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Comparative effectiveness trials in asthma – how will I recognize one?

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Abstract

Purpose of review—Comparative efficacy trials are designed to evaluate the harms and benefits of healthcare in a research environment. There is increasing interest in the results of comparative effectiveness trials, which are intended to fill gaps in evidence to inform decision-making in real-life clinical environments. The objective of this report is to review various tools to classify trials along the efficacy to effectiveness continuum.

Recent findings—Three tools (PRECIS, PRECIS-2, and PRACTAS) are available that use a star diagram to illustrate where each element of a clinical trial design falls along the efficacy to effectiveness continuum (e.g., selectivity of eligibility criteria, supports to promote participant adherence). The number and type of design element to be classified varies (e.g., ten elements for PRECIS and PRACTAS vs. nine elements for PRECIS-2; only the PRACTAS tool includes stakeholder engagement). There is substantial inter-rater reliability when using all three tools and inter-rater reliability varies across the different design elements (intra-class correlation of coefficient 0.4 to 0.8).

Summary—The PRECIS, PRECIS-2, and PRACTAS tools are options when classifying trials along the efficacy to effectiveness continuum. Researchers and decision-making stakeholders are likely to disagree about the extent to which clinical trials employ efficacy or effectiveness designs.

Keywords/short phrases

Pragmatic trials; efficacy trials; stakeholder engagement; PRECIS tool; PRACTAS tool

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CONFLICTS OF INTEREST

None.

INTRODUCTION

The design of clinical trials has traditionally focused on comparing different strategies of care (e.g., pharmacotherapy or self-management training options) under conditions in which opportunities for confounding and bias have been minimized. Such efficacy trials (or ‘explanatory’ trials) are designed to address the question, “Can this intervention work under optimal circumstances?” (1,2)

Clinical settings include a wide spectrum of patients, including patients with multiple chronic conditions or a history of non-adherence that may preclude participation in efficacy trials. Also, clinicians often have varying levels of expertise, and healthcare settings have become increasingly resource-constrained – these factors may affect how interventions are delivered and increase the likelihood of variations in care (Table 1). Such considerations have raised concerns about the relevance and external validity of results of efficacy trials in guiding clinical practice and increased interest in effectiveness (or pragmatic) trial designs that address the question: “Will this intervention work when delivered in clinical practice?” To address the need for comparative effectiveness trials, the Patient Centered Outcomes Research Institute (PCORI) in the United States has funded several comparative effectiveness trials, including eight trials that are underway to evaluate promising interventions to reduce asthma disparities across the age spectrum of African Americans and Hispanics/Latinos.(3)

Each element of the clinical trial design (e.g., selection of patients; delivery of intervention) can fall somewhere along a continuum between efficacy to effectiveness. Even if a specific element is at one end of the continuum (e.g., efficacy design to enroll highly adherent study population), other elements may be closer to the effectiveness end of the continuum (e.g., interventions delivered by clinicians who are likely to use the intervention in practice). The Pragmatic Explanatory Continuum Indicator Summary (PRECIS) tool (4,5) and an adaptation that includes stakeholder engagement as a separate design element (PRAGmatic Clinical Trial Assessment Scale, PRACTAS) (6) were developed as a communication support tool for researchers in ensuring that the study design was consistent with their intended purpose. These tools can also be used by clinicians, patients, and other decision-makers to systematically evaluate the relevance of completed clinical trials and to decide which trial results are appropriate to their decision-making context.

The objective of this report is to review the PRECIS, PRECIS-2, and PRACTAS tools for classifying clinical trials along the efficacy to effectiveness continuum. Such information could help researchers and decision-making stakeholders select the tool appropriate for the intended use.

PRECIS and PRECIS-2 tools

The 2009 PRECIS tool has 10 elements,(4) each of which can be rated along the continuum from efficacy to effectiveness and displayed on a star diagram (Figure 1): 1) *selectivity of eligibility criteria* (inclusion and exclusion criteria compared to the full range of people who may receive the intervention or comparator interventions in clinical practice), 2) *flexibility*

of the experimental intervention (extent of leeway in applying the intervention compared to what would occur in clinical practice), 3) *practitioner expertise for the experimental intervention* (level of experience among individuals implementing the study intervention compared to the full range available in clinical settings), 4) *flexibility of the comparison intervention* (extent of leeway in usual or comparator care), 5) *practitioner expertise for the comparison intervention* (level of experience among individuals implementing the comparator compared to full range available in clinical settings), 6) *follow-up intensity* (frequency and extent of study-specific data collection from participants compared to what would occur in clinical practice), 7) *outcomes* (relevance and feasibility in clinical practice), 8) *participant compliance* (measurement and supports to promote adherence to assigned study regimen compared to what would occur in clinical practice), 9) *practitioner adherence* (measurement and supports to promote fidelity to study protocol compared to what would occur in clinical practice), 10) *primary analysis* (intention to treat vs. per protocol).

For example, the eligibility criteria would be considered closer to the efficacy end of the efficacy to effectiveness continuum if patients with a history of smoking more than 5 pack-years, presence of comorbid conditions (e.g., obesity), and a history of non-adherence to therapy are excluded. By contrast, the eligibility criteria would be considered closer to the effectiveness end of the continuum if patients with asthma were identified on the basis of physician-reported diagnosis, irrespective of lung function testing or smoking status. Similarly, the flexibility of the experimental intervention would be considered low (efficacy end of the continuum) if the starting dose, dose escalation, and formulation (e.g., inhaled budesonide) of inhaled corticosteroids were pre-specified and patients and their physicians were not permitted to modify the dosing regimen or formulation.

The PRECIS tool does not include a formal scoring system and some studies suggest that the PRECIS tool may have limited inter-rater reliability.^(7–9) The PRECIS tool star diagram was therefore updated in 2017 to include 9 elements, each scored on a five-point scale (1 for the efficacy end of the continuum, 5 for the effectiveness end to the continuum; Figure 2).⁽⁵⁾ Based on feedback from clinical trialists, clinicians, and policymakers, the “eligibility” element in the original PRECIS tool was separated into two elements (*eligibility, setting*) in PRECIS-2. The latter was included to describe whether the trial was done in a setting that approximates the environment in which the results would be applied. For example, if the trial was performed in routine clinical settings as patients receive care for asthma from their usual asthma provider (rather than in clinical research suites in a different building than where they receive their routine asthma care), the setting would be closer to the effectiveness end of the efficacy to effectiveness continuum.

Two new elements were added in PRECIS-2 (*recruitment* [effort devoted to recruit patients in the trial compared to what would be used to engage patients in usual care] and *organization* [differences in resources, provider expertise, and organization of care in the intervention arm compared to what would be available in usual care]). For example, if patients were offered enrolling in the trial as they presented for a routine clinical visit with their primary care physician (rather than being called by phone to recruit them into a study), the recruitment approach would be closer to the effectiveness end of the continuum.

Four elements in the original PRECIS tool were removed (*practitioner expertise* [experimental], *practitioner expertise* [comparison], *flexibility* [comparison intervention], *flexibility* [experimental intervention]). Several of the other design elements were renamed to facilitate interpretation (e.g., *practitioner adherence* was renamed to be *flexibility: delivery*). The PRECIS-2 tool also has brief explanations for each study design element on the star diagram. Reliability testing of the PRECIS-2 tool by the developers indicates intraclass correlation coefficients (ICC) of fair (0.5 for *recruitment* and for *flexibility: adherence* elements) to excellent (0.8 for *eligibility*, *setting*, *flexibility: delivery* elements). (10)

PRACTAS tool

The PRECIS tools (PRECIS, PRECIS-2) do not include an assessment of the extent to which stakeholders contributed to the study design. Meeting the expressed needs of stakeholders (e.g., patients, clinicians, purchasers) is considered a key criterion for comparative effectiveness research by the U.S. Department of Health and Human Services and the Patient Centered Outcomes Research Institute.(11,12) In recent years, effectiveness trials that address the expressed needs of end-users, such as patients, clinicians, and other stakeholders, have attracted substantial interest by study sponsors as a strategy to accelerate the uptake of new health-related information into clinical practice.

The PRAGmatic Clinical Trial Assessment Scale (PRACTAS, Figure 3) tool(6) is an adaptation of the original PRECIS tool to include *stakeholder engagement* as a design element, defined as non-researchers participating in specifying the research question or informing decisions about one or more other aspects of the study design (e.g., defining eligibility criteria; selection of outcomes). The *primary analysis* element in the PRECIS tool was removed because it does not generally distinguish between efficacy and effectiveness designs. In both cases, an intent-to-treat analysis is preferred and can be supplemented with a per-protocol analysis. Thus, the PRACTAS tool includes the same number as the original 10-item PRECIS tool. As with the PRECIS-2 tool, each element of the PRACTAS tool is scored on a five-point scale on a star diagram (1 for the efficacy end of the continuum, 5 for the effectiveness end to the continuum), but the overall intraclass correlation coefficient for the PRACTAS tool was poor (0.4).(6) The low intraclass correlation coefficient suggests limited agreement between different raters when using the PRACTAS tool to evaluate the same trial.

Conclusion

There is increasing interest in comparative effectiveness trials in asthma and other conditions to guide clinical decision-making to complement the information gained from traditional efficacy trials. Decision-makers who use the PRECIS, PRECIS-2, or PRACTAS tools to distinguish between comparative effectiveness and efficacy trials are likely to disagree. There is a need to develop and validate tools that could be used to more reliably classify clinical trial designs along the efficacy to effectiveness continuum.

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KEY POINTS

- There is increasing interest in comparative effectiveness trials to guide clinical decision-making.
- The PRECIS, PRECIS-2, or PRACTAS tools were developed to distinguish between comparative efficacy and effectiveness trials, but inter-rater reliability crosses the range from fair to excellent, depending on the element of study design. Thus, there are likely to be disagreements about whether trials are predominantly using an efficacy or effectiveness design.
- Validated tools to more reliably classify clinical trial designs along the efficacy to effectiveness continuum are needed.

Figure 1. Pragmatic Explanatory Continuum Indicator Summary (PRECIS) (Reproduced with permission from reference 4)

PRECIS tool has 10 elements, each of which can be rated along the continuum from efficacy to effectiveness and displayed on a star diagram: 1) selectivity of eligibility criteria, 2) flexibility of the experimental intervention, 3) practitioner expertise for the experimental intervention, 4) flexibility of the comparison intervention, 5) practitioner expertise for the comparison intervention, 6) follow-up intensity, 7) outcomes, 8) participant compliance, 9) practitioner adherence, 10) primary analysis. An assessment of where, on the efficacy-effectiveness continuum, a clinical trial lies for each element is made. The lines for each element are arranged like spokes of a wheel and a “tick” is placed on the line representing the trial’s location on the continuum. The “E” denotes efficacy end of the efficacy to effectiveness continuum. The locations of each “tick” are joined by a line and create a star diagram.

Figure 2. Pragmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2) (Reproduced with permission from reference 5)

The 9-item PRECIS-2 tool is adapted from PRECIS tool, and separates eligibility into two elements (eligibility, setting) and includes two new elements: recruitment and organization. Four elements in the original PRECIS tool were removed (practitioner expertise [experimental], practitioner expertise [comparison], flexibility [comparison intervention], flexibility [experimental intervention]). Several of the other elements were renamed to facilitate interpretation (e.g., practitioner adherence was renamed to be flexibility: delivery). PRECIS-2 is scored using a numerical scale (1–5) for each element: 1 (very explanatory-efficacy) to 5 (very pragmatic-effectiveness).

Figure 3. PRAGmatic Clinical Trial Assessment Scale (PRACTAS)

Adapted from PRECIS tool, the 10-item PRACTAS includes stakeholder engagement as a design element. The primary analysis element in the original PRECIS tool was removed because it does not generally distinguish between efficacy and effectiveness designs. The PRACTAS score for each design element ranges from 1 (efficacy end) to 5 (effectiveness end). One unit increments are used to provide a score and marked on the star diagram. “E” denotes efficacy end of the efficacy to effectiveness continuum. The locations of each element are joined by a line and create a star diagram.

Table 1

Comparative efficacy vs. effectiveness clinical trials

	Advantages	Disadvantages
Efficacy trials	<ul style="list-style-type: none"> Intended to assess harms and benefits of healthcare in a research environment with multiple supports to promote high fidelity to study protocol (high internal validity). Optimized to answer the proof-of-concept question: "Can this intervention work" Reduced risk of missing an effect when the intervention is used as directed in a highly selected population. 	<ul style="list-style-type: none"> Requires substantial resources to identify eligible patients due to selective eligibility criteria), to identify, train, and monitor study investigators and research staff in the use of study protocol, and to support study-specific activities (e.g., in-person study visits or specialized tests) Implementation of intervention as studied in the efficacy trial may be delayed or not be possible in a clinical environment, because of resource constraints in routine practice settings.
Effectiveness trials	<ul style="list-style-type: none"> Intended to assess harms and benefits of healthcare as it would be used in a routine care setting (high external validity) Optimized to answer the question "Does this intervention work" when applied in clinical settings Requires fewer resources than efficacy trial because of limited study-specific supports. Easier to identify eligible patients, because eligibility criteria are intended to mimic practice Harms and benefits observed in study more likely to reflect what would occur if the intervention is used in routine practice settings (higher external validity compared to efficacy trial) Stakeholder engagement in the study design and implementation may facilitate uptake of study results 	<ul style="list-style-type: none"> Due to practice variation in clinical settings, there may be underdiagnosis or misdiagnosis. Patients enrolled in effectiveness trials may therefore not be the same as those enrolled in efficacy trials. Patient adherence to study interventions and fidelity of implementing interventions by providers may mimic clinical practice, which could increase the likelihood of confounding or observing no difference in outcomes between study interventions Co-therapies often permitted during effectiveness trials, which could lead to confounding.