholder identification for dissemination and implementation • Evaluating the impact of dissemination and implementation • Communication and dissemination research

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Self-Assessment for Category 2: Standards Associated with Patient-Centeredness

Select the single best answer to each question.

1. Which of the following is true regarding meaningful patient and stakeholder engagement?
    a. Collecting data from electronic medical records to determine which medication is most effective is a good example of meaningful engagement because the data is coming from patients.
    b. The stages of research and ways in which patients and other stakeholders are engaged may vary from study to study.
    c. For a study to demonstrate adequate engagement, at least one person from each of the PCORI stakeholder groups must be included as a member of the research team.
    d. The advice and involvement of stakeholders is unlikely to improve the relevance of research to, or its understanding by, wide audiences.

2. Which of the following is an important reason for having representative participants in a research study?
    a. Enable focus on a highly selected group of individuals, leaving out those who are reflective of the "real world"
    b. Establish which PRO has the best test-retest properties
    c. Help minimize bias and to ensure generalizability of results
    d. Allow the exclusion of people from underrepresented minorities

3. Which of the following is true concerning PROs?
    a. Patients should not be involved in determining which symptoms are most important to them because this would bias a study's results.
    b. An example of a PRO is asking a doctor how he or she thinks a patient is doing during a visit.
    c. PROs are the only measures that should be used as outcomes in PCOR.
    d. It is important to document the measurement properties for PROs.

4. Which of the following is true concerning research dissemination?

    a. The principal investigator is always the best communicator of study results.
    b. Asking patients and stakeholders for advice in developing a dissemination strategy is unlikely to provide useful information.
    c. When developing a dissemination strategy, it is important to consider who the end users of research will be.
    d. The optimal means to disseminate research findings to the public is through peer-reviewed scientific journals and research meetings.

5. Which of the following is true regarding stakeholders for PCOR?

    a. The types and numbers of stakeholders will be the same for every study.
    b. Patients and their caregivers are important stakeholders.
    c. It is never appropriate to include stakeholders in identifying research questions.
    d. Stakeholders should not contribute to research dissemination.

6. Which of the following is an example of meaningful engagement?

    a. Including patients as research participants
    b. Using data from an electronic medical record to evaluate the effectiveness of new medication
    c. Asking a group of patients to review a questionnaire to see if it is understandable
    d. Naming a patient as an author on a paper without his or her having been involved in planning the study, contributing data, evaluating the results, or reviewing the manuscript

7. Which of the following is true regarding engaging patients and stakeholders throughout the research process?

    a. It helps ensure that the questions being asked are meaningful, and the data are understandable and usable.
    b. It requires minimal additional effort or planning.
    c. It adds considerable bias to study results.
    d. It is the same for every PCOR project.

8. Which of the following is true concerning the recruitment of study participants?

    a. Asking patients and stakeholders for advice is unlikely to provide useful information.
    b. Study inclusion criteria and numbers of visits may need to be reevaluated and modified in the case of slow recruitment.
    c. It is reasonable to assume that almost all patients who enroll in a longitudinal study will complete the study.
    d. A single approach using fliers to recruit study subjects typically ensures the highest yield.

9. Which is a good strategy to enhance study participant retention?
    a. Providing additional payments to subjects without first seeking Institutional Review Board (IRB) or ethics board approval
    b. Telling patients in a double-blind randomized trial that they are receiving the best therapy
    c. Asking patients to arrive early for a study visit and having them wait beyond their scheduled time to be called in
    d. Regular check-in calls and newsletters providing information on recruitment or early findings, or education about participants' conditions

10. Which of the following is *not* a PRO?
    a. Patient experience with an ambulatory care provider
    b. Patient diagnosis of depression
    c. Patient rating of pain severity
    d. Patient-reported limitation in physical function

11. Are physician reports of pain more reliable than patient self-reports?
    a. Yes
    b. No

12. Which of the following is *not* an important property to evaluate for a PRO measure?
    a. Reliability
    b. Validity
    c. Responsiveness
    d. Specificity

13. Are the only costs to consider for dissemination budgeting related to publication costs in peer-reviewed journals?
    a. Yes
    b. No

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Answer Key for Category 2: Standards Associated with Patient-Centeredness

1. b
2. c
3. d
4. c
5. b
6. c
7. a
8. b
9. d
10. b
11. b
12. d
13. b

Category 3: Standards for Data Integrity and Rigorous Analyses

This category contains nine modules and an interview. The learning objectives for this category are

Cognitive

- Compare the content of different types of secondary data to select data appropriate to study goals
- Describe the characteristics of a well-validated exposure or outcome variable, including scales
- Explain the key threats to validity of exposure and outcome variables in secondary data sets
- State the purpose of control of confounding in secondary data analyses
- Define internal and external validity of a study using secondary data

Attitudinal

- Appreciate the challenge of assessing the causal effects of exposures on outcomes from observational or experimental studies
- Commit to protecting data from breaches of confidentiality and privacy
- Recognize the importance of capturing the diverse sources of uncertainty in estimates of causal effects through sensitivity and other analyses

Skills

- Draw a causal graph that represents the major observed variables, unobserved variables, and assumptions that constitute the proposed analysis
- Select one or more data sets that meet the project's needs
- Develop an analytic plan to address the specific aims of the project
- Choose validated exposure and outcome variables, when available
- Prepare a satisfactory description of a plan for control of confounding
- Prepare a plan to address potential bias and variance in effect estimates caused by unobserved variables—for example, using instrumental variables or sensitivity analyses
- Formulate a thoughtful plan for subgroup analyses and/or sensitivity analyses as needed to address specific aims
- Apply tools to assess a proposed study's internal validity at the time of study design.
- Conduct analyses that are reproducible by others

The contents of this category include

Module 1	**Introduction** • Attention to data integrity • Rationale for this set of standards • Standards for data integrity and rigorous analyses
Module 2	**Objectives and Objectives Illustration** • Review of attitudinal and skills objectives o Select a dataset that meets the project's needs o Develop an analytic plan to address the specific aims of the project o Choose validated exposure and outcome variables, when available o Prepare a satisfactory description of a plan for control of confounding o Formulate a thoughtful plan for subgroup analyses and/or sensitivity analyses as needed to address specific aims • Apply appropriate tools for assessment of a proposed study's internal validity at the time of study design. • Presentation of example: example from the literature of a completely described study with smart choices
Module 3	**Initial Considerations regarding Data Integrity and Rigorous Analyses** • Introduction to the topic and its importance to PCOR • Introduction to EQUATOR (Enhancing the QUAlity and Transparency Of health Research)
Module 4	**Thinking about Causality** • Discussion of causal frameworks • Developing causal graphs with examples
Module 5	**Data Options for Observational Designs**
Module 5a	**Primary Data** • Observational data • Primary data • Registry data • Cross-sectional survey data • Prospective cohort study data

Module 5b	**Secondary Data** • Claims data • Electronic health record (EHR) data • Repurposed trial or cohort data
Module 6a	**Imperfect Exposure Variables** • Imperfect exposure data o Measures of agreement o Exposure invalidity o Solutions
Module 6b	**Imperfect Outcome Variables** • Imperfect outcome data o Validation studies o Sensitivity analyses
Module 6c	**Attention to Scales and Instruments** • Reliability • Validity • Responsiveness
Module 7a	**Planning Analyses of Observational Data** • Common study designs and importance of specifying choices when designing research
Module 7b	**Describing a Data Analysis Plan** • Key elements in formulating and describing a data analysis plan o Choice of study design best suited to question o Choice of data o Description of exposures and measurement o Description of outcomes and measurement o Plan for exploratory data analysis o Plans for testing hypotheses about relationship between exposures and outcomes o Considerations regarding confounders of the relationship and how these will be approached o Considerations regarding sensitivity analyses
Module 8	**Control for Confounding by Observed Covariates**

Module 8a	**Matching and Restriction**
Module 8b	**Standardization, Stratification, and Regression**
Module 8c	**Introduction to Propensity Scores**
Module 9	**Summary** • Review • Where to go for additional information
Interview	**Protection of Privacy**

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Self-Assessment for Category 3: Standards for Data Integrity and Rigorous Analyses

Select the single best answer to each question.

1. What might be considered a drawback to conducting a randomized controlled trial (RCT) of the comparative safety of two drugs?
    a. Treatment groups are not similar.
    b. Safety events are rare.
    c. Data quality is poor.
    d. Internal validity is less than that of observational designs.

2. Which is a benefit of using existing data for research?
    a. Data validity is usually higher than when using newly collected data.
    b. Existing data are considered more valid than trials of the efficacy of a medicine under development.
    c. Study participants can receive care in their usual care settings.
    d. Funding agencies prefer use of these data for nearly all questions.

3. Which of the following is an example of a cross-sectional study?
    a. National Health and Nutrition Examination Survey (NHANES)
    b. Women's Health Initiative Observational Study (WHIOS)
    c. Framingham Heart Study
    d. Cystic Fibrosis Patient Registry

4. Which of the following is the best reason for preparing a conceptual model at the beginning of proposal development?
    a. It provides the necessary information for sample size calculations.
    b. It illustrates the rationale for the choice of statistical model.
    c. It identifies key confounders and effect modifiers of the relationships being tested.
    d. It allows exclusion of populations with low prevalence of disease.

5. Which type of data is typically available in both electronic health record (EHR) data and administrative billing data?
    a. Results of laboratory tests
    b. Out-of-pocket cost of a mammogram
    c. Tobacco-use status
    d. Date of hospitalization

6. Why might Medicare data be preferred over local health system medical record data to answer a comparative effectiveness question?
    a. Medicare data are clean and simple to use.
    b. IRBs will not permit use of local health system data.
    c. Cost data are essential for any comparative effectiveness question.
    d. Results from a study using Medicare data will be generalizable to most of the US elderly population.

7. Which of the following is true?
    a. Nesting a cohort study within data collected for a trial is typically *not* permitted by the National Institutes of Health.
    b. Participants enrolled in multicenter trials are representative of the US population.
    c. Data from children can never be used as observational data for research.
    d. Observational studies using existing data are often less expensive than prospective cohort studies.

8. When assessing medication adherence, are pharmacy records necessarily more valid than patient self-report of medication use?
    a. Yes
    b. No

9. What does a kappa statistic of 80 percent indicate?
    a. If the study is repeated 100 times, then 20 percent of the time the results will differ by two standard deviations from the mean.
    b. Two reviewers of the test results agree 80 percent of the time.
    c. There is a high degree of agreement between two reviewers of test results that is not due to chance.
    d. A third reviewer of test results is needed 80 percent of the time to resolve discrepancies between two reviewers.

10. In comparing the effectiveness of two rapid diagnostic tests used in the emergency room to detect influenza, which of the following is most important?
    a. High sensitivity
    b. High specificity
    c. Absence of false negatives
    d. Noninvasiveness

11. What problem arises from misclassifying people's exposures when conducting a retrospective cohort study?
    a. Individuals may receive inappropriate treatment.
    b. Conclusions about the relationship between exposure and outcome may be wrong.
    c. It may be difficult to identify the appropriate people for follow-up testing.
    d. Outcomes cannot be verified appropriately.

12. In a case-crossover design, who makes up the control population?
    a. Individuals who did not have the exposure of interest
    b. Individuals without the outcome of interest
    c. There is no control population; it is a case-only design.
    d. There is no control population; the investigator assigns the intervention.

13. What is the reason to perform matches in a case-control study?
    a. An equal number of cases and controls is essential for statistical modeling.
    b. Performing matches controls for potential confounders.
    c. Performing matches provides a way to rigorously understand the impact of the variables used for matching.
    d. Performing matches reduces the risk of doing an underpowered study.

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Answer Key for Category 3: Standards for Data Integrity and Rigorous Analyses

1. b
2. c
3. a
4. c
5. d
6. d
7. d
8. b
9. c
10. a
11. b
12. c
13. b

Module 3	**Methods to Prevent and Monitor Missing Data** • Discuss, using examples, steps taken in study design and conduct to monitor and limit the impact of missing data • Describe actions by design and management teams to reduce missing data • Discuss actions by investigators and site personnel to reduce missing data
Module 4	**Record and Report Missing Data** • Discuss issues of participant drop-out within data analysis • Provide examples on documenting participant drop-out • Introduce, using examples, reporting standards and guidance
Module 5	**Describe Statistical Methods to Handle Missing Data (Advanced)** • How missing data will be handled: an example from a PCORI grant application • SPIRIT (Standard Protocol Items: recommendations for Interventional Trials) 2013 statement • Example of description of imputation procedure for missing data
Module 6	**Statistical Methods to Handle Missing Data and Methods of Examining Sensitivity of Inferences to Missing Data Methods and Assumptions (Advanced)** • Hypothetical study: two time points • Observed and unobserved data • Distribution of observed and unobserved data • Examples of assumptions (worst case and best case) • Missing at random/missing not at random • Case study • Other approaches • Sensitivity analysis • Properly account for statistical uncertainty • Single imputation (e.g., last observation carried forward) should not be the primary analytic approach • Examine sensitivity to assumptions

6. Which of the following are good practices for reporting missing data? *(Select all that are correct.)*
   a. *Reporting on data completeness*
   b. Accounting for all participants who entered into a study
   c. Describing how missing data were handled in the analysis
   d. Omitting patients who are lost to follow-up from the reporting
   e. Interpreting the study results in light of missing data

The following four questions are based on this scenario:

Consider a randomized study in which patients are randomized to either a new or a control treatment. Suppose patients are scheduled to be followed for one year, with outcomes scheduled to be measured at 6 and 12 months. Suppose the outcome takes on values between 0 and 100, with higher values representing better health. While there are no missing outcomes at 6 months, some patients drop out of the study between 6 and 12 months and their outcomes are missing. The investigators are interested in comparing the mean outcomes at 12 months between the new and control treatments. Suppose that outcomes are missing on some patients.

7. Is it possible to estimate the means of interest without assumptions?
   a. Yes
   b. No

8. When evaluating whether the new treatment is better than the control treatment, what is the most conservative assumption that can be imposed?
   a. Assume the outcomes for all patients with missing data in the new treatment arm are 0 and the outcomes for all patients with missing data in the control arm are 100.
   b. Assume the outcomes for all patients with missing data in the new treatment arm are 100 and the outcomes for all patients with missing data in the control arm are 0.
   c. Missing at random in each treatment arm
   d. Maintained response after drop-out

9. Does the assumption of missing at random posit that missingness is unrelated to the outcome under investigation?
   a. Yes
   b. No

10. Is ad-hoc sensitivity analysis the preferred approach to conducting sensitivity analysis?
   a. Yes
   b. No

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Answer Key for Category 6: Standards for Data Registries

1. b
2. c
3. a
4. c
5. d
6. a
7. d
8. b
9. a

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Answer Key for Category 7: Standards for Data Networks as Research-Facilitating Structures

1. c
2. b
3. e
4. b
5. a
6. b
7. e
8. e
9. c
10. d
11. e
12. e
13. d
14. e
15. a
16. a
17. c
18. d
19. d
20. a

Category 8: Standards for Causal Inference Methods

This category contains 10 modules. The learning objectives for this category are

Cognitive

- Explain how causal effects are defined
- Describe the benefits of randomized experiments for estimating causal effects
- Recognize the danger of confounding in nonexperimental studies
- Determine whether there is covariate balance across treatment groups

Attitudinal

- Value careful and thoughtful design of causal inference studies

Skills

- Prepare an analytic plan that clearly states the causal hypothesis of interest, populations, exposures, comparators, and outcomes
- Demonstrate the timing of an outcome assessment relative to the initiation and duration of exposure
- Choose the strongest study design for estimating causal effects for the question of interest (i.e., randomized designs, self-controlled case series)
- Show how to balance bias and variance in study design and analysis
- Report the key assumptions underlying propensity score and instrumental variable approaches

The contents of this category include

Module 1	**Introduction** • Attention to causal inference • Rationale for causal inference standards • Description of the standards
Module 2	**Objectives** • Cognitive • Skills

Module 3a	**Defining Causal Effects** • What do we mean by the term *causal effect*? • Define clearly the causal hypothesis of interest, populations, exposures, comparators, and outcomes. • Example: treatment of gestational diabetes
Module 3b	**Confounding, Randomized Experiments, and Nonexperimental Studies** • Confounding: the challenge • Example of confounding • Randomized experiments as a solution to confounding • Complications of randomized experiments • Nonexperimental designs
Module 4	**Planning a Nonexperimental Study** • Clear specification of treatment and comparison conditions, population of interest, and outcomes and their timing • Example: CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) • Develop an understanding of why people receive different treatments. • Confounding by indication • Danger in adjusting for posttreatment variables • Choice of study designs and datasets
Module 5	**Common Nonexperimental Study Designs** • Case-control designs • Case-crossover • Propensity score/matching designs for cohort studies • Instrumental variables • Interrupted time series and comparative interrupted time series • Regression discontinuity
Module 6a	**Considerations When Using Propensity Score Methods** • Propensity score designs for cohort studies • Main idea of propensity scores • Ways of using propensity scores • Covariate balance as the goal • Overlap in propensity score distributions • Unobserved confounders

Module 6b	**Example of Propensity Score Approach** • Connors et al.: right heart catheterization • Population, treatment and comparison conditions, outcomes, and confounders • Propensity score matching approach • Covariate balance, before and after matching • Outcome results
Module 7a	**Considerations When Using Instrumental Variables Methods** • The idea of an instrumental variable • Brief examples of instruments • Assumptions underlying the approach • Assessing the assumptions: Randomly assigned? Influence the treatment received? No direct effect on outcomes?
Module 7b	**Example of Instrumental Variable Analysis** • Brookhart et al.: physician prescribing preference as instrument for looking at effect of COX-2 inhibitors versus nonselective NSAIDs (nonteroidal anti-inflammatory drugs) • Population of interest, treatment and comparison conditions, outcomes, and instruments
Module 8	**Sensitivity Analysis** • Value in doing sensitivity analyses • Sensitivity to unobserved confounding in propensity score approaches • Sensitivity to instrumental variables assumptions
Module 9	**More Complex Temporal Settings** • What if I have treatments and covariates measured repeatedly over time? • What if I want to control for posttreatment variables? • Need to be careful about time ordering and clearly define covariate time periods and outcome time periods • Idea of principal stratification • Marginal structural models as one strategy

Module 10	**Key Points** • Clear definitions of treatments, outcomes, and populations of interest • Need to think clearly about study design and select one that is appropriate for research question and data available • Value in careful design of nonexperimental studies • Revisit original learning objectives

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Self-Assessment for Category 8: Standards for Causal Inference Methods

1. Which of the following is a benefit of an RCT? *(Select the single best answer.*)
    a. Potential outcomes for each unit are available.
    b. Comparisons of outcomes are not confounded by observed or unobserved covariates.
    c. Comparisons of outcomes are not confounded by observed covariates.
    d. The results are always relevant to target populations.

2. What are the properties of a confounder? *(Select all that are correct.)*
    a. Moderates treatment effects
    b. Related to the exposure of interest
    c. On the causal pathway between exposure and outcomes
    d. Related to the outcome of interest

3. Which of the following is not an example of a nonexperimental study design? *(Select the single best answer.)*
    a. Propensity score matching
    b. Comparative interrupted time series
    c. Instrumental variables
    d. Fidelity assessment

4. Which of these designs can be used to estimate a causal effect with data from just one unit? *(Select the single best answer.)*
    a. Regression discontinuity
    b. Instrumental variables
    c. Interrupted time series
    d. Propensity score matching

5. To control for a posttreatment variable, such as medication adherence, in a randomized trial, can it be included as a predictor in the outcome model?
    a. Yes
    b. No

6. Are the assumptions underlying instrumental variables analyses fully testable?
    a. Yes
    b. No

7. In a randomized trial it is okay to subset the data analyzed to those individuals in the treatment group who were fully adherent to the treatment under study.
    a. Yes
    b. No

8. Does a good instrument directly affect the outcomes of interest?
    a. Yes
    b. No

9. Which of the following designs takes advantage of a treatment that was administered on the basis of a threshold on some predictor variable? *(Select the single best answer.)*
    a. Propensity scores
    b. Instrumental variables
    c. Randomized experiment
    d. Regression discontinuity

10. Does the propensity score represent the probability of experiencing the outcome of interest?
    a. Yes
    b. No

11. Which of the following is not a useful diagnostic for propensity score methods? *(Select all that apply.)*
    a. Overlap between propensity score distributions in exposed and unexposed groups
    b. Assessment of the validity of the exclusion restriction
    c. The standardized difference in means between exposed and unexposed groups on a covariate
    d. The standardized difference in means between exposed and unexposed groups on the outcome

12. Which of the following is not a benefit of using propensity score methods? *(Select the single best answer.)*
    a. Adjusting for observed confounders
    b. Adjusting for observed and unobserved confounders
    c. Helping analysts see the overlap between exposed and unexposed groups
    d. Reducing sensitivity to specific regression models by reducing extrapolation

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Answer Key for Category 8: Standards for Causal Inference Methods

1. b
2. b, d
3. d
4. c
5. b
6. b
7. b
8. b
9. d
10. b
11. b, d
12. b

Category 9: Standards for Adaptive and Bayesian Trial Designs

This category contains 10 modules and an interview. The learning objectives for this category are

Cognitive

- Compare the different types of adaptive trial designs
- Describe the inferential philosophy underlying Bayesian statistics and its advantages over non-Bayesian approaches to inference
- Evaluate the statistical properties of adaptive trial designs
- Outline a structure and analysis plan for a Bayesian or adaptive randomized clinical trial (RCT) design

Attitudinal

- Value considerations of clinical equipoise in relation to the implications of adapting randomization during an RCT

Skills

- Formulate appropriate prior distributions for Bayesian trial designs
- Demonstrate that clinical trial infrastructure is adequate to support planned adaptations
- Select factors that will lead to successful adaptive or Bayesian trial designs
- Choose appropriate considerations for interim and final analyses of data from adaptive and Bayesian clinical trials
- Report adaptive RCTs using the CONsolidated Standards Of Reporting Trials (CONSORT) statement

The contents of this category include

Module 1	**Introduction** • Attention to clinical trial design • Rationale for adaptive and Bayesian trial design standards • Statement of the standards for adaptive and Bayesian trial designs
Module 2	**Review of the Objectives (Skills)** • Learning objectives • Examples from the literature of adaptive and Bayesian clinical trials

Module 3a	**Overview** • Statistical inference: Bayesian or frequentist? • How have clinical trialists generally designed RCTs? • Error probabilities • Bayesian and frequentist statistical inference • Bayesian advantages/criticism • Predictive distribution • Conditional inference
Module 3b	**Background** • Bayesian inference applied to an RCT • Relationship of Bayesian inference to frequentist inference • Why might we consider adaptive and Bayesian clinical trials for PCOR? • Adaptive designs/controversy
Module 4	**Planning an Adaptive Clinical Trial** • Prospective planning and clear documentation • Details to include in the protocol • Details to include in a statistical analysis plan
Module 5	**Statistical Properties of Adaptive Clinical Trials** • Operating characteristics of a study (definition) • Methods for assessing operating characteristics • Describing statistical properties of the proposed design • Ensuring that you have "covered the bases" • Stakeholder feedback on simulation scenarios and operating characteristics • Examples of ways to present simulation results
Module 6	**Specifying the Structure and Analysis Plan** • Rationale for this standard • Statistical models • Aspects of the Bayesian model: prior distributions • How Informative is the prior distribution? • Example: More data will lead posterior distributions to converge, regardless of prior distributions • Utility functions • Assumptions • Structure and analysis plan • Computational issues

Module 7	**Infrastructure for Adaptive Clinical Trials** • Key infrastructure requirements for a successful adaptive clinical trial
Module 8	**Reporting Results of Adaptive Clinical Trials** • Sections of the CONSORT statement one can use to report key dimensions of adaptation • Additional elements to consider when reporting results
Module 9	**Other Considerations and Recommendations for Adaptive and Bayesian Clinical Trials** • Considerations of operational bias • Proper oversight of adaptive RCTs
Module 10	**Summary** • Review of methodology standards • Where to go for additional learning (references)
Interview	**Ethical Issues Related to Adaptive Trials** Drs. Gary Rosner and Nancy Kass

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Self-Assessment for Category 9: Standards for Adaptive and Bayesian Trial Designs

Select the single best answer to each question.

1. What is the difference between the traditional clinical trial designs of the past few decades and adaptive clinical trials?
    a. Adaptive trials allow changes in the way the trial is run, at will, at any time during the trial.
    b. Traditional clinical trial designs require much more preparation and pre-study planning than adaptive trials do.
    c. Adaptive trials incorporate predefined rules for changing certain aspects of the clinical trial in response to accruing data.
    d. Adaptive clinical trials never incorporate randomization.

2. Do Bayesian statistical inference conditions on the clinical trial's data make inference about the study's treatment effects?
    a. Yes
    b. No

3. Is Bayesian posterior inference always heavily influenced by the prior distribution?
    a. Yes
    b. No

4. How might an adaptive clinical trial provide randomized evidence to support individualizing therapies?
    a. By altering randomization probabilities within predefined patient subgroups to favor a treatment that appears to be more beneficial
    b. By maintaining equal randomization of patients to trial treatments, but always allowing *post hoc* analyses of trial data in subgroups that were not defined prior to opening the study
    c. By changing the trial's entry criteria to enrich for patients who do not appear to benefit from any treatments in the trial
    d. By allowing the trial's sponsors to change the study chair in response to the accruing trial data

5. Which of the following statements represents a reason for intensive and extensive planning for an adaptive trial?
    a. Specification and evaluation of trial details during the planning stage allow key stakeholders to fully evaluate the trial's design and potential outcomes.

b. Completely describing the adaptive trial's design, assumptions, and decision making help ensure that the scientific community and key stakeholders will consider the study results to be valid and credible.
c. Evaluation of the trial's design under a broad range of scenarios allows one to estimate important characteristics of the design, such as the probabilities of possible erroneous conclusions and misstatements.
d. All of the above

6. Should all possible adaptations be described before the study begins?
   a. Yes
   b. No

7. Do adaptive trials' statistical considerations typically include more than simply Type I error, power, and sample size?
   a. Yes
   b. No

8. Do pre-specified adaptations that are part of an adaptive trial typically occur as protocol amendments, and do these amendments occur subsequent to the opening of the trial, rather than as part of the protocol?
   a. Yes
   b. No

9. Which of the following statements relating to the infrastructure needs of an adaptive trial is *incorrect*?
   a. The trial's registration and randomization systems should interact with the data management system if the accruing data may alter randomization probabilities.
   b. The study team needs to consider the logistics relating to drug distribution in order to maintain an adequate supply of drugs, as randomization probabilities change.
   c. A system for capturing and archiving the trial's database at the time each adaptation occurs is not necessary for an adaptive design, because archiving of the study data is not necessary each time an adaptation or interim analysis occurs.
   d. Testing the infrastructure (including, but not limited to, the randomization system, the data collection system, and processes for implementing the adaptation) ensures that the trial can run successfully as designed.

10. Why should the committee overseeing an ongoing adaptive trial (e.g., the trial's data safety and monitoring board) refrain from modifying the trial's design, except to ensure patient safety?
    a. The study team worked very hard to develop the trial's design, write the protocol, and initiate the study.
    b. Another committee will make such changes if its members see fit.
    c. The oversight committee does not include anyone with expertise on adaptive trials.
    d. *Ad hoc* modifications to the trial's design could affect the statistical properties of the trial.

11. Do the CONSORT 2010 guidelines include recommendations for reporting on adaptive trials?
    a. Yes
    b. No

12. Which of the following is an example of operational bias in a trial that incorporates adaptive randomization?
    a. The trial randomizes between a medical and a surgical treatment.
    b. A physician participating in a three-armed trial in which one arm may be dropped midcourse does not enroll older patients who are eligible for the trial because the physician believes that older patients are not good candidates for one of the arms.
    c. In a trial that masks patients and their treating physicians to treatment assignments, a participating physician figures out the randomization codes and tells patients which treatment they received.
    d. The trial uses different follow-up schedules for the randomized treatments, evaluating patients randomized to one treatment more frequently for the primary study endpoint than patients randomized to another treatment.

13. Do Interim analyses require the same degree of data cleaning as final analyses, even though these procedures may lead to lengthy delays or implementation of an adaptation using a subset of available data?
    a. Yes
    b. No

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Answer Key for Category 9: Standards for Adaptive and Bayesian Trial Designs

1. c
2. a
3. b
4. a
5. d
6. a
7. a
8. b
9. c
10. d
11. b
12. b
13. b

Category 10: Standards for Studies of Diagnostic Tests

This category contains seven modules. The learning objectives for this category are

Cognitive

- Define diagnostic testing, list the developmental phases of a testing modality, and highlight the correct stage when comparative clinical effectiveness research (CER) should be undertaken
- Describe the strengths and limitations of different diagnostic testing study designs on patient-centered outcomes, including randomized controlled trials (RCTs), observation studies, simulation or modeling, and systematic reviews
- Outline accepted structures for reporting diagnostic comparative effectiveness study results, including CONsolidated Standards Of Reporting Trials (CONSORT), Standards for Reporting Diagnostic Accuracy (STARD), and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)

Attitudinal

- Appreciate the need to address short-term, intermediate-term, and long-term patient-centered outcomes in diagnostic testing studies
- Value transparency and accessibility when reporting study results to patients and stakeholders

Skills

- Design an appropriate diagnostic testing study to match the clinical context
- Incorporate patient-centered outcomes in plans for evaluation of a diagnostic test
- Prepare an approach for testing the influence of factors known to affect a diagnostic test under evaluation
- Demonstrate application of reporting standards

The contents of this category include

Module 1	**Introduction** • Statement of standards
Module 2	**Objectives**

Module 3	**Study Designs** • Definition of diagnostic testing and CER • A review of the developmental phases of a testing modality • Uneven development of evaluation methods • Study designs for CER on diagnostic tests • Review of different study designs, including RCT, observational studies, simulation/modeling studies, and systematic reviews
Module 4	**Assessing the Effect of Factors Known to Affect Diagnostic Test Evaluations** • Test characteristics • Patient characteristics • Test interpreter characteristics • Care-setting characteristics • Statistical planning
Module 5	**Designing Studies to Reflect Clinical Practice Pathways and Incorporating Patient-Centered Outcomes in the Evaluation of Diagnostic Tests** • Studies that appropriately integrate diagnostic tests into clinical pathways • Process of care as an intermediate outcome • Documentation of posttest care • Measuring short-term and long-term patient-centered outcomes
Module 6	**Structured Reporting of Diagnostic Comparative Effectiveness Study Results** • Structured checklists for reporting study results and assessing study quality • CONSORT (example) • STARD (example) • QUADAS (example) • Analytical validity, Clinical validity, Clinical utility and Ethical, legal and social implications (ACCE) framework (example)
Module 7	**Communicating with Patients and Stakeholders** • Complexity of clinical decisions • Communicating benefits and harms • Patient-accessible information formats

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Self-Assessment for Category 10: Standards for Studies of Diagnostic Tests

Select the single best answer to each question.

1. In which phase of development is a diagnostic test compared to other testing modalities in prospective, multi-institutional studies?
   a. Phase 1 (Discovery)
   b. Phase 2 (Introductory)
   c. Phase 3 (Mature)
   d. Phase 4 (Disseminated)

2. Processes of care and patient outcomes are generally studied in which developmental stage(s) of a diagnostic test?
   a. Phase 1 (Discovery)
   b. Phase 1 (Discovery) and Phase 2 (Introductory)
   c. Phase 3 (Mature)
   d. Phase 3 (Mature) and Phase 4 (Disseminated)

3. Study designs for CER on diagnostic tests include which of the following?
   a. Prospective randomized design
   b. Observations design
   c. Modeling, simulation, and decision analysis
   d. Systematic reviews and meta-analysis
   e. All of the above

4. Which of the following is a strength of a randomized control study design?
   a. Minimizes selection bias and confounding due to indication
   b. Generally contains homogenous study populations
   c. Generally takes less time to complete relative to an observational study
   d. Yields study results that are broadly generalizable

5. Do the technical specifications of a test include criteria for a positive test result, machines types and settings, and assays?
   a. Yes
   b. No

6. Is standardization of testing technology and testing results across settings (e.g., sites, platforms, laboratories, institutions, geographic regions) essential to draw reliable and generalizable scientific conclusions?
    a. Yes
    b. No

7. Which of the following is not a process of care outcome?
    a. Time to initiation of treatment
    b. Test sensitivity
    c. The number and nature of subsequent tests or treatment
    d. Time until a definitive diagnosis is procured

8. The STARD checklist is used to do which of the following?
    a. Report on diagnostic accuracy tests
    b. Assess the quality of diagnostic accuracy tests in systematic reviews
    c. Report RCTs
    d. Ensure that all components of the PCORI funding application are complete

9. Which of the following aspects of a diagnostic test is not examined by CDC's ACCE framework?
    a. Infiltration into the healthcare market
    b. Clinical validity
    c. Clinical utility
    d. Analytical validity

10. Should the findings of comparative effectiveness studies of diagnostic tests be presented in a way that is assessable to patients and a broad range of stakeholders, and should they address patient-centered outcomes?
    a. Yes
    b. No

Category 11: Standards for Systematic Reviews

This category contains 10 modules and an interview. The learning objectives for this category are

Cognitive

- Define the basic search strategy elements required for a systematic review on a specific topic
- Outline the process of identifying and assessing studies for inclusion in a systematic review
- Explain the purpose of initiating a systematic review and define the essential elements of forming a systematic review question
- Describe the methods for synthesizing a body of evidence qualitatively and quantitatively (i.e., meta-analysis) and for critically appraising a published systematic review
- Delineate recommended ways of reporting systematic reviews

Attitudinal

- Value the importance of designing and conducting of a comprehensive literature search for a systematic review

Skills

- Demonstrate a comprehensive process of identifying studies for inclusion in a systematic review (including choice of tools for assessing the risk of bias of included studies)
- Identify an appropriate source of up-to-date standards for performing a systematic review
- Formulate a research question for a systematic review
- Prepare the outline of a protocol for a systematic review on a specific topic
- Design a strategy for grading the strength of evidence of a systematic review
- Summarize and synthesize extracted data (characteristics of included studies, risk of bias of included studies, and numerical results)

Module 7	**Step 5—Evaluate Study Quality and Applicability**
	• Decide how evaluation will be used
	• Focus on most important aspects of quality and applicability
	• How is Step 5 vulnerable to bias and error?
	• What can be done to minimize bias and error?
	  o Use established instruments
	  o Establish quality control

Module 8	**Step 6—Summarize and Synthesize Evidence** • Assemble evidence tables • Prepare written summary of evidence • Consider meta-analysis after examining heterogeneity • Assess the strength of the evidence • Review PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance on reporting systematic reviews. • How is Step 6 vulnerable to bias and error? • What can be done to minimize bias and error?
Module 9	**Putting It All Together: Appraising a Systematic Review** • Present an example of a systematic review in name only • Present an example of a systematic review that follows IOM standards
Module 10	**Putting It All Together: Designing a Systematic Review** • Give an example of a topic and ask participants to formulate the question, then show some options, and ask them to self-rate their own formulation of the question. • Ask participants to draft main elements of a protocol, then show good and bad protocols, and ask them to self-rate their own protocol draft. • Ask participants to design a strategy for grading the strength of evidence, then show good and bad examples, and ask them to self-rate their own strategy. • Present an example of extracted data, ask participants to suggest a strategy for summarizing and synthesizing, then show good and bad examples, and ask them to self-rate their own strategy compared to the examples.
Interview	**Engaging Stakeholders in Systematic Reviews and CER** Dr. Eric Bass and Ellen Tambor

5. Which of the following is important when searching for studies to include in a systematic review? *(Select all that are correct.)*
    a. Use electronic databases to maximize the identification of relevant studies
    b. Search multiple databases and other sources
    c. Keep meticulous documentation of the details of the search process
    d. Avoid using controlled vocabulary when developing a Boolean search strategy

6. What is the best way to minimize bias and error when searching for relevant studies to include in a systematic review? *(Select the single best answer.)*
    a. Use experienced reviewers with appropriate training in systematic review methods.
    b. Prepare detailed instructions for the reviewers.
    c. Ask a second reviewer to check the work of the first reviewer.
    d. Use an independent dual review process with trained reviewers, clear instructions, and a process for monitoring quality of performance.

7. What are important elements to consider when extracting data on an outcome of interest? *(Select the single best answer.)*
    a. Type of measurement and time points
    b. Domain, type of measurement, and metric
    c. Type of measurement, metric, and time points
    d. Domain, type of measurement, metric, aggregation method, and time points

8. Which of the following is a true statement about the accuracy of data extraction in systematic reviews? *(Select the single best answer.)*
    a. The error rate is relatively high even when reviewers have substantial experience.
    b. The error rate is very low when experienced reviewers extract data from eligible studies.

9. Which criteria should be used to assess potential selection bias in RCTs? *(Select the single best answer.)*
    a. Fidelity to protocol, use of co-interventions, and unintended interventions
    b. Blinding of outcome assessors and validity of outcome measures
    c. Completeness of follow-up and outcome data, and use of intention-to-treat analysis
    d. Randomization, allocation concealment, and sequence generation