



ORIGINAL ARTICLE

## Systematic review of the implementation and evaluation of Pharmaceutical Care in hospitalised patients (Pharmaceutical Care implementation in hospitalised patients. Systematic review)

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### KEYWORDS

Pharmaceutical care practice;  
Pharmaceutical care; Programme evaluation;  
Effectiveness; Efficiency; Systematic review of literature

### Abstract

**Introduction:** The persistence of drug-related morbidity and mortality of patients admitted to hospital means scientific criteria need to be identified for implementing and evaluating Pharmaceutical Care (phC) in a hospital setting.

**Objective:** To conduct a systematic review of the literature to identify, select and analyse studies on the implementation and evaluation of phC in hospitalised patients.

**Material and methods:** A search for articles related to clinical pharmacy (CP) and phC published between 1990 and 2006 was performed using a restricted search strategy combining all descriptors. The databases searched were Medline, Embase, Drug & Pharmacology and Cochrane Library. Original and review articles, available in English or Spanish, describing CP and phC programmes which had a participating pharmacist and were carried out on hospitalised patients were selected.

**Results:** Sixty-six articles were found, of which 49 (74.2%) were included and 17 (25.8%) excluded. 15 (22.7%) regarding the integration between CP and phC in hospitals were selected, as well as 18 (27.3%) on implementing phC and 16 (24.2%) related to the evaluation of phC programmes.

**Conclusions:** In the studies described, pharmacists have managed to incorporate phC programmes in the care activities of pharmacy services. Efforts to unify CP and phC criteria should be a common plan for the future in this profession. Patients treated must obtain specific health benefits from phC and medical institutions must recognise they have beneficial effects at a reasonable cost.

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**PALABRAS CLAVE**

Seguimiento  
farmacoterapéutico;  
Atención  
farmacéutica;  
Evaluación de  
programas;  
Efectividad;  
Eficiencia;  
Revisión sistemática  
de la literatura

## Revisión sistemática sobre la implantación y la evaluación del seguimiento farmacoterapéutico en pacientes hospitalizados

**Resumen**

**Introducción:** La persistencia de la morbimortalidad relacionada con la farmacoterapia del paciente ingresado hace necesario identificar evidencia científica sobre la implantación y evaluación del seguimiento farmacoterapéutico (SFT) a nivel hospitalario.

**Objetivo:** Realizar una revisión sistemática de la literatura para localizar, seleccionar y analizar estudios sobre la implantación y evaluación del SFT en pacientes hospitalizados.

**Material y métodos:** Se realizó una búsqueda de artículos relacionados con la farmacia clínica (FC) y el SFT publicados entre 1990 y 2006, mediante una estrategia de búsqueda restringida combinando todos los descriptores. Las bases de datos consultadas fueron Medline, Embase-Drug & Pharmacology y Cochrane Library. Se seleccionaron artículos originales y revisiones que describían un programa de SFT y de FC, que contaban con la participación del farmacéutico, que se hubieran efectuado en pacientes hospitalizados y que estuvieran disponibles en inglés o español.

**Resultados:** Se localizaron 66 publicaciones, incluyendo 49 (74,2%) y excluyendo 17 (25,8%). Se seleccionaron 15 (22,7%) sobre la integración entre la FC y el SFT en el ámbito hospitalario, 18 (27,3%) respecto a la implantación del SFT y 16 (24,2%) relacionadas con la evaluación de programas de SFT.

**Conclusiones:** En los estudios descritos, los farmacéuticos han logrado incorporar el SFT a las actividades asistenciales de los servicios de farmacia. Aunar esfuerzos para unificar los criterios de la FC y el SFT debe ser un plan para un futuro común en esta profesión. Del SFT, los pacientes atendidos deben obtener resultados en salud concretos y las instituciones hospitalarias deben reconocer sus efectos beneficiosos respecto a unos costes razonables.

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## Introduction

For more than twenty years, pharmacy services have been established allowing reciprocal intervention of the pharmacist as pharmacotherapy has constantly developed.<sup>1</sup> However, there are numerous published studies that show that many admissions to hospitals,<sup>2,3</sup> emergencies,<sup>4,5</sup> and health problems during admission are due to the medication given to patients.<sup>6,7</sup> It is essential for pharmaceutical services to continue evolving towards a healthcare perspective, as preventable morbidity and mortality related to drug dispensing are still unresolved.<sup>8</sup> Therefore, it is a priority to implement a pharmaceutical care programme (phC) in hospital units, consisting of strategies devised in this field, to obtain better drug therapy results.<sup>9</sup> To provide this solution, pharmacists have been incorporating phC in the design, implementation and optimisation of hospital pharmaceutical services, alongside concepts of continuous improvement and quality assurance.<sup>10,11</sup> Such integrated clinical actions by pharmacists have led to pharmacological treatment being optimised in the patients they serve every day, regardless of the care setting.<sup>12,13</sup>

As a result, phC programmes have increased and developed in recent years in different care fields in many countries. However, in many cases, phC has lost its focus as a clinical practice for evaluating and monitoring drug therapy as a way to improve or achieve health outcomes that depend on the particular needs of the patient. Many programmes have

lost sight of the fact that it is a process focused on patient care, and must be implemented by a method with a logical sequence which is systematic, continuous and documented. Drug therapy must be monitored and evaluated by a standardised methodology to allow phC to be implemented. Using a systematic procedure provides for consistent performance. Standardised methods and specific documentation provided for each patient provide not only a record of the care process, but allow other pharmacists and other health team members to promote continuity in this type of care.<sup>14</sup>

There is evidence that phC is able to promote both the improvement of health care for patients, with its consequent health benefits, and strategies aimed at developing the abilities and skills of pharmacists and physicians, who evaluate the overall quality of pharmacotherapy.<sup>15</sup> However, this does not provide convincing evidence of changes in health outcomes, as it is distorted by other pharmaceutical interventions which are not oriented towards patient care; therefore, the effectiveness and efficiency of phC has not been conclusively shown.

Therefore, a systematic review of the literature is needed to identify, select and analyse scientific evidence to help in understanding the possibilities of implementing and evaluating phC in hospital units. The purpose is to make a critical analysis of existing literature to provide theoretical and practical support for the development of phC in patients.

## Objectives

To systematically review the published scientific literature on the implementation and evaluation of pHc in hospitalised patients with regard to the following:

- Integration between clinical pharmacy (CP) and pHc caring for hospitalised patients.
- Methods, procedures and programmes used for implementation of pHc for admitted patients.
- Evaluation of pHc from the perspective of effectiveness, efficiency and care practice research.

## Materials and methods

A systematic review of scientific literature on the implementation and evaluation of pHc programmes within a hospital environment was performed. Studies dealing with the integration between CP and pHc in the care of inpatients were also identified. A search for articles relating to CP and pHc, published between 1990 (the year of publication of the concept of *Pharmaceutical Care*<sup>16</sup>) and 2006, was conducted. The databases searched were Medline, Embase-drug and Pharmacology and the Cochrane Library. MeSH terms were chosen that were the most appropriate descriptors: Programme evaluation, methods, research, economics analysis, pharmaceutical services. Keywords directly related to pHc which were not MeSH terms were chosen: *Pharmaceutical Care, Clinical Pharmacy, Drug related problem, Implementation, hospital*. A limited search strategy was performed, combining all descriptors using Boolean operators as follows:

Pharmaceutical Care		Methods	
		Implementation	
Clinical Pharmacy	AND	Programme Evaluation	AND Hospital
Pharmaceutical Services		Economic analysis	
		Research	

Then, independently of the databases, specialist journals on the subject were consulted, such as the *Australian Journal of Hospital Pharmacy*,<sup>17</sup> *Atención Farmacéutica*,<sup>18</sup> the *Canadian Journal of Hospital Pharmacy*,<sup>19</sup> *Farmacia Hospitalaria*,<sup>20</sup> *Pharmaceutical Care España*,<sup>21</sup> *Revista de Calidad Asistencial*,<sup>22</sup> and *Seguimiento Farmacoterapéutico*.<sup>23</sup> Information from specialist books on pHc was included<sup>24</sup> as well as pharmacotherapy.<sup>25,26</sup> Original articles and reviews that met the following criteria were selected:

- 1) Those describing a pHc and/or CP programme, either comparing the two concepts or separately. To be included in the review they had to meet the following conditions
  - i) For pHc programmes, the patient care process had to include the following:
    - a) The establishment of a direct therapeutic relationship with the patient.
    - b) Patient assessment and identification of health problems related to drugs.

- c) Development of a pharmaceutical care plan.
    - d) Evaluation and continuous monitoring of the patient.
  - ii) For a CP programme, it had to include:
    - a) Establishment of a pharmaceutical health team relationship benefitting the patient.
    - b) Implementation of any clinical activity altering a patient's health outcomes.
    - c) Assessment and monitoring of the patient.
- 2) Those involving the pharmacist.
- 3) Those implemented on patients admitted to a hospital.
- 4) Those found in English or Spanish.

Selection was performed independently by two researchers and differences resolved by consensus. The study data were imported from the databases for their selection, extraction and analysis. The contents were processed using the programme Reference Manager Professional Edition, version 11.0.0.

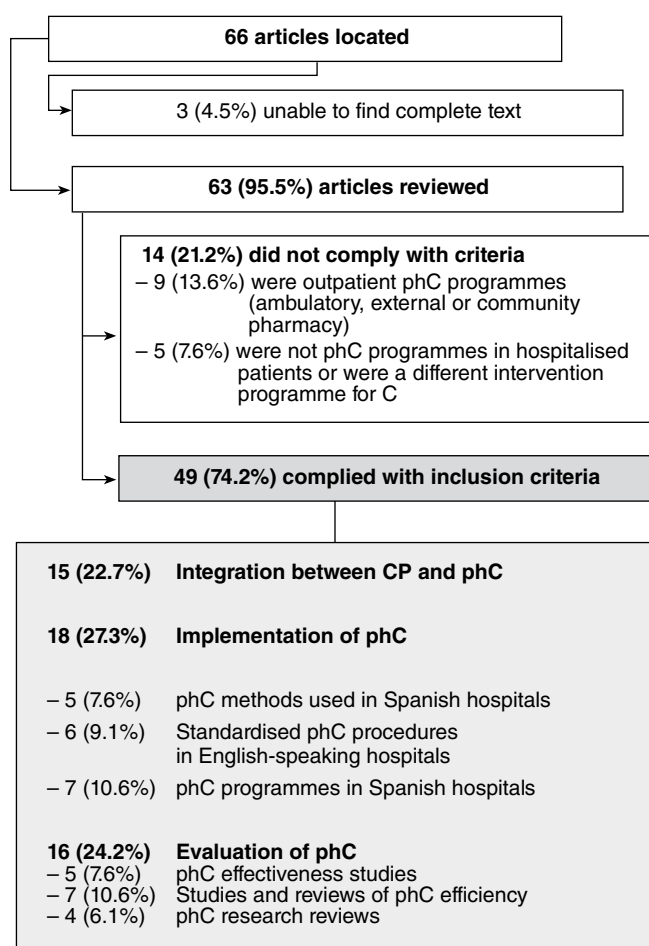
## Results

After performing the search, 66 articles were located, of which 49 (74.2%) were included and 17 (25.8%) excluded. Those excluded are found in Appendix. Based on the findings in the 49 selected studies, it was necessary to form study groups and subgroups for the extraction, description and analysis of the information. Figure shows the distribution and classification of the articles found.

### Integration between Clinical Pharmacy and Pharmaceutical Care in Hospital Settings

Fifteen studies and reviews (22.7%) were selected to study the integration between CP and pHc in the hospital setting.<sup>27-41</sup>

Wang et al<sup>41</sup> established that the contribution of pharmacists in the health care of hospitalised patients showed a healthcare cost containment and an improvement in the quality of pharmacotherapy in hospital units. In fact, pharmacist intervention in the studies of Mutnick et al<sup>31</sup> and Suseno et al<sup>39</sup> demonstrated a reduction in costs during hospitalisation and resolved drug therapy problems that were affecting the quality of life of patients admitted. As Milloning et al<sup>33</sup> and McCreddie et al<sup>32</sup> established, clinical pharmacists use data from patients' hospital records (medical history, medication profiles, etc.), to provide information to help in the pharmacotherapy decision-making of clinicians. Tabish et al<sup>40</sup> confirmed that CP had actively promoted the integration of the pharmacist with the medical team and the implementation and control of a series of analytical processes, both for monitoring pharmacological treatments and for conducting the pharmacokinetic determinations required for some drugs, especially those with a narrow therapeutic margin. From these studies, the results of Bjornson et al<sup>27</sup> and Morrison et al<sup>34</sup> are significant: both confirm the benefits of CP by proving their effectiveness at the level of hospital care, with a significant contribution to a better quality of drug administration for hospitalised patients. Steffen<sup>38</sup> also discussed the quality guarantee component of CP. Bosso<sup>28</sup>



**Figure 1** Breakdown of studies found. CP indicates clinical pharmacy; phC, Pharmaceutical Care.

clearly reflects the sense of integration between CP and phC in clinical practice. He insists that the intention of implementing phC in hospitals is to take a step forward in the practice of pharmacists (by adoption of the philosophy and implementation in health care operations) from the structure and clinical processes already developed in the pharmacy department. Of these studies, three were systematic reviews of the literature. Two were performed by Schumock,<sup>36,37</sup> summarising the economic benefits of CP services, even prior to the formal appearance of *Pharmaceutical Care* in 1990. Meanwhile, the systematic review of Kaboli et al<sup>29</sup> suggested that future studies should be multicentre, have larger sample sizes, reproducible interventions and an identification of specific patient factors affecting improved outcomes from the participation of clinical pharmacists.

### Implementation of pharmaceutical care

Eighteen publications (27.3%) were selected concerning the *implementation of phC*. Three subgroups were formed from

this group to address three different themes: methods used, procedures and/ or programmes in Spain or English speaking countries.

Five reviews<sup>24,26,42-44</sup> were devoted to describing *phC methods* (7.6% of the total) used in Spanish hospitals. Spain has used the US method proposed by Cipolle (1998)<sup>24</sup> of the then *Minnesota Pharmaceutical Care Project*, which was updated in 2004 in the *Pharmaceutical Care Practice* book.<sup>26</sup> A modification of the *SOAP approach* is also used to perform phC, which was first published by Kradjan et al<sup>43</sup> and later revised by Cornelli et al.<sup>42</sup> In Spain, Silva-Castro et al<sup>44</sup> modified the Dáder method to the peculiarities of phC in hospitalised patients. Table 1 summarises and compares the stages of the care process regarding phC standards.

Six articles on *standard phC procedures implemented in hospitals* (9.1%) were selected. Several procedures have been proposed for standardising this pharmaceutical care practice: in the United States,<sup>45</sup> Canada<sup>46,47</sup>, and Australia,<sup>48,49</sup> based on the responsibility of pharmacists in implementing individual patient care.

To investigate the possible differences in the deployment of phC between English-speaking countries and Spain in this health care environment, 7 articles (10.6%) were grouped describing *phC programmes conducted in Spanish hospitals*. Despite the different approaches adopted from the interpretation of the concept of *Pharmaceutical Care* and its various applications, various phC programmes<sup>a</sup> have been implemented in hospital units in Spain.<sup>50-56</sup> Table 2 compares the procedures introduced in certain Spanish hospitals.

### Evaluation of pharmaceutical care programmes

In practice, various studies in hospitals have shown that phC is effective and also efficient.

Sixteen articles *evaluating phC programmes*<sup>57-72</sup> were evaluated (24.2% of total). In turn, different subgroups were formed according to different study subjects: phC effectiveness, efficiency and research.

Five articles were analysed (7.6% of total) regarding the *effectiveness of the phC*.<sup>57-61</sup> In this regard, studies such as Holdford<sup>57</sup> measured the effect according to *clinical outcomes*, such as length of stay, transfers to ICU, hospital mortality and readmission within 30 days. Lee and McPherson<sup>58</sup> checked that the recommendations of pharmacists positively influenced health outcomes for patients, not only due to associating health problems with the medication but also for modifying pharmacotherapy recommendations. Smythe et al<sup>60</sup> implemented and evaluated a phC programme in an intensive care unit. They conducted a cohort study with an intervention group of 152 patients, monitored over two months, which reduced the appearance of drug side effects and reduced the average hospital stay by 1.2 days. They established significant differences in favour of phC

<sup>a</sup>A slightly different term is used for the names of these programmes (in Spanish "*Atención Farmacéutica*"). However, after reviewing the studies, they are interpreted to refer to procedures that correspond to phC or Pharmaceutical Care programmes.

**Table 1** Methods for pharmaceutical care in hospital patients used in Spain

<b>Standard</b>	<b>Cipolle et al (1998)</b>	<b>Kradjan et al (2000)</b>	<b>Silva-Castro et al (2003)</b>
	<b>Cipolle et al (2004)</b>	<b>Cornelli et al (2005)</b>	
<b>Obtaining patient information</b>	The pharmacist collects relevant and specific information from the patient to make decisions about drug therapy	The patient record consists of: 1. Pharmaceutical knowledge 2. Patient information sources in the health environment 3. Patient interview	After assessment by the doctor, information is received from direct pharmaceutical patient interviews and/or caregiver: 1. Health concerns before and during hospitalisation 2. Description of drugs 3. Review of systems 4. Information about emotional states, habits, drug allergies and other info not in the hospital records
	It is based on direct interviews with the patient where a therapeutic relationship is established The below is obtained from the patient: 1. Demographic information 2. Experience with medication 3. Clinically relevant information	The patient's record is organised as follows: 1. Medical history 2. Pharmacological history 3. Social history	The information is incorporated in successive interviews that support the pharmacotherapy relationship in light of developments in the patient during the hospital stay
<b>Pharmacotherapy evaluation</b>	<i>Pharmacotherapy Workup®</i> Describes the rational process, hypothesis, therapeutic relationship established and resolution of health care problems  It is a rational decision-making process assessing patient needs related to medication, any drug-related problems are identified, therapeutic goals are established, interventions are selected and the results evaluated	<i>SOAP approach</i> Standard medical model to organise health problems information with records geared towards patient problems  Each clinical problem is identified, <i>subjective</i> and <i>objective</i> data are <i>analysed</i> and a <i>plan</i> established to solve it	<i>Dáder method</i> Systematic, continuous and documented process using pharmacotherapeutic history  Pharmacotherapy evaluation consists of evaluating the need, effectiveness and safety of medication, based on analysis of the patient clinical condition regarding their pharmacotherapy (situation status) and the review of clinical evidence adjusted to the patient circumstances (study phase)

## A. Evaluation of patient needs

- a) From the *relationship with the patient*, the pharmacist has information about patient identity, his complaint, his medication experience and establishes other relevant clinical information
- b) Determines patient *pharmacotherapy* needs according to whether they are
  - 1) appropriate, 2) effective,
  - 3) safe, and 4) complied with by the patient

For each health problem identified in the patient, the following information is obtained and recorded

1. *Subjective*: problems reported by the patient according to what he feels and suffers. These are not quantifiable or reproducible (equivalent to the symptoms)
2. *Objective*: problems that can be observed, measured and quantified in the patient (equivalent to signs and measurable parameters)

1. The patient is known (general health status, medical history review and participation in clinical sessions)
2. Pharmacotherapy relationship is established from *pharmaceutical interviews* reflecting the health concerns and patient's knowledge of medication
3. *Situation status* is prepared (patient's clinical picture listing health problems and medications used to treat them)
4. The *study phase* is conducted (review of current evidence on health problems and medication use)

## B. Pharmacotherapy analysis or evaluation

*Evaluation of pharmacotherapy* is done by associating a health problem with a drug to identify medication-related problems

3. *Analysis*: assessment made by the pharmacist on the subjective and objective information. To identify any problems with the drugs proposed adaptation of the Newton algorithm<sup>82</sup> which states:

5. From the situation status and study phase, the *evaluation phase* is conducted, which consists of pharmacotherapy assessment regarding necessity, effectiveness and safety

Pharmacotherapy needs	Category	Pharmacotherapy evaluation	Category
Indication	1. Pharmacotherapy	For each drug unnecessary	1. Indication
	2. Need for therapy		2. Effectiveness
Effectiveness	3. Ineffective pharmacotherapy		3. Side effects
	4. Dose too low		4. Cost
Safety	5. Adverse drug reaction	For the full regime	5. Duplication
	6. Dose too high		6. Interactions
	7. Non-compliance	For adherence	7. Self-medication
Adherence			8. Adherence

Pharmacotherapy evaluation

1. Untreated health problem
2. Effect of unnecessary imedcine

Effectiveness

3. Non-quantitative ineffectiveness
4. Quantitative ineffectiveness

Safety

5. Non-quantitative unsafety
6. Non-quantitative unsafety



Table 1 (continued)

Standard	Cipolle et al (1998)	Kradjan et al (2000)	Silva-Castro et al (2003)
	Cipolle et al (2004)	Cornelli et al (2005)	
<b>C. Care plan</b>	<p><i>Action plan</i> consists of:</p> <ul style="list-style-type: none"> <li>a) Therapeutic goals established with the patient</li> <li>b) Interventions designed to address those drug-related problems detected</li> <li>c) A timetable for evaluating the results of clinical interventions</li> </ul>	<p>4. <i>Plan</i>: interventions and recommendations for resolving problems identified. Includes a description of the recommendations, aspects of treatment, health education and programming to evaluate results</p>	<p>6. The <i>intervention phase</i> is performed</p> <ul style="list-style-type: none"> <li>a) The <i>action plan</i> is designed with the patient and health team, where <i>pharmacotherapeutic objectives</i> determining <i>pharmaceutical interventions</i> are prioritised and set</li> <li>b) The patient's daily agenda is established</li> <li>c) Patient health education and/or medical reports are prepared</li> </ul>
<b>D. Control and evolution of the patient</b>	<ul style="list-style-type: none"> <li>a) Clinical results are obtained and compared with the therapeutic aims to assess effectiveness and safety</li> <li>b) Any new health problems emerging are evaluated</li> <li>c) The new health status is documented</li> <li>d) The time for evaluating clinical outcomes is programmed</li> </ul>	<p>Clinical findings are reviewed (signs, symptoms and measurable parameters) to check whether the therapeutic objectives set for each patient have been reached or not</p>	<p>7. <i>Successive pharmaceutical interviews</i> are conducted during daily patient visits where it is checked whether expected <i>clinical results</i> have been obtained according to the pharmacotherapy objectives pursued. A new status report is given depending on any changes that have occurred, and a new assessment is made and acted upon as often as deemed necessary during the hospital stay</p> <p>8. The <i>pharmacotherapy report</i> is prepared at <i>hospital discharge</i></p>

Adapted from: Silva-Castro MM, Tuneu L, Calleja MA, Faus MJ. Pharmaceutical care in the hospital. Pharm Care Esp 2008; 10(4):180-1.

**Table 2** Hospital pharmaceutical care programmes in Spain

		Farré et al (2000)	Carmona et al (2001)	Castillo et al (2000)	Jiménez et al (1998)	Silva-Castro (2004)
		Clopés et al (2000)	Valencia	Madrid	Valencia	Campos-Vieria (2004)
		Barcelona				Córdoba
<b>Definition of the process</b>	Name:	Pharmaceutical care programme	Name: Pharmaceutical care programme	Name: Pharmaceutical care programme	Name: Pharmaceutical care programme	Name: Pharmaceutical care programme (phC)
	(pharmaceutical monitoring)					
	Continuous process, whose purpose is to identify, prevent and resolve problems related to medication, through which the pharmacist can make interventions to increase effectiveness and reduce the risks of pharmacotherapy	It was set up in hospital units with unit dose dispensing medications through the preparation of the Pharmacotherapy history in the Pharmacy Service	Includes a systematic method of collecting patient data and a methodology to detect, resolve and prevent problems related with medication	A pharmaceutical programme compiling and processing information to identify problems and needs of the patient, establishing pharmaceutical objectives, selecting optimal therapy in collaboration with other care workers and the patient, establishing the monitoring plan and communication of the pharmacist proposal to the care team or patient	Dáder phC method application For hospital patients. Systematic, continuous and documented process through the pharmacotherapy record	
<b>Procedures</b>	1. Detection of patient pharmacotherapy profile associated with UDDDS	1. Preparation of pharmacotherapy record in Pharmacy Service	1. Selection of patients based on clinical history and critical indicators during pre-treatment and treatment	1. Screening of patients by medications prioritised by CFT, pharmacotherapy history review and clinical laboratory programme	1. Knowledge of the patient (general health status, medical history review and participation in clinical sessions)	
	2. Detection and analysis of problems (such as medical diagnosis and symptoms related to drugs, such as prescription errors or adverse effects)	2. Identification of problems related to medication (active: by the pharmacist; passive: by doctor, nurse or patient)	2. Identification of health problems related to medication (according to Robertson <sup>63</sup> )	2. Medical and medication history review	2. Establishing the pharmacotherapeutic relationship from pharmaceutical interviews that reflect the health concerns and knowledge of medication from the patient's perspective	
	3. Collecting the necessary data	3. Pharmaceutical action (intervention)	3. Communication with the doctor in the service	3. Identification of medication-related problems (according to Robertson <sup>63</sup> )	3. Preparation of the situation status	
		4. Pharmaceutical action appraisal, regarding gravity, acceptability				



Table 2 (continued)

	Farré et al (2000)	Carmona et al (2001)	Castillo et al (2000)	Jiménez et al (1998)	Silva-Castro (2004)
	Clopés et al (2000)	Valencia	Madrid	Valencia	Campos-Vieria (2004)
	Barcelona				Córdoba
	4. Carrying out intervention (communication sheet) 5. Evaluation of intervention according to impact and significance	and clinical appropriateness	4. Monitoring proposals 5. Recording results (according to Canaday <sup>84</sup> ) 6. Assessment of interventions by type of medication-related problems and clinical impact	4. Pharmaceutical action 5. Monitoring the progress of the patient and documentation 6. Evaluating the adequacy of pharmacist interventions	4. Updated evidence review of health problems and medication use 5. Evaluation of pharmacotherapy regarding necessity, effectiveness and safety 6. Design of action plan and implementation of pharmaceutical interventions
<b>Form of treatment</b>	Therapeutic monitoring linked to the medicine distribution system of the pharmacists assigned to UDDDS	Performed by Resident Pharmacist in a 3-month period	Performed during the rotation of resident pharmacists for internal medicine and surgery services	Performed by a consultant clinical pharmacist as part of the multidisciplinary team responsible for patients	Performed by pharmacists expert in pHc, accompanied by assistant pharmacists
<b>Patient selection</b>	By analysis of pharmacotherapeutic profile of hospitalised patients (age, condition, number of medications and high-risk drugs)	By pharmacotherapy records in the Pharmacy Service	By clinical history of particular hospital services	Drug preselection prioritised by the Pharmacy and Therapeutics Committee, pharmacotherapy record and clinical analysis. Selected by clinical history	As belonging to a particular hospital service; pHc offered to patients as admitted
<b>Sources of information</b>	Pharmacotherapeutic profile Information available on hospital computer system	Unit dose drug dispensation system	According to medical history If necessary, personal interview with the patient	According to medical history Unit dose drug dispensation system	According to medical history Pharmacotherapeutic profile Nursing records

<b>Information required</b>	<ul style="list-style-type: none"> <li>• Patient information (age, sex, weight, height)</li> <li>• History of current illness, previous medical history and social history</li> <li>• Allergies, habits, diet, compliance</li> <li>• Laboratory tests, vital signs</li> <li>• Current or previous pharmacotherapy received</li> <li>• Patient, doctor and service details</li> <li>• Medication details</li> <li>• Data from problems associated with medication</li> <li>• Pharmaceutical treatment data</li> </ul>	<p>Critical pre-treatment indicators: age, sex, chronic illnesses and organ dysfunction, additional tests, diagnosis</p> <p>Critical indicators during treatment: subjective and objective data of the patient's situation that vary regarding disease and patient characteristics</p>	<p>From computerised sources (prescription)</p> <ul style="list-style-type: none"> <li>• Pharmacological treatment</li> <li>• Pharmacotherapy record details</li> <li>• Biochemical and microbiological data</li> </ul> <p>From clinical history</p> <ul style="list-style-type: none"> <li>• Anthropometric data</li> <li>• Diagnosis and clinical situation</li> <li>• Kidney or liver disorders</li> <li>• Pharmacotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Health concerns before and during hospitalisation</li> <li>• Description of drugs</li> <li>• Review of systems</li> <li>• Information about emotional state, behaviour, drug allergies and other information not in the hospital records</li> </ul>
<b>Documentation</b>	Pharmacotherapeutic profile Intervention record Intervention sheet with medical team	Records according to Canada <sup>83</sup>	Individual pharmacotherapeutic monitoring sheet	Pharmacotherapeutic history
<b>Classification and identification of problems related to medication</b>	Adapting Qpolle <sup>24</sup> Intervention coding system (indication, dosage, administration, route, interactions, adverse reactions, medication not included in the guide, others)	According to Qpolle <sup>24</sup> (7 medication-related problems). Identification of problems associated with active medication (by pharmacist) and passive (by doctor, nurse or patient)	According to Qpolle <sup>24</sup> (7 medication-related problems) For identification, the algorithm according to Robertson <sup>83</sup> is applied	According to the 2nd Granada Consensus on Drug-Related Problems. <sup>86</sup> 3 supra-categories (necessity, effectiveness, safety). 6 categories (need for medication, unnecessary medication, non-quantitative ineffectiveness, non-quantitative unsafety, quantitative unsafety)
<b>Definition of intervention</b>	Pharmaceutical intervention: including those arising from the pharmacist due to prescribing drugs not	Treatment from the pharmaceutical care programme: aimed at the identification, prevention or resolution	Pharmaceutical intervention: action taken by the pharmacist in response to a problem with the medication or care	Pharmaceutical intervention: action arising from a clinical decision attempting to modify a feature of the treatment, the patient undergoing it or

Table 2 (continued)

	Farré et al (2000)	Carmona et al (2001)	Castillo et al (2000)	Jiménez et al (1998)	Silva-Castro (2004)
	Clopés et al (2000)	Valencia	Madrid	Valencia	Campos-Vieria (2004)
	Barcelona				Córdoba
	included in the pharmaceutical guide, and therapeutic interventions which are those related to a drug, its indication, dosage, interaction	of problems related to medication from the programme It does not include activities resulting from the prescription of drugs not included in the guide, or those resulting from defects in the prescription form, filling out of prescriptions or transcription or preparation errors	of clinical implications arising from health problems related to medication	need for a patient. There are 3 types: 1) designed to optimise treatment, 2) preventive, and 3) educational	conditions surrounding it to modify the patient's health
<b>Evaluation of intervention</b>	Intervention indicators (IF/day, IF/bed, IF/prescription, IF/admission, IF/stay). Impact: qualitative measure by improving the effectiveness, safety or cost Significance: measure of contribution to improving the quality of care - appropriate, indifferent or inappropriate	Acceptability: measures the evaluation of the proposal made by the receiver. Severity of medication-related problems (according to Llopis <sup>85</sup> ): from absence to permanent damage or death Adequacy of pharmaceutical treatment (according to Llopis <sup>86</sup> ): from having importance for patient care to preventing vital organ failure or death	Clinical impact indicators: percentage of interventions that prevent serious events involving increased stay or permanent damage, and interventions that prevent events threatening the patient's life Acceptance indicator: percentage of interventions accepted by the physician Resolution indicator: number of drug related-problems solved for every 100 interventions accepted by the physician	Severity of medication-related problems (according to Schneider <sup>87</sup> ): from not causing harm to the patient to producing permanent damage or death Adequacy of pharmaceutical treatment: from having importance for patient care to preventing vital organ failure or death Clinical outcome: from negative to full recovery using objective and subjective data	Acceptability • Number of interventions accepted • Accepted interventions/health problem solved • Accepted interventions/health problem not solved Activity indicators • Problems with medication prevented and resolved • Interventions performed Avoidability Process measures • Duration of pharmacotherapy • Length of stay • phC patient-day time

CFT indicates Commission of Pharmacy and Therapeutics; phC, Pharmaceutical Care; UDDDS, unit dose drug distribution system.

Adapted from: Silva-Castro MM, Tuneu L, Calleja MA, Faus MJ. Pharmaceutical care in the hospital. Pharm Care Esp 2008;10(4):18.

for hospital stay duration and readmissions requiring treatment, with significant improvements for patients receiving phC when compared with those not receiving it. Also Varma et al<sup>61</sup> established significant improvements in readmissions requiring treatment. Moreover, in this study, the quality of life related to health was measured via a general questionnaire (*SF-36® Health Survey*) and a specific questionnaire for heart failure (*MLHF-Minnesota Living with Heart Failure questionnaire*), which also considered measures regarding medication knowledge and adherence to pharmacotherapy. In this study, the intervention group scored higher in the 8-dimensional SF-36, indicating that the quality of life was not affected negatively. However, significant differences were found only in physical function (at 9 and 12 months), social function (at 12 months) and mental health (at 9 and 12 months). Regarding knowledge and adherence, no significant differences were found between the control and intervention groups. Results published by Strand et al,<sup>59</sup> regarding impact on the care of 2,985 patients is also notable. 11,626 documented encounters were made with the pharmacist. 16,312 clinical conditions were evaluated, of which 5,166 (32%) improved by identifying and solving health problems related to medication. Moreover, 9,134 (56%) of these clinical conditions showed no change in health status while receiving phC, which means that patients' health status regarding chronic conditions remained stable.

As regards *phC efficiency*, we selected various studies and reviews (7 articles, 10.6% of total).<sup>62-68</sup>

Etemad et al<sup>63</sup> showed that phC reduces costs during hospitalisation, and resolves health problems related to medication, which were diminishing the quality of life of patients admitted. Similarly, Nesbit et al<sup>66</sup> concluded that this leads to a decrease in health care costs and improved the quality of the pharmacotherapy. Gandhi et al<sup>64</sup> conducted a cohort study of patients in the coronary care unit of a university hospital where they sought to determine the clinical impact of clinical pharmacy services in the direct costs of drugs, and estimated the reduction in total cost for drugs associated with pharmaceutical intervention. They found that the average cost of medications per patient in the control group was US\$ 374.05, while in the intervention group it was US\$ 233.74 ( $P < .05$ ). Weidle et al<sup>68</sup> documented 68,000 interventions made by 45 pharmacists. Of these, 90% affected the quality of the therapeutic process; costs during the survey reduced by US\$ 374,000 to US\$ 783,000. Smythe et al<sup>60</sup> also evaluated costs and established that the decrease in total drug cost was US\$ 6,534.53 with the annual projected savings estimated to be US\$ 42,474.45. McMullin et al<sup>65</sup> evaluated the impact of phC in cost savings for patients in internal medicine and the intensive care unit, and a prospective cohort study was performed. In the intervention group, the pharmacists contacted the doctors to carry out their recommendations, while in the control group they were observers. Patients in the intervention group had an average medication cost lower than the control group ( $P < .001$ ; control US\$ 73.7, intervention: US\$ 43.5). There were no statistically significant differences in the duration of stay, 30-day rate of readmission and mortality, probably because these

were not measures of effects that could be related exclusively with drug therapy problems. In Spain, Climente-Martí and Jiménez<sup>62</sup> conducted a cost-benefit study to describe the methodology, clinical and pharmacoeconomic outcomes of pharmacist interventions for hospitalised patients. The savings were US\$ 70,939 with the reduced cost being US\$ 49,402. The cost/benefit ratio was 3.7: 1, and return on investment was 268.7%.

For *phC research*, four reviews were selected (6.1% of total).<sup>69-72</sup>

In 1998, Kennie et al<sup>71</sup> reported the need to improve the quality of research and clarify the descriptions of phC as a care process to evaluate its clinical and economic impact. In 2005, Rangel et al<sup>72</sup> conducted a systematic review of the current state of pharmaceutical care research including studies published between 1999 and 2004 in hospital and community pharmacy; the results were very similar to those previously described by Kennie et al.<sup>71</sup> They concluded that the methodology of the work should be more rigorous, they recommended observational, prospective, multicentre studies to measure the effectiveness and efficiency of these care activities. The work would measure quality of life related to the health of patients (for example, by using questionnaires to assess the quality of life associated with health) and the degree of satisfaction they receive from them, as well as using universally accepted methods to increase study quality. The findings of the systematic review by Beney et al<sup>72</sup> regarding concerns about the extrapolation of studies, poor definition of interventions and the absence of cost evaluation and patient outcome data alerted pharmacists in all care areas. It should be noted that more rigorous research is needed to document the effects of pharmaceutical interventions. Although the results did not reflect the care work involved in implementing phC, they were the starting point for improving research seeking to establish the effectiveness and efficiency of the care process with more certainty.

## Discussion

### Integration between clinical pharmacy and pharmaceutical care in hospitals

As mentioned by Kaboli<sup>29</sup> in his systematic review, direct problems experienced by hospitalised patients are not resolved in many cases, as patients continue to suffer health problems from using drugs. As a result and despite CP being implemented in many hospitals, several questions are raised by the fact that there is still high morbidity and mortality related to drugs. At the same time, doubts arise over the degree of implementation of phC, also intended to solve health problems suffered and derived from drugs taken.

CP and phC are closely related when put into practice. In fact, they ought to be mutually dependent, as phC provides the original purposes for CP, when it is seen as a professional practice rather than as an applied health science. In addition, phC describes the format for pharmacists to coordinate their work around a process focused on patient care. phC is the health care practice which is part of a

philosophy incorporating the patient as the central focus. This comprehensive and holistic vision of health and patient promotes an entire philosophy of action seeking the participation of the pharmacist to obtain specific results on patients and their health.

The concept of CP adds essential clarity to the components of the participation process for the pharmacists and strengthens the academic platform of pHc. CP is the basis for pHc and, without it, it is not possible to assess the medication according to necessity, effectiveness and safety. What changes in the pHc is active participation and the systematic and objective incorporation of the individual needs of each patient. CP has developed the drug quality processes for patient improvement, but without the integrative perspective of pHc, with CP being limited to processes. Moreover, it is the vision of the patient at the centre of the treatment and the integration of knowledge and skills provided by pHc that create seamless global care. It is clear that the patient should be the focus of the caring practice, and also for the pharmacist. CP has indeed been set as a target, although its primary recipients are physicians who receive information, documentation and knowledge on the rational use of medicines.

In fact, as stated by Hepler,<sup>30</sup> CP has defined and developed processes to provide the best quality of care related to drug therapy. Currently these quality systems should be patient-centred, cooperative and inter-professional. Thus clinical tasks should be organised around the needs of patients and direct results searched for them. Therefore, clinical practice is no longer an option as the mainstream practice in the profession.

Nowadays, there are circumstances preventing the work of CP being focused towards individualised care processes for each patient. Although it takes place in some hospital services or health care units for outpatients, dealing directly with patients admitted in hospitals is not as easy and does not occur as often as in the community pharmacy, where contact is constant.<sup>9</sup> Specialisation of care staff may entail the risk of losing patient focus and being diverted to care models based more on theoretical developments than on incorporating the pharmacotherapeutic needs of patients in normal clinical practice.

pHc should be enriched with CP to develop the knowledge and skills necessary for quality contributions from the pharmacist. Also CP has to incorporate pHc to understand health and drug therapy as a unit, and to measure the specific results provided by each of the processes. Bosso<sup>28</sup> recommends changing CP services to include the following pHc assumptions:

1. Changing the focus of professional practice directly towards the patient's perspective.
2. The primary objective of this practice should be to obtain tangible results on the health of one patient at a time, which should translate into individual pharmacotherapy that is necessary, effective and safe.
3. To consider that the patients are not only the centre of the process but should be involved in clinical decisions related to their medication.
4. To integrate all clinical activities necessary for the best result in one patient at a time.

5. The integration of the pharmacist with the health team should be done via and for the patient.
6. Establish a pharmacist-patient relationship, and with the caregiver if necessary, to improve the health outcomes resulting from pharmacotherapy.
7. To provide a systematic and continuous process of care for each patient.
8. To support the decisions taken for the patient in the literature based on scientific evidence.

Therefore, pharmacists have much to offer in terms of clinical, humanistic and economic outcome issues linked with morbidity and mortality associated with medications. Unifying CP and pHc criteria should be a plan for a common future in this profession.

### Implementing pharmaceutical care

*Regarding pHc methods*, the most important difference between *Pharmacotherapy Workup*<sup>®</sup> and the *SOAP approach*<sup>®</sup> is the rational process undertaken by the care worker in the evaluation of pharmacotherapy (as reflected by differences in the documentation). Basically, the most relevant differences are in the sequence of the analysis, the detection of drug-related problems and in making clinical decisions. Cipolle et al<sup>26</sup> proposed the *Pharmacotherapy Workup*<sup>®</sup>, which is a process of analysis and decision-making designed specifically to evaluate drug therapy, whereas Cornelli et al<sup>42</sup> used the *SOAP approach*<sup>®</sup> which is a process used by other health care workers to solve clinical problems. In the first method, drug-related problems are identified as a result of health problems associated with the medication, while in the second method the existing health problem is treated like any other clinical event. This is because the problem is treated primarily as a health problem, which may be because of the drug used, the whole regime or even cost. The *Dáder method*, which is modified according to the hospital patient pHc method<sup>37</sup> is more similar to the *Pharmacotherapy Workup*<sup>®</sup> than the *SOAP approach*<sup>®</sup> in the rational process of decision making. They are also similar in the pharmacotherapy evaluation, which is performed by considering the health issues of the medications used in treatment, unlike the *SOAP approach*<sup>®</sup>. However, the form of assessment is different because the *Pharmacotherapy Workup*<sup>®</sup> considers adherence as a separate category in the evaluation. This category refers to situations where the patient is unable or unwilling to take the medication properly and must be evaluated at the end because, it is explained, it leads to a failure of the regime even if it complies with the indication, effectiveness and safety. The *Dáder method* does not have this category, as it considers these situations as causes of quantitative ineffectiveness when taking lower doses than established, quantitative unsafety when taking more doses than recommended, an untreated health problem when no dose is taken and an unnecessary drug effect when a medicine no longer needed is still being taken. Unlike the *Pharmacotherapy Workup*<sup>®</sup> and the *SOAP approach*<sup>®</sup>, the *Dáder method* has a specific phase to ensure the review of scientific evidence suited to the circumstances of the patient (study phase). Finally,

regarding the plan of action, the three methods are based on observing the results of pharmaceutical interventions through clinical variables that reflect whether the pursued pharmacotherapy objectives have been reached or not.

Regardless of the method used, the most important thing is to develop a rational organised sequence to properly identify and resolve health problems associated with drugs.

As for the differences between the *procedures for conducting phC*, it must be stressed that the procedures proposed by the ASHP Guidelines<sup>45</sup> and Naumann and Tsuyuki<sup>47</sup> do not require a pharmaceutical interview with the patient and are “flexible” regarding obtaining the pharmacotherapy record. This may lead to a lot of medical history data being taken from the hospital computer systems without establishing a pharmacist-patient relationship, which is fundamental for phC. The procedure proposed by Naumann and Tsuyuki<sup>47</sup> stress the importance of being consulted as the doctors “make their rounds”. This is now essential to being considered a part of the health team. The procedure suggested by Smioni and Brien<sup>49</sup> emphasises the need to include phC notes within the medical record. This facilitates the communication of individual results in the phC. The US procedure emphasises establishing pharmacotherapeutic aims with their respective strategies, including the patient and the members of the health team. Any phC procedure to perform must be based on a pharmacist-patient therapeutic relationship. Developed according to the needs of the patient, this relationship determines the capacity of care to be provided throughout the care process.

Among *phC programmes in Spanish hospitals*, there are several differences that must be analysed:

- In the five programmes, the information is obtained from medical records plus other hospital or pharmacy service records (drug profiles). It is clear only in the Silva-Castro et al<sup>56</sup> and Campos-Vieira et al<sup>50</sup> studies that specific pharmaceutical interviews were done during phC and that the pharmacists established a direct and permanent relationship with patients during hospitalisation.
- Regarding sources of patient clinical information, other pharmacy processes (pharmacotherapeutic profiles) are used as well as those prepared by other health team members (from the hospital computer system and medical records). The importance of using these sources is undeniably important, however, it is essential that they consist of pharmacotherapy information sources which reflect results from the whole care process provided by pharmacists for each of the patients in their care.
- Therapeutic monitoring linked to the drug distribution system described by Farré et al<sup>54</sup> is a general healthcare activity which makes use of every clinical unit depending on the working structure established with the pharmacist in charge of the unit dose drug distribution system (UDDDS).
- Performance of the programme by a single consultant pharmacist described by Jiménez and Climente-Martí<sup>55</sup> is a more specialised consultation type model leading to more specific interventions. This will benefit only a

certain number of patients, although they may be those who most need it.

- There are differences both in the concept of medication-related problems and their classification. Using different classifications may hamper comparison of results and pharmaceutical interventions may have different approaches. The programmes described by Carmona et al<sup>52</sup> and Jiménez and Climente-Martí<sup>55</sup> evaluate problems related with medication according to their gravity.
- There are various concepts of pharmaceutical and pharmacist intervention; a number of studies use different names to refer to the same concept. However, in other cases, pharmaceutical activities refer to the process of using drugs without focusing on measures aimed at changing the outcome of pharmacotherapy in clinical terms, as is strictly the case for pharmaceutical interventions. For phC, pharmaceutical intervention refers to the pharmacist trying to improve the clinical outcome, achieved after the use of drugs, by modifying some characteristic of the treatment the patient is taking or the conditions surrounding it. This action is part of the plan agreed with the patient and the health team to fulfil the pharmacotherapy objectives.
- Regarding the evaluation of the intervention, the approval of the health team and gravity are taken into account when measuring clinical impact. None of the studies makes it clear how the pharmacotherapy objectives were assessed or the action plan continued.

Baena<sup>73</sup> commented on some of the methodological difficulties related to the implementation of phC, and referred to slight differences in the definition and method of the care process regarding what was being measured. He suggested that it is not just about different definitions being used for the same procedure (which is sometimes done), as this would mostly be irrelevant because it would be corrected with appropriate specification; the problem is when different things are being measured or different methods used within the same article. There should be an effort to clarify the definitions worked with (being measured). This would lead to the “same language” being used, and would make it easier to compare results and make progress with the research. In any event, the programmes analysed in this section were instrumental in developing pharmaceutical care work in Spanish hospitals, and have brought phC care activities into pharmacy services. Now there is a need for this to become a continuous, more permanent and more extensive care process, which may be the link that the vision and priority of the patient can provide.

## Evaluation of pharmaceutical care programmes

phC should demonstrate its efficiency within the health system to be considered as a new viable health technology.<sup>74</sup> Several of the studies described have established the economic impact of pharmaceutical interventions in hospitals. These assessments have been specifically targeted at the economic evaluation of CP services,<sup>36,37</sup> but do not specifically refer to phC programmes as a patient-centred care process.



Despite the evidence described in this section for the effectiveness and efficiency of care at the hospital level, the Cochrane review by Beney et al<sup>69</sup> referring to the role of pharmacists in patient care, concluded that there are doubts about the efficiency due to the difficulty of extrapolating results, poorly defined interventions and the scarce assessment of costs and patient outcomes. In addition, the Silva-Castro et al<sup>75</sup> technical report also concluded that evidence to demonstrate the effectiveness of pHc programmes in hospitals has not yet been provided, agreeing with the Cochrane review written by Beney et al.<sup>69</sup> It is clear that the studies published in this technical report have methodology limitations that prevent any decisive conclusions about the efficiency or effectiveness of programmes for patients. From the point of view of measuring the effects and costs, the methodology used in the reviewed studies shows that measurement of the clinical impact on patients who received pHc is still an unexplored area.<sup>76,77</sup> Therefore, regarding the implementation of pHc, there is a need to review methodological aspects of previous studies and establish areas for improvement in future research and of efficiency studies for this care practice.

Even if the results seem disappointing, it should be made clear that the objectives of the published studies were to describe the implementation of pHc, and not to assess it by measuring effectiveness (which involves evaluation of health outcomes<sup>78</sup>) or efficiency (which involves economic evaluation studies for the pharmaceutical care process<sup>79</sup>). Learning from those who have implemented pHc may help in alerting care workers to the errors made previously and advances to be incorporated.

In Spain, there are probably not as many studies published as programmes that exist. This is reflected in the limited scientific output on the professional practice determined by Rangel et al,<sup>72</sup> who state that only 4% of the publications covered in a systematic review of pharmaceutical care research can be considered. They also state that the results of further studies of its implementation in our environment would be needed before any changes to this care practice in our own health conditions. Baena<sup>73</sup> commented on the systematic review of Rangel et al<sup>72</sup> and commented that increased rigour in the study method is the only component missing to give the final support for the efficiency and effectiveness of pHc. He added that good interpretation of results from the field work carried out cannot be obtained if they have no common denominator with respect to the research methodology bases. He also reiterated that at this time where scientific evidence is the criterion for making health decisions on the use of a particular technology, it is obligatory to seek demonstration of the effectiveness of pharmaceutical intervention in patients. And also, so that doubts over the ability of the technology to improve health care quality should not be raised in the rest of the healthcare team. There are two reasons why this may be the case:

1. The limited scientific output about a professional practice such as pHc, as it is little more than 15 years old. It may be that the slow penetration of pHc research within the Spanish health system may be inevitable.<sup>73</sup>

2. The implementation of pHc in hospital patients has taken place in controlled conditions under the coordination of hospital and pharmacy services with specific experience in the provision of clinical services. Currently there are studies with greater methodological rigour that have compared it with the alternative of "not performing pHc". The following step must be to compare it with another pharmaceutical intervention, such as a programme of intensive pharmacovigilance, drug monitoring, among others, within the CP field.<sup>76</sup>

For these reasons it may be logical that these types of study have not yet been published (perhaps they are currently being done) and that many institutions have decided to implement pHc based on studies such as Smythe,<sup>60</sup> Varma,<sup>61</sup> Gandhi,<sup>64</sup> and McMullin<sup>65</sup> which demonstrate that this care process offers benefits to patients.

This phenomenon has happened in other areas of health, such as the implementation of health technologies and health programmes that are already in place from the emerging evidence of health technologies that demonstrate their benefits, in terms of effectiveness, despite their efficiency not being proven.<sup>74,80</sup> Under the premise of ensuring patient safety, no medical technology should be implemented without prior evaluation. However, this is not always the case. Some technologies are used in practice with no good quality studies or expert advice. There are cases such as controlled uses where technology is deployed in a controlled environment, subject to research or compassionate use, when the technology is available for situations where no other alternative is available.<sup>81</sup>

The challenge for pharmaceutical care is to move forward in implementing pHc, and apply suitable methods that comply with relevant ethical conditions to assess the effectiveness and efficiency of this care process. Patients cared for this way must obtain specific health outcomes, and medical institutions must recognise their beneficial effects with respect to reasonable costs.

## Conclusions

A systematic review of the literature provided valid scientific evidence and is an accurate source of technical support for the implementation of this care practice. Ninety-five point five percent of the publications located were reviewed and 74.2% of these met the inclusion criteria to extract and analyse the information.

Pharmacists have much to offer for the clinical and economic outcomes associated with morbidity and mortality related to medication. Efforts to unify the criteria of CP and pHc should be made for a future common plan for this profession.

The studies described managed to incorporate pHc in the care activities of the pharmacy services. There is now a need for a continuous, more permanent and extensive care process to form the missing link that the vision and priority of the patient can provide. Patients cared for this way must obtain specific health outcomes, and medical institutions must recognise their beneficial effects with respect to reasonable costs.

## Conflicts of interest

The authors declare no conflict of interest.

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## Appendix. List of studies not included

### The full text was not found (3 articles)

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