Published in final edited form as:

J Clin Epidemiol. 2018 January ; 93: 66–75. doi:10.1016/j.jclinepi.2017.10.015.

Use of the PRECIS-II instrument to categorize reports along the efficacy-effectiveness spectrum in an hepatitis C virus care continuum systematic review and meta-analysis

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Abstract

There is increasing recognition of the importance of the distinction between efficacy and effectiveness research in the design, conduct, and evaluation of interventions and program outcomes. There is a concurrent increase in the application of systematic reviews and meta-analyses. These two lines of inquiry are only beginning to meet. There is an emerging need for systematic reviews and meta-analyses to account for differences in degrees to which included studies reflect either efficacy and effectiveness designs. Based on on-going work on a formal systematic review of the hepatitis C virus care continuum, this paper describes and discusses the rationale for, and how the PRECIS-II instrument can be used on, and modestly adapted to, studies included in the systematic review examining the extent to which studies include elements of efficacy or effectiveness, or a combination of the two. We also highlight that use of such an instrument may have general applicability to and value in the conduct of systematic reviews and meta-analysis.

Keywords

Efficacy; effectiveness; systematic reviews and meta-analyses; hepatitis c virus; care continua

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Disclosures

The authors declare that they have no competing interests or disclosures to make.

Author Contributions

AEJ, DP, and HH conceived of the manuscript. AEJ wrote the first draft and incorporated edits on revised versions. AEJ, DP, HH, DS, and JR contributed to the adaptation of the instrument, provided feedback as the adapted instrument was piloted by AEJ, and provided feedback on drafts of the manuscript. All authors approved the final manuscript.

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1.0 Introduction

Efficacy and effectiveness studies provide two distinct ways to examine the impact of an intervention (e.g., a pharmacologic treatment, or a behavioral intervention). They address two distinct research questions.[1, 2] All aspects of study design, including methods for sampling, recruiting, and data analysis, inform whether the study is asking (and answering) an efficacy or effectiveness research question.[1–3] It is critical to recognize what differentiates questions of efficacy and effectiveness, to situate published studies along a spectrum of efficacy and effectiveness, to specify the research question being addressed and to understand which type of study provides answers to which research questions.[4–7]

Efficacy studies are designed to focus attention on the impact of a specified intervention on a specified outcome under precisely defined, and often idealized, conditions.[2, 3, 8] These study design elements help ensure high internal validity, which improves causal inference with respect to the direct impact of that specified intervention, but only under those precisely defined circumstances (e.g., on a precisely defined population, and under precisely defined conditions of intervention implementation).[6, 9] As such, some have referred to efficacy studies as “explanatory studies”; in some settings, these studies may best “explain” biologic mechanisms or the idealized potential of an intervention, such as a pharmacologic agent, to yield a specific outcome.[2, 3, 10] In general, efficacy studies can be seen as addressing the question “can an intervention work” when the investigators do everything possible to help the intervention work.

In contrast, effectiveness studies are designed to focus attention on the impact of an intervention as applied in practice on specified outcomes, under conditions experienced in general practice, facilitating generalizability by focusing on the question of “will an intervention work” in general practice. In other words, while an effectiveness study can examine the impact of an intervention, and in fact may do so with a randomized controlled trials design, this type of study asks whether an intervention “will work” in general practice. [3, 11] These studies more robustly demonstrate the impact of interventions in general practice but not idealized settings; as such, some have referred to effectiveness studies as ‘pragmatic’ studies as they aim to examine the impact of an intervention in practice.[2]

Of note, a study examining the use of the terms efficacy and effectiveness in the published literature, found that they were used inappropriately and inconsistently, and consequently, often lead to the misclassification of studies.[12] Further, while some scholars use the terms synonymously, for some readers the terms “explanatory” and “pragmatic” may be taken to imply superior scientific rigor through the term “explanatory” and inferior scientific rigor through the term “pragmatic”; we will use the terms efficacy and effectiveness in attempt to highlight their equal importance in addressing different but simultaneously important research questions.[3]

Studies can be thought of as existing along a continuum of efficacy and effectiveness, in which the ends of the spectrum are characterized by either a pure efficacy study design or a pure effectiveness study design, with a range of studies in between having some

characteristics of both.[2, 13] Further, it should be noted that both efficacy and effectiveness questions can be addressed using either randomized controlled trial or observational study designs, and that conversely randomized controlled trials can be designed to more fully address either questions of efficacy or effectiveness. The design features of randomization in randomized controlled trials contributes potentially to achieving higher internal validity and minimization of potential confounding, but randomized controlled trials can nonetheless focus on questions of efficacy or effectiveness to varying degrees.

Systematic reviews and meta-analyses are increasingly used to synthesize the enormous amounts of published material, including published data from observational and experimental studies related to hepatitis C virus and drug use epidemiology.[14] Concomitantly, the results generated from systematic reviews and meta-analyses are increasingly being used to inform policy.[14] The reliance on the results of systematic reviews and meta-analyses for policy decisions requires that they generate sound and unbiased syntheses and pooled estimates. As has been noted by Stroup, *et al.* and others, because of existing pressures for timely data, and because some data are only available or are more quickly available from observational studies, systematic reviews and meta-analyses have increasingly included and examined observational studies as well as randomized controlled trials.[15–17] Guidelines for the optimal reporting of systematic reviews of observational data have been proposed.[15, 18]

We are currently conducting a systematic review of the hepatitis c virus care continuum among people who use drugs.[19] This paper describes and discusses the rationale for, and how the PRECIS-II instrument can be used on, and modestly adapted to, studies of the hepatitis C virus care continuum, examining the extent to which studies include elements of efficacy or effectiveness, or a combination of the two.[19] We discuss how included studies may reflect efficacy or effectiveness designs to varying degrees overall, and for each of the care continuum steps considered, and how such assessments may inform the design, conduct, and results of systematic reviews and meta-analyses. We also highlight that use of such an instrument may have general applicability to and value in the conduct of systematic reviews and meta-analysis.

2.0 Definitions

Efficacy

In efficacy studies, patient eligibility and exclusion criteria are generally restrictive in order to create an ideal environment that eliminates or holds constant as many potential confounding factors as possible, so as to maximize the chances of assessing whether an intervention (e.g., a pharmacologic or a behavioral intervention) has the desired impact under these idealized circumstances. For example, if comorbid conditions might diminish the potential efficacy of a drug or intervention, those with such conditions often are excluded from studies. As such, response rates would generally reflect the maximum achievable outcomes with the intervention under study. However, analyses that focus on any group other than all randomized participants (i.e., anything other than a pure intention-to-treat analysis), such as “on treatment analyses” or subgroup introduce considerations that shift the position of the study (even if slightly) on the efficacy-effectiveness spectrum.[2, 20]

Effectiveness

Effectiveness studies explore the impact of a treatment under conditions more typical of routine clinical practice; that is, when applied in varying contexts, to varying populations, and with more variable components of implementation. Effectiveness studies may be either observational or may be randomized controlled trials. When they are randomized controlled trials, they may have well-specified inclusion criteria, but these criteria may be broader in an attempt to enhance potential generalizability. For example, in an effectiveness study, if those with comorbid conditions might benefit from an intervention shown to have efficacy in idealized circumstances, such persons would not be excluded from the study. As such, response rates may not reflect the maximum achievable outcomes under idealized and optimized circumstances, but the (likely lesser) outcomes would be more representative of those achieved when an intervention is applied more widely in practice.

Hybrid Efficacy-Effectiveness Studies

Some models of the phases or spectrum of healthcare research, such as those proposed by both the National Cancer Institute and the National Heart, Lung, and Blood Institute suggest a sequence of research inquiry in which efficacy studies should generally precede effectiveness studies.[21–23] In a key article on efficacy trials Flay wrote “it can be argued that randomized experiments (clinical trials) are necessary for tests of efficacy, and that only when a treatment procedure has been shown to cause desirable changes under optimum conditions is it worthwhile to evaluate its effectiveness when delivered in real world settings”.[21] While there are in fact situations in which an effectiveness study might well be the best first step, common models of the phases of research, and in particular of drug development, often rely on the sequence of efficacy studies followed by effectiveness studies.[21–23] Whether related to reliance on these models of sequential efficacy-effectiveness studies or not, data show that there can be long time lags between demonstrations of intrinsic efficacy, and demonstrations of population-level effectiveness.[24]

Some have concluded that a solution to these long time lags would be a greater and earlier emphasis on effectiveness studies.[8, 9] Another approach to address these gaps that has been proposed is the use of ‘hybrid’ study designs.[25–27] Hybrid studies reflect some aspects of both efficacy and effectiveness design elements, and hence have been proposed to potentially provide some information about both questions; causal inference may be diminished due to a trade-off between optimizing external and internal validity.[11, 25] Yet, most studies contain a mix of efficacy and effectiveness features (for various reasons) [10, 28] and so referring to a category of efficacy-effectiveness hybrids may not really be creating a new category, as much as recognizing and highlighting that studies routinely exist on a spectrum and may emphasize different features to different degrees. Some have proposed finding an optimal “balance-point” between efficacy and effectiveness in study design.[28] Still others have highlighted that a premature emphasis on effectiveness studies could inadvertently lead to an acceptance of “usual care” of untested or suboptimal efficacy, and consequently thwart efforts to identify new interventions that may improve care.[29]

While all of these considerations are relevant, we take the position that a critical first step is understanding where on an efficacy-effectiveness spectrum any given study lies, that efficacy and effectiveness studies by design address different relevant questions and provide complementary information, and that there is likely no optimal balance appropriate for all study questions. Understanding the extent to which a study reflects an efficacy design and analysis, or an effectiveness design and analysis, is important in the initial planning of a study (choosing what the study questions are), interpretation of a study, and very likely, the conduct of systematic reviews and meta-analyses.

3.0 Developing an instrument to assist in the differentiation of efficacy and effectiveness design elements

There have been various approaches proposed to assist scientists in formulating their study designs as more efficacy or effectiveness in nature and similarly in categorizing published studies as reflecting efficacy or effectiveness outcomes.[2, 30] Gartlehner, *et al.* developed an instrument enumerating criteria for distinguishing between efficacy and effectiveness studies in systematic reviews.[31] This instrument dichotomized studies as being either an efficacy or effectiveness design. While this instrument was shown to have a high specificity for identifying effectiveness studies, we sought an instrument that would allow us to categorize studies included in our systematic review on a spectrum of efficacy-effectiveness. [30] We anticipated that studies addressing the hepatitis C virus care continuum were likely to address both questions of diagnosis and treatment, as well as questions of behavioral and structural interventions to improve the application of these interventions. Categorizing studies along a spectrum of efficacy-effectiveness would be more meaningful and precise than relying on a dichotomous measure.

Loudon, *et al.* published a useful tool, the PRECIS-II, to assist scientists in designing and carrying out studies that are consistent with their research questions.[4] The PRECIS-II instrument is a useful, validated tool intended to guide study design, and characterize degrees of efficacy and effectiveness in studies, and it has been applied to trial design in various settings and to some post-hoc analyses.[53] Unlike the instrument developed by Gartlehner, *et al.*, the PRECIS-II examines 9 design domains, each rated on a 5-point scale allowing categorization of studies along a spectrum.[2, 30] Although primarily intended to assist in study design, the PRECIS-II instrument was also applied to several trials post-hoc to assess for the degree of efficacy or effectiveness of the study trial in the primary PRECIS-II publication.[2] Further, while the PRECIS instruments (both the initially proposed PRECIS instrument and the subsequently revised PRECIS-II) have been mainly applied to randomized controlled trials, these instruments are being increasingly applied to a wider range of studies (including cluster-randomized trials, trials with factorial designs, and observational studies).[32–34]

4.0 Significance of distinguishing effectiveness and efficacy studies in systematic reviews and meta-analyses

In systematic reviews and meta-analyses, sound syntheses and pooled effect size estimates must come from data from studies examining the same phenomenon and analyzing data in statistically analogous ways. If data are pooled inappropriately, this can introduce substantial variability in the measured effect and lead to erroneous inferences. Since efficacy and effectiveness studies have different goals and are expected to yield different outcomes, some assessment of whether (or the degree to which) a study is an efficacy study or an effectiveness study may be essential in systematic reviews and meta-analyses. Combining studies addressing efficacy questions and effectiveness questions in a single systematic review or meta-analysis, without treating them distinctly, may raise several considerations. This may result in either increased heterogeneity and/or biased pooled estimates of effect sizes. Further, combining heterogeneous studies to generate a net pooled estimate may yield an estimate that is not in fact meaningful, as the study questions are, in fact, different. Systematic reviews and meta-analyses may generally need to either consider such studies separately or have appropriate methods to assess the degree of effectiveness and efficacy design components and consider such measures as an important covariate in analysis. Systematic reviews and meta-analysis can examine how outcomes vary in relation to factors that reflect degrees of efficacy and effectiveness in study design.

While few systematic reviews and meta-analyses have directly addressed this issue, the critical potential for heterogeneity to be introduced into data pooled for meta-analysis through variability in which the included studies reflect efficacy or effectiveness questions or design elements has been increasingly recognized. In a systematic review and meta-analysis of the effectiveness of brief alcohol interventions in primary care populations, a sub-group analysis assessed the impact of the interventions in ideal or real-world trials using a coding scale that examined domains similar to those in the PRECIS-II instrument.[2, 35] The authors summed scores for the separate domains to develop a measure examined as a co-variate in meta-analysis; in meta-regression they did not identify an impact of efficacy-effectiveness differences on estimated treatment effects. However, the lack of an observed impact of the efficacy-effectiveness measure may have been due to the measure's insensitivity or the inappropriateness of the summary score in that context.[35]

A systematic review by Ankarfeldt, *et al.* explored a potential efficacy-effectiveness gap as a driver of the differences in observed impact of glucose-lowering drugs between observational studies and randomized controlled trials.[5] They dichotomized papers as either being pure randomized controlled trials reflecting efficacy designs or observational studies reflecting effectiveness designs and compared mean observed effect sizes in each group. Although, Ankarfeldt, *et al.* did not identify an efficacy-effectiveness gap (possibly as a result of limited sample size and confounding), significant gaps between efficacy and effectiveness outcome have been observed for many interventions.[24, 36–39] An alternative explanation for the lack of a gap identified in Ankarfeldt, *et al.* may have been the use of a dichotomous efficacy-effectiveness outcome measure. With regard to hepatitis C virus, gaps between the efficacy and effectiveness of hepatitis C virus treatment are substantial;

treatment efficacy rates generally exceed 90%, while numerous reports find net effectiveness often under 20%.[40, 41]

5.0 Adapting the PRECIS-II instrument for use in hepatitis C virus care continuum systematic reviews

We are conducting a systematic review and meta-analysis of the hepatitis C virus care continuum, with pre-defined care continuum steps of screening or testing, linkages to care, treatment acceptance, initiation and adherence, treatment completion, the biologic outcome of a sustained virologic response, and subsequent risk of re-infection.[19] Based on our pre-existing familiarity with the hepatitis C virus care continuum literature, we designed this systematic review to include both randomized controlled trials and observational studies (e.g., evaluation studies assessing the implementation of programs or models of testing and care delivery).[19] The care continuum construct is being increasingly applied as a tool to examine outcomes of care for a range of conditions in which care typically consists of a series of sequential steps. For example, the care continuum construct has been formally applied to public health evaluations of HIV care and to outcomes for several infectious and non-communicable diseases.[36, 42–44] In studies of the hepatitis C virus care continuum, use of an instrument such as the PRECIS-II may be critical to understanding the degree to which study findings provide data addressing questions of intervention efficacy or effectiveness. The nine domains of the PRECIS-II instrument are: 1) eligibility, 2) recruitment, 3) setting, 4) organization, 5) flexibility of delivery, 6) flexibility of adherence, 7) follow-up, 8) outcome, and 9) analysis.

Our main adaptation to the PRECIS-II was to modify the prompts to reflect their application to post-hoc analysis of studies and to reflect considerations specifically relevant to hepatitis C virus care continuum studies. Using the PRECIS-II toolkit and guided by Loudon, *et al.*, we adapted each domain of the PRECIS-II instrument; prompts were tailored to address the post-hoc nature of the review, and instructions were included that were informed by both subject matter expertise and expertise in trial design, statistical analysis and the conduct of systematic reviews and meta-analyses.[2, 45] Figure 1 presents the modestly adapted PRECIS-II instrument; the purpose of this instrument is to guide the assessment of the study design elements in each PRECIS-II domain and to score each domain on an efficacy-effectiveness spectrum in which a score of 1 represents full efficacy and a score of 5 represents full effectiveness. (See Figure 1)

One additional consideration specific to the adaptation of the PRECIS-II to our hepatitis C virus care continuum study is that some studies present more than one hepatitis C virus care continuum outcome (e.g., testing and linkage to care), in which case eligibility criteria, recruitment method, and data analysis plan may differ between outcomes. We therefore anticipated that PRECIS-II assessments may need to be applied multiple times to a single study. As an example, Figure 2, shows the PRECIS-II wheel for one of the papers to be included in the systematic review, which examined two sequential steps of the hepatitis C virus care continuum.[46] One application of the instrument related to the study's examination of testing and the other to the study's examination of a linkage to care

intervention. Note that the study's design tended towards a predominance of effectiveness features in all domains, but that the examination of HCV testing was more effectiveness-focused across all domains.

6.0 PRECIS-II domains and their relationship to the HCV care continuum literature

Care continuum models are useful in evaluating the net population or group-level effectiveness of interventions and in identifying gaps in the (usually) sequential steps of care processes, which can be addressed to improve population level outcomes. [43] While the diagnosis, management, and treatment for hepatitis C virus infection has improved over recent years, gaps in continuity of care persist, particularly among people who use drugs, who constitute the largest group of HCV infected people.[43, 47] The HCV care continuum includes a series of clinical evaluations, often requiring time between steps and sometimes requiring patients to receive care at different venues (e.g., patients may be tested at a substance use treatment program, referred to a primary care clinic for confirmatory testing, and then be linked to a more specialized hepatitis C virus treatment setting such as hepatology clinic). Once they complete these steps the majority of patients receiving highly efficacious HCV therapeutic agents will be effectively cured (i.e., achieve sustained virologic responses), lowering their risk of hepatitis C virus-related morbidity and mortality. Alternatively, individuals who are lost at any given step of the care continuum will remain at risk of hepatitis C virus attributable morbidity and mortality, and they will remain infectious and potentially contribute to ongoing transmission if they engage in risk behaviors.[36] Thus, engagement in the care continuum through to a cure may have important benefits to individual and population health.

Published literature and programs may address progress through the multiple steps of the care continuum (reporting or evaluating progress from screening through to hepatitis C virus treatment and sustained virologic response) or may focus more specifically on outcomes of either single steps or selected steps of the care continuum (e.g., receipt of antibody screening and subsequent confirmatory testing for those antibody positive). In doing so, published literature may examine interventions (pharmacologic, behavioral, or structural) to increase testing, engagement in care, treatment initiation, or treatment adherence and completion, and may do so using any combination of efficacy, effectiveness or hybrid study designs.

Initial pre-specified plans for our systematic review were to: 1) adapt the PRECIS-II instrument to apply post-hoc to the hepatitis C virus care continuum reports and 2) examine and categorize reports and outcomes with respect to hepatitis C virus care continuum steps that include a) screening and testing, b) linkage to and completion of clinical evaluations in care, c) interventions to increase treatment acceptance, initiation, adherence, d) completion of treatment, e) achieving sustained virologic response, and f) re-infection post-sustained virologic response.[19] Plans also included characterizing each report or the intervention applied for each care continuum step in a report using our adaptation of the PRECIS-II.

We will briefly review each of the PRECIS-II domains and discuss how these domains are relevant to reviews of HCV care continua.

6.1 Domain: Eligibility

This domain considers the extent to which participants in the report are similar to those who would receive this intervention if it was part of usual care. For hepatitis C virus studies, we anticipated that some reports may focus on samples of the general population, others on individuals with certain behavioral or demographic characteristics (such as age cohort, engaging in injection drug use, or engaging in substance use treatment or syringe exchange programs), and others on specific populations already known to have hepatitis C virus exposure or active hepatitis C virus infection. Reports may examine hepatitis C virus treatment outcomes among all people treated as part of routine care (e.g., in a Veterans Health Administration system setting) or examine treatment outcomes among people specifically recruited for a study (e.g., a behavioral or technological intervention to promote treatment adherence) for which participants were required to have certain specific characteristics and consent to being randomized to different treatment arms.

6.2 Domain: Recruitment

This domain considers how much additional effort is made to recruit participants over and above that which would be used in the usual care setting to engage with patients. Studies might examine rates of acceptance of alternate hepatitis C virus testing methods routinely offered to all new program entrants or report on testing acceptance rates of people reached via respondent-driven sampling methods, through which incentives are offered.

6.3 Domain: Setting

This domain considers how different the trial setting is from usual care settings. Studies of HCV screening may be conducted in research settings (e.g., study field sites conducting outreach to reach participants) or in care and prevention settings that a high-risk population may regularly access (e.g., a substance use treatment program). Additionally, settings might include general medical clinics where people born in the CDC-defined “hepatitis C virus birth cohort” (i.e., those born between 1945–1965) may be tested for HCV when they present for general medical evaluations. With respect to hepatitis C virus treatment, studies of new therapeutic agents may be conducted in highly specialized research settings that facilitate the conduct of associated pharmacokinetic analyses and rigorous measures of medication adherence, while other studies may focus on the acceptance and tolerability of licensed treatment agents by a wide range of patients in settings they may routinely use for care or other services, such as substance use treatment programs.

6.4 Domain: Organization

This domain asks how the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial compared to those available in usual care. Hepatitis C virus intervention studies may utilize existing clinical staff without relying on additional training or resources, or utilize specifically trained research staff or routine staff who have been given special or additional training in order to conduct the intervention (i.e., having providers receive specific training in motivational interviewing skills to apply to the provision of steps of care). The type of measures taken by the study staff to ensure that patients adhere to the intervention can vary both in type of adherence technique (e.g., phone

call reminder, providing on-site treatment) and in intensity (e.g., allowing only one attempt to be linked to HCV medical evaluation or allowing multiple attempts).

6.5 Domain: Flexibility of delivery

This domain asks how flexible intervention delivery is compared to the flexibility likely in to exist in usual care; greater flexibility is likely to be provided in usual care whereas a stricter adherence to protocol in the delivery of an intervention may be seen in clinical trials or specialized settings. Studies may vary in whether the intervention applied is highly scripted, delivered by highly trained staff, and assessed for fidelity, or is applied by non-study staff, where intervention content is allowed to vary and fidelity is unmeasured. Here for example, studies using motivational interviewing as part of an intervention may include assessments of interventionist fidelity to a strictly protocol-based intervention. Alternatively, studies may use motivational interviewing but allow interventionists to have flexibility in intervention delivery and not perform fidelity assessments.

6.6 Domain: Flexibility of adherence

This domain evaluates the difference in the flexibility participants are afforded in adherence to an intervention compared to what might be seen in usual care. Hepatitis C virus studies might examine the utility of a multi-session education and motivation intervention on treatment initiation or completion. Patients might be required to complete all the sessions to be considered in the population for which outcomes are reported (in a efficacy design). Alternatively, patients may be allowed to attend as few or as many sessions as they deem useful (in an effectiveness design).

6.7 Domain: Follow-up

This domain considers differences in the intensity of measurement and follow-up of participants in the report, compared to that which might be found in usual care. This domain could be reflected in either the degree of patient time and effort, and/or the time and effort of the study or clinical team. For example, it may be appropriate to assess some studies according to the extent to which an interventionist's time is devoted to data collection beyond that performed as part of usual care, whereas other studies may be assessed according to the intensity of the follow-up schedule required of patients (e.g., weekly blood testing for patients on hepatitis C virus treatment). Studies with more intensive follow-up may result in a Hawthorne-like effect, in that a greater number of follow-up visits or a less flexible follow-up schedule may adversely influence adherence and thereby reduce measured effect size.[48]

6.8 Domain: Outcome

The outcome domain assesses the extent to which the primary outcome of the report is relevant to participants. In hepatitis C virus treatment studies, cured infection or improvement in quality of life may be the most relevant outcomes to patients. Virologic responses measured during or immediately after completion of treatment serve as an early surrogate of likely sustained virologic response and actual cure; other studies may report sustained virologic response measured at least 24 weeks after treatment completion, more

definitely measuring cure. Similarly, reports might consider differences in participant adherence to treatment with or without reporting rates of virologic cure.

Care continuum studies may present outcome data for one more sequential care continuum steps, as discussed above, resulting in the need for distinct assessments of the PRECIS-II domains for a single report. For this domain, therefore, consideration should focus first on identifying the outcome(s) (e.g., just initial linkage to care, or retention in care through to treatment completion). This step will determine whether the adapted PRECIS-II instrument would be applied once or more than once. This domain also considers how outcomes are measured (e.g., self-reported or medical record confirmed attendance at first medical evaluation appointment), and how the study design may or may not have affected the achievement of the outcome (e.g., patients were given patient navigators who would schedule their hepatitis C virus medical evaluation appointment, provide reminders and follow-up).

6.9 Domain: Analysis

The focus of this domain is the assessment of the extent to which all data are included in the analysis of the primary outcome. A key aspect is the degree to which the methods applied promote internal and/or external validity.[3, 10] Intention-to-treat analyses in studies with randomized designs are key methods to promote internal validity. Therefore, whether a study uses “on treatment analyses” or subgroup analyses as opposed to pure intention-to-treat analysis will be one consideration in measures of its efficacy or effectiveness focus.

With respect to hepatitis C virus, these considerations specifically may relate to whether individuals who have absolute or relative contraindications to treatment are included or excluded from analysis, whether those with potentially modifiable individual-level barriers to treatment are excluded or addressed in analyses, or whether structural or programmatic factors, such as an individual’s health insurance status, are treated as exclusions or as important factors impacting net effectiveness.

7.0 Limitations

Limitations of this paper include that we not conduct a strict, formal adaptation of our very slightly adapted PRECIS-II leading to a new validated version. However, our adaptations to the existing PRECIS-II tool were quite modest. We changed the syntax of the prompts to reflect post-hoc nature of the planned application of the instrument, although we highlight that the instrument has been used for post-hoc analyses previously. [2, 32, 33] The PRECIS-II instrument has been found to have good interrater reliability and most discriminate validity.[49]

Further, as the PRECIS-II tool has been increasingly applied to a wider range of study questions and study designs, potential reconsideration of how the tool is applied arise. For example, Forbes, *et al.* proposed that for analyses of cluster randomized trials, more detailed information would be obtained by applying the tool twice, once at the individual-level and once at the cluster-level.[34] Similarly, we identified that studies of the hepatitis C virus care continuum that examined two or more care continuum outcomes may need to be assessed

with multiple applications of the PRECIS-II instrument, one for each step. Further, some studies employing the PRECIS-II have noted that some raters felt a need for more information than was sought by the prompts in the formal PRECIS-II Toolkit.[34] Our ‘adaptation’ of the instrument took note of this and embellished the prompts to attempt to give raters guidance on specific elements we expected to encounter in the hepatitis C virus care continuum literature. (See Figure 1)

Given that our ‘adaptations’ merely changed the prompts with respect to the post-hoc nature of its application and added some further guidance for raters, we do not feel or suggest that new formal instruments need be redeveloped for each application of the PRECIS-II to each new health condition. In fact, we feel that the existing instrument is applicable to many conditions with only modest tailoring of prompts based on expert knowledge of the specific conditions under study. We have not yet completed the systematic review to which the modestly adapted PRECIS-II is being applied. Further, assessments of both the instrument’s validity and reliability, and of the potential impact of heterogeneity with respect to efficacy-effectiveness features in included papers on identified hepatitis C virus care continuum outcomes and potential impacts on observed effect sizes await completion of the study. Further, data regarding a more general potential impact of variability in efficacy and effectiveness on observed outcomes across randomized controlled trials of interventions for a variety of conditions will hopefully be forthcoming through a recently planned other study. [50]

8.0 Conclusion

The considerations reviewed reflect key issues in the meeting of two lines of inquiry: those related to understanding and distinguishing questions of efficacy and effectiveness in study design, and those related to anticipating and addressing the impact of these distinctions on the conduct of systematic reviews generally, and as applied to the care continuum in particular.

Care continuum models are proving to be useful tools in public health assessments of, and efforts to improve, the outcomes of sequential steps of care.[43] The outcomes identified reflect both the efficacy and effectiveness of sequential healthcare or prevention interventions. Therefore, systematic reviews of care continua, such as our systematic review of the hepatitis C virus care continuum among people who use drugs, will identify, include, and need to appropriately characterize studies with varying mixtures of efficacy or effectiveness design. Our adaptation of the PRECIS-II instrument will be useful in generating valid and meaningful syntheses of the available literature.

The distinction between efficacy and effectiveness is sometimes conflated or ignored, and greater priority is sometimes given to one or the other. [8, 25, 28] However, the distinction is critical in focusing attention on the separate but ultimately on outcomes and the outcomes that might be obtainable in actual clinical or public health practice. Identifiable design and analytic features imbue studies with elements that array them on a spectrum of efficacy and effectiveness.[13] Some systematic reviews and meta-analyses may appropriately focus exclusively on either intervention efficacy or intervention effectiveness; however, even these

reviews must be able to characterize studies with respect to efficacy or effectiveness design and recognize that studies may not fit purely into either category. Systematic reviews and meta-analyses would be more informative if efficacy and effectiveness are examined.

Acknowledgments

The HCV Synthesis Project is supported by a grant from the National Institutes of Health (RO1DA034637-01). Support was also received from the Center for Drug Use and HIV Research, an NIH P30 Center (P30 DA011041).

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Highlights

Authors are asked to provide a text box entitled “What is new” that summarized what this paper adds to the existing literature, with up to 5 items/points addressing: 1) key findings, 2) what this adds to what is known, 3) What is the implication, what should change now

Key findings

- a. The PRECIS-II instrument can be modestly adapted to assess studies of the HCV care continuum, and to categorize them with respect to the degree they address questions of efficacy and effectiveness.

What this adds to what was known?

- a. For studies examining more than one step in the HCV care continuum (e.g., testing, linkage to care, and treatment) the instrument may need to be applied more than once.
- b. Systematic reviews, which increasingly examine both observational and RCT data, may need to consider the degree to which included studies rely on efficacy and effectiveness design elements.
- c. The PRECIS-II instrument, modestly adapted, may be a useful tool allowing systematic reviews to categorize included papers with respect to variability in efficacy or effectiveness design.

What is the implication and what should change now?

- a. Systematic reviews and meta-analyses would be more informative if included reports were categorized along the efficacy-effectiveness spectrum and this categorization were taken into account in analyses.

Date _____
 Coder (Last name, first name) _____
 Study ID: _____

Question 1: What is the research question as defined by the authors?
 Question 2: Do the authors state what type of study they conducted in order to test their research question(s) (i.e., do they say whether the study was efficacy, effectiveness, or hybrid)?
 Question 3: If Question 2's response is "Yes" then: What did the authors explicitly state was their study design and/or intent: efficacy, effectiveness, or a hybrid?
 Question 4: At an initial assessment, from the perspective of the coder, what is the type of study employed by the authors to investigate the research question? (circle one of four options)

is the study operating under "idealized"/"optimized" conditions? a) Efficacy
 is the study operating under "usual"/"real world" conditions? b) Effectiveness
 is the study operating under a mix of these conditions? c) "Hybrid"
 Unclear d) Unclear

PRECIS-II Domain	PRECIS-II Prompt	Domain explanation and instruction	Score (1-5)*	Examples from paper that illustrate rationale for score
Eligibility criteria	Who is selected to participate in the trial? To what extent are the people who use drugs in the trial similar to those who would receive the intervention if it was part of usual care?	A study would be given a high effectiveness score (5) if eligibility criteria were identical to the standard of care for people who use drugs (PWUD) whereas a study would be given an efficacy score (1) if there were many exclusions not experienced by PWUD as part of standard care. Other inclusion/exclusion criteria that would lower the PRECIS-II score would be excluding persons with co-morbidities or other common barriers to good outcomes (e.g., mental health disorders, people whose adherence or follow-up may pose difficulties, homelessness, poor motivation, etc.).		
Recruitment path	How are participants recruited into the trial? To what extent are the people who use drugs in the trial similar to those who would receive the intervention if it was part of usual care?	If studying or evaluating recruitment strategies is part of the focus of the intervention or analysis, then score 1 if the recruitment strategy or efforts are substantially beyond those currently used in routine care or beyond those likely to be easily added to routine care (e.g., use of an outreach worker who will spend several hours a day to find a potential participant would be such an example); score 5 for recruitment efforts commonly employed in routine care (e.g., providers asking at a routine visit) or score 5 or close to 5 for efforts likely to be easily or plausibly added to routine care (e.g., sending one letter or making one phone call). If a study used incentives to encourage participation in the intervention, then the study should be considered more of an efficacy study unless the incentives are part of the intervention itself.		
Setting	Where is the trial being done? How different is the setting of the trial and the usual care setting for people who use drugs?	Consider that the study site may be part of the study question. Since some studies are likely to be conducted in settings specific to the needs of PWUD, e.g., field sites, drug treatment programs, syringe exchange programs (SEPs), use of a particular site may be part of (or the focus of) the study question itself. The study will be given a score reflecting a more predominately effectiveness design the closer the care setting is to standard care for PWUD.		
Organization intervention	What expertise and resources are needed to deliver the intervention? How different are the resources, provider expertise and the organization of care delivery in the intervention arm of the trial and those available in usual care for people who use drugs?	Consider whether the setting is one where even if the intervention was not currently part of routine practice or care, it is one that could be easily implemented outside of a study or a pilot project, without major additions of staff, new funding streams, equipment or policy change. If this is the case, then score 5. If the intervention could not be implemented (or sustained) post-study without ongoing research funding or substantial new clinical/public health funding, the addition of substantial new staff, equipment or policy change, then score 1.		
Flex of experimental intervention delivery	How should the intervention be delivered? How different is the flexibility in how the intervention is delivered and the flexibility in usual care for people who use drugs?	If there was a very strict study protocol which utilized monitoring or measures to improve or ensure compliance, with specific advice on allowed co-interventions and complications, then the study would be given a high efficacy rating (1). Fidelity monitoring would be an example of a measure that contributes to a lower PRECIS-II score. Think about the flexibility of both intervention delivery as referring to the intervention itself, even if the goal of the intervention is to improve adherence, we would still rate the study in terms of whether or not there were measures in place to increase adherence to the intervention. For example, measures to improve attendance at sessions promoting adherence to the intervention would contribute to lower scores.		
Flex of experimental intervention adherence	What measures are in place to make sure participants adhere to the intervention? How different is the flexibility in how participants must adhere to the intervention and the flexibility in usual care?	Think about the degree of allowed flexibility of adherence within the intervention as referring to the intervention itself. Even if the goal of the intervention is to improve adherence, we would still rate the study in terms of whether or not there were rigorous measures in place to increase adherence to the intervention and not the range of observed adherence itself. For example, use of measures to improve the attendance at sessions would lead to a lower PRECIS-II score. However, when addressing/promoting adherence is part of the study question or after goal of the intervention, score 1 for adherence promoting interventions that utilize or require (staff or participant) time, effort, cost or technology substantially beyond those in (or easily added to) routine care (e.g., attendance at 8 two-hour training sessions during a work day run by a professional with advanced training); score 5 for efforts part of, or could easily be added to routine care (e.g., by virtue of being able to use existing staff without added training, cost, equipment or substantial additions of time or effort).		
Follow-up	How closely are participants followed-up? How different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care?	An efficacy trial (rated 2 or 1 depending on intensity of follow-up schedule) would have more frequent and/or longer visits, unscheduled visits triggered by primary outcome events or intervening events, and/or more extensive data collection. A key point here is whether follow-up for the trial results in care that differs from usual conditions. A concern is whether follow-up has an impact on engagement in care. Studies that only examine outcomes that are early surrogates, for example early viral response (EVR) of ultimate outcomes (e.g., 12 week sustained viral response) and not the ultimate outcomes themselves would receive lower scores.		
Outcome	How relevant is it to participants? To what extent is the trial's primary outcome relevant to participants?	A efficacy approach (score 1 or 2) would make use of early surrogate outcomes, central adjudication or use assessment expertise that is not available in usual care. Effectiveness trials will have outcomes that are of obvious importance to PWUD and would be routinely observed in usual care. Approaches to the primary outcomes that are likely to reduce the PRECIS-II score include using a composite primary outcome in which some of the elements are less important to participants or patients than others (such as incidence of death, liver cancer, or elevated liver tests). This is relevant, for example, with respect to HCV testing if the endpoint included both the validated receipt of viral load testing and with self-reported receipt of testing. Another example would be the combination of those achieving SVR and those completing prescribed HCV treatment. Measuring an outcome that is important but is measured earlier than it would be in usual practice would be given a lower score: time horizons may vary from short-term after a one-time intervention (more efficacy) to long-term (more effectiveness).		
Analysis	To what extent are all data included in the analysis of the primary outcome?	Other analytic practices that would lower the PRECIS-II score would be excluding those with adherence lower than some threshold (in studies where adherence is not the outcome), or excluding those where intervention fidelity assessments suggest lower than some threshold fidelity to the planned intervention. Analyses that focus on secondary endpoints, post-hoc derived subgroups, or data merged from more than one study, would also lower PRECIS-II scores. Efficacy trials may notably have new eligibility criteria applied post-randomization that includes only completers or those following the treatment protocol, for example.		

*Scores 1 - 5 represent the following categories:
 1: Full efficacy
 2: Partial efficacy
 3: Equally effectiveness/efficacy
 4: Partial effectiveness
 5: Full effectiveness

Figure 1.
Data Collection Form: Adaptation of the PRECIS-II Instrument for HCV Care Continuum Systematic Review

Figure 2.
PRECIS-II wheel chart for two HCV Care Continuum outcomes in McGovern, *et al.* 2006⁴⁶