



Economic evaluations of clinical pharmacy services in the United States: 2011-2017

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Abstract

Studies evaluating the cost-effectiveness of clinical pharmacy services (CPS) are needed to justify implementation and reimbursement. Through a systematic review, we describe services provided by pharmacists and their economic outcomes. We conducted a literature search of published studies in PubMed, Ovid, and Embase from January 2011 through December 2017. Manuscripts evaluating a CPS with patient-level economic outcomes and conducted in the United States were included. Study risks of bias were classified by study design characteristics. Economic evaluations were classified according to the presence of a comparator, and cost and outcome measures included. The quality of full economic evaluations was assessed using the Quality of Health Economic Studies (QHES) instrument. Descriptive statistics were used to summarize CPS characteristics. After screening, 115 studies were included. Type of service provided included general pharmacotherapy (41%), disease management (30%), and targeted drug program (17%). Settings included hospital (34%), ambulatory care (28%), and community pharmacy (17%). Study designs were considered high risk of bias (use of a historical control group or no control group) in 69% of cases while 25% were medium risk of bias (non-randomized with a concurrent control group) and 6% were low risk of bias (randomized experimental or multigroup interrupted time series). Economic evaluation types were descriptive studies that measured cost and/or outcomes of a CPS (55%), comparative studies that measured cost or outcomes of a CPS and a comparator (37%), and full evaluations that measured cost and outcomes of a CPS and a comparator (8%). Among nine full evaluations, the median (range) QHES score was 74 (59-95) and four reported the CPS as being more effective at a lower cost. Few full economic evaluations were conducted, but supported the cost-effectiveness of CPS. Use of a comparator group and measurement of economic inputs and outcomes would strengthen the body of evidence.

KEYWORDS

cost-benefit analysis, health services research, pharmacoeconomics, pharmacy

Over the past three decades, the profession of pharmacy has continued to advance from the traditional dispensing role toward a clinically focused role integrated within a health care team.^{1,2} The American College of Clinical Pharmacy defines clinical pharmacy as a discipline in which pharmacists provide individualized patient care that optimizes medication therapy, promotes health, and advocates for disease prevention. The scope of pharmacy practice has now expanded to roles such as management of chronic conditions in the outpatient and community settings, disease prevention through vaccination administration, and inclusion in team-based care practice models.^{3,4} Pharmacists also serve as experts in drug information, medication use, and evidenced-based care within health care teams.^{5,6}

Contemporary health policy changes and legislation have contributed to the advancement of the profession and the expansion of clinical practice in the United States. In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act expanded patients' access to medication therapy management (MTM) services and required that Medicare Part D prescription drug plans reimburse MTM providers, including pharmacists, for such services.⁷ The Patient Protection and Affordable Care Act of 2010 included pharmacists as key players in patient-centered medical home primary care teams, which are eligible for capitated payments.⁸ Recent implementation of new legislation has also given pharmacists a higher degree of autonomy in practice with 48 of 50 states currently allowing collaborative practice agreements between pharmacists and physicians, although the degree of autonomy may be dependent on the state and setting.⁹ These collaborative practice agreements authorize pharmacists to autonomously manage patient therapy. In Oregon and California, pharmacists are allowed to prescribe short-acting hormonal contraception for women based on a defined treatment algorithm, and several states allow pharmacist prescribing of naloxone for opioid overdose under a defined protocol or in emergent situations.^{10,11}

Given the resource constraints placed on the current 2019 US health care system, the cost-effectiveness of such services must be evaluated to inform health systems on implementing and operating clinical pharmacy services (CPS) and to inform payers of coverage decisions and reimbursement for CPS. We previously conducted four systematic reviews on the economic evaluations of CPS from 1988 to 2010.¹²⁻¹⁵ The most recent systematic review, summarizing economic evaluations published between 2006 and 2010,¹⁴ identified 25 economic evaluations and highlighted several deficiencies in the body of evidence, in addition there was a high proportion but low number of studies, which utilized a randomized controlled design, and that the majority of studies were subject to a high potential for bias. The review also highlighted that during this timeframe, CPS focused on general management of drug therapy and, surprisingly, was still mostly focused on hospital-based services. Given the overall shift in health care from an inpatient to an outpatient setting and increasing opportunities for pharmacist reimbursement in the ambulatory clinic and community settings, the cost-effectiveness of such programs has still not been sufficiently assessed. In this current review, we sought to evaluate whether the focus of economic evaluations of innovative pharmacy services has shifted to different types of services or settings, if the quality of these evaluations has improved, and to assess the overall cost-effectiveness of these new and innovative CPS. Furthermore, because studies with a

medium or high potential for bias contribute little to the overall body of evidence and incomplete economic evaluations do not measure cost-effectiveness, we instead chose to focus our results on key findings from studies identified as having a low potential for bias and full economic evaluations. Therefore, the aim of this study was to describe the characteristics and outcomes of economic evaluations of CPS conducted in the United States and published between 2011 and 2017 to inform health system administrators and payers as to their cost-effectiveness.

1 | METHODS

1.1 | Search strategy and study selection

A literature search for published economic evaluations of CPS was conducted between January 2011 through December 2017 in PubMed, Ovid, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and International Pharmaceutical Abstracts (IPA). Search terms and search restrictions have been described previously.¹⁴ All titles, abstracts, and manuscripts were evaluated by two reviewers. First, titles were screened for articles that potentially evaluated any pharmacist service. A title identified as relevant by at least one reviewer was included for abstract screening. Abstracts passing the first review were screened for articles that specifically evaluated a clinical pharmacy service. Any abstract identified as potentially relevant by at least one reviewer was included for full manuscript review. Full manuscripts meeting the above preliminary review criteria were then screened for inclusion or exclusion. Included manuscripts had to evaluate a clinical pharmacy service, defined as the evaluation of a service provided by a pharmacist for a patient, caregiver, or provider. Manuscripts also had to include and describe some types of economic input (eg, pharmacist's labor and salary, overhead costs, or operating costs) or economic outcome (eg, medical procedure costs, pharmaceutical therapy costs, patients' out-of-pocket costs, incremental cost-effectiveness ratio [ICER], return on investment [ROI], and cost-benefit ratios). Manuscripts in which CPS cost and economic outcomes were not measured at all or not measured in monetary terms were excluded. Other exclusion criteria were manuscripts not written in English and those that evaluated the effects of team-based care that included a pharmacist, but for which the impact of the pharmacist on patient outcomes could not be discerned. A manuscript that was classified as using nonempirical data, an editorial, unoriginal report, narrative review, or systematic review was excluded. Finally, due to the large amount of included manuscripts, only studies conducted in the United States were included in this review. Inclusion of a manuscript for full review required that both reviewers agree on inclusion, otherwise, discrepancies were discussed among a group of three senior reviewers to achieve consensus.

1.2 | Data abstraction

After screening, manuscripts were fully reviewed by two reviewers. Abstracted data included study objective, country, study design and

TABLE 1 Study design types, notation, threats to internal validity, and study design quality

Type	Notation	Threats to internal validity	Risk of bias
Randomized experimental designs			
Pretest/posttest	R O _ O R O X O	<ul style="list-style-type: none"> • Randomization at the cluster level or individual level minimizes the risk of selection bias • Cluster randomization minimizes the risk of contamination bias in group-level interventions 	Low
Posttest	R _ O R X O		
Nonrandomized designs with a control group and multiple observations			
Multigroup interrupted time series	O O O _ O O O O O X O O O	<ul style="list-style-type: none"> • Multiple observations pre- and post-intervention accounts for time trends, but differential effects of events throughout time can result in bias 	Low
Nonrandomized designs with a concurrent control group			
Pretest/posttest	O _ O	<ul style="list-style-type: none"> • Self-selection of patients to a group or the propensity of certain patients to be placed in a group greatly increases the risk of selection bias 	Medium
	O X O		
Posttest	_ O X O		
Nonrandomized designs with a historical control group			
Pretest/posttest	O _ O	<ul style="list-style-type: none"> • The use of a historical control group further increases the risk of bias if events in time differentially affect both groups 	High
	O X O		
Posttest	_ O X O		
Designs without a control group			
Pretest/posttest	O X O	<ul style="list-style-type: none"> • The lack of a control group presents the highest risk of bias 	High
Posttest	X O		
Economic models			
Decision tree	Not applicable	<ul style="list-style-type: none"> • The validity of economic models is limited by the model structure, model assumptions, and quality of inputs derived from the literature 	QHES score
Markov cohort	Not applicable		

Notes: Time elapses from the left to right and the vertical alignment of O between groups indicate simultaneous outcome measurement. Economic modeling studies were evaluated separately using the QHES checklist.

Abbreviations: O, outcome observation; QHES, Quality of Health Economic Studies; R, patient or cluster may be the unit of randomization; X, application of an intervention; _, absence of an intervention.

sample size, study duration, type and description of the clinical pharmacy service, clinical setting, description of pharmacist service costs, type of economic evaluation, economic results summary, a quality assessment for manuscripts which were full economic evaluations, journal of publication, whether the journal was indexed in Medline, and whether the journal was pharmacy related as indicated by having “pharmacy” or “pharmacotherapy” in the journal title. Data were collected using a data abstraction form in RedCap (Center for Clinical and Translational Science [CCTS] UL1TR002003) and downloaded into Microsoft Excel 2016 (Microsoft Corp., Redmond, WA). Abstracted review data were collated, and discrepancies were discussed among reviewers until consensus was achieved.

1.3 | Data reporting and classification of abstracted data

The objective of each included study was described using a population, intervention, comparator, outcomes, timeframe (PICOTS) framework

using the following categories: population receiving the intervention, pharmacist intervention, comparator intervention if present, primary and secondary outcomes, and study evaluation timeframe defined as the time at which outcomes were assessed.¹⁶ Sample size was reported according to the number of subjects in the intervention and control groups. Study design classification was based on the presence of a comparator group, whether the comparator group was concurrent or historical, use of random allocation to a concurrent control group, whether randomization was at the individual or cluster level, and if repeated observations were used before and after the implementation of the CPS service (Table 1).¹⁷ Study designs based on economic models were classified as either decision trees or Markov cohort models.

The type of clinical pharmacy service was classified according to several categories based on the prior systematic reviews¹²⁻¹⁵: disease state management (focused management of a single disease state or diseases in a common class), general pharmacotherapeutic management (management of several disease states and medications), pharmacokinetic monitoring (management of medication[s] strictly through kinetic monitoring), targeted drug program (therapeutic

management of a single drug or drugs from a common class), patient or provider education program (providing education only without therapeutic intervention or monitoring), wellness program and/or immunization service (focus on promotion or maintenance of good health and not treatment of disease), health screening (point of service screening only without pharmacotherapeutic intervention), or other. Although services provided by clinical pharmacists may encompass several categories, the single category that best designated the service was selected for each study. The specific role of the pharmacist was described and the interventions provided by the CPS were listed and briefly described. The CPS was further described by classifying the practice setting as hospital, long-term care facility, community pharmacy, clinic or hospital-based outpatient pharmacy, ambulatory care clinic, urgent care clinic, emergency department, multiple care settings, or other.

Studies were also classified according to the type of economic evaluation based on the presence of a comparator group and whether inputs (program costs) and consequences (economic outcomes) of the groups were evaluated (Table 2).¹⁸ When available, initial costs (ie, one-time investments to develop the CPS) and ongoing costs (ie, continually accruing costs to maintain operation of the CPS) were described. Studies that measured program costs and economic outcomes of a CPS and a comparator were defined as full economic evaluations. Studies that measured program costs or economic outcomes between a CPS and a comparator were defined as an analytic economic evaluation. Studies that measured program cost and/or economic outcomes of a CPS without a comparator group were defined as a descriptive economic evaluation. Additional data were collected for full economic evaluations, including the study's perspective (societal, payer, provider, or patient), threshold or willingness-to-pay to define cost-effectiveness, currency year, and CPS program cost. Finally, the economic results of each study were briefly described.

The risk of bias for each study was assessed based on the type of study design utilized and categorized as high, medium, or low based on the judgment of the authors. Studies with low risk of bias implemented an experimental randomized design or an interrupted time-series design (ITSD) with a control group. Studies with a medium risk of bias implemented a nonrandomized study design with a

TABLE 2 Type of economic evaluation based on measurement of inputs and/or outputs, and presence of a comparator

Presence of comparator?	Inputs and outputs measured?		
	Outputs ^a only	Inputs ^b only	Both measured
Yes	Outcomes analysis	Cost analysis	Full economic evaluation
No	Outcomes description	Cost description	Cost-outcome description

Abbreviation: CPS, clinical pharmacy services.

^aOutputs refer to consequences and outcomes of the CPS such as changes in health care utilization or costs, cost-effectiveness ratios, return on investment, or cost-to-benefit ratios.

^bInputs refer to program costs such as labor costs, capital costs, and operating costs.

concurrent control group. Finally, studies with a high risk of bias utilized a design including a historical control group or a single group design without a control group. The strengths and weaknesses of each study design with respect to the risk of bias are briefly described in Table 1. For studies that used a full economic evaluation, the quality of the evaluation was assessed and quantified separately using the Quality of Health Economics Studies (QHES) checklist.¹⁹ This tool was chosen for its ease of application and calculation of a numerical score to judge economic evaluation quality. The QHES consists of 16 yes or no questions assessing specific study criteria. Each question is assigned a weighted point value based on the potential impact of the criterion on the study quality. The QHES scores a study on a discrete scale from 0 (lowest quality) to 100 (highest quality). Finally, pooled benefit-to-cost ratios were calculated among full economic evaluations, data permitting. The PRISMA checklist for systematic reviews was also provided in Data S1.

1.4 | Data analysis

Descriptive statistics were calculated to summarize study classifications using R version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria).

2 | RESULTS

2.1 | Search results

The search terms yielded 19 555 articles for title screening. After deduplication, 17 169 potential titles were screened, 1865 of which entered abstract screening. Of the abstracts screened, 973 manuscripts were screened for inclusion and exclusion criteria. Two hundred fourteen manuscripts were identified for full data abstraction, which was composed of 115 US studies and 99 studies conducted outside of the United States (Figure 1). Because of the considerable differences between pharmacy practice in the US and non-US settings, studies conducted outside of the United States were not included in this review. Results are presented stratified by the type of clinical service and included a focused descriptive narrative of low bias studies and full economic analyses. Tables S1-S5 summarize all of the studies identified in this systematic review.

2.2 | Type of study design and economic evaluation

Fifty percent of study designs utilized a comparator group, 43% were single-group studies, 6% were classified separately as economic models, and 1% was classified as other. Among the studies comparing the CPS to a comparator group, 57% utilized a concurrent control group, 58% of which used a paired design that measured outcomes before and after CPS implementation. The remaining 43% used a

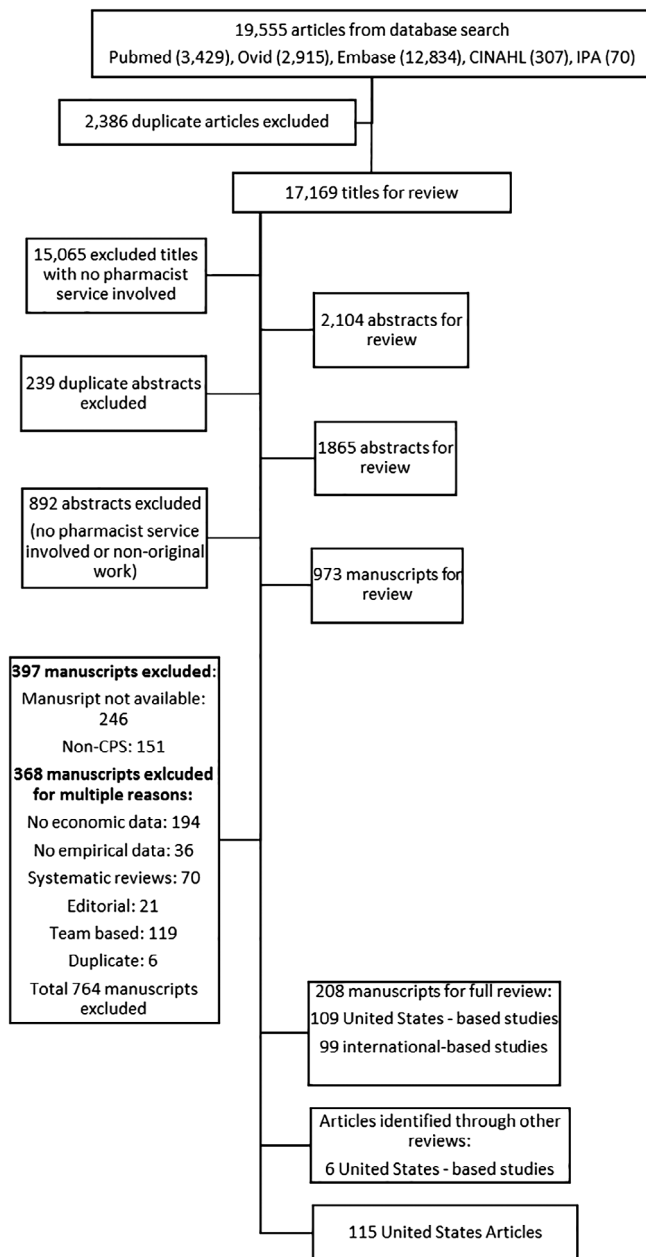


FIGURE 1 PRISMA diagram depicting exclusion of articles based on study criteria. CPS, clinical pharmacy services; PRISMA, preferred reporting items for systematic reviews and meta-analyses

historical control group with only one study using a paired design. Among the studies that utilized a concurrent control group, 15% were experimentally randomized designs and the remaining were non-randomized designs. Of the randomized studies, three were individually randomized and two were cluster randomized, all of which used a paired design. Decision trees and Markov cohort models comprised 4% and 2% of the economic model-based study designs. The single study identified as “other” was a work-sampling study that did not fit the classification scheme. When classified according to the risk of bias, high-, medium-, and low-risk study designs were utilized in 69%, 25%, and 6% of studies, respectively (Table 3).

TABLE 3 Frequency of study design types and of study design quality

Study design type	Frequency (%) N = 115	Risk of bias	Frequency (%) N = 107
Cluster randomized experimental pretest-posttest	2 (2)	Low	6 (6)
Randomized experimental pretest-posttest	2 (2)		
Randomized experimental posttest	1 (1)		
Multigroup ITSD	1 (1)		
Nonrandomized pretest-posttest	15 (14)	Medium	27 (25)
Nonrandomized posttest	12 (11)		
Historical control pretest-posttest	1 (1)	High	74 (69)
Historical control posttest	24 (22)		
One-group pretest-posttest	18 (17)		
One-group posttest	31 (29)		
Decision tree model	5 (4)	N/A	N/A
Markov cohort model	2 (2)		
Other	1 (1)		

Notes: Study design quality classification was not applied to studies utilizing economic models because these designs warrant a different method for quality assessment. The single study defined as “other” was a work-sampling study and did not fit our study design classification criteria. Abbreviations: ITSD, interrupted time-series design; N/A, not applicable.

Outcome analysis comprised 35% of all economic evaluation types, followed by outcome description (30%), cost and outcome description (23%), and full economic evaluations (8%) (Table 4). Cost analysis and cost description comprised 3% and 1%, respectively, of the type of economic evaluations utilized.

2.3 | Type of CPS, setting, and journal of publication

The types of CPS (N = 115) evaluated are general pharmacotherapeutic management (41% of studies), disease state management (30%), targeted drug programs (17%), patient or provider education programs (8%), and wellness and/or immunization programs (4%). No studies were assessed as primarily evaluating a pharmacokinetic monitoring program or health screening program. Most economic evaluations of CPS (N = 115) occurred in the hospital setting (34%), followed by the ambulatory care clinic (28%), community pharmacy (17%), long-term care setting (2%), clinic or hospital-based outpatient pharmacy (2%), emergency department (1%), multiple settings (6%), and other (10%). No CPS was evaluated as occurring in an urgent care clinic.

TABLE 4 Frequency of economic evaluation type

Evaluation type	Frequency (%) N = 115
Full economic evaluation	9 (8)
Outcome analysis	40 (35)
Cost analysis	3 (3)
Cost and outcome description	27 (23)
Cost description	1 (1)
Outcome description	35 (30)

Eighty-two percent of articles were published in Medline-indexed journals. Manuscripts (N = 115) were published in 39 different journals with the majority published in pharmacy journals: *Journal of the American Pharmacists Association* (14%), *American Journal of Health-System Pharmacy* (14%), *Journal of Pharmacy Practice* (8%), *Journal of Managed Care Pharmacy* (6%), *Journal of Managed Care & Specialty Pharmacy* (6%), *American Journal of Pharmaceutical Education* (4%), *The American Journal of Managed Care* (4%), *The American Journal of Pharmacy Benefits* (3%), *Pharmacotherapy* (3%), and *Annals of Pharmacotherapy* (3%). The remaining journals each contributed between 1% and 3% to the total.

2.4 | Summary of CPS stratified by type of service

2.4.1 | General pharmacotherapeutic management

A total of 47 (41%) economic evaluations focused on general pharmacotherapeutic management (Table S1).²⁰⁻⁶⁶ Most studies used study designs with a high risk of bias—38% were single-group posttest, 15% were nonrandomized posttest using a historical control group, and 11% were single-group pretest-posttest. Study designs with a medium risk of bias comprised the rest of the studies: 15% were nonrandomized pretest-posttest and 11% were nonrandomized posttest. Among these studies, 14 were described to be MTM programs.^{20,22,24,25,29,30,35-37,45-47,54,63} Among studies that measured program cost, measured costs included pharmacist salary, fringe benefits, and administrative costs. Program cost ranged from \$57000²⁵ to \$281000.⁶³ These studies generally reported cost savings based on avoided medication-related problems and decreases in medical or pharmaceutical health care expenditures. Per patient cost savings due to avoided expenses attributed to pharmacist intervention ranged from an average of \$103⁴⁶ to \$3191.15.²⁹ Four studies reported that the MTM service decreased health care utilization relative to a control group,^{24,45,47,54} while two other studies reported no changes in medication costs³⁵ or health care utilization.³⁶ The remaining studies, primarily consisting of single-group designs, generally reported cost savings through identification and resolution of drug therapy problems.

There were two studies with a low risk of bias by randomizing individual patients or using repeated observations.^{43,60} One study utilized an experimental pretest-posttest control group design to

evaluate the impact of a pharmacist medication therapy management (MTM) program.⁴³ In an ambulatory care setting, pharmacists evaluated prescription and nonprescription drugs of employees and their dependents and provided them with medication action plans. The MTM group had a statistically significant decrease in annual prescription drug out-of-pocket cost from \$1334 at baseline to \$1100 at 12 months, while the control group did not experience a significant reduction in prescription out-of-pocket costs (\$1293 at baseline and \$1123 at 12 months, $P = .062$). The other study conducted a two-group ITSD to evaluate coordinated hospital and community pharmacist medication management (Pharm2Pharm program) on hospitalizations of elderly adults.⁶⁰ Prior to inpatient discharge, hospital pharmacists performed medication reconciliation and discharge counseling. Upon discharge, community pharmacists provided continuation of care through identifying and resolving drug therapy problems among other interventions. Analysis using a linear mixed-effect model adjusted for case-mix estimated that hospitals adopting the Pharm2Pharm program resulted in a 36.5% reduction in medication-related hospitalizations as compared with nonintervention hospitals (46/1000 admissions vs 72/1000 admissions, respectively). The predicted cost saving from avoided hospitalizations was \$6 626 913. At an annual intervention program cost of \$1 820 454, the intervention's return on investment was 2.64.

Another study classified as general pharmacotherapeutic management was a full economic evaluation.²⁸ The study evaluated the cost-effectiveness of a comprehensive medication review (CMR) service provided by pharmacists compared with usual care over a 1-year period using a decision tree model. Pharmacists conducted comprehensive medication reviews and contacted prescribers to resolve identified drug-related problems. The average cost per adverse event prevented was \$192.60 with CMR and \$157.02 with usual care.

2.4.2 | Disease state management

Thirty-four studies evaluated disease state management programs.⁶⁷⁻¹⁰⁰ Among these, the most common conditions addressed were: diabetes (35%), infectious diseases (eg, human immunodeficiency virus, hepatitis C) (15%), cardiovascular disease (15%), transplant (9%), psychiatric disorders (9%), and chronic obstructive pulmonary disease (6%) (Table S2). The majority of disease state management studies utilized study designs with a high risk of bias: single-group pretest-posttest design (21%), single-group posttest (18%), and non-randomized posttest with a historical control group (12%). Study designs with a medium risk of bias included nonrandomized pretest-posttest design (15%) and nonrandomized posttest design (15%). Although the studies that measured program costs varied in specific services delivered, measured costs typically included pharmacist salary, overhead cost, and patient materials. The types of outcomes ranged from cost savings based on improvement of clinical measures (eg, blood pressure and CD4 count), cost savings, revenue, and reduction in health care utilization. Most studies demonstrated cost savings ranging from \$23000⁶⁷ up to \$210000⁷⁹ or a decrease in health care

utilization. However, some studies reported no beneficial effects of pharmacy services on health care utilization or cost.^{68,80,82,88,90,95,96}

Three studies utilized experimental randomized designs with a full economic evaluation, all of which focused on management of hypertension.^{89,99,100} One study utilized a cluster randomized pretest-posttest control group design to evaluate the cost-effectiveness of a physician-pharmacist collaboration intervention on patients with hypertension compared with usual care in an ambulatory care setting.⁸⁹ Pharmacists conducted patient interviews to obtain a medication history, ascertain patient medication knowledge, and assess medication barriers. Pharmacists then created a care plan for the patient and notified the physician of necessary therapy modifications. The authors reported an ICER of \$33.27/mmHg reduction in systolic blood pressure and \$69.98/mmHg reduction in diastolic blood pressure. Another study also utilized a cluster randomized pretest-posttest design to evaluate the cost effectiveness of a pharmacist-delivered education and monitoring intervention for patients with uncontrolled hypertension relative to usual care in a community pharmacy.¹⁰⁰ Pharmacists identified and assessed medication adherence barriers, provided support for behavioral changes conducive to adherence, and provided a tool-kit containing education materials and a pill box. Pharmacists also reviewed medication regimens and provided feedback to physicians. The incremental cost to reduce systolic blood pressure by 1 mmHg was \$22.20. The ICER for an additional patient to achieve blood pressure control was \$665.20, and \$463.30 for an additional person to achieve an adherence measure of proportion of days covered >0.80. The third study was an experimental randomized posttest design to evaluate the cost-effectiveness of home blood pressure monitoring of hypertensive patients with patient access to the medical record for communication combined with pharmacist care provided in an ambulatory care clinic.⁹⁹ Patients were given access to a website to communicate with their health care provider and to view their medical records. Pharmacists obtained medication histories, developed an action plan for blood pressure control, and recommended changes to therapy. Patients were given a home blood pressure monitoring kit for continued follow-up of blood pressure control. The ICER was \$16.65 per percent improvement in hypertension control and \$65.29/mmHg reduction in systolic blood pressure. Additionally, the ICER per life saved was \$1850 for men and \$2220 for women.

Four studies conducted full economic evaluations using economic models.^{70,72,83,85} Irwin and colleagues conducted a full economic evaluation using a decision tree to evaluate a pharmacist osteoporosis management program, where pharmacists recommended interventions for fracture prophylaxis and identified and resolved drug-related problems.⁷⁰ Compared with nursing management alone, the higher rates of bisphosphonate initiation in the pharmacist-managed group resulted in 2.2 fewer fractures per 1000 women, and the total annual cost of care per 1000 patients was \$619 736 in the pharmacist-managed group and \$762 887 in the nursing group. Olvey and colleagues also used a decision tree to conduct a full economic evaluation that compared a pharmacist telephone-delivered MTM service with a letter-based MTM service.⁷² Pharmacists identified diabetic patients who were not

receiving, but who did have an appropriate indication for a statin or angiotensin-converting enzyme inhibitor. Pharmacists notified patients and recommended them to discuss treatment initiation with their prescriber. The service provided more benefits at a greater cost compared with a letter-based MTM service with a resulting ICER of \$4684 per additional treatment success, defined as initiation of a guideline-recommended medication without a subsequent cardiovascular event. Klepser and colleagues conducted a full economic evaluation using a decision tree to compare pharmacist diagnosis and treatment of strep throat to several alternatives.⁸³ Pharmacists diagnosed strep throat via the use of rapid antigen detection tests (RADT) and treatment with antibiotics under a collaborative practice agreement. The average cost of pharmacist management and treatment was \$53.56, which resulted in 0.2707 quality-adjusted life-days (QALDs) lost. Pharmacist management provided more improvement by way of fewer QALDs lost at an equal or lower cost compared with several alternatives: walk-in clinic with RADT alone (\$79.12 for 0.2707 QALDs lost), physician observation (\$80.42 for 0.2753 QALDs lost), physician empiric therapy (\$84.92 for 0.4072 QALDs lost), and physician RADT alone (\$88.97 for 0.2707 QALDs lost). Pharmacist management was more costly and more effective than physician culture (ICER of \$6042/QALD) and physician RADT with culture (ICER of \$40 745/QALD). Finally, Yu and colleagues used a Markov model to conduct a full economic evaluation of pharmacist management of type 2 diabetes with prescribing authority compared with usual care.⁸⁵ Pharmacist-managed treatment of diabetic patients consisted of prescribing, dose adjustments, and laboratory orders in an ambulatory care clinic. The total average cost of service, medications, and cardiovascular events was \$35 740 with pharmacist management and \$44 528 with usual care. Pharmacist management was associated with 5.518 QALYs gained compared with 5.020 in the usual care group.

2.4.3 | Targeted drug program

Twenty studies evaluated targeted drug programs (Table S3).¹⁰¹⁻¹²⁰ The majority of these evaluations utilized study designs at high risk of bias. Nonrandomized posttest designs with a historical control comprised 55% studies, followed by single-group posttest (15%), single-group pretest-posttest (10%), and nonrandomized pretest-posttest with a historical control (5%). The remaining studies consisted of those with a medium risk of bias: nonrandomized pretest-posttest (5%) and nonrandomized posttest (5%). Five studies evaluated pharmacist antimicrobial stewardship programs.^{101,103,106,115,117} These studies typically measured costs related to antimicrobial utilization or length of stay. Antimicrobial cost per patient day was reported to be lower with pharmacist stewardship, which ranged from \$3.09¹¹⁷ to \$64.13.¹¹⁵ Other targeted drug programs evaluated stewardship of other drug types such as erythropoietin¹⁰⁴ and acid suppression.^{109,116} These studies reported cost savings, which ranged between \$37000¹¹⁶ and \$198352¹⁰⁴ annually.

Only one study evaluated a targeted drug program that conducted a full economic evaluation.¹⁰⁷ This study compared pharmacist-managed erythropoiesis-stimulating agent (ESA) therapy

compared with usual care. Pharmacists independently managed ESA therapy in concordance with hospital guidelines. Pharmacist-managed ESA therapy was more effective providing 2.096 QALYs compared with 2.093 QALYs provided by usual care. Annual average cost of care was \$13 412 with pharmacist care, which was lower than \$16 173 with usual care.

2.4.4 | Patient or medical provider education

Among the nine studies evaluating pharmacist education of patients or medical providers, only a single study utilized a study design at low risk of bias and no study conducted a full economic evaluation (Table S4).¹²¹⁻¹²⁹ Eight of the nine studies primarily used designs at high risk of bias: single-group pretest-posttest (33%) and non-randomized posttest with a historical control group (22%). One third of studies were of medium quality consisting of nonrandomized pretest-posttest (22%) and nonrandomized posttest (11%). Measured program costs included pharmacist salary, training, and medication costs. Program cost ranged from \$57.44 per hour of pharmacist time¹²⁵ to \$1.7 million annually.¹²² Outcomes measured included decrease in patient out-of-pocket cost and cost savings. Studies generally reported cost savings attributed to pharmacist services, which ranged from \$456.67¹²⁶ to \$1655¹²³ per patient.

One study utilized a randomized experimental pretest-posttest design.¹²⁹ Patients with diabetes enrolled in an employer-based health care plan were randomized to a pharmacist counseling and empowerment intervention or a control group, which consisted of printed education materials. Pharmacists provided patient education and patient empowerment in community pharmacies and ambulatory care clinics. The authors reported that there were no statistically significant changes in mean medication costs and mean all-medical care costs between the intervention and control groups.

2.4.5 | Wellness program and immunization services

Among five studies evaluating pharmacist-provided wellness programs or immunization services, none utilized a study design at low risk of bias nor conducted a full economic evaluation (Table S5).¹³⁰⁻¹³⁴ All studies utilized the single-group design. Measured costs included pharmacist salary, vaccine products, and vaccine administration materials. The studies reported net revenues for pharmacy services, which ranged from \$6354¹³⁰ to \$14 749.¹³¹

2.4.6 | Study quality of full health economic evaluations

A description and summary of all full economic evaluations and the associated QHES score is displayed in Table 5. A total of nine full economic evaluations were identified and the median (range) QHES score

was 74 (59-95).^{28,70,72,83,85,89,99,100,107} Six studies utilized decision analytic models to evaluate the cost-effectiveness of CPS and four of which reported the CPS as being more effective at a lower cost relative to the comparator (ie, dominant comparator).

2.4.7 | Benefit-to-cost ratio

Benefit-to-cost ratios could not be calculated due to the format of results, in which benefits were not valued in monetary units and cost off-sets were not disaggregated from total costs.

3 | DISCUSSION

In this continuation of a series of economic evaluations of CPS dating back to 1988,¹²⁻¹⁵ we found that the literature on evaluating the economic benefits of CPS was primarily composed of manuscripts using study designs with high risk of bias, either without a control group or with a historical control group. The most common type of study design used was a descriptive design without a comparator group (43%). This is in stark contrast to the 2006 to 2010¹⁴ review, in which 70% of studies utilized a control group. The prior review found 72% of studies to be full economic evaluations,¹⁴ whereas only 8% of studies in this current review were full economic evaluations. However, of the nine full economic evaluations reported here, the average QHES score was 77.3, which was higher than the 60.4 reported in the prior review.¹⁴ Most CPS economic evaluations assessed general pharmacotherapeutic services or management of a specific disease state, which is consistent with the prior review.¹⁴ Hospitals remained the most common setting of CPS; however, we found a substantial expansion in the proportion of services in the ambulatory care setting from 16% in the 2006 through 2010 review¹⁴ to 28% in the current review. Additionally, a greater number of CPS were implemented in the community pharmacy setting (n = 20) compared with the prior review in which only eight studies were in the community setting.

Given the enactment of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 that recognized pharmacists' role in MTM,⁷ there were surprisingly only two MTM studies in the 2006 through 2010 review.¹⁴ In contrast, we found 15 studies for this time period that were explicitly stated as being MTM services.^{20,22,24,25,29,30,35-37,43,45-47,54,63} We also observed seven economic evaluations of CPS focused on antibiotic use, five of which were explicitly stated as antimicrobial stewardship programs.^{101,103,106,115,117} In comparison with the reviews encompassing 2001 through 2010,^{14,15} there were a total of 14 targeted drug programs focusing on antimicrobials, but none were described as being antimicrobial stewardship programs. Finally, with the enactment of the 2010 Patient Protection and Affordable Care Act⁸ that recognized pharmacists as part of a patient-centered medical home, we found no such studies that described pharmacists in this setting. However, these studies may have been classified as providing "team-based" care, and if the outcomes could not be

TABLE 5 Description, summary, QHES score, and incremental cost-effectiveness ratios of full economic evaluations

Service and perspective	Currency year and costs	Benefits	ICER ^a	QHES score
Pharmacist osteoporosis management compared with nursing management from the payer perspective ⁷⁰	Total annual cost of care and labor in 2012 US dollars Intervention: \$619 736 Comparator: \$726 887	2.2 fewer hip fractures per 1000 women in the intervention group	Not reported, but dominant	59
Pharmacist telephone-delivered MTM compared with letter-delivered MTM from the payer perspective ⁷²	Total average cost of program, medications, adverse drug reactions, and cardiovascular events in 2010 US dollars: Intervention: \$7110 Comparator: \$5471	Average treatment success: Intervention: 0.247 Comparator: 0.056	\$4684 per additional treatment success	89
Pharmacist managed erythropoiesis-stimulating agent clinics compared with usual care from the payer perspective ¹⁰⁷	Total average cost of service, drugs, office visits, laboratory testing and hospitalizations in 2012 US dollars: Intervention: \$13 412 Comparator: \$16 173	QALYs: Intervention: 2.096 Comparator: 2.093	Dominant	95
Community pharmacist-as-provider program for the diagnosis and treatment of pharyngitis compared with standard of care from the payer perspective (assumed) ⁸³	Total average cost of service, drugs, adverse effects, and diagnostic testing in 2010 US dollars: Intervention: \$53.62 Walk-in clinic: \$79.12	Quality-adjusted life-days lost: Intervention: 0.2707 Comparator: 0.2707	Dominant	74
Pharmacist diabetes management vs usual care from the payer perspective ⁸⁵	Total average cost of service, medications, and cardiovascular events in 2011 US dollars: Intervention: \$35 740 Comparator: \$44 528	QALYs: Intervention: 5.518 Comparator: 5.020	Dominant	87
Comprehensive medication of review interventions compared with no comprehensive medication reviews from the payer perspective ²⁸	Total average cost per adverse event prevented in 2012 US dollars: Intervention: \$192.60 Comparator: \$157.02	Average probability of avoiding an adverse event: Intervention: 0.93 Comparator: 0.94	Dominated	74
Pharmacist management of hypertension with the physician compared with usual care from the societal perspective ⁸⁹	Total average cost of service and drugs in 2013 US dollars: Intervention: \$1462.87 Comparator: \$1259.94	Average systolic blood pressure at study end: Intervention: 131.6 mmHg Comparator: 138.2 mmHg	\$33.27/mmHg reduction in systolic blood pressure	82
Home blood pressure monitoring with pharmacist care for hypertensive patients compared with usual care from the payer perspective ⁹⁹	Total average cost per patient in 2009 US dollars: Intervention: \$400.36 Comparator: \$67.36	Average systolic blood pressure at study end: Intervention: 137.7 mmHg Comparator: 146.8 mmHg Percent of population with controlled hypertension at study end: Intervention: 56% Comparator: 36% Change in life expectancy in years at study end: Intervention: 0.53 (men), 0.44 (women)	\$65.29/mmHg reduction in systolic blood pressure \$16.65/% improvement in hypertension control \$1850/life-year saved for men, and \$2220/life-year saved for women	69

(Continues)

TABLE 5 (Continued)

Service and perspective	Currency year and costs	Benefits	ICER ^a	QHEs score
		Comparator: 0.35 (men), 0.29 (women)		
Pharmacist education and monitoring for hypertensive patients compared with usual care from the provider perspective ¹⁰⁰	Total average cost per patient in 2007 US dollars: Intervention: \$104.80 Comparator: not reported	Average reduction in systolic blood pressure from baseline: Intervention: 11.8 mmHg Comparator: 6.2 mmHg % of population with controlled hypertension at study end: Intervention: 53.8% Comparator: 36.7% % of patients with PDC >0.80 at study end: Intervention: 59.7% Comparator: 36.1%	\$22.2/mmHg reduction in systolic blood pressure \$665.5/additional person to achieve hypertension control \$463.3/additional person to achieve a proportion of days covered >0.80	67
				Median (range) 74 (59–95)

Abbreviations: ICER, incremental cost-effectiveness ratio; MTM, medication therapy management; PDC, proportion of days covered; QALYs, quality-adjusted life-years; QHEs, Quality of Health Economics Studies questionnaire.

^aDominant indicates that the pharmacist service was more effective at a lower cost relative to the comparator. Dominated means that the pharmacist service was less effective at a higher cost relative to the comparator.

attributable directly to pharmacist care, they were excluded from this review.

As the profession of pharmacy continues to expand services to new populations, practice settings, and models of care, as well as seek reimbursement for those services, it is imperative that we justify the additional costs of our services with the incremental benefits provided. This is evident in that 21% of articles in this review were in journals with a managed care audience. In comparison with the prior reviews, the only journal among these to publish such studies was the *Journal of Managed Care Pharmacy*, which published eight evaluations from 2001 through 2010. Health care administrators and insurers require valid estimates of costs and benefits through well-designed studies and a comparison of such costs and benefits with a standard of care. Of the nine full economic evaluations reported, four reported the CPS as demonstrating a greater effect at a lower cost relative to the comparator.^{70,83,85,107} Two studies with low-risk of bias demonstrated that the CPS resulted in cost savings,^{43,60} and three other studies with low risk of bias demonstrated that the CPS was more efficacious in hypertension patients relative to the comparator groups.^{89,99,100} However, the proportion of studies at high risk of bias without a control group has increased substantially compared with the prior review, and the proportion of full economic evaluations has also decreased.

The bulk of evidence identified in this review is unlikely to support the continued expansion of CPS and its reimbursement. Decisions to implement and reimburse CPS based on evidence at high risk of bias, or on studies that did not measure input costs, may lead to misallocation of health system resources, inefficiency in the health care system, and provision of cost-ineffective care to patients. Additionally, full economic evaluations did not present enough information to calculate benefit-to-cost ratios. Health system decisionmakers often rely on interpretation

of benefit-to-cost ratios instead of ICERs, and this poses a limitation on the interpretability of the results of full economic evaluations from the perspective of the health system decision maker.

Future research on the economic evaluations of CPS must improve upon the deficiencies of studies highlighted in this current review to justify CPS and demonstrate its cost-effectiveness. Primarily, researchers should implement a study design that incorporates an appropriate control group. If conducting an economic model-based study, inputs for CPS effectiveness should be derived from studies judged to be high quality (eg, studies with comparator groups or that used randomization). Researchers should also report more complete economic data, which include measurement of input costs such as labor in addition to economic outcomes. With the use of a comparator group and measurement of economic inputs and outputs, the difference in outcomes between a CPS and a comparator can be weighed against the difference in costs to judge whether the CPS is cost effective. Additionally, financial costs and benefits can be disaggregated to present cost-to-benefit ratios or ROI, which are more readily interpreted by decision makers compared with ICERs. Finally, the measure of effectiveness should ideally avoid surrogate outcomes and use actual health outcomes such as mortality or QALYs.

Our review has several limitations. We restricted our current review to studies conducted in the United States, whereas prior reviews included foreign-based studies, which constituted 44% (2001 through 2005)¹⁵ and 52% (2006 through 2010)¹⁴ of included studies. Therefore, our review has limited generalizability and neither captures the overall study quality of economic evaluations nor its overall cost-effectiveness. Although we utilized five different databases to conduct our search, we may not have identified or included all relevant manuscripts. We did not search for unpublished work, which

increases the risk of publication bias. Furthermore, we did not obtain unreported economic data, which increase the risk of reporting bias if the results of studies reporting economic data differed systematically. The risk of bias for each study was based on the type of design utilized and not the specific characteristics of each study. Therefore, our classification may not truly capture the quality of the body of evidence and we encourage readers to critically evaluate individual studies of interest. Finally, the quality of full economic evaluations was assessed using the QHES, which may not accurately measure study quality. Although it captures the presence of important aspects of study conduct, it does not necessarily capture the rigor of study conduct.

4 | CONCLUSIONS

Most studies we evaluated lacked a comparator group and are at high risk of bias. However, full economic evaluations comprised a small percent of studies, and they were of relatively good quality and demonstrated cost-effectiveness of CPS interventions. Future studies should incorporate an appropriate control group and conduct more complete economic evaluations by measuring economic inputs and outcomes to strengthen the body of evidence.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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