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Research Paper

Effect of strategic purchasing of antiviral drugs and the clinical pathway for the treatment of Chronic Hepatitis C in Colombia (hepC-STRATEGY): study protocol for a quasi-experimental study

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Abstract

Objective: Describe a study protocol to establish the effect of DAA's strategic purchase and the clinical pathway in the clinical outcomes, general costs, and quality of healthcare of patients with CHC in Colombia.

Methods: A quasi-experimental study will be carried out to compare clinical outcomes (treatment effectiveness), healthcare quality (access to treatment, time to treatment, patient's satisfaction and barriers/facilitators perceived) and direct costs before/after the implementation of the mentioned strategies. Patients ≥18 years old initiating DAA treatment between January 2015 and December 2019 in an outpatient pharmacist-led center in Colombia will be included. In order to reduce selection bias, the propensity score method will be used. In the bivariate analysis, χ^2 tests and *t* student will be used to analyse the study outcomes. A regression analysis will be used to explain the association of multiple variables with access to treatment, time to treatment and effectiveness. Descriptive statistics will be used to analyse the patient's satisfaction and barriers/facilitators perceived.

Key findings: Implementing local government policies is necessary to improve access to medicines and decrease disease burden. The strategies adopted by the Colombian Ministry of Health to manage CHC needs to be evaluated. Therefore, studies are required to establish their effects on clinical outcomes, overall costs, and quality of care.

Conclusions: This study will provide evidence on the effect of Colombian strategies to address the problem of HCC. It will provide information to policymakers in low- and middle-income countries that could reduce disease burden.

Keywords: hepatitis C; direct-acting antivirals; health policy; patient care management; health services research; pharmaceutical services

Introduction

Chronic Hepatitis C (CHC) is a disease caused by the Hepatitis C Virus (HCV) infection. It is considered a public health problem by the World Health Organization[1] because it affects 2–3% of the world population. Also, it is associated with high morbidity and mortality, since 70–90% of infected patients progress to chronic liver diseases, such as cirrhosis and hepatocellular carcinoma, which, in some cases, need liver transplantation.[2, 3] Additionally, this disease affects vulnerable and largely unattended populations such as people who inject drugs, people with inadequate healthcare, among others.[4–6]

Another relevant condition that makes CHC a public health problem is the access limitation to highly effective drugs -Direct-acting Antivirals (DAA)-, which can eradicate HCV in up to 90% of cases with a high tolerability profile.[7] Among the obstacles to accessing DAA are the high prices that can put at risk the financial sustainability of health systems worldwide[8, 9]; the health systems fragmentation, where, in general, the interconnections between healthcare and administrative processes are ignored; and the complex relationships between medicines and healthcare.[10] Therefore, it is necessary to establish and implement strategies that allow patient-centered care, access to medicines, health services, and other interventions.[11, 12]

In Colombia, the Ministry of Health and Social Protection (MoHSP) has made progress in addressing the CHC problem to control the infection and resolve barriers to access to medicines. One of the strategies implemented was the purchase of DAA treatment through the Pan-American Health Organization-PAHO's Strategic Fund (first Sofosbuvir/Ledipasvir, Sofosbuvir, Daclatasvir, and later, Sofosbuvir/Velpatasvir), and the instauration of a Clinical Pathway for the treatment of CHC. It integrates the healthcare and administrative processes to favor treatment access and proper monitoring of the medicines' safety and effectiveness.[13, 14]

The implementation of the Clinical Pathway has required integrating healthcare processes and reporting in health information systems, allowing a high level of control in CHC follow-up and the subsequent indicators generation. However, the indicators only present information on the percentage of patients who have completed treatment and achieved the elimination of HCV.[15] They do not present evidence of the general costs of healthcare or the improvements that have occurred in dimensions related to the quality of care, such as access to medicines, time to treatment, safety, and patient satisfaction.[16] Besides, barriers or facilitators within the healthcare process are unknown.

In conclusion, there is limited information on the effects of the strategies adopted by the MoHSP to manage CHC in Colombia. For this reason, this study aims to establish the effect of strategic purchasing and the Clinical Pathway for CHC treatment in outcomes related to clinical results, general costs, and quality of healthcare of CHC patients of the Colombian health system's contributory regime.

Methods

Study design

A retrospective, quasi-experimental study with a non-equivalent control group, will be carried out to compare the clinical outcomes before/after strategic purchase and clinical pathway implementation. The intervention group includes patients treated under the strategic purchase and the clinical pathway. The control group includes patients who did not receive healthcare under those strategies. An economic "top to bottom" method[17] will be used to estimate and compare the direct costs of healthcare of CHC patients in both groups. Additionally, a questionnaire will be applied to the intervention group to identify barriers and facilitators in CHC healthcare and to evaluate the patient's satisfaction with the healthcare process under the clinical pathway.

Study setting

The study will be conducted in a specialized healthcare provider institution in Colombia that treats outpatients with CHC.

Study population

The study population will be outpatients with a diagnosis of CHC confirmed by quantitative HCV RNA test, affiliated to one health insurance company from Colombia under the contributory regime (There are two types of insurance schemes into the healthcare system in Colombia: contributory regime and subsidized regime. In contributory regime, link to healthcare is made through the payment of a quotation by the patient, his/her family, or by the patient and his/her employer. The subsidized regime is for the poor and vulnerable population of the country).[18]

Patients will be eligible to participate if they are aged at least 18 years and have any prescription of pharmacological treatment for CHC. Patients with incomplete information in at least one of the following variables: fibrosis, cirrhosis (if applicable), an antiviral drug, will be excluded.

Intervention

Intervention group: Patients treated under the Direct-acting Antiviral's (DAA) strategic purchase and clinical pathway

The components of the intervention include: (1) Strategic purchase of DAA (Sofosbuvir/Ledipasvir, Sofosbuvir, Daclatasvir, Sofosbuvir/Velpatasvir) by the MoHSP through the PAHO's strategic fund; and (2) healthcare process established in the clinical pathway proposed by the MoHSP.[14]

In the study setting, the clinical pathway has been complemented with pharmaceutical service activities (Figure 1). This healthcare process includes:

a) Screening and patient diagnosis (confirmation by quantitative HCV RNA test). The notification of the diagnosed patients to the National Public Health Surveillance System (SIVIGILA) is mandatory.
b) Evaluation for the start of treatment and medicines prescription (this process is made by a specialist in internal medicine, hepatology, or infectious disease). The DAA prescription has to be made through the MIPRES platform (MIPRES is a technological platform of the MoHSP that allows health professionals to report the prescription of medicines not included in the health benefits plan because they are not financed with health system resources[19]).
c) Pharmaceutical Care (includes pharmacist interview, pharmacotherapeutic review, labs review, evaluation of Drug-Related Problems, pharmacist's interventions). It is a continuous process in which the pharmacist focuses on the patient's evolution and is in constant communication with the nursing staff in charge of the medicines supply and the patient's physician.

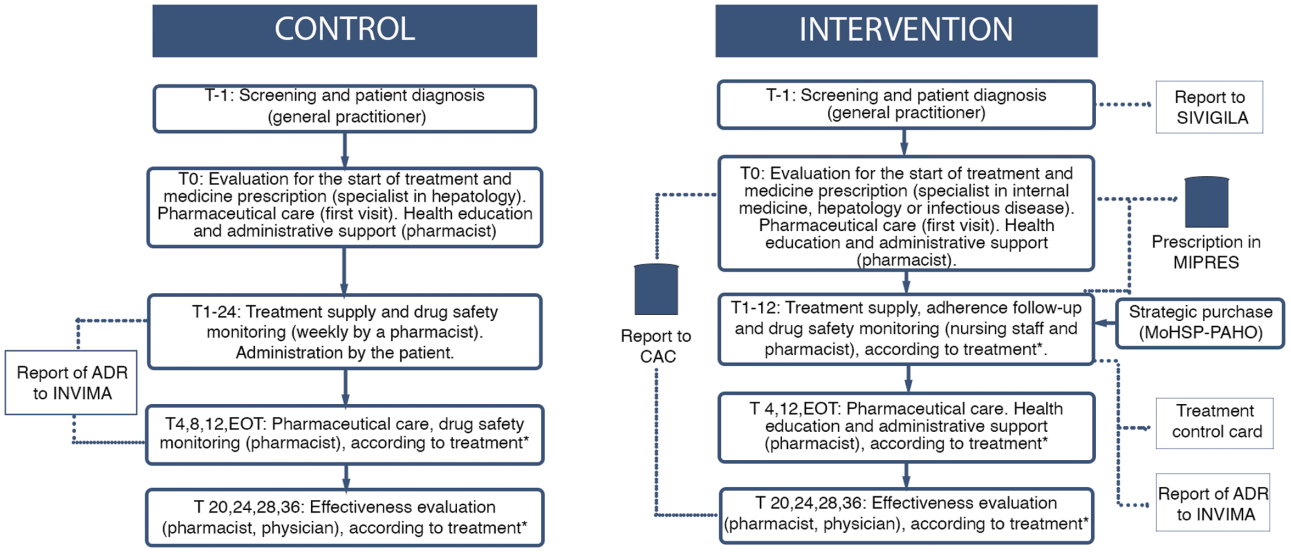

Figure 1 General overview of the HepC-STRATEGY study Time (*t*) measured in weeks *According to the treatment, the duration of the therapy can be of 8, 12, 16 or 24 weeks, with evaluation of the Sustained Virological Response at week 12 or 24; the performance of laboratory tests depends on the treatment and its duration and are defined in the MoHSP's Clinical Pathway (14). Abbreviations: ADR: Adverse Drug Reaction; EOT: End of treatment; CAC: National Account of High Cost; SIVIGILA: National Public Health Surveillance System; MIPRES: My Prescription (MIPRES – Platform of the MoHSP to prescribe drugs that are not included into the health benefits plan); MoHSP: Ministry of Health and Social Protection; PAHO: Pan American Health Organization; INVIMA: National Institute for Drug and Food Surveillance.

It includes "face to face" consultation at weeks 0, 4, the week of the End Of Treatment -EOT- (8, 12 or 24) and the week of evaluation of effectiveness (week 12 or 24 after EOT).

d) Health education: the pharmacy staff provides education to the patient/caregiver about CHC (generalities of the disease, mechanisms of transmission and strategies to prevent reinfection/transmission, complications of liver disease), and their treatment, focusing on the therapeutic plan, possible precautions (compatibility of the use with food or other medicines), possible contraindications, recommendations of use (administration form, dose, frequency, duration of treatment, what to do if he/she forget a dose, storage conditions and final disposition); effectiveness and safety parameters (tests necessary to monitor treatment, most common adverse reactions, how to detect and manage them); with particular emphasis on the importance of adherence. Educational materials and tools for medication management are provided.
e) Administrative support: the pharmacy staff provides support to the patient to complete administrative procedures related to the CHC treatment.
f) Treatment supply and adherence follow-up: Patients have two types of treatment supply according to his/her needs:

- *Daily-supervised medicine administration*: the patient receives his/her medicine daily by a nurse at the patient's home or work. In this way, adherence is monitored daily and registered in the control treatment card.
- *Weekly or monthly dispensing and daily tele-supervised administration*: the patient receives a weekly or monthly treatment by the nursing staff at the patient's home or work. Daily medicine administration by the patient is supervised through telepharmacy (telephone, social networks). This modality of medicines supply is made in patients who have manifested the need for a weekly/monthly delivery and have signed a commitment to demonstrate the tele-supervised administration and the delivery of the empty blisters of the medication. This process is carried out with the prior authorization of the National Leader of the Hepatitis C Program of the specialized healthcare provider institution.

Any Adverse Drug Reaction (ADR) detected during this process is notified to the pharmacist in charge of patient follow-up.

g) Drug safety monitoring: The pharmacist assesses the incidence of ADR through a review of laboratory tests (ordered by the physician according to the DAA and treatment duration[14]), pharmacist's interviews, and notifications of the nurse responsible for the treatment administration/delivery. In case of suspicion of ADR, the respective notification is made to the national medicines' agency (National Institute for Drug and Food Surveillance -INVIMA-) and classifies its severity. The pharmacist establishes with the hepatologist the appropriate management of the ADR.
h) Effectiveness evaluation: the pharmacist evaluates treatment effectiveness by the analysis of the HCV viral load. Patients with suspected therapeutic failure are discussed with the hepatologist to define management (dosage adjustment, change of DAA, evaluation of Resistance Associated Substitutions).

The pharmacist register the clinical data in a control treatment chart and the database from the National Account of High-Cost Medications (Cuenta de Alto Costo, CAC).

The time of treatment and evaluation of effectiveness depends on the antiviral treatment, so the total time of the patient in follow-up can vary between 20 and 36 weeks (Table 1).

The patients included in this group will be invited to answer a questionnaire to identify the barriers, facilitators, and patient satisfaction with the healthcare process.

Table 1 Follow-up treatment duration in patients with DAA

	Weeks				
Treatment regime*	A	B	C	D	E
Treatment duration	8	12	16	24	12
Effectiveness evaluation	12	12	12	12	24
Total time of intervention	20	24	28	36	36

*Treatment regime depends on the genotype, cirrhosis status and previous treatment. Weeks for treatment are defined in the MoHSP's Clinical Pathway.[14]

Comparator

Control group: patients treated under usual care before the establishment of the strategic purchase and the Clinical Pathway.

In this group, the healthcare provider purchased the medicine, and the healthcare process included:

a) Screening and patient diagnosis (confirmation by quantitative HCV RNA test).
b) Evaluation for the start of treatment and medication prescription (this process was made by hepatology).
c) Pharmaceutical Care (includes pharmacist interview, pharmacotherapeutic review, labs review, evaluation of Drug-Related Problems, and pharmacist interventions).

It includes "face to face" consultation at weeks 0, 4, 8, the week of the EOT (12 or 24), and the week of evaluation of effectiveness (week 12 or 24 after the EOT).

d) Treatment supply: The treatment dispensing was made weekly by the pharmacist, and the patient was responsible for the administration.
e) Drug safety monitoring: The pharmacist assesses the incidence of ADR through a review of laboratory tests (ordered by the physician) and pharmacist's interviews during "face to face" consultation. In the case of ADR suspicion, the notification was made to the INVIMA. Before the start of treatment, laboratory tests included pregnancy test and TSH, in addition to tests of renal function, hepatic function, and blood count.
f) Health education, administrative support, and effectiveness evaluation were made as described in the intervention group.

Outcome measures

The outcomes selection responds to the objectives of the strategies implemented by the MoHSP, aiming to improve access to treatment and clinical outcomes through the medicine cost reduction achieved by the strategic purchase. In this sense, the primary outcome to be measured is *access to treatment*, defined as the proportion of patients who initiate treatment, compared with the total number of patients with an indication of treatment (confirmed diagnosis and prescription of treatment).

The secondary outcomes to be measure are:

- *Time to treatment*: difference in days between the date of the first antiviral prescription and the treatment start date;
- *Effectiveness*: the proportion of treated patients that achieved Sustained Virological Response (SVR) -undetectable HCV viral load (lower than the Lower Quantification Limit), 12 weeks after the end of the DAA therapy (SVR12) or 24 weeks after the end of treatment for therapy that include interferon (SVR24)[14];
- *Drug-related problems-DRP*: the proportion of patients who initiated treatment and experienced any undesirable event that is associated or suspected associated with drug therapy and that interferes or potentially interferes with the desired outcome for the patient[20];
- *Cost of care*: direct costs of healthcare of CHC patients from the third payer perspective, the Colombian General System of Social Security in Health.

In patients from the intervention group, *barriers and facilitators* perceived and *patient's satisfaction* with the healthcare process will be evaluated.

Figure 2 presents the activity carried out in each group, their frequency, and the time for the outcomes' evaluation.

Sample size

The sample size was calculated with EpiDat Version 4.2 (Consellería de Sanidade, Xunta de Galicia, Spain, Pan American Health Organization, CES University). Assuming an access/start of treatment of 70% in the control group and 90% in the intervention group, with a 95% confidence and 80% power, will be required at least 62 patients in each arm. This data was used in the sample size calculation, considering the lack of reports of access to DAA in Colombia before implementing the MoHSP strategies and that some countries had reported initiation of antiviral in 28–70% of patients.[21–23] According to the Colombian MoHSP, the strategies implemented can generate access superior to 90% in the patients in the contributory regimen.[15]

Recruitment

The health insurance company will provide the list of patients with International Classification of Diseases code (ICD-10) for CHC (B182) and the list of patients with DAA prescription between 1 December 2015 and 31 December 2019. After analyzing the criteria of eligibility, patients who have been diagnosed/treated before 1 August 2017 will be considered as potential candidates for the control group; those that were diagnosed/treated under the MoHSP strategies after 1 August 2017, will be considered potential candidates for the intervention group.

Blinding

Blinding of participants and the health team involved in care is not possible due to the intervention's nature.

Data collection, management and analysis

Data on patient demographics, clinical information, and variables related to CHC healthcare processes' costs will be extracted from the health insurance company and the healthcare provider databases, patient's clinical record, and pharmacovigilance reports.

A questionnaire will be applied to identify the barriers, facilitators' and patients' satisfaction with the healthcare process under the clinical pathway. The questionnaire on barriers and facilitators has multiple-choice answers, and the satisfaction questionnaire has a Likert scale-response design. The questionnaires were created based on a narrative review of the literature and the experience of the researchers. Its usability was evaluated.

TIMEPOINT	STUDY PERIOD																											
			TREATMENT/FOLLOW-UP																			CLOSE-OUT							
	t-1	t0	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21	t22	t23	t24	t28	t32	t36
INTERVENTION GROUP																													
Screening and patient diagnosis	X																												
Evaluation for the start of treatment and drug prescription		X																											
Administrative support		X	X	X	X	X	X	X	X	X	X	X	X	X				X				X		X		X			
Pharmaceutical Care, Health education, Drug safety monitoring		X				X				X*				X				X				X				X	X		X
Treatment supply and adherence follow-up; Drug safety monitoring			X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X			
Effectiveness evaluation																						X				X	X		X
CONTROL GROUP																													
Screening and patient diagnosis	X																												
Evaluation for the start of treatment and drug prescription		X																											
Administrative support		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X			
Pharmaceutical Care, Health education, Drug safety monitoring		X				X				X				X				X				X				X	X		X
Treatment supply, Drug safety monitoring			X		X		X		X		X		X		X		X		X		X		X		X				
Administration by the patient			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Effectiveness evaluation																						X				X	X		X
ASSESSMENTS																													
HCV Viral Load		X				X				X				X				X				X				X	X		X
Blood count, Renal and Hepatic Function		X	X+	X+		X				X+				X+												X+			
Pregnancy test and TSH test (only in the Control Group)		X																											
Outcomes																													
Access to treatment			X																										
Opportunity in the beginning of treatment			X																										
Effectiveness (SVR12 o 24)																						X				X	X		X
DRP		X				X				X				X				X				X				X	X		X

Figure 2 Schedule for enrolment, interventions, and assessments. Made according to recommendations for intervention trials (SPIRIT).Time (*t*) measured in weeks. Abbreviations: HCV: Hepatitis C virus; SVR: Sustained Virological Response; DRP: Drug-related problems. ☐The time to perform these activities depends on the treatment duration chosen for each patient. + Applies to Direct-acting Antivirals (DAA) therapies that include Ribavirin or Ribavirin/pegylated interferon in the intervention group.* This "face to face" consultation is made at week 8 ONLY with patients that ends treatment in that week.

The estimated completion of the study is 31 March 2021, after the end of patients' follow-up, questionnaire application, and statistical analysis.

Estimation of resources and costs in healthcare

The time horizon considered for the cost analysis will be six months, which corresponds to the average time elapsed between the start of treatment and completion of follow-up in patients with CHC.

The estimation of resources and costs will be developed in three phases:

a) Identification of the events generating costs in healthcare according to MoHSP recommendations[14] includes general and specialized medical care consultations, treatment costs, and laboratory, among others.
b) Consumption of resources: The amount and frequency of use of each resource in the healthcare process in the intervention and control groups will be identified to build a standard case for each group.
c) Cost assessment: All monetary units will be expressed in Colombian pesos (COP) of 2019.

- Drug costs: the search for the drug's prices used before the strategic purchase will be carried out in the Colombia Drug Price Information System (SISMED) between December 2015 and July 2017. Those prices will be adjusted to current prices of the year 2019 according to the inflation or the Consumer's price index in health.

If the drug's price is under government regulation, the price will be obtained from the respective price regulation document. If the price reported in SISMED is lower than the regulated price, it will be chosen in the standard case.

The price of DAA purchased through the strategic purchase will be extracted from the Purchase and Delivery Reports of Drugs published by the MoHSP.

- Procedures costs: The costs of the procedures will be estimated using the manual suggested by the Technological Health Assessment Institute from Colombia (IETS), adding up to 30%.[24]

Data management

A Microsoft Access 2010 database will be used to hold the study-related data. The researchers involved in this study will be the only ones with access to information.

The information will be collected retrospectively using the databases provided by the health insurance company and the healthcare provider, as follow:

1) the lists of patients with ICD-10 codes for CHC (B182) and with prescription of DAA will be crossed;
2) the clinical record of patients diagnosed with CHC without a prescription of DAA, will be reviewed to establish if the diagnosis was confirmed or discarded, according to the report of the HCV RNA quantitative test;
3) the eligibility criteria will be evaluated, and patients will be distributed in the intervention or control group, according to the date of treatment;
4) the variables related to CHC diagnosis, treatment, outcomes, and healthcare costs will be collected;
5) the answers to the questionnaires will be registered into the study database.

The participants' files and questionnaires will be strictly confidential and archived in the healthcare provider institution.

Researchers involved in this study would be the only ones with access to the information. The principal investigator will perform a complete data backup every day, and the information will be stored in two different hard drives as a safety measure.

Statistical methods

Statistical analysis will be performed using SPSS version 25 (Statistical Package for the Social Sciences – IBM, USA).

Matching

Given the absence of randomization, to reduce the possible selection biases and establish a balance in the covariates between the control and treatment group, the matching technique by propensity score will be used.[25, 26] Initially, propensity scores will be calculated for each patient by logistic regression to model the inclusion probabilities within the intervention group given their observable characteristics (sex, age, stage of fibrosis and cirrhosis, history of use of previous antiviral drugs).[27]

Later, the balance of propensity scores between the intervention and control group will be examined using frequency histograms. Then, each patient of the intervention group will be matched with a control group patient according to the assigned propensity score. Matching will be made with the nearest neighbor.[27]

Statistical analysis

Following the matching, a univariate, bivariate, and multivariate analysis will be performed. Questionnaires will be summarized using descriptive statistics.

For the categorical variables, absolute and relative frequencies will be calculated. For the quantitative variables analysis, the Shapiro-Wilk test will be carried out to analyse the normality of the distribution. If so, the mean and standard deviation will be estimated. Otherwise, the median and interquartile range will be calculated. The minimum and maximum values will also be calculated.

In the bivariate analysis, χ^2 tests will be used for the categorical variables. Depending on the distribution of the quantitative variable, t student or U-Mann Whitney will be performed for independent samples. These measures will be presented with the respective 95% CI and statistical significance will be assumed if the *P*-value is less than 0.05 ($P < 0.05$).

A regression analysis will be performed to explain the association of multiple variables with the outcomes of interest (access to treatment, time to treatment and effectiveness). The effect of sex, age, genotype, degree of fibrosis/cirrhosis, and HIV co-infection will be evaluated for access to treatment, and time to treatment outcomes.[21, 23, 28] The effect of genotype, prior exposure to treatment, cirrhosis, duration of treatment, and existence of Resistance Associated Substitutions will be analysed for the effectiveness outcome.[29]

Cost evaluation

The total cost of the base case for each group will be estimated using the information of the type case (frequency of use of medicines and procedures) and the respective costs of each resource.

The base case will be used to report the conclusions of the study. In the same way, the difference between the total costs of the groups will be calculated, and a sensitivity analysis will be carried out to estimate the variability given by the changes in the unit costs of the parameters,[30] for this, the maximum and minimum values of the medications and procedures will be considered.

Missing data

In case of missing data in the outcomes of interest, two analyses will be made:

1) complete case analysis where patients with missing information will be eliminated[31]; and
2) multiple imputation to consider all matched patients, in which each missing data will be replaced with two or more acceptable values representing a distribution of probabilities.[32]

To generate the imputed estimates, the reported outcomes, and the patient's demographic information will be included in the model.

Discussion

The 2030 Agenda for Sustainable Development has the aim of eliminating viral hepatitis as a public health problem. It focuses on the global goals of reducing new infections of viral hepatitis by 90% and reducing deaths from viral hepatitis by 65% by 2030.[12, 33] Those goals require improvement in access to diagnosis and treatment, helping people to become aware of their disease and treating at least 80% of patients by the year 2030.[34, 35]

Colombia is making significant changes in policies to improve access to treatment and contribute with VHC elimination; therefore, it is necessary to make visible the strategies made by the government and generate scientific evidence of its results.

To our knowledge, this is the first quasi-experimental study designed to evaluate the effect of the strategic purchase and the Clinical Pathway in patients with CHC in Colombia, in which the outcomes are related to the objectives of the implemented strategies. In this sense, besides evaluating treatment effectiveness, we want to estimate the costs of healthcare since the strategic purchase sought to reduce costs for the system and facilitate access, which is our primary outcome. Likewise, the Clinical Pathway aimed to standardize the healthcare process and improve its quality. Therefore, we decided to evaluate patient satisfaction and the barriers/facilitators identified by them.

The results could be subject to potential biases because our study setting had performed an integrated healthcare process for several years, even before the establishment of the Clinical Pathway, which was not the rule in other contexts. Besides, given the retrospective nature of this study, we depend on the quality of the information registered in the clinical databases, especially in the control group. At that time, it was not mandatory to report some information. We will try to mitigate this limitation by using a patient recruitment period of 2.4 years and the review of clinical records.

The realization of this research by an independent organization will generate objective evidence of the effects of the strategies adopted in Colombia for CHC management. The analysis of this information would allow defining possible improvements and, perhaps, analyse the feasibility of the strategies' extrapolation to other regimes and other high-cost diseases. Furthermore, this information could help other policymakers in lower- and middle-income countries adopt some of these strategies to decrease the CHC burden disease.

Conclusions

This study will provide evidence on the effect of the strategies adopted by the policymakers in Colombia to address CHC problems

in terms of access to medicines, time to treatment, effectiveness, safety, costs, and patient satisfaction. The analysis of the barriers and facilitators perceived by patients during the treatment received under the Clinical Pathway, could allow the instauration of improvements into the process.

The details of the interventions evaluated in this research could help other policymakers in lower- and middle-income countries adopt some of these strategies to decrease the CHC burden disease.

Supplementary Material

Supplementary data are available at Journal of Pharmaceutical Health Services Research online.

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Author contributions

M.L.-M., and P.A.: Conceptualization, Methodology, Writing - Original Draft, Funding acquisition, Writing - Review & Editing. A.S.-O.: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing. N.D.-Z., C.M.V.-P., and F.A.R.: Methodology, Writing - Review & Editing. J.G.C.: Conceptualization, Methodology, Writing - Review & Editing.

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Conflict of Interests

None declared.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study protocol.

Informed Consent

Only the participants who had authorized the use of their data will be included in the study. The participants who will be answering the questionnaires will receive verbal and written information about the study. Those who agree to participate must sign a consent form [see Supplementary File 4].

Study results will be published in national or international indexed scientific journals and presented to Colombian policymakers. Press releases or explanatory brochures of the project results will be published for public communication.

The SPIRIT checklist is available in Supplementary File 5.

Ethics Approval

The study was approved by the Medical Research Institute Bioethics Committee from the University of Antioquia (Ref: 2019-004) [see Bioethics Committee approval, English version, in Supplementary File 3]. It has been registered in the U.S. National Library of Medicine database clinicaltrials.gov (Protocol Version 1, 28 February 2019, registration number NCT03895294).

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