



An Official American Thoracic Society Research Statement: Comparative Effectiveness Research in Pulmonary, Critical Care, and Sleep Medicine

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Background: Comparative effectiveness research (CER) is intended to inform decision making in clinical practice, and is central to patient-centered outcomes research (PCOR).

Purpose: To summarize key aspects of CER definitions and provide examples highlighting the complementary nature of efficacy and CER studies in pulmonary, critical care, and sleep medicine.

Methods: An *ad hoc* working group of the American Thoracic Society with experience in clinical trials, health services research, quality improvement, and behavioral sciences in pulmonary, critical care, and sleep medicine was convened. The group used an iterative consensus process, including a review by American Thoracic Society committees and assemblies.

Results: The traditional efficacy paradigm relies on clinical trials with high internal validity to evaluate interventions in narrowly defined populations and in research settings. Efficacy studies address the question, "Can it work in optimal conditions?" The CER paradigm employs a wide range of study designs to understand the effects of interventions in clinical settings. CER studies address the question, "Does it work in practice?" The results of efficacy and CER studies may or may not agree. CER incorporates many attributes of outcomes research and health services research, while placing greater emphasis on meeting the expressed needs of nonresearcher stakeholders (e.g., patients, clinicians, and others).

Conclusions: CER complements traditional efficacy research by placing greater emphasis on the effects of interventions in practice, and developing evidence to address the needs of the many stakeholders involved in health care decisions. Stakeholder engagement is an important component of CER.

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OVERVIEW

- Efficacy studies rely on clinical trials with high internal validity (explanatory trials) to answer the question "Can it work in optimal conditions?" Comparative effectiveness research (CER) is intended to answer the question, "Does it work in practice?"
- CER embraces a range of study designs, including pragmatic trials and observational studies. The research methods in CER are similar to those used for outcomes research or health services research, but CER emphasizes engagement and involvement of diverse perspectives of stakeholders, including patients, in prioritizing research questions and study designs.
- Although efficacy and CER designs complement each other, results of efficacy and CER studies may not agree.
- The Patient-Centered Outcomes Research Institute, an independent research agency funded by the 2010 United States Affordable Care Act, was developed to help patients and their caregivers communicate and make informed health care decisions. The Patient-Centered Outcomes Research Institute funds CER and other research methodologies, but not cost-effectiveness research.
- To respond effectively to funding opportunities in CER, the pulmonary, critical care, and sleep research communities will need to understand CER and how it complements efficacy-based designs.
- The American Thoracic Society and its members are well positioned to promote multistakeholder engagement in the design, conduct, and dissemination of CER and efficacy research in pulmonary, critical care, and sleep medicine.

INTRODUCTION

Comparative effectiveness research (CER) has received considerable attention in recent years, including in the lay press (1–3). Funding opportunities for CER have grown with the recognition that, with an increasing number of health care options, patients, clinicians, and other stakeholders need better evidence to guide decision making in practice settings (4). In the past, most of these decisions were guided by *efficacy research*. Efficacy research is designed to determine if an intervention (prevention, screening, or treatment) works under conditions that maximize internal validity

and the likelihood of detecting an intervention effect, while minimizing harm. As such, efficacy research often excludes patients who have comorbidities and who do not adhere to study procedures. Moreover, studies employing the efficacy paradigm are generally conducted in research settings by trained research personnel and with sufficient resources to ensure that the intervention is delivered appropriately. Efficacy studies intend to answer the question “Can it work in optimal conditions?” Therefore, they are well suited to identifying potential health care options, but ill equipped to determine how well the intervention works in clinical practice.

In contrast to efficacy research, *effectiveness research* is designed to compare the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in clinical practice settings (5). Clinical practice settings are characterized by incomplete patient adherence, variable levels of provider expertise, and limited resources. In other words, there is increasing concern that efficacy models of evidence generation may not always provide actionable information to support clinical decision making between patients and health care providers at the point of care (6, 7). CER research offers the opportunity to generate the evidence needed to choose among the various treatment options available in clinical practice, and to determine which is most appropriate for a given patient. There is hope that the CER paradigm can supplement traditional efficacy-driven research by providing more relevant data to support quality improvement initiatives, clinical practice guidelines, health insurance coverage decisions, and patient-centered outcomes research (PCOR) (8–10). The Patient Centered Outcomes Research Institute (PCORI), an independent research agency, funded by the 2010 United States Affordable Care Act, was developed specifically to help patients and their caregivers communicate and make informed health care decisions (11, 12). PCOR uses CER and other methodologies to achieve its goals. In many respects, CER methods are not entirely unique or new. CER incorporates many attributes of outcomes research and health services research (13, 14), although CER provides a substantially greater emphasis on meeting the expressed needs of nonresearcher stakeholders in the design, conduct, and dissemination of findings.

Although there have been other general reports about CER (15, 16), guidance from the American Thoracic Society (ATS) about the specific role of CER for pulmonary, critical care, and sleep disorders is needed. To address this gap, we convened an *ad hoc* Working Group of ATS members with expertise in clinical trials, health services research, observational research methodologies, quality improvement, and behavioral sciences in pulmonary, critical care, and sleep medicine to develop this *Research Statement*. The objectives of this *Statement* are to summarize key aspects of CER definitions and provide illustrative examples that highlight the complementary nature of efficacy and CER studies in pulmonary, critical care, and sleep medicine. Elements of study design include the patient population (eligibility criteria), intervention and comparators (dose, frequency, duration, use of inactive or active control groups, interventions to promote adherence to study protocols), primary and secondary outcomes (selection, prioritization, frequency, and measurement tools), timeframe (assessment period), and setting (practices involved in research). Few clinical studies adhere exclusively to efficacy or effectiveness principles in all elements of their design. Instead, some design elements may be more consistent with an efficacy design (e.g., highly selective eligibility criteria that exclude patients with multiple chronic conditions and a history of nonadherence to therapy), whereas others may be aligned with an effectiveness design (e.g., consistent with clinical practice, both patients and clinicians are aware of treatment assignment). Moreover, each element of a study design

may exist along a continuum between efficacy and effectiveness. However, to best illustrate the contrast between efficacy and effectiveness designs, this *Research Statement* will include examples that represent extreme ends of the efficacy and effectiveness continuum across most or all study design elements.

DEFINITIONS

The Institute of Medicine (IOM), the Department of Health and Human Services (DHHS), and the Affordable Care Act have each promulgated the need for CER (5, 15–17). Yet each has proposed somewhat different working definitions of CER. The broadest definition, from the IOM (15), defines CER as “*the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care ... to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care*” (15). This expansive definition can be interpreted to include both efficacy and effectiveness research.

The DHHS defines CER as the “*conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in ‘real world’ settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances*” (5, 16). The DHHS definition emphasizes the need for CER to directly inform clinical practice, and, like the IOM, recognizes a role for patients, clinicians, and other stakeholder needs when designing studies.

The Affordable Care Act authorized the formation of PCORI to promote “patient-centered outcomes research” to inform patients and their caregivers (11, 17). Under the Act, PCOR is defined as research that “*helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options*” (18). Not surprisingly, PCOR has substantial overlap with definitions of CER cited here, but also provides particular emphasis on studies that address “*outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life.*” PCOR uses CER designs to address some questions (e.g., “What are my options and what are the potential benefits and harms of those options?”), but PCOR also includes research activities to address issues of importance to patients (e.g., research to support systematic collection of key patient-reported and patient-centered outcomes; identifying optimal methods for engaging patients in the research process) (19).

Common to the various definitions of CER is the importance of explicitly meeting the needs of a wide group of health care decision makers, developing evidence that directly informs clinical practice, and evaluating outcomes that are meaningful to patients. To ensure that CER answers relevant questions, a broad representation of stakeholders must be engaged to develop research priorities and specific research questions (20). Although there is no single or standard definition of a “stakeholder” for CER, the term is typically used to denote a broadly defined end-user group: patients and their caregivers, practicing clinicians, policymakers, industry representatives, private and public health care purchasers, and researchers. For applications submitted in response to PCORI funding announcements, stakeholder engagement involves more than simply creating an advisory committee to assist researchers with dissemination

activities after study completion. PCORI emphasizes patient and caregiver engagement, but also encourages partnerships with other stakeholders throughout the research plan, including formulation of research questions, selecting essential features of the study design (defining participants, comparators, outcomes of interest), monitoring study conduct and progress, and disseminating study results. PCORI asks that applicants provide justification in cases where more limited approaches to stakeholder engagement are selected. Definitions of stakeholders and adequate stakeholder engagement are likely to depend on the funder, so should be reviewed before developing research applications. Nevertheless, stakeholder engagement is likely to lead to a stronger focus on “real-world” problems and ensure that the information generated through CER provides actionable information applicable to clinical practice.

As an example of stakeholder engagement on a broader level to establish a research agenda, the Agency for Healthcare Research and Quality COPD Outcomes-Based Network for Clinical Effectiveness and Research Translation (CONCERT) convened a wide base of stakeholders, including patients, clinicians, researchers, policymakers, industry representatives, and private and public health care purchasers, to develop priorities for effectiveness and implementation research in chronic obstructive pulmonary disease (COPD) (21). Results of the work by CONCERT highlighted the challenges of establishing research priorities, as different stakeholder groups have overlapping or contrasting views about what is needed. The CONCERT

investigators recommended the use of a structured, transparent, multicriteria decision analysis tool (e.g., analytic hierarchy process) to help understand why preferences for CER varied across stakeholder groups. The optimal methods for engaging patients, clinicians, and other end users in the research process, however, are unclear.

EXAMPLES COMPARING EFFICACY AND EFFECTIVENESS STUDY DESIGNS

As stated previously here, there is a continuum between efficacy and effectiveness, and, depending on the study question, investigators may select a specific dimension of study design (e.g., selection of participants) to approximate the effectiveness end of this continuum, whereas other aspects of study design (e.g., fidelity with which the intervention is applied) may be more consistent with the efficacy end of this continuum (22). Efficacy designs emphasize use of clinical trials with high internal validity (efficacy or explanatory trials). CER designs include clinical trials (effectiveness or pragmatic trials), but also observational studies (e.g., cohort studies) and quasiexperimental studies (e.g., interrupted time series and regression discontinuity designs) (Table 1). CER also includes evidence synthesis activities, such as systematic reviews with meta-analyses. The most appropriate design (e.g., efficacy trial, effectiveness trial, observational study) depends on the study question and priorities of stakeholders who will develop, use, and disseminate

TABLE 1. COMMON STUDY DESIGNS IN COMPARATIVE EFFECTIVENESS RESEARCH

Study Design	Some Key Advantages and Limitations
Randomized clinical trial (unit of randomization is an individual subject or groups of subjects, such as a clinical practice)	<p><i>Advantages:</i> Randomization is the superior method for limiting threats to internal validity, such as measured and unmeasured factors confounded with exposure status (e.g., symptom severity and use of long-acting bronchodilators).</p> <p><i>Limitations:</i> Some patient subgroups may be less likely to provide informed consent for participation in randomized clinical trials, which could limit generalizability of study findings. Randomization may not be ethical or possible to conduct (e.g., due to inadequate equipoise among patients or clinicians; intervention of interest is already in widespread use). May be difficult to design in cases where there is insufficient information about dose, frequency, duration, effect size, or populations likely to benefit or be harmed. Resources needed to conduct randomized clinical trials limit the number of questions that can be addressed.</p>
Quasiexperimental designs (e.g., interrupted time series, regression discontinuity)	<p><i>Advantages:</i> Permits evaluation of an intervention effect when randomized clinical trials are not possible (see above for explanation). Design well suited for large-scale evaluations of policy changes with sufficient power to evaluate and identify sources of heterogeneity of treatment effects (e.g., by region, patient population, provider, health care setting).</p> <p><i>Limitations:</i> Need adequate data about timing and spread of intervention in study population and outcomes before and after intervention implementation, which may not be routinely collected, archived, or available. Potential for confounding or bias that limits internal validity (e.g., unmeasured factors that lead to secular trends in outcome other than intervention of interest).</p>
Observational studies (e.g., cohort, secondary analyses of electronic health records or administrative data sets)	<p><i>Advantages:</i> Permits evaluation of an intervention effect when randomized clinical trials are not possible (see above for explanation). Design well suited to evaluate clinical practice (clinician behavior [e.g., adherence to asthma guidelines]) or natural history of outcomes by region, patient population, and health care setting. Can inform design of clinical trials or quasiexperimental studies.</p> <p><i>Limitations:</i> Need adequate data about timing and spread of intervention in study population and outcomes, which may not be routinely collected, archived, or available. Risk of missing data or inadequate data especially high in retrospective studies or when using administrative data. Some data types (e.g., patient reported outcomes) may be incomplete or missing in existing data sources; prospective data collection may be necessary. Potential for confounding or bias that limits internal validity (e.g., unmeasured factors that lead to secular trends in outcome other than intervention of interest).</p>
Evidence synthesis (e.g., qualitative systematic literature reviews or meta-analyses)	<p><i>Advantages:</i> Systematic reviews provide opportunity to synthesize evidence developed by different studies, identify need for additional evidence.</p> <p><i>Limitations:</i> Publication bias may limit available evidence. Existing data largely based on efficacy designs, which may limit generalizability to clinical practice.</p>

the information: *timeliness* (e.g., how quickly is the information needed?); *relevance* to specific populations and settings (e.g., to whom is the evidence intended to apply: smokers, nonsmokers, or both? Urban, rural, or both?); *tolerance for bias and confounding* (e.g., would study findings be informative if nonadherence was common in one or more of the comparison groups?); and *resources* available to answer the study question (e.g., is there an infrastructure for clinical trial?). More details about the various CER designs are presented in recent reviews (23–25).

To illustrate the complementary information gained from efficacy and effectiveness designs, we provide illustrative examples of studies in three clinical areas relevant to ATS. Within each area, we provide hypothetical descriptions in Tables 2–4 of an efficacy trial and two different effectiveness study designs (a trial and an observational study).

1. Pulmonary medicine (among patients hospitalized for an exacerbation of COPD, is initial therapy with high-dose intravenous corticosteroids superior to low-dose oral corticosteroids?) (Table 2).
2. Critical care medicine (in patients with acute respiratory distress syndrome due to sepsis, does therapy guided by pulmonary artery catheters [PACs] improve outcomes compared with therapy without PAC guidance?) (Table 3).
3. Sleep medicine (among patients with obstructive sleep apnea [OSA] who have failed continuous positive airway pressure [CPAP], is uvulopalatopharyngoplasty [UPPP] superior to oral appliances in improving daytime sleepiness?) (Table 4).

Patient Populations

Eligibility criteria for efficacy trials are generally based on strict disease definitions (e.g., diagnosis of COPD based on airflow obstruction on spirometry, even though most patients with a physician diagnosis of COPD have not had spirometry, and some patients with radiographic evidence of emphysema have normal spirometry). Efficacy trials generally exclude patients likely to be nonadherent with the research protocol to optimize the opportunity for detecting a treatment effect (even though nonadherence is common). By contrast, effectiveness studies employ more inclusive eligibility criteria to determine what is likely to occur in clinical practice (25–27). Prospectively defined subgroup analyses, if adequately powered, could then determine if the patterns of harms and benefits vary depending on the criteria used to define the patient population. For example in the case of OSA, diagnosis based on local sleep laboratory findings could be used in effectiveness studies, rather than requiring central overreading (a commonly used approach to standardize disease definitions in efficacy studies) (26). Alternatively, central overreads could be used in a random sample to assess the robustness of the results using alternative entry criteria.

The tightly controlled settings and high resource needs of efficacy trials often necessitate that they be performed in large academic institutions. With a greater emphasis on providing the evidence to guide clinical practice, CER needs to address care delivered not only in academic institutions, but also in community settings (e.g., health maintenance organizations, federally qualified health centers, or other practice-based research networks).

Data sources for observational studies include clinical registries (e.g., cystic fibrosis registry) or data collected expressly for research. Claims data or electronic health records can also be

used for observational designs. Although observational designs are particularly helpful for answering questions in populations that are underrepresented in clinical trials (e.g., elderly or minorities or those with multiple comorbid conditions), they are associated with increased risk of confounding and bias (26). Whether the benefits of observational studies are outweighed by their downside risks depends on the needs of the stakeholder.

Intervention and Comparators

The experimental and comparator interventions in the efficacy framework are specific, including dose, frequency, and duration (Tables 2–4). Efficacy trials are conducted with trained and, often, expert clinicians and infrastructure to carefully implement study procedures. For example, in a study of PACs in sepsis and acute respiratory distress syndrome, an efficacy study would use a single standard catheter with a strict protocol for placing and interpreting findings from the PACs (28). By contrast, interventions and comparators in effectiveness studies are intended to reflect real-life options and how such options would be implemented in practice (e.g., implemented by clinicians, not researchers). In an effectiveness study of PAC use, catheter placement, measurement, and data interpretation would occur according to local practice (29, 30). If assessing whether an oral appliance or UPPP is better for patients with OSA who have failed CPAP, an effectiveness trial might permit the use of any available mandibular advancement device without the use of a prespecified, single-titration protocol.

Efficacy studies may employ inactive (placebo or sham) or active (prevention, screening, or treatment alternative) comparators to establish the potential benefit of an intervention. Understanding the relative effectiveness of alternatives used in clinical practice is of particular importance in CER studies, so CER studies generally use active comparators. For example, an efficacy study of CPAP for sleep apnea may use sham CPAP as the comparator, whereas an effectiveness study might compare CPAP to available oral appliances or a weight loss program in a community setting.

Comparison to usual care is also acceptable in effectiveness studies, although usual care typically includes a range of practices, and therefore introduces ambiguity about how to evaluate the results. If a study results in positive findings, it may not be possible to know whether the intervention was superior to all of the combinations of usual care, or whether the effect was driven by a subset of usual care. Negative studies could occur if there were convergence between groups and both groups received similar care over the course of the study. Carefully recording the care, including cotherapies, and clinician perceptions of the effectiveness of the care used in the intervention and usual care groups could help interpret study results and examine the potential for heterogeneity of treatment effects. An alternate strategy is to standardize the care in the control group, but this creates a single practice standard as a comparator, and precludes the opportunity to compare differences between the intervention and multiple comparators. Standardizing care in the control group may also not be feasible without substantial resources to monitor and promote specific care patterns—resources not available in clinical practice.

In observational studies, administrative records data can be used to identify interventions and comparators (Table 1–3). Claims data, however, are susceptible to measurement error (e.g., patient may not be receiving the intervention, or may receive the intervention at a lower or higher dose or frequency

TABLE 2. PULMONARY STUDY EXAMPLES—QUESTION: AMONG PATIENTS HOSPITALIZED FOR AN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE, IS INITIAL THERAPY WITH HIGH-DOSE INTRAVENOUS CORTICOSTEROIDS SUPERIOR TO LOW-DOSE ORAL CORTICOSTEROIDS?

	Efficacy Trial	Effectiveness	
		Trial	Observational Study
Participant eligibility criteria	Physician diagnosis of COPD exacerbation Age > 50 yr 20 pack-years or more smoked FEV ₁ < 50% of predicted Excluded patients with clinically important comorbid conditions (e.g., heart failure) or concerns about adherence to therapy after discharge	Physician diagnosis of COPD exacerbation Age > 50 yr 20 pack-years or more smoked Excluded patients only for safety reasons or could not tolerate oral medications (e.g., vomiting or poor gastric mobility)	ICD-9 billing code for primary discharge diagnosis of COPD, or ICD-9 billing code for primary discharge diagnosis of respiratory failure, with a secondary diagnosis of COPD Age > 50 yr No exclusions
Experimental intervention	Oral corticosteroids initiated within 6 h of presentation Specified dose, frequency, and duration (40 mg/d × 10 d) Promote fidelity to study interventions; deviations from the recommendations are considered protocol violations	Oral corticosteroids initiated as soon as possible, within 24 h of hospital admission Suggested dose, frequency, and duration (40 mg/day × 10 d) Treating physician may modify if patient has problems tolerating regimen (e.g., may switch to intravenous corticosteroids if develop problems with oral treatment)	Oral corticosteroids initiated within 1 calendar day of hospital admission Received prednisone via mouth, at least 40 mg/d for 2 calendar days
Comparison intervention	Intravenous corticosteroids initiated within 6 h of presentation Specified dose, frequency, and duration (methylprednisolone 125 mg intravenous every 6 h × 72 h, then oral prednisone 40 mg × 7 d) Promote fidelity to study interventions; deviations from the recommendations are considered protocol violations	Intravenous corticosteroids initiated as soon as possible, within 24 h of hospital admission Suggested dose, frequency, and duration (methylprednisolone 125 mg intravenous every 6 h × 72 h, then oral prednisone 40 mg × 7 d) Treating physician may modify if patient has problems tolerating regimen (e.g., if there are problems with insomnia or hyperglycemia)	Intravenous corticosteroids initiated within 1 calendar day of hospital admission Received methylprednisolone (or similar medication) 125 mg intravenous every 6 h for at least 2 calendar days
Practitioner expertise	Research network, includes a high proportion of specialist physicians and dedicated staff with expertise in clinical trials Intense training in study procedures	Full range of expertise, specialists and nonspecialists; no dedicated staff to ensure adherence	No exclusions
Primary trial outcomes	Treatment failure (initiation of mechanical ventilation after the second hospital day, inpatient mortality, or readmission for acute exacerbation of COPD within 30 d of discharge)	Patient-centered outcome: return to baseline level of functional health (e.g., able to work) Hospital length of stay Readmission or death within 30 d Stakeholder input used to select primary outcome	Hospital length of stay Readmission or death within 30 d
Follow-up intensity	Daily measurement of clinical status by study team while in the hospital, weekly phone calls after hospital discharge; in-person study visit after hospital discharge at 30 d	Nonobtrusive, such as administrative review of employment records, electronic medical records, and National Death Index	Nonobtrusive, such as administrative review of employment records, electronic medical records, and National Death Index
Practitioner and patient adherence	Audits and feedback for protocol fidelity	Fidelity and adherence measured without feedback	Difficult to assess practitioner or patient adherence
Analysis of primary outcome	ITT; Adjusted analysis based on baseline values; sufficient power for subgroups of interest may or may not be part of the study design	ITT; sufficient sample size in subgroups of interest, particularly those who are generally excluded from efficacy trials (e.g., those with clinically important comorbidity or those requiring noninvasive mechanical ventilation)	Patients who received intervention and comparison treatments; effects of confounding/selection bias minimized using propensity scores

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICD-9 = *International Classification of Diseases*, Ninth Revision; ITT = intention to treat; PAC = pulmonary artery catheter.

than recorded). Claims data can be supplemented with clinical data stored in electronic health records. These linked administrative-clinical data sources are available within some health care organizations (e.g., the Veterans Administration) (8). Research organizations, such as the DARTNet Institute (www.dartnet.info), the Health Maintenance Organization Research Network (27), and CONCERT (31), have developed

these linkages across health systems, but only in a relatively modest number of institutions. The available data will likely shape how one assesses the intervention and the comparator. For example, to study the impact of intravenous versus oral steroids on COPD exacerbations, billing codes for these agents can be used to identify the intervention and comparator (Table 2).

TABLE 3. CRITICAL CARE STUDY EXAMPLES—RESEARCH QUESTION: IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME DUE TO SEPSIS, DOES THERAPY GUIDED BY PULMONARY ARTERY CATHETERS IMPROVE OUTCOMES COMPARED TO THERAPY WITHOUT PULMONARY ARTERY CATHETER GUIDANCE?

	Efficacy Trial	Effectiveness Designs	
		Trial	Observational Study
Participant eligibility criteria	Consensus criteria definitions for ARDS and sepsis Exclusions of high-risk and low-risk patients	Physician diagnosis of ARDS and sepsis Exclusions only for contraindication to PAC	ICD-9 billing codes for ARDS plus codes for sepsis, pneumonia, trauma, surgical complications, etc.
Experimental intervention	Catheter placed within 4 h of randomization One catheter type Placement protocol Measurement protocol Management protocols for shock and volume status	Catheter placed when physician available Placement, measurement, and management however and how often data are measured, interpreted, and used by physician in local practice	CPT code for PAC
Comparison intervention	Central venous pressure measurement to assess volume status	No PAC Allow central venous pressure measurement when present or noninvasive methods to assess filling pressure and cardiac output	No CPT code for PAC
Practitioner expertise	PAC team—intense training in catheter placement and measurements	Existing staff expertise	No exclusions based on physician type
Primary trial outcome	14-d organ failure-free days	6-mo all-cause mortality	6-mo all-cause mortality
Follow-up intensity	Daily measurement of organ function variables	6-mo follow up through EMR or National Death Index	6-mo follow up through EMR or National Death Index
Practitioner adherence	Audits and feedback for protocol use	Fidelity and adherence measured without feedback	Difficult to assess practitioner adherence
Analysis of primary outcome	ITT; adjusted analysis based on baseline values	ITT; effects overall and within subgroups defined by presence of shock and ARDS severity	Patients who received intervention and comparison treatments; effects of confounding/selection bias minimized using propensity scores

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CPT = current procedural terminology; EMR = electronic medical record; ICD-9 = *International Classification of Diseases*, Ninth Revision; ITT = intention to treat; PAC = pulmonary artery catheter.

Outcomes

Choosing appropriate outcome measures is an important challenge facing researchers involved in any clinical research. Physiology or biomarkers as endpoints (because such measures link directly to mechanisms of disease) may be sufficient for efficacy studies. In CER studies, the views of patients and other stakeholders should be considered when selecting outcomes. For example, efficacy trials in pulmonary medicine have traditionally used spirometry measures of lung function (32); it is likely that patients and other stakeholders (e.g., payers) would prefer exacerbations, acute care use, and other endpoints in effectiveness studies. It is likely that different stakeholders would have divergent views about what outcomes are of particular importance; researchers need to carefully consider how best to incorporate input from different stakeholders in such cases. Effectiveness studies also tend to emphasize primary outcome measures that are practical to use for decision making in clinical practice (e.g., patient-reported outcome), rather than outcomes that require specialized tools, personnel, or infrastructure (e.g., 6-min walk distance to measure exercise tolerance).

In observational studies, outcomes generally focus on measures of health care use (length of stay, all-cause mortality, and total health care costs), as these outcomes are generally available in administrative and electronic health record data. Limitations of observational studies based on these data sources include missing data for outcome measures not routinely collected in practice (e.g., anxiety or patient satisfaction scores) or misclassification (e.g., pneumonia versus asthma exacerbation).

Cost effectiveness as an outcome in effectiveness studies is poised to take on greater importance in the United States, given the national attention devoted to controlling health care expenditures. Dollars-per-quality-adjusted life years can be used as

an outcome measure to inform discussions about health care expenditures associated with strategies of care. Dollars-per-quality-adjusted life years simultaneously capture multiple dimensions of benefit (e.g., both “better” and longer life) (33, 34). In some areas of the world (e.g., the United Kingdom), a combination of clinical and cost effectiveness is considered before making therapies broadly available in clinical practice (35). In the United States (36–38), there is little public support for the use of cost effectiveness for decision making, because it may reduce options available to patients and providers (39). By statute, PCORI is not allowed to fund cost-effectiveness studies, or studies in which cost is an outcome measure (even if cost is specified as a secondary outcome) (36, 40). PCORI-funded studies, however, may collect detailed measures of resource use for the interventions and comparators, permitting cost-effectiveness analyses through other mechanisms (41).

INTERPRETING RESULTS OF EFFICACY AND EFFECTIVENESS STUDIES

Results of efficacy and effectiveness studies may or may not agree. For example, efficacy trials generally support the use of inhaled corticosteroids (ICS) as first-line agents in patients with mild or moderate persistent asthma (42, 43). However, a recent effectiveness trial found leukotriene receptor antagonists (LRAs) to be as effective as ICS for long-term control, likely due to better adherence to LRAs (44). These results do not imply that the efficacy studies are wrong; ICS may still be the best choice for those patients who are willing and able to maintain high levels of adherence to ICS. The efficacy studies demonstrate that, under ideal conditions, where study patients are trained to use inhaler devices correctly and regularly, ICS yield

TABLE 4. SLEEP STUDY EXAMPLES—QUESTION: AMONG PATIENTS WITH OBSTRUCTIVE SLEEP APNEA WHO HAVE FAILED CONTINUOUS POSITIVE AIRWAY PRESSURE, IS UVULOPALATOPHARYNGOPLASTY SUPERIOR TO ORAL APPLIANCES IN IMPROVING DAYTIME SLEEPINESS?

	Efficacy Trial	Effectiveness Designs	
		Trial	Observational Study
Participant eligibility criteria	AHI > 15/h using standardized measurement and scoring procedures using polysomnography Documented failure of CPAP Excessive daytime sleepiness based on MSLT No contraindications for oral appliance or UPPP No prior use of oral appliances and no prior upper airway surgery except tonsillectomy Exclusions for comorbidities related to disability in 3 mo, depression, other sleep disorders, confounding medications	Clinical diagnosis of moderate to severe OSA Not interested in CPAP therapy Self-report of daytime sleepiness No contraindications for oral appliance or UPPP	Patients with a billing diagnosis of OSA in the past 10 yr who have an insurance claim for either an oral appliance or UPPP
Experimental intervention	UPPP performed using standardized protocol with concomitant nasal procedure only allowed as per protocol	UPPP performed as per surgeon with no restrictions on concomitant nasal surgery	Any UPPP
Comparison intervention	Oral appliance using the Herbst device and following a fixed titration algorithm	Any mandibular advancement device with no specified titration algorithm	Any mandibular advancement device with no specified titration algorithm
Practitioner expertise	Sleep medicine boarded surgeons with a high volume of UPPP cases and sleep medicine boarded dentists Intense training in study procedures	Any practitioner who offers UPPP or oral appliance	Any practitioner who offers UPPP or oral appliance
Primary trial outcomes	AHI, MSLT scored by blinded central reading center	Epworth Sleepiness Score, quality of life, costs of OSA care	Motor vehicle accident injuries (based on billing claims and National Death Index) Work productivity (based on absenteeism rates from employer databases) Overall health care costs
Follow-up intensity	Weekly by telephone, monthly in person for up to 3 mo	Nonobtrusive, such as administrative review of electronic medical records	None
Practitioner and patient adherence	Audits and feedback for protocol fidelity	Fidelity and adherence measured without feedback	None
Analysis of primary outcome	ITT	ITT; overall and within subgroups defined by age strata or specific comorbid conditions (e.g., coexisting COPD or not)	Multivariate regression analysis adjusting for propensity to get UPPP versus oral appliance and baseline levels of outcome measures

Definition of abbreviations: AHI = apnea-hypopnea index; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; MSLT = multiple sleep latency testing; OSA = obstructive sleep apnea; UPPP = uvulopalatopharyngoplasty.

better outcomes than LRAs. However, under real-world conditions that take into account patient preferences and adherence, ICS and LRAs are equally effective.

Another example demonstrates the need to understand why results can differ between efficacy and effectiveness designs. In a landmark observational study of the impact of PACs in 5,735 critically ill patients, Connors and coworkers (45) found an increased risk of death associated with PACs. These findings, based on an observational CER study that used propensity score matching to minimize the risk of confounding by indication between those who received versus those who did not receive PACs (e.g., minimizing imbalance in the severity of illness between the two groups), provided the motivation to conduct efficacy trials in 1,000 patients with acute lung injury (46), 433 patients with congestive heart failure (47), and 1,994 patients undergoing high-risk surgery (48). The efficacy trials included careful patient selection, high levels of fidelity to the intervention and control conditions (including how the PAC data were to be used on decision making), and sufficient power to detect small differences in mortality. The results of the three efficacy

trials failed to detect differences in benefit or harm (including mortality) in the PAC and comparator groups in the study populations. Taken together, the results of these three efficacy trials indicate that, under conditions in which patient selection is narrowly defined and appropriate placement and use of PAC is monitored and promoted, PACs did not lead to harm (49).

Two subsequent studies that incorporated some elements of a pragmatic trial design (PAC placement and data interpretation at the discretion of local physicians) (29, 30) also failed to detect a higher risk of death with the use of PACs. Some elements of these two trials, however, were more aligned with the efficacy framework (e.g., excluding patients with comorbid cardiogenic shock or thrombocytopenia in one study [29]), raising questions about direct comparisons with the previously published observational CER study (45).

Differences in the results of the five trials (29, 30, 46–48) and the observational CER study (45) suggest that propensity scores for case matching in the observational CER study may have been inadequate in fully preventing confounding by indication. Alternatively, differences in patient populations, how PAC data

were used, and clinical settings (including expertise of practitioner using PACs) may have contributed to differences in findings regarding mortality between the observational CER study and the subsequent clinical trials. Moreover, the lack of benefit in the PAC group (versus the comparison group) was a consistent finding across the various study designs. This example demonstrates the complexity of making inferences when efficacy trials, pragmatic trials, and observational CER studies offer different conclusions.

CONCLUSIONS

Efficacy and CER study designs complement each other. Efficacy studies are designed to answer the question “Can it work in optimal conditions?,” so emphasize the use of clinical trials with high internal validity. By contrast, CER focuses on answering “Does it work in practice?” and, therefore, embraces a range of study designs, including pragmatic trials and observational studies. Many investigators blend efficacy and effectiveness design options in a single study, which may contribute to differences in results across studies. The current emphasis on CER has led to significant changes in funding opportunities for health research, including through PCORI. Although the fundamental research methods in CER are similar to those used for outcomes research or health services research, CER emphasizes engagement and involvement of diverse perspectives of stakeholders, including patients, in prioritizing research questions and study designs and disseminating results. This emphasis in CER will likely engender a shift for some research towards directly addressing the needs of end users of health-related information. In the United States, there is currently insufficient public support for the use of cost-effectiveness analyses for health care–related decision making. Moreover, PCORI explicitly prohibits the inclusion of cost-effectiveness research designs in applications submitted in response to its funding opportunities.

To respond effectively to funding opportunities in CER, the pulmonary, critical care, and sleep research communities will need to understand CER and how it complements efficacy-based designs. ATS is home to researchers, clinicians, and patients, and it actively engages policymakers, representatives of industry, and other health-related decision makers. ATS is thus well positioned to serve as an exemplary organization to promote multistakeholder engagement in the design, conduct, and dissemination of CER and efficacy research in pulmonary, critical care, and sleep medicine.

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