METRICS
META-RESEARCH INNOVATION CENTER AT STANFORD

Minimal reporting standards for pre-clinical research

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Concepts poorly taught or understood by junior (and senior?) lab scientists

- Basic elements and formal logic and purpose of experimental design
- Foundations of statistical inference and the meaning of basic statistical summaries.
- How to link Question – Design – Measurement – Conduct – Analysis – Inference – Conclusions/Implications – Generalizations.
- Virtually every gap in training or understanding is created or reinforced by the literature they read.

A funder's attempt to improve methodology: Minimal standards are not enough

The case of the PCORI methods standards

(Patient-centered Outcomes Research Institute)

PCORI's Methodology Standards

- Required by PCORI's authorizing law
- Developed by the Methodology Committee & adopted after public comment
- Represent minimal standards for design, conduct, analysis, and reporting of research.
- Used to:
  - ✓Assess the rigor of applications
  - ✓Monitor study conduct
  - ✓Evaluate final research reports

PCORI METHODOLOGY REPORT

January 2019

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The Methodology Standards were updated in February 2019 and are available at www.pcori.org/methodology-standards.
An update to the Methodology Report will be posted later in 2019.

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

2019 PCORI Methodology Standards

65 standards grouped in 16 topic areas

Cross-Cutting Standards (5)

- Formulating Research Questions
- Patient Centeredness
- Data Integrity & Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects

Design-Specific Standards (11)

- Data Registries
- Data Networks
- Causal Inference Methods
- Adaptive & Bayesian Trial Designs
- Studies of Medical Tests
- Systematic Reviews
- Research Designs Using Clusters (2016)
- Studies of Complex Interventions (2018)
- Qualitative Methods (2019)
- Mixed Methods Research (2019)
- IPD-MA (2019)

Standards for Preventing and Handling Missing Data

- **MD-1: Describe methods to prevent and monitor missing data.**
- **MD-2: Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.** …..Estimates of treatment effects or measures of association should ….account for statistical uncertainty attributable to missing data. Methods used for imputing missing data should produce valid confidence intervals and permit unbiased inferences. … Single imputation methods, such as last observation carried forward, baseline observation carried forward, and mean value imputation, are discouraged…
- **MD-3: Record and report all reasons for dropout and missing data, and account for all patients in reports.**
- **MD-4: Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.**

PCORI Methodology Standards Checklist

Follow the instructions provided below. Upload the completed template as an Excel file into PCORI Online. Detailed instructions are included in the Application Guidelines for this PCORI Funding Announcement (PFA). Refer to the PCORI Methodology Report for explanations about the standards. Note that the Methodology Standards in red text indicate those that are newly adopted, as of February 26, 2019, by the Board of Governors.

In the checklist below, you will see a complete list of the PCORI Methodology Standards. In column D, using the drop-down menu options, indicate whether or not each methodology standard applies to your research. If the standard applies, in column E, provide the page number and section of your research plan where the text illustrates how you addressed the standard. Lastly, in column F, indicate whether your study may deviate from the standard and provide a rationale. Repeat the sequence for each standard. Note: Do not alter any formatting of this template.

Application ID					
PI Name					
Application Title					
Standard Category	Abbrev.	Standard	Have you addressed how you plan to adhere to the standard in your application?	List page numbers	Notes
Cross-Cutting Standards for PCOR					
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence			
	RQ-2	Develop a formal study protocol			
	RQ-3	Identify specific populations and health decision(s) affected by the research			
	RQ-4	Identify and assess participant subgroups			
	RQ-5	Select appropriate interventions and comparators			
	RQ-6	Measure outcomes that people representing the population of interest notice and care about			
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context			
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants			
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest			
	PC-4	Support dissemination and implementation of study results			
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for data analysis that correspond to major aims			
	IR-2	Assess data source adequacy			
	IR-3	Describe data linkage plans, if applicable			
	IR-4	Document validated scales and tests			
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity			
	IR-6	Masking should be used when feasible			
	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.			

Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data			
	MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness			
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports			
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation			
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base			
	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods			
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed			
Standards for Specific Study Designs and Methods					
Standards for Data Registries	DR-1	Requirements for the design of registries			
	DR-2	Documentation and reporting requirements of registry materials, characteristics, and bias			
	DR-3	Adapting established registries for PCOR			
	DR-4	Documentation requirements when using registry data			
Standards for Data Networks as Research-Facilitating Structures	DN-1	Requirements for the design and features of data networks			
	DN-2	Selection and use of data networks			
Causal Inference Standards	CI-1	CI-I: Specify the causal model underlying the research question ***CROSS-CUTTING STANDARD***			
	CI-2	Define and appropriately characterize the analysis population used to generate effect estimates			
	CI-3	Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure			
	CI-4	Measure potential confounders before start of exposure and report data on potential confounders with study results			
	CI-5	Report the assumptions underlying the construction of propensity scores and the comparability of the resulting groups in terms of the balance of covariates and overlap			
	CI-6	Assess the validity of the instrumental variable (i.e. how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable			

Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations			
	AT-2	Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs			
	AT-3	Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses			
	AT-4	When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications			
Standards for Studies of Medical Tests	MT-1	Specify the clinical context and key elements of the medical test			
	MT-2	Assess the effect of factors known to affect performance and outcomes			
	MT-3	Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials			
Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate			
Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level			
	RC-2	Justify the choice of cluster randomization			
	RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level			
	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude			
	RC-5	Stratified randomization should be used when feasible			
Standards for Studies of Complex Interventions	SCI-1	Fully describe the intervention and comparator and define their core functions			
	SCI-2	Specify the hypothesized causal pathways and their theoretical basis.			
	SCI-3	Specify how adaptations to the form of the intervention and comparator will be allowed and recorded			
	SCI-4	Plan and describe a process evaluation			
	SCI-5	Select patient outcomes informed by the causal pathway			
Standards for Qualitative Methods	QM-1	State the qualitative approach to research inquiry, design, and conduct			
	QM-2	Select and justify appropriate qualitative methods sampling strategy			
	QM-3	Link the qualitative data analysis, interpretations, and conclusions to the study question			
	QM-4	Establish trustworthiness and credibility of qualitative research			
Standards for Mixed Methods Research	MM-1	Specify how mixed methods are integrated across design, data sources, and/or data collection phases			
	MM-2	Select and justify appropriate mixed methods sampling strategy			
	MM-3	Integrate data analysis, data interpretation, and conclusions			
Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)	IPD-1	Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information it will provide that other approaches would not			
	IPD-2	Describe the proposed governance structure for the IPD-MA in the protocol and study reports			
	IPD-3	Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA			
	IPD-4	Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications			

METHODOLOGY STANDARDS

Please report how your project meets PCORI's Methodology Standards that apply to your ongoing research (enter N/A if appropriate). The following Standards should be addressed at the appropriate study phases (see table below):

Methodology Standards to address	Report how these Methodology Standards are being met
Standards for Formulating Research Questions	The trial design was developed using PRECIS-2 framework and adheres to PCORI methodology standards. Per RQ-1, the research question was determined based on identification of practice variation with clinicians equally committed to each intervention, and gap analyses from two recent systematic reviews from the investigative team and others establishing clinical equipoise between INTERVENTION X and INTERVENTION Y. A formal study protocol was developed stating research objectives, study design, exposures, analysis and outcomes and has been registered on clinicaltrials.gov per RQ-2. The primary objective of the trial is to compare the effectiveness of INTERVENTION X versus INTERVENTION Y among patients with CONDITION Z; which are in accordance to RQ-3 and RQ-6 Standards. Effectiveness will be measured based on reduced duration of feeding tube dependency, an outcome valued equally by patients, caregivers and clinicians (RQ-6). In addition, we have identified several participant subgroups for whom differences in treatment response or swallowing outcomes may exist, per PCORI Methodology Standard (RQ-4): namely, age at diagnosis, HPV status, prior surgery, radiation therapy dose, addition of chemotherapy, and use of prophylactic feeding tube.
Standards Associated with Patient Centeredness	Through stakeholder engagement, we continue to give ongoing feedback to the Trial Executive Committee by engaging several groups of stakeholders partners (patients, family caregivers, policy makers and payer representatives, as well as clinicians from multiple disciplines) at all phases of the study, from conception through dissemination. Stakeholders engage in meaningful input and decision-making in collaborative settings as part of homogeneous stakeholder groups as well as a multi-disciplinary Stakeholder Advisory Board (PC-1). In Module 01, stakeholders informed the implementation of the criteria for 'trigger' in Arm 01 INTERVENTIN X patients. In Module 02, stakeholders reviewed and provided recommendations for secondary outcomes aligning with PCORI Methodology Standard (PC-3), some of which following review by the Trial executive Committee have now been incorporated in the last REB/IRB amendment. In year 04, stakeholders will also engage in review and interpretation of study findings and together, we will design and execute the implementation and dissemination plan (PC-4). This is a patient-centered trial. All patients eligible for the trial will be approached by study coordinator for consent to capture a representative spectrum of the target population, in accordance with PCORI Methodology Standard PC-2.
Standards for Data Integrity & Rigorous Analyses	A quantitative data analysis plan have been determined a priori that correspond to major aims (PCORI Methodology Standards IR-1). For Aim 1, an intention-to-treat (ITT) approach will be applied incorporating a gate-keeper method to control risk of Type I error in the setting of multiple comparisons. The initial analysis will compare the INTERVENTION X to the combined INTERVENTION Y groups in terms of the duration of outcome within the 12-month study period by means of a multiple linear regression model with covariate adjustment. If this test yields $p < 0.05$, the two INTERVENTION Y groups will be compared using the same linear analysis method. The meaningful variables proposed to include in the regression model are: age; HPV status; surgery (yes/no); chemotherapy (yes/no); radiation dose; and facility. The data management plan was developed in accordance with PCORI Methodology Standards for Data Integrity and Rigorous Analysis (Consortium Contractual Arrangements –) (IR-7). Data sources include the electronic health record, imaging data (videofluoroscopy), and a mixture of clinician-graded and patient-reported outcomes reported using validated scales and tests (IR-4). Linkage of study, clinical, and imaging source data (IR-3) will be maintained in the secure central database via unique study identifiers. All source data will derive from individual level patient records maintained in each participating site's health record or study forms although patient information will be de-identified in study database.

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Patient-Centered Outcomes Research Institute (PCORI) Methodology Standards to Improve the Design and Reporting of Research

Evan Mayo-Wilson,[1] Kelly Vander Ley,[2] Kay Dickersin,[1] Mark Helfand[2]

Objective The Patient-Centered Outcomes Research Institute (PCORI) began receiving funding applications in September 2011 and published Methodology Standards in November 2013 addressing issues related to research design and transparent reporting. PCORI requires that investigators of funded studies submit a draft final research report (DFRR) that is peer reviewed by an external team; after revision, in response to peer-review, the final report is published on the PCORI website. We sought to determine whether research described in DFRRs adheres to the PCORI standards.

Mayo-Wilson Results

- **0 of 31 final reports adhered to all the standards.**
- Due to incomplete reporting and nonadherence with recommendations.
- (1) Most reports neither included nor cited a systematic review, and most did not include or cite a study protocol
- (4) Many reports did not use appropriate methods for handling missing data
- (5) Most reports examined heterogeneity with subgroup analyses, but few studies conducted confirmatory tests for heterogeneity.

Implications

- **Even a funder with substantial leverage and resources has difficulty changing dominant paradigms of practice, no less paradigms of reasoning.**
- **We are now conducting a portfolio review to see which manuscript problems are detectable or preventable in the initial stages of the proposed research.**
- **The difference between technical solutions (the standards) and true policy solutions (getting them used, no less understood) is enormous; *the latter is more important and much harder.***

nature research
Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

www.thelancet.com Vol 374 August 8, 2009

The art of medicine

Reality check for checklists

*Charles L Bosk, Mary Dixon-Woods, Christine A Goeschel, Peter J Pronovost

[Peter Pronovost's commentary on the misinterpretation of his celebrated "checklist" that purportedly eliminated central line infections in Michigan hospitals.]

The study was widely reported in the popular media and elsewhere as a triumph of the "simple checklist" as a solution to patients' safety problems. Yet the widespread interest in this study is a dual-edged sword.

It was a great story…The problem is that the story may well have been oversimplified. The emphasis on checklists is a Hitchcockian "McGuffan", a distraction from the plot that diverts attention from how safer care is really achieved…**widespread deployment of checklists without an appreciation of how or why they work is a potential threat to patients' safety and to high-quality care**.

www.thelancet.com Vol 374 August 8, 2009

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The mistake of the “simple checklist” story is in the assumption that a technical solution (checklists) can solve an adaptive (sociocultural) problem…

Emphasising checklists as the explanatory mechanism for the reduction in catheter related infections obscures the complex labour necessary to create a collective local faith in checklists. How support was mobilised for coordinating work around infection control is the real story of the Keystone ICU project.

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Another important feature is the emphasis of the model on conferring legitimacy on the intervention. This was achieved by allowing teams to customise the implementation of evidence locally, and challenging assumptions about who has relevant knowledge, who counts as an expert, and who is able and ought to act to improve safety. **Indeed, it would be a mistake to say there was one "Keystone checklist": there was not a uniform instrument, but rather, more than 100 versions**. Each ICU, informed by evidence and a prototype, was encouraged to develop their own checklist to fit their unique barriers and culture. Taken together, what the Keystone programme did was change workers' motives for cooperating so that they internalised new norms.

www.thelancet.com Vol 374 August 8, 2009

The art of medicine

Reality check for checklists

When we begin to believe and act on the notion that safety is simple and inexpensive, that all it requires is a checklist, we abandon any serious attempt to achieve safer, higher quality care. Reporting the Keystone initiative as a success of checklists teaches the wrong lesson: namely, that reliable, safe care requires nothing more than insisting upon routine, standardised procedures.

The “simple checklist” stories in the press created excitement about progress in achieving patients’ safety and reassurance for the public and policy makers, but the real story of Keystone is messier and more complex. Although we all hope for the simple solution that with ease and no additional expense makes a stay in the ICU safer, there is some danger in mistaking hope for reality. The answer to the question of what a simple checklist can achieve is: on its own, not much.

Where do we go from here?

- Technical fixes alone will not work. Checklists/minimal reporting standards are *reminder* systems; they do not substitute for understanding how the plane flies.
- If the users don't have that understanding, enforcing de minimus reporting requirements can require de maximus effort with de minimus results.
- Pressure & legitimacy needs to be exerted at all levels, from funders, journals, regulators, professional societies, but change occurs at the ground level, and must include education + the means to operationalize it.
- Improving research practices must be driven by scientists reforming their own fields with the help of R&R experts, impelled by institutional leadership, manifest by structures & metrics.
- We need to partner with and learn from those who study institutional and disciplinary change, e.g. sociologists and organizational experts.