

Application of an adapted PRECIS-2 instrument to assess efficacy- and effectiveness-study designs in a systematic review of intervention studies of the hepatitis C virus-care continuum among people who use drugs

Ashly E Jordan^{1,2}
David C Perlman^{2,3}
Daniel J Smith¹
Holly Hagan^{1,2}

¹New York University, Rory Meyers College of Nursing, New York, NY, USA; ²Center for Drug Use and HIV Research, ³Icahn School of Medicine, Mount Sinai Beth Israel, New York, NY, USA

Introduction: Systematic reviews and meta-analyses examining intervention studies may need to categorize studies by the degree to which they reflect efficacy or effectiveness study-design elements when reporting systematic reviews and meta-analysis results.

Materials and methods: We identified reports presenting data from intervention studies eligible for evaluation with an adapted PRECIS-II instrument as part of a larger systematic review of the hepatitis C virus (HCV)-care continuum among people who used drugs. We applied the instrument to score reports examining any of the HCV-care-continuum steps of testing, linkage to care, and treatment on an efficacy–effectiveness spectrum. Composite scores are presented in tabular format and in stacked dot plots.

Results: The adapted PRECIS-II instrument was applied to 37 unique reports that presented data on 51 HCV-care-continuum outcomes of testing (n=16), linkage to care (n=12), and treatment (n=23). Totals of 28, six, and three reports had been produced on one, two, or all three outcomes, respectively. Ten and eight studies described themselves as having efficacy or effectiveness designs, respectively; 33 did not specify. PRECIS-II composite scores for reports produced on testing, linkage to care, and treatment ranged widely: 1.22–5. Composite scores for reports examining HCV treatment indicated study designs that tended toward effectiveness (3.35), but those examining testing (3.85) or linkage (3.8) had more effectiveness-study designs ($P=0.003$, $P=0.013$, respectively).

Conclusion: Reviewed reports varied widely in their use of efficacy/effectiveness-study designs, suggesting that systematic reviews and meta-analyses need to consider heterogeneity in efficacy/effectiveness study design in analyses. Most reports tended modestly toward having effectiveness designs, and treatment studies contained the most elements of efficacy-study designs. When assessing large numbers of reports with the PRECIS-II instrument, stacked dot plots may aid visually in depicting the range of scores. This review suggests that studies of the effectiveness of HCV treatment of people who use drugs at a population level is a research gap.

Keywords: efficacy, effectiveness, HCV-care continuum, systematic review and meta-analysis, evidence base

Correspondence: Ashly E Jordan
Center for Drug Use and HIV Research,
Rory Meyers College of Nursing, New
York University, 433 First Avenue – 7th
floor, New York, NY 10010, USA
Tel + 1 212 992 7180
Email aj924@nyu.edu

Plain-language summary

Systematic reviews and meta-analyses are important methods for synthesizing existing knowledge to inform public health policy and identify research gaps. Efficacy and effectiveness studies

provide two distinct ways to examine the impact of an intervention and address two distinct research questions, and the degree to which studies examine efficacy or effectiveness is an important form of study design that systematic reviews must address. The PRECIS-II instrument is a validated tool intended to guide intervention design and characterize degrees of efficacy and effectiveness in studies. It has been applied to trial design in various settings and in a few post hoc analyses. Using a modestly adapted PRECIS-II instrument, we sought to examine the degree to which efficacy- and effectiveness-design elements were present in intervention studies included in a systematic review on the hepatitis C virus-care continuum among people who use drugs. We found that most study designs tended toward effectiveness, consistent with the recognized gap between efficacy and effectiveness in the hepatitis C virus-care continuum. An important gap identified is the need for more data on the population-level effectiveness of hepatitis C virus treatment in broader populations of people who use drugs treated in appropriate but routine models of care.

Introduction

Systematic reviews and meta-analyses are important methods for synthesizing existing knowledge to inform public health policy and identify research gaps.^{1–3} There is an emerging need for systematic reviews and meta-analyses examining intervention reports to account for differences in degrees to which included reports reflect either efficacy or effectiveness designs.^{4,5}

Systematic reviews must make assessments of the similarity of studies for inclusion on parameters, including those of study design.⁶ Intervention studies in particular may vary in design elements intended to maximize either internal validity, with the goal of addressing questions of the intrinsic efficacy of an intervention, or to maximize elements favoring external validity, with the goal of addressing questions of generalizability and the effectiveness of an intervention in routine practice.⁴ Efficacy and effectiveness studies provide two distinct ways to examine the impact of an intervention; in fact, they address two distinct research questions.^{7,8} Combining results from studies designed to answer different questions may lead to imprecise and possibly invalid inferences.⁹ The degree to which studies examine questions of efficacy or effectiveness is an important form of study-design heterogeneity that systematic reviews must address. All aspects of study design, including methods of sampling, recruiting, and data analysis, inform whether the study is asking (and answering) an efficacy- or effectiveness-research question.^{4,10}

Hepatitis C virus (HCV) infection causes substantial morbidity and mortality.^{11,12} Morbidity and mortality persist in part due to incompletely effective and underimplemented

programs to prevent primary infection and reinfection, and to very low rates of implementation of highly efficacious HCV treatment for those chronically infected.^{13–16} New, oral direct-acting antivirals with treatment regimens lasting only 8–12 weeks have more than 90% efficacy, creating the potential for HCV treatment as prevention (TasP) through lowering community HCV viral load (ie, resultant lower probabilities of HCV acquisition [forward transmission] among current people who inject drugs [PWID]).¹⁷ HCV TasP also has the ability to reduce morbidity and mortality by curing people of their infection and thus reducing HCV-induced hepatic injury (eg, development of cirrhosis) over the life course. However, the high cost of these medications has severely restricted access in the US, particularly for PWID, reducing the population-level effectiveness of HCV TasP.¹⁸ Modeling suggests that effective population-level HCV prevention and treatment will require broader implementation of needle-exchange programs, medication-assisted treatment, and expanded treatment to serve as TasP.^{19–24}

Published literature examining steps of the HCV-care continuum have addressed questions of both the intrinsic efficacy of antiviral agents and biobehavioral interventions, and questions of the effectiveness of these interventions in practice and at the population level.^{25,26} Despite the availability of HCV-testing methods with high sensitivity and specificity and treatment regimens of high efficacy, HCV has been identified as an area in which large gaps between efficacy and observed clinical and population-level effectiveness have been and in many settings continue to exist.^{26–29} As such, systematic reviews of aspects of HCV care are likely to encounter studies reflecting various degrees of efficacy- and effectiveness-study design.^{4,30,31} Indeed, given the recognized efficacy–effectiveness gap, it could be argued that there is a need for the development and implementation of interventions to improve the effectiveness of HCV-care-continuum steps.

We are conducting a systematic review and meta-analysis of the HCV-care continuum, with predefined care-continuum steps of screening or testing, links to care, treatment acceptance, initiation, and adherence, treatment completion, the biologic outcome of a sustained virologic response, and subsequent risk of reinfection.³¹ The intent of the systematic review was to examine data specifically for the HCV-care continuum among people who use drugs (PWUD) as a distinct population. The rationale for the focus on this population is that PWUD as a population have distinct characteristics impacting outcomes and thus require analysis as a separate group.³² The care-continuum construct is increasingly being

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.²⁵ For example, the care-continuum construct has been formally applied to public health evaluations of HIV care and to outcomes for several infectious and incommunicable diseases.^{25,26,33,34} We sought to explore and characterize the degree of heterogeneity with respect to efficacy- and effectiveness-study design components among papers identified in systematic reviews examining the outcomes of HCV testing, link to care, and treatment in intervention studies using the adapted PRECIS-2 instrument⁸ and to develop methods to represent pooled PRECIS-2 scores and their distribution.

Materials and methods

Systematic review

The data reported here were derived from ongoing analyses being conducted as part of our systematic review/meta-analysis titled “The HCV care continuum among people who use drugs” (PROSPERO CRD42016034113). The methods of our systematic review/meta-analysis have been defined in detail.³¹ In brief, this protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.³⁵ A PRISMA flow diagram is presented in Figure 1.

The primary exposures examined in this review were PWUD or a PWID and thus at risk of HCV infection and being a former PWUD or PWID and having HCV infection. The term “PWUD” is used herein to refer to those who use or have used any illicit drug(s) by any route, but excludes those who use or have used alcohol, tobacco, or marijuana only. The term “PWID” is used to refer to those who use or have used any illicit drug by injection.

This study includes published data from both observational and experimental study designs. To be eligible, the reports needed to present outcomes of interest on any one or more of three specific HCV-care-continuum steps (testing, linkage to care, and treatment), present data from the US, be published in English between January 1, 1990 and February 20, 2016, and include data on PWUD and/or PWID.³¹ Inclusion criteria required that reports presented data from the US, as the progression through steps in the care continuum is highly dependent on the types of health-care delivery systems in a given country.

Initial prespecified plans were to examine and categorize reports and outcomes with respect to HCV-care-continuum steps of screening and testing, linkage to and completion of clinical evaluations in care, interventions to increase treatment acceptance, initiation, and adherence, completion of treatment, achieving a sustained virologic response (SVR),

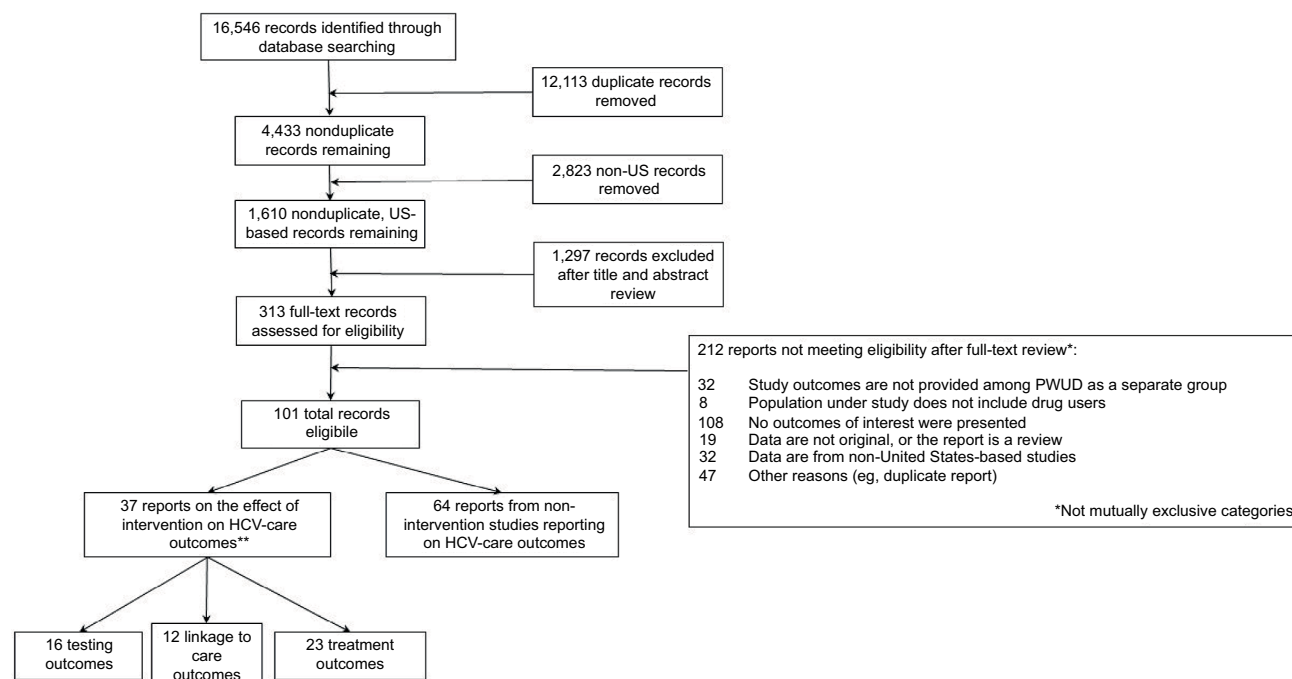


Figure 1 PRISMA diagram for systematic review.

Note: **Some reports reported on more than one outcome.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HCV, hepatitis C virus; PWUD, people who use drugs; US, United States.

and reinfection post-SVR. Because identified reports included data on a heterogeneous mix of these steps, each defined variously, for the current analyses we recategorized these six outcomes into the following three sequential care-continuum-step outcomes: HCV screening and testing (included screening for primary infection and for recurrent infection in PWUD who may have had spontaneous clearance of initial infections), linkage to HCV care, including data addressing completion of HCV clinical evaluation, and HCV treatment that included treatment offers, acceptance, initiation, and completion, and outcomes of treatment (including SVR and reinfection post-SVR).

Studies were characterized by specific clinic settings, geographic location, study time period, and whether the study described itself as having an efficacy- or effectiveness-study design. Treatment studies were further categorized as to whether they examined licensed or unlicensed HCV-treatment agents. Studies were also characterized as to whether they were intervention studies (evaluating outcomes of a program or care model in either a randomized or observational design) or not. Nonintervention studies included those presenting such data as reports presenting factors associated with HCV-treatment initiation at the individual level providing no data on any implementation of a program or intervention, reports presenting prevalence data on anti-HCV and HCV RNA testing in a nonrandom selection of clinics across an area, and chart reviews of HCV-positive patients to find reasons that they did not initiate treatment. We then applied the PRECIS-2 to identified intervention studies.

Scoring on the spectrum of efficacy–effectiveness study design

The PRECIS-2 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 a few post hoc analyses.^{30,36–38} PRECIS-2 has been shown to have good interrater reliability.³⁹ The nine domains of PRECIS-2 are eligibility, recruitment, setting, organization, flexibility of delivery, flexibility of adherence, follow-up, outcome, and analysis.

We modestly adapted the PRECIS-2 to modify the prompts to reflect its application to the post hoc analysis of studies and to reflect considerations specifically relevant to HCV-care-continuum studies. Using the PRECIS-2 toolkit and guided by Loudon et al, we adapted the prompts and instructions for each domain of PRECIS-2: prompts were tailored to address the post hoc nature of the review, and instructions were included that were informed by both HCV subject-matter expertise and expertise in trial design, statistical analysis, and the conduct

of systematic reviews and meta-analyses.^{8,40} One additional consideration specific to the application of PRECIS-2 to care-continuum studies is that some studies present more than one outcome (eg, HCV testing and linkage to care), in which case eligibility criteria, recruitment method, and data-analysis plan may differ between outcomes. In such cases, we applied the PRECIS-2 instrument separately for each outcome for which data were presented.

Studies that presented results from intervention studies were scored with the adapted HCV PRECIS-2 instrument and were rated for each of the nine PRECIS-2 domains for each of the three possible study outcomes on which data were presented. After pilot testing, the adapted reports were reviewed by one coder (AEJ), with scores reviewed by the study team. Each domain was scored on a 5-point Likert scale from full efficacy (1) to full effectiveness (5), with a score of 3 indicating that a study-design domain was equally one of efficacy and effectiveness. In addition, a composite score is reported for each report to characterize the overall position of the design on an efficacy–effectiveness spectrum. PRECIS-2 scores for each of the included reports were depicted as wheel charts, and four of these are shown as examples (see Figures 2 and 3). Mean and median scores were calculated for each domain for all reports contributing data on each HCV-care-continuum outcome. A series of stacked dot plots was used to represent the distribution of PRECIS-2 scores by domain and outcome (Figure 4). Statistics were calculated in SPSS and the stacked dot plots were generated in Stata.^{41,42}

Results

The process of the systematic review is presented in Figure 1 as a PRISMA flow diagram. The initial search yielded a total of 16,546 reports. After removal of duplicate reports and studies that presented data not based in the US, 1,610 reports were assessed for eligibility by title and abstract review, 1,297 excluded for ineligibility, and the remaining 313 assessed for eligibility by full-text review. A total of 101 reports were deemed eligible for the overall systematic review; 37 reports were identified as being intervention studies specifically addressing PWUD and thus eligible for PRECIS-2 evaluation and the subject of this report.

These 37 reports presented data on 51 HCV-care-continuum outcomes of testing (n=16, Table 1),^{43–58} linkage to care (n=12, Table 2),^{44–46,49,51,52,54,57–61} and treatment (n=23, Table 3).^{44,45,51,61–80} A total of 28 papers reported on precisely one outcome, six papers reported on two outcomes, and three papers reported on all three outcomes. One report provided national data, four reports presented data from multiple sites, and the remaining reports were single-site studies. Reports

presented data from 12 US states. A third of the outcomes reported data from New York. The types of settings in which the data were collected varied, but they were generally characteristic of settings where PWUD receive services (eg, needle-exchange program, methadone-maintenance-treatment program) (Tables 1–3).

Each of the nine PRECIS-2 domains was assessed for each separate outcome presented in any given report. As an example of how study design may vary with respect to efficacy–effectiveness elements in each of the PRECIS-2 domains, we describe variations identified in the domain flexibility of intervention adherence. For outcome linkage to care, an example of full efficacy was when a study required that researchers providing the intervention be highly trained and follow a strict study protocol,⁶³ a study that used a specified protocol but that allowed for some modest protocol deviation was rated as a partial-efficacy design,⁵⁹ a study that provided standard-of-care referral for off-site HCV care following an HCV-positive test but in which staff received some specialized training was considered to exhibit both efficacy and effectiveness elements equally,⁴⁵ when a linkage to care intervention included reproducible components beyond the standard of care but that could be implemented selectively as needed, it was considered to represent a partial-effectiveness design,^{46,59} and a study in which linkage to care relied on off-site referral without specialized staff training or additional measures was an example of a full-effectiveness design.⁴⁴

For each outcome of the HCV-care continuum, scores for each domain are presented in Tables 1–3, along with the composite score. Composite scores for reports examining HCV treatment were lower (3.35) than those for either testing (3.85) or linkage (3.80) ($P=0.003$ and $P=0.013$, respectively). For reports on HCV testing, composite scores ranged from 1.89 (SD 1.36) to 5 (SD 0). For reports on HCV linkage to care, composite scores ranged from 2.44 (SD 0.53) to 5 (SD 0). For reports on HCV treatment, composite scores ranged from 1.22 (SD 0.67) to 5 (SD 0). Reports on either testing or linkage to care tended toward effectiveness designs with means for all nine domains >3.5 . Reports on treatment tended toward having more efficacy-design elements, particularly for the domains of analysis, delivery, and eligibility.

Most studies did not describe themselves as being efficacy or effectiveness studies (64.7% or 33 of 51 outcomes), while ten (19.6%) described themselves as having an efficacy design and eight (15.7%) as having an effectiveness design. Overall composite scores for those describing themselves as an efficacy design ($n=10$), effectiveness design ($n=8$), and for those not specifying ($n=33$) were 3.31 (SD 1.04), 3.95

(SD 0.54), and 3.68 (SD 1.1), respectively. A total of 22 of the 23 papers reporting on HCV treatment among PWUD were studies of agents that were already licensed at the time of the study; one report that examined the use of an investigational treatment regimen had the lowest composite score (1.22).

Wheel charts were constructed for each of the reports (four are shown). Harris et al was one of three reports reporting on all three care-continuum steps.^{44,45,51} As an example, a visual depiction of adapted PRECIS-2 scores for each of the domains for each of the three outcomes reported in Harris et al is depicted in Figure 2. Figure 3 depicts the adapted PRECIS-2 scores for three of the 12 reports presenting data on linkage to care.^{46,49,58} A series of stacked dot plots (Figure 4) visually depict the range and distribution of all of the individual PRECIS-2 scores for each of the domains by outcome. Mean and median scores for each of the nine domains for each of the three outcomes (testing, linkage to care, and treatment) and for composite score for each reported outcome are shown in Table 4.

Discussion

There have been various approaches proposed to assist scientists in formulating their study designs to address questions of efficacy or of effectiveness, and similarly in categorizing published studies as reflecting efficacy- or effectiveness-study designs.^{8,81,83} Gartlehner et al developed an instrument for distinguishing between efficacy and effectiveness studies in systematic reviews.⁸² This instrument dichotomized studies as being either an efficacy or effectiveness design. While the instrument was shown to have 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.⁸¹ We anticipated that studies addressing the HCV-care continuum would be likely to address questions of both the efficacy and effectiveness of diagnosis, linkage to care, and treatment efforts, as well as the impact of behavioral and structural interventions to improve the outcomes of each of these HCV-care-continuum steps. Categorizing studies along a spectrum of efficacy–effectiveness would be more meaningful and precise than relying on a dichotomous measure.

Loudon et al⁸ published a useful tool, the PRECIS-2, to assist scientists in designing and carrying out studies that are consistent with their research questions. Although primarily intended to assist in study design, PRECIS-2 has also been applied post hoc to assess for the degree of efficacy or effectiveness in published trials.^{8,37} We have modestly adapted the PRECIS-2 instrument to allow post hoc assessments of where

Table 1 PRECIS-2 assessments for testing outcome (n=16)

First author, publication year	Recruitment site	Location	Stated study design	Time period
D'Souza, 2003 ⁴³	STD ^a clinic	Houston, TX	Effectiveness	February 1 - May 21, 2001
Gunn, 2005 ⁴⁴	Nonresidential alternative sentencing drug rehabilitation	San Diego, CA	n/s ^b	April 1999 - December 2002
Harris, 2010 ⁴⁵	MMTP ^c	New York, NY	n/s	July 2003 - July 2005
Hennessy, 2007 ⁴⁶	STD clinic	New York, NY	n/s	May 2000 - March 2004
Kapadia, 2007 ⁴⁷	Community	New York, NY; Baltimore, MD; Seattle, WA	Efficacy	April 2002 - May 2004
Kim, 2013 ⁴⁸	Correctional facility	Concord and Framingham, MA	n/s	October 2006 - March 2008
Lally, 2005 ⁴⁹	Short-term drug treatment program	Fallriver, MA	n/s	January 2001 - March 2001
Mallette, 2008 ⁵⁰	VA ^d	Providence, RI	Effectiveness	October 1998 - March 2004
Martinez, 2012 ⁵¹	MMTP	New York, NY	Effectiveness	July 2006 - June 2008
Masson, 2013 ⁵²	MMTP	New York, NY	Efficacy	2008 - 2011
McGarry, 2002 ⁵³	NEP ^e , MMTP	RI	n/s	July 1997 - March 1998
McGovern, 2006 ⁵⁴	Correctional facility	MA	n/s	November 2001 - May 2004
Merchant, 2014 ⁵⁵	ED ^f	Providence, RI	n/s	February 2011 - March 2012
Merchant, 2015 ⁵⁶	ED	New England	n/s	July 2010 - December 2012
Morano, 2014 ⁵⁷	Mobile medical clinic	New Haven, CT	n/s	2012 - 2013
White, 2016 ⁵⁸	ED	Oakland, CA	n/s	April 2014 - October 2014

Note: PRECIS-2 domain scale: 1 = full efficacy, 2 = partial efficacy, 3 = neither efficacy nor effectiveness, 4 = partial effectiveness, 5 = full effectiveness. ^aSexually transmitted disease; ^bNot specified; ^cmethadone maintenance treatment program; ^dVeterans Affairs; ^eneedle exchange program; ^femergency department.

Abbreviations: STD, sexually transmitted disease; n/s, not specified; MMTP, methadone-maintenance-treatment program; VA, Veterans Affairs; NEP, needle-exchange program; ED, emergency department.

Table 2 PRECIS-2 assessments for linkage to care outcome (n=12)

First author, publication year	Recruitment site	Location	Stated study design	Time period
Brady, 2007 ⁵⁹	VA ^a gastroenterology and liver clinics	Durham, NC	Effectiveness	January 2002 - November 2004
Fishbein, 2004 ⁶⁰	MMTP ^b	New York, NY	Not specified (n/s)	November 1999 - n/s
Gunn, 2005 ⁴⁴	Nonresidential alternative sentencing drug rehabilitation	San Diego, CA	n/s	April 1999 - December 2002
Harris, 2010 ⁴⁵	MMTP	New York, NY	n/s	July 2003 - July 2005
Hennessy, 2007 ⁴⁶	STD ^c clinic	New York, NY	n/s	May 2000 - March 2004
Lally, 2005 ⁴⁹	Short-term drug treatment program	Fallriver, MA	n/s	January 2001 - March 2001
Martinez, 2012 ⁵¹	MMTP	New York, NY	Effectiveness	July 2006 - June 2008
Masson, 2013 ⁵²	MMTP	New York, NY	Efficacy	2008 - 2011
McGovern, 2006 ⁵⁴	Correctional facility	n/s, MA	n/s	November 2001 - May 2004
Morano, 2014 ⁵⁷	Mobile medical clinic	New Haven, CT	n/s	2012 - 2013
Rifai, 2006 ⁶¹	VA 28-day inpatient substance-use treatment program	Rural Virginia	n/s	January 2000 - October 2001
White, 2016 ⁵⁸	ED ^d	Oakland, CA	n/s	April 2014 - October 2014

Note: PRECIS-2 domain scale: 1 = full efficacy, 2 = partial efficacy, 3 = neither efficacy nor effectiveness, 4 = partial effectiveness, 5 = full effectiveness. ^aVeterans Affairs; ^bmethadone maintenance treatment program; ^csexually transmitted disease; ^demergency department.

Abbreviations: STD, sexually transmitted disease; MMTP, methadone-maintenance-treatment program; VA, Veterans Affairs; ED, emergency department.

PRECIS-II Domain									
Eligibility criteria	Recruitment	Setting	Organization	Flexibility of intervention delivery	Flexibility of intervention adherence	Follow-up	Outcome	Analysis	Composite score (SD)
4	4	4	5	5	5	5	5	5	4.67 (0.50)
5	5	5	4	5	5	5	5	5	4.89 (0.33)
2	5	5	3	4	4	4	3	2	3.56 (1.13)
3	5	3	2	4	3	5	2	1	3.11 (1.36)
5	5	5	3	3	3	3	4	4	3.89 (0.93)
5	5	5	5	5	5	5	5	5	5.00 (0.00)
5	4	5	5	5	5	5	5	5	4.89 (0.33)
2	5	3	5	1	1	5	2	2	2.89 (1.69)
5	5	5	5	4	4	5	5	2	4.44 (1.01)
5	5	5	4	5	3	4	5	5	4.56 (0.73)
5	5	5	5	5	5	5	5	5	5.00 (0.00)
4	4	5	4	5	4	5	5	5	4.56 (0.53)
2	1	5	1	1	1	1	3	2	1.89 (1.36)
2	1	5	1	1	1	1	2	3	1.89 (1.36)
5	5	5	3	5	5	5	5	5	4.78 (0.67)
2	5	3	3	3	2	2	3	3	2.89 (0.93)

PRECIS-II Domain									
Eligibility criteria	Recruitment path	Setting	Organization	Flexibility of intervention delivery	Flexibility of intervention adherence	Follow-up	Outcome	Analysis	Composite score (SD)
2	3	4	5	4	5	4	5	5	4.11 (1.05)
4	4	5	5	3	5	3	4	4	4.11 (0.78)
5	5	5	5	5	5	5	5	5	5.00 (0.00)
2	5	5	5	3	3	3	2	2	3.33 (1.32)
3	5	3	2	4	4	5	2	2	3.33 (1.22)
5	4	5	5	5	5	5	5	5	4.89 (0.33)
5	5	5	3	4	4	4	3	3	4.00 (0.87)
5	5	5	4	5	4	4	5	5	4.67 (0.50)
5	4	5	4	4	4	5	3	3	4.11 (0.78)
5	5	5	3	5	5	5	5	5	4.78 (0.67)
3	5	3	2	2	2	4	2	2	2.78 (1.09)
2	2	3	2	3	2	2	3	3	2.44 (0.53)

Table 3 PRECIS-2 assessments for treatment outcome (n=23)

First author, publication year	Recruitment site	Location	Stated study design	Time period	Treatment drug licensed or unlicensed
Adeyemi, 2004 ⁶²	Viral hepatitis clinic	Cook County, IL	n/s ^a	July 2001 - December 2002	Licensed
Allen, 2003 ⁶⁴	Correctional facility	Cranston, RI	Efficacy	1997 - 2001	Licensed
Bonkovsky, 2008 ⁶³	MMTP ^b	n/s	Efficacy	n/s	Licensed
Bruce, 2012 ⁶⁵	MMTP	New Haven, CT	n/s	2007 - 2010	Licensed
Butt, 2016 ⁶⁶	VA ^c	Multiple VA sites throughout USA	Efficacy	October 1 2001 - June 30 2015	Licensed
Gunn, 2005 ⁴⁴	Nonresidential alternative sentencing drug rehabilitation	San Diego, CA	n/s	April 1999 - December 2002	Licensed
Harris, 2010 ⁴⁵	MMTP	New York, NY	n/s	July 2003 - July 2005	Licensed
Ho, 2013 ⁶⁷	Primary care co-located in a homeless shelter	San Jose, CA	n/s	n/s	Licensed
Ho, 2015 ⁶⁸	VA HCV clinic	San Diego, CA; Palo Alto, CA; New York, NY	n/s	March 2009 - February 2011	Licensed
Lalezari, 2015 ⁶⁹	MAT ^d clinic	8 sites across the USA	Efficacy	April 2013 - n/s	Unlicensed
Litwin, 2009 ⁷⁰	MMTP	New York, NY	n/s	January 1 2003 - December 15 2005	Licensed
Litwin, 2015 ⁷¹	MAT clinic	New York, NY	n/s	January 21 2011 - April 2 2013	Licensed
Martinez, 2012 ⁵¹	Viral hepatitis clinic	New York, NY	Effectiveness	July 2006 - June 2008	Licensed
Mehta, 2006 ⁷²	HIV clinic	Baltimore, MD	Effectiveness	June 1998 - December 2003	Licensed
Miller, 2012 ⁷³	Liver clinic	Atlanta, GA	n/s	2002 - 2007	Licensed
Nelson, 2014 ⁷⁴	VA	Entire USA	Efficacy	January 1 2004 - December 31 2009	Licensed
Rifai, 2006 ⁶¹	VA 28-day inpatient substance-use treatment program	Rural Virginia	n/s	January 2000 - October 2001	Licensed
Stein, 2012 ⁷⁵	MMTP	New York, NY	Effectiveness	March 2009 - October 2010	Licensed
Sylvestre, 2002 ⁷⁶	MMTP	Oakland, CA	Efficacy	n/s	Licensed
Sylvestre, 2005 ⁷⁷	MMTP	Oakland, CA and New York, NY	n/s	n/s	Licensed
Taylor, 2011 ⁷⁸	MMTP	Providence, RI	Efficacy	n/s	Licensed
Van Thiel, 2003 ⁷⁹	Hospital clinic	Maywood, IL	n/s	August 1997 - December 2000	Licensed
Woodrell, 2015 ⁸⁰	Primary care liver clinic	New York, NY	n/s	2011 - 2013	Licensed

Note: PRECIS-2 domain scale: 1 = full efficacy, 2 = partial efficacy, 3 = neither efficacy nor effectiveness, 4 = partial effectiveness, 5 = full effectiveness. ^aNot specified;

^bmethadone maintenance treatment program; ^cVeterans Affairs; ^dmedication assisted treatment.

Abbreviations: n/s, not specified; MMTP, methadone-maintenance-treatment program; VA, Veterans Affairs; HCV, hepatitis C virus; MAT, medication-assisted treatment.

on an efficacy–effectiveness spectrum studies identified and included in this systematic review of outcomes of the steps of the HCV-care continuum lie.⁸⁴ We have now applied this adapted instrument in the context of this systematic review of outcomes of the steps of the HCV-care continuum.³¹

There was significant heterogeneity in the distribution of efficacy- and effectiveness-study design elements among reports examining the HCV-care continuum identified in this systematic review. The majority of reports did not specify whether the study was intended to examine efficacy or effectiveness. This might reflect a recognition that study designs

exist along a spectrum of efficacy and effectiveness, but it might also reflect incomplete consideration of these issues at the time of study design. As highlighted by Loudon et al,³⁹ use of the PRECIS-2 instrument may be invaluable during the process of study planning to help ensure that investigators select study-design elements that most appropriately answer the study question, whether that be one of efficacy, effectiveness, or some combination.

The PRECIS-2 toolkit gives guidance on how to score each domain, and rather than suggesting a composite score, suggests scores be depicted visually in a wheel.⁸

PRECIS-II Domain									
Eligibility criteria	Recruitment path	Setting	Organization	Flexibility of intervention adherence	Flexibility of intervention adherence	Follow-up	Outcome	Analysis	Score (SD)
2	5	4	5	4	4	4	4	4	4.00 (0.87)
4	5	5	5	5	4	4	4	2	4.22 (0.97)
1	3	5	1	1	1	1	2	2	1.89 (1.36)
2	3	5	3	1	1	1	1	1	2.00 (1.41)
1	3	4	3	2	2	3	2	2	2.44 (0.88)
5	5	5	5	5	5	5	5	5	5.00 (0.00)
2	5	5	2	2	3	3	2	1	2.78 (1.39)
3	4	5	3	3	2	4	2	2	3.11 (1.05)
3	3	4	3	2	3	3	4	3	3.11 (0.60)
3	1	1	1	1	1	1	1	1	1.22 (0.67)
2	5	3	5	2	2	2	5	2	3.11 (1.45)
3	5	5	3	4	4	4	5	3	4.00 (0.87)
5	5	5	3	4	4	3	3	2	3.78 (1.09)
4	4	5	5	3	5	3	4	3	4.00 (0.87)
2	2	2	3	2	4	4	2	4	2.78 (0.97)
2	5	5	4	2	4	2	4	4	3.56 (1.24)
2	3	5	4	1	1	1	2	1	2.22 (1.48)
5	3	3	5	4	3	3	3	4	3.67 (0.87)
2	5	3	3	2	3	4	2	2	2.89 (1.05)
3	5	5	4	3	3	4	4	3	3.78 (0.83)
3	5	5	3	3	3	3	5	4	3.78 (0.97)
3	5	4	3	2	3	2	3	4	3.22 (0.97)
5	5	5	5	5	5	5	5	5	5.00 (0.00)

Wheel charts do serve as potent infographics representing the degrees of heterogeneity or homogeneity found in the efficacy–effectiveness design of studies. As demonstrated by the heterogeneity in efficacy–effectiveness study design identified among the included reports, studies of any given care–continuum step can vary significantly in efficacy–effectiveness design and in their positions on the efficacy–effectiveness spectrum. As seen in Figures 2 and 3, for a given outcome and even within a single publication examining all three HCV-care–continuum steps, the balance of efficacy–effectiveness study-design elements may vary.

Studies of HCV testing and linkage to care had mean scores for all nine domains that tended toward effectiveness, particularly for the domains of setting, recruitment path, and follow-up. For testing studies, this is consistent with the fact that throughout the period studied in the systematic review, HCV-diagnostic tests of high sensitivity and specificity have been available and key questions have been on how to engage more PWUD in testing. While behavioral and structural interventions to promote linkage to care could in theory be evaluated to assess their efficacy or for questions of effectiveness, linkage to care reports identified in this review

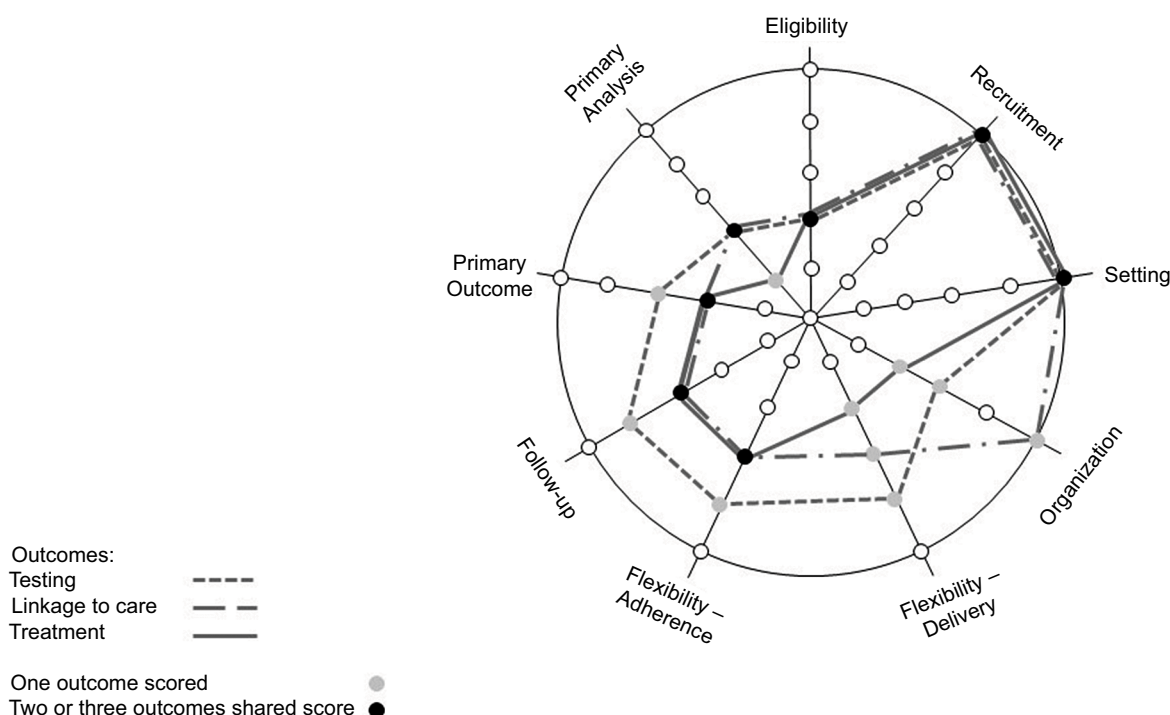


Figure 2 PRECIS-2 wheel chart for three outcomes in Harris et al.⁴⁵

tended to have effectiveness-study designs, as appropriate in a situation in which the efficacy of testing and treatment have been well demonstrated.^{44,49,52}

It is notable that mean PRECIS-2 composite scores for treatment studies were significantly lower than for those examining testing or linkage to care, despite the fact that all except one of the treatment studies were studies of already licensed treatment regimens. While treatment studies tended modestly toward effectiveness designs overall, and especially with respect to recruitment path and study setting, they tended toward efficacy designs with respect to eligibility, the flexibility of delivery, and analysis. Reasons for this are uncertain; however, one possibility is a “carryover” to studies of licensed drugs of the study-design methods appropriately employed in the evaluation of investigational drugs. The tendency toward effectiveness-study design with respect to study setting and recruitment path may reflect a recognition of the need to engage PWUD in settings they attend. Use of efficacy-design elements may have been prompted by efforts to examine whether HCV-treatment outcomes among PWUD can be as good in idealized conditions as among non-PWUD. These data may have been needed to influence policy-makers to include PWUD in treatment guidelines.^{85,86} Addressing the other critical question of how good HCV-treatment outcomes among PWUD are in routine care and at the population level

may be more appropriately examined and addressed by use of effectiveness-study designs.

While wheel charts have been utilized in reviews of modest numbers of publications,^{36,37} they lose their visual clarity and potency as the number of reviewed reports increases. It becomes impractical either to depict each paper separately or as superimposed wheel charts. We thus sought alternative ways to present PRECIS-2 score data visually for larger numbers of studies. We used stacked dot plots to represent the distribution of scores for each domain for each paper included in a systematic review. We also represented scores by their means (with standard deviations) in tabular form. These formats may be useful approaches for other studies applying the PRECIS-2 instrument to large numbers of reports.

Several issues arise in incorporating measures of a study’s efficacy–effectiveness status in systematic reviews/meta-analyses. Dichotomous assessments, such as that of Gartlehner et al, yield a dichotomous variable that is easily incorporated in meta-analyses.⁸¹ However, as demonstrated by the heterogeneity of efficacy–effectiveness study designs identified among the included reports (see Tables 2–4), papers in this systematic review are more richly and accurately categorized along a spectrum of efficacy–effectiveness in numerous domains.

The use of a measure with nine domains, each scored with a 5-point Likert-like scale, poses choices as to the best way

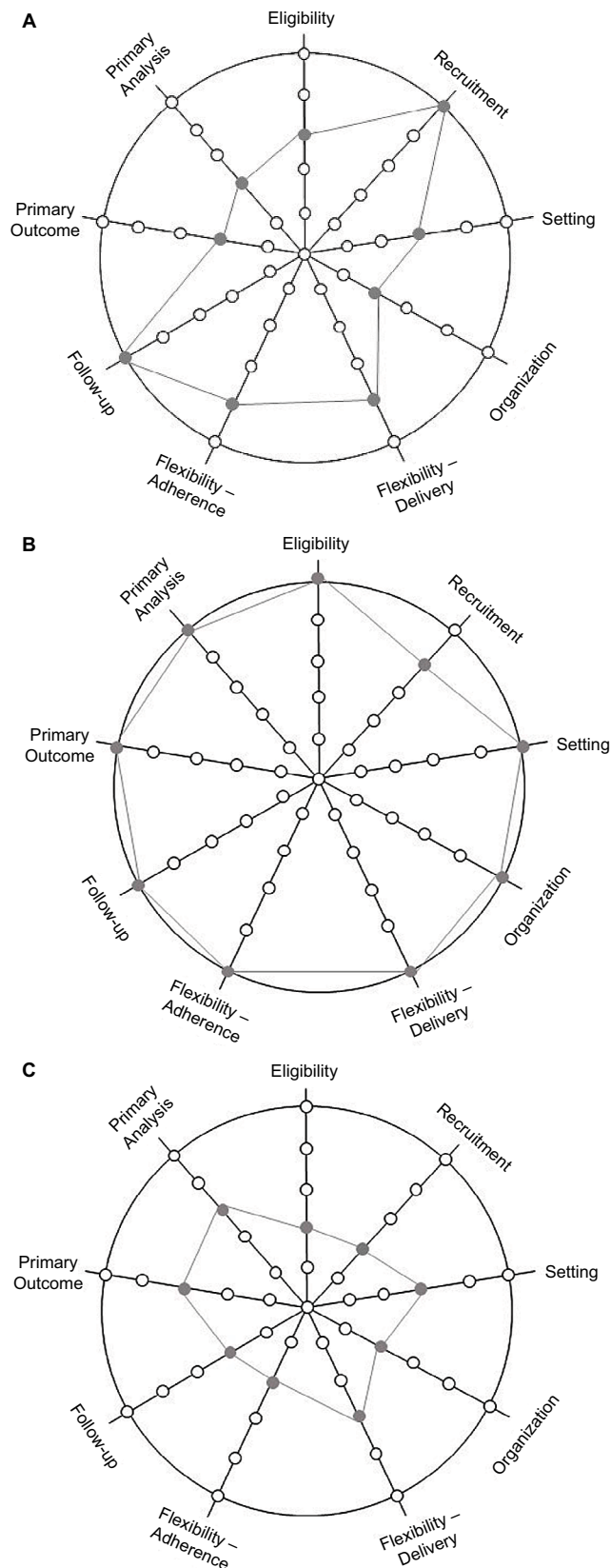


Figure 3 PRECIS-2 wheel charts.

Notes: (A) Linkage to care outcome in Hennessy et al.⁴⁶; (B) linkage to care outcome in Lally et al.⁴⁹; (C) linkage to care outcome in White et al.⁵⁸

to incorporate these measures of efficacy–effectiveness study design into meta-analyses. One could consider each domain a separate variable with a range of 1–5, and examine each domain as a covariate in metaregression. If one particular domain were found to differentiate included studies more potentially, one could examine that domain exclusively in meta-analysis, as opposed to incorporating all nine domains as covariates. A study would have to include a sufficient number of papers to examine nine separate efficacy–effectiveness domains as covariates. Some studies have utilized composite PRECIS-2 scores for each report in metaregression, rather than examining each domain as a distinct covariate.^{30,37}

This study is subject to limitations. One limitation is that the systematic review examined only reports that specifically included PWUD and that reported data for PWUD separately. We note that many studies of HCV may include PWUD without explicitly saying so or without reporting data separately for PWUD as a group (and hence would not be included in this systematic review), and also note that many studies (particularly treatment-randomized controlled trials) may specifically exclude PWUD. Nonetheless, the intent of the systematic review was to examine data specifically for the HCV-care continuum among PWUD as a distinct population. The rationale for the focus on this population is that PWUD as a population have distinct characteristics impacting outcomes and thus require analysis as a separate group.³² One limitation was that reports were coded by a single rater, with scores then reviewed by the study team; however, the PRECIS-2 instrument has been shown to have good interrater reliability.³⁹ Numerous studies did not either specify their recruitment time periods or present data that spanned multiple years, precluding sound analyses of any temporal trends. The level of data provided in the included reports with respect to some of the domains was variable, and could have contributed to misclassification of studies with respect to PRECIS-2 scores.

Conclusion

The heterogeneity identified in efficacy–effectiveness study design suggests that variability needs to be accounted for in systematic reviews and meta-analyses of the HCV-care continuum. Use of an adapted PRECIS-2 instrument with scores depicted in stacked dot plots and in tabular form will help guide how to incorporate these data in meta-analysis. Studies presenting outcomes of interventions to improve the steps of the HCV-care continuum would be enhanced by more clearly framing their study design and results with respect

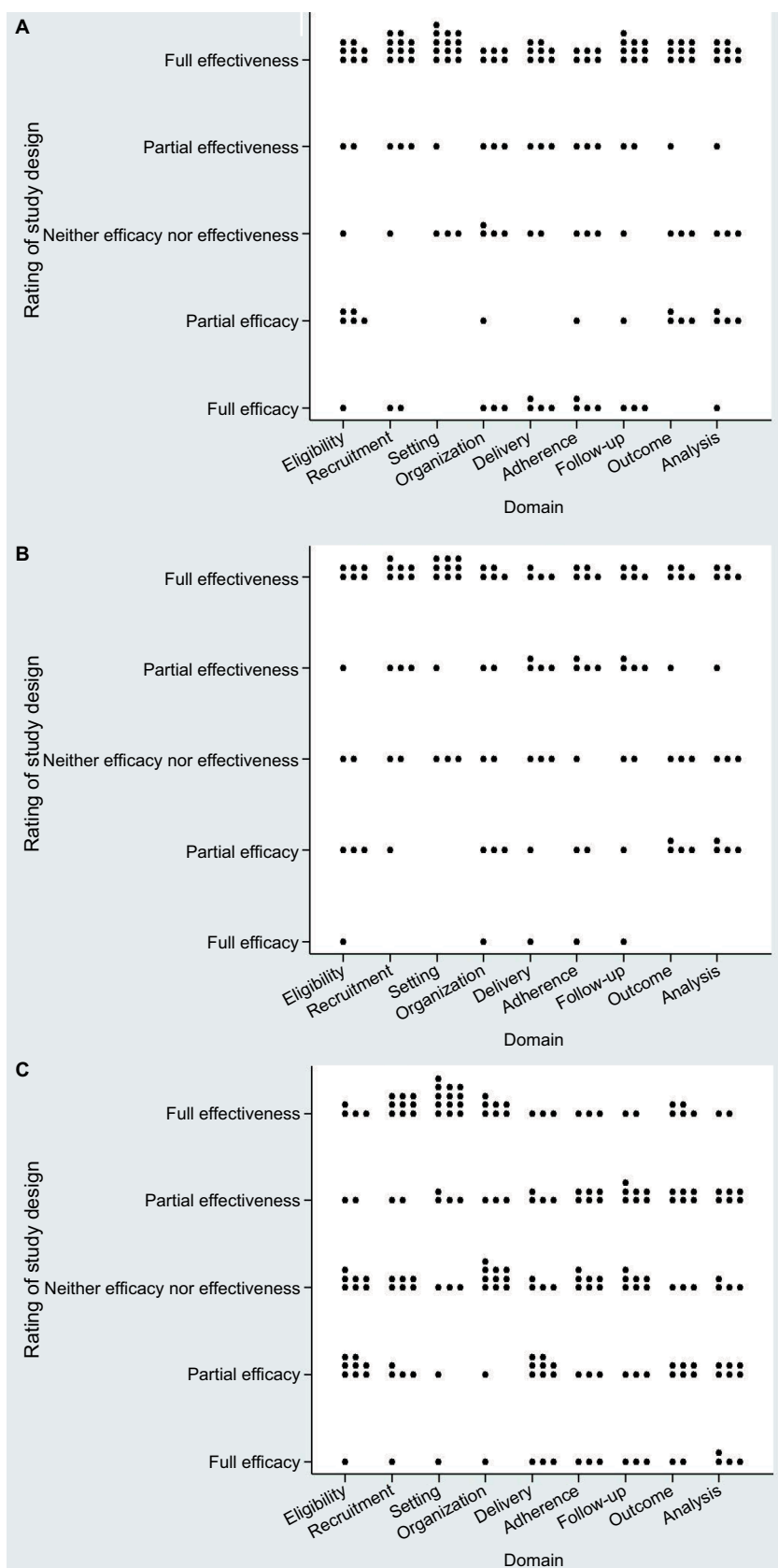


Figure 4 (A) HCV-testing outcome; (B) HCV linkage to care outcome; (C) HCV-treatment outcome.

Abbreviation: HCV, hepatitis C virus.

Table 4 Composite score results from PRECIS-2 assessment for 37 reports in HCV-care-continuum systematic review

PRECIS-II Domains (n = 9)	Testing (n = 16 outcomes)		Linkage to care (n = 12 outcomes)		Treatment (n = 23 outcomes)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Eligibility	3.81 (1.50)	4.50	3.83 (1.50)	4.50	2.91 (1.20)	3.00
Recruitment path	4.31 (1.35)	5.00	4.33 (1.01)	5.00	4.09 (1.21)	5.00
Setting	4.56 (0.80)	5.00	4.42 (0.88)	5.00	4.26 (1.15)	5.00
Organization	3.63 (1.50)	4.00	3.75 (1.45)	4.00	3.52 (1.14)	3.00
Flexibility of delivery	3.81 (1.66)	4.50	3.92 (1.25)	4.00	2.74 (1.30)	2.00
Flexibility of adherence	3.50 (1.62)	4.00	4.00 (1.36)	4.00	3.04 (1.25)	3.00
Follow-up	4.06 (1.62)	5.00	4.08 (1.28)	4.00	3.00 (1.19)	3.00
Outcome	4.00 (1.32)	5.00	3.67 (1.33)	3.50	3.22 (1.35)	3.00
Analysis	3.69 (1.46)	4.50	3.67 (1.33)	3.50	2.78 (1.30)	3.00
Mean (SD) PRECIS-II summary score by outcome	3.85 (0.34)	–	3.80 (0.27)	–	3.35 (0.56)	–

Note: PRECIS-2 domain scale: 1 = full efficacy, 2 = partial efficacy, 3 = neither efficacy nor effectiveness, 4 = partial effectiveness, 5 = full effectiveness.

Abbreviation: HCV, hepatitis C virus.

to the extent to which they are measuring and reporting on efficacy or effectiveness. This review of intervention studies examining the HCV-care continuum found that most study designs tended toward effectiveness designs, consistent with the recognized still-existing population-level gap between the efficacy of testing, linkage, and treatment interventions and the current population-level net effectiveness of HCV-care systems in moving individuals and populations through the HCV-care continuum to SVR and cure. Treatment studies, nonetheless, were more likely to utilize efficacy study-design elements, particularly in the domains of eligibility, flexibility of delivery, and analysis. This is notable, given the solid evidence of the efficacy of current HCV-treatment agents. It suggests that one important gap in the literature may be the need for more data on the population-level effectiveness of HCV treatment in broader populations of PWUD treated in appropriate but routine models of care.

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