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## Development and validation of a pharmacoeconomic tool for decision making in the implementation of pharmaceutical care for hypertensive patients in the Brazilian public health system (SUS)

Maurílio de Souza Cazarim<sup>a,\*</sup>, Rodrigo Reis<sup>b</sup>, Olívia Wu<sup>c</sup>, Rui Pedro Charters Lopes Rijo<sup>d</sup>, André Luiz Teixeira Vinci<sup>b</sup>, Domingos Alves<sup>b</sup>, Leonardo Régis Leira Pereira<sup>a</sup>

<sup>a</sup>*Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil*

<sup>b</sup>*Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil*

<sup>c</sup>*Health Economics and Health Technology Assessment, University of Glasgow, United Kingdom*

<sup>d</sup>*School of Technology and Management, Polytechnic Institute of Leiria, Leiria, Portugal*

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### Abstract

Systemic Arterial Hypertension (SAH) is a risk factor for 9.4 million deaths worldwide. In Brazil, the condition attributes an annual cost of approximately USD640,000,000 to the SUS. The epidemiological and economic analysis of Pharmaceutical Care (PC) in the management of hypertensive patients showed an improvement in blood pressure control, a reduction of the risk of SAH complications, and an investment return of over USD1.7 million after ten years. Therefore, this article aims to present a pharmacoeconomic tool capable of assisting decision making in the implementation of PC in the SUS. A systematic review is being conducted for the robustness of the estimation of clinical and epidemiological impact of SAH, its results will be tabulated and applied in the improvement of the tool together with the direct medical and non-medical costs, indirect costs and costs of the SAH. In addition, a Markov model will be designed to estimate the incidence of cardiovascular diseases and SAH's associated diseases by studies of proteomics that address the Human Network Disease. We hope to validate this auxiliary tool and thus to improve blood pressure control among hypertensive patients, quality of life, to reduce comorbidities and deaths, as well as optimizing the use of health resources.

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\* Corresponding author. Tel.: +0-000-000-0000 ; fax: +0-000-000-0000 .  
E-mail address: [maurilio.jf@gmail.com](mailto:maurilio.jf@gmail.com)

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## Nomenclature

CVD	Cardiovascular Diseases
PC	Pharmaceutical Care
SAH	Systemic Arterial Hypertension
SIASUS	Information System of Outpatient (Sistema de Informações Ambulatórias do SUS)
SIH	Information System of Hospital Admissions (Sistema de Informações de Internações Hospitalares)
SUS	Unified Health System (Sistema Único de Saúde)
WHO	World Health Organization

## 1. Introduction

According to the WHO<sup>1</sup>, of 56.4 million deaths worldwide in 2015, 39.5 million were due to non-communicable diseases and almost 75% of these deaths occur in low- and middle-income countries. In Brazil, they account for the highest rates of morbidity and mortality and for a significant portion of outpatient and hospital care expenses which represent 70% of health care expenditures in the country<sup>2,3</sup>. SAH is among the most important non-communicable morbidities which is a multifactorial condition characterized by elevated and sustained blood pressure levels<sup>3,4</sup>.

SAH affects about a third of the Brazilian population, reaching more than 50% of the elderly individuals and 5% of the children and adolescents. Its severity is related to the damage of target organs, such as kidneys, heart and brain<sup>1,5,6</sup>. According to the WHO<sup>7</sup> SAH is considered a major risk factor for the occurrence of CVD. The increase of 10 mmHg in systolic blood pressure increases by up to 25% the risk of developing CVD<sup>8</sup>.

This context delineates a reality in which investment to improve access to health and treatment in the case of SAH has not shown the expected effectiveness<sup>9,10</sup>. This is exacerbated by the underfunding of the Brazilian Public Health System, the SUS, and its difficulties at improving the use of health resources. Hence, the SUS has sought alternatives to overcome this panorama of hypertension in Brazil, outlining strategies and care proposals that promote the improvement of clinical outcomes and patient care, and seeking health technologies that are capable of being integrated into pre-existing health services<sup>11</sup>. A health technology that has shown effectiveness in the control of chronic diseases such as hypertension<sup>12,13,14</sup>, and can optimize health resources is the PC<sup>15,16</sup>.

PC is a model of professional practice where the pharmacist promotes patient care through consultations for pharmacotherapeutic follow-up. Some studies have shown that PC has been effective not only in blood pressure control but also in the reduction of health complications caused by hypertension<sup>13,17,18,19,20</sup>. As evidenced by Souza et al. (2007)<sup>21</sup> this practice can reduce systolic blood pressure by 20 mmHg and diastolic blood pressure by 10 mmHg in hypertensive patients.

In this context, this article aims to present a pharmacoeconomic tool capable of predicting the epidemiological and economic impact for the planning of the care of hypertensive patients by the PC in the SUS with proposed methods to its improvement and validation and, thus, to help reduce the morbidity and mortality associated with SAH and to improve the use of resources in health.

In the next section, we will present some background information for the construction of the proposed tool. Then, in the third section, we will describe the steps taken and planned to build the system. At last, in the section four, we will present a brief description of the importance of such work.

## 2. Background

The planning of the care of hypertensive patients by PC was structured in a proposal of pharmacoeconomic tool. This tool was grounded in a previous study, which has evidenced the reach of 98% of blood pressure control associated with PC and the reduction of 30.3% in cardiovascular risk in ten years<sup>22</sup>. The study presented an economic methodology of analysis, which was based on the development of a Markov model to predict the incidence and deaths from CVD and chronic kidney disease in a long time.

Markov modeling is a mathematical tool attributed to the analysis of pharmacoeconomic decisions with the purpose of designing health states and death to predict complications of a treatment. This mathematical model is widely used for chronic diseases since they constitute more complex outcomes over a long period of time. With the application of the model, it is possible to attribute health state transitions over the years, determined by Markov cycles, which allows projection according to probabilities in a time horizon and, in the end, to obtain the individuals allocated in different health states, including the state of absorption (death), thus enabling the calculation of the years of life saved by different health technologies. For each health condition a cost can be assigned to perform pharmacoeconomic analyzes comparing different medications or interventions<sup>23,24</sup>.

Therefore, the study of Cazarim<sup>25</sup> measured the reduction in health costs associated with PC, showing a growing savings in health resources over a period of ten years. The liquid return of the investment in this pharmaceutical practice was USD \$1,712,709.74 and the cost-benefit ratio was 30.03 (26.74 - 34.28), with the rate of return of investment of 303%. This has fostered the development of a pharmacoeconomic tool that can help health managers in the implementation of PC in the SUS, as well as in the allocation of health resources and epidemiological planning for hypertension and associated complications (chronic kidney disease, heart failure, ischemic heart disease, stroke and peripheral artery disease).

For the improvement of the tool, an important point to be incorporated in a separate module are the costs of the morbidities associated with the complications of SAH which are not correlated to their treatment, not being considered the effect of SAH as a risk factor. This association of one disease as predisposing factor to another morbidity has been studied by a recent line of research, the Human Network Disease<sup>26</sup>. The approach and development of this line of research is done by methods of proteomic studies<sup>27</sup>, which are based on the mapping of proteins transcribed by mRNA precursors of diseases. This mapping is visualized in an integrated network form between diseases, which determines the association between their predisposition<sup>26</sup>.

This modern conceptualization of the association between diseases has brought advances and expectations for treatments by the prospects of customizing medicine and making health care more preventive and effective. Because an avoided disease can prevent numerous other morbidities, and the disease initially avoided is not considered a risk factor for the others<sup>26,28,29,30</sup>.

The prevention of associated diseases can have a positive epidemiological and financial impact on the SUS. This impact has not been measured in the literature. However, this reinforces the need to create methods that evaluate and collaborate for the scientific development of the recent area. In addition, the measurement of the epidemiological and financial impact incorporated into the pharmacoeconomic tool tends to contribute to health planning, resources saving and optimization of the application of resources in health. In this context, we hypothesize that clinical results achieved by PC programs for hypertensive patients can avoid related complications, such as CVDs, and morbidities that have been associated with their complications. Moreover, this analysis incorporated in the development of the pharmacoeconomic tool can predict the epidemiological and economic impact associated with the implementation of PC in ten years, it collaborates for the reduction of morbidity and mortality associated with SAH and, consequently, for the planning of the application of resources in the SUS.

## 3. Methods

The pharmacoeconomic tool was developed according to the methods reported in the previous work of Cazarim<sup>25</sup>. A systematic review is being performed and its finds will be tabulated and applied to restructure the tool. In addition, a Markov model to estimate the incidence of diseases that has been associated with the complications of SAH will be structured. The probabilities for the model will be calculated according to the epidemiological indicators extracted from the diseases associations of proteomic studies. This serves to create a new field in the tool that assists a projection

of the epidemiological impact and morbidity costs. With this, the tool will be improved for its validation and applicability. The steps to elaborate the tool were presented in Fig. 1.

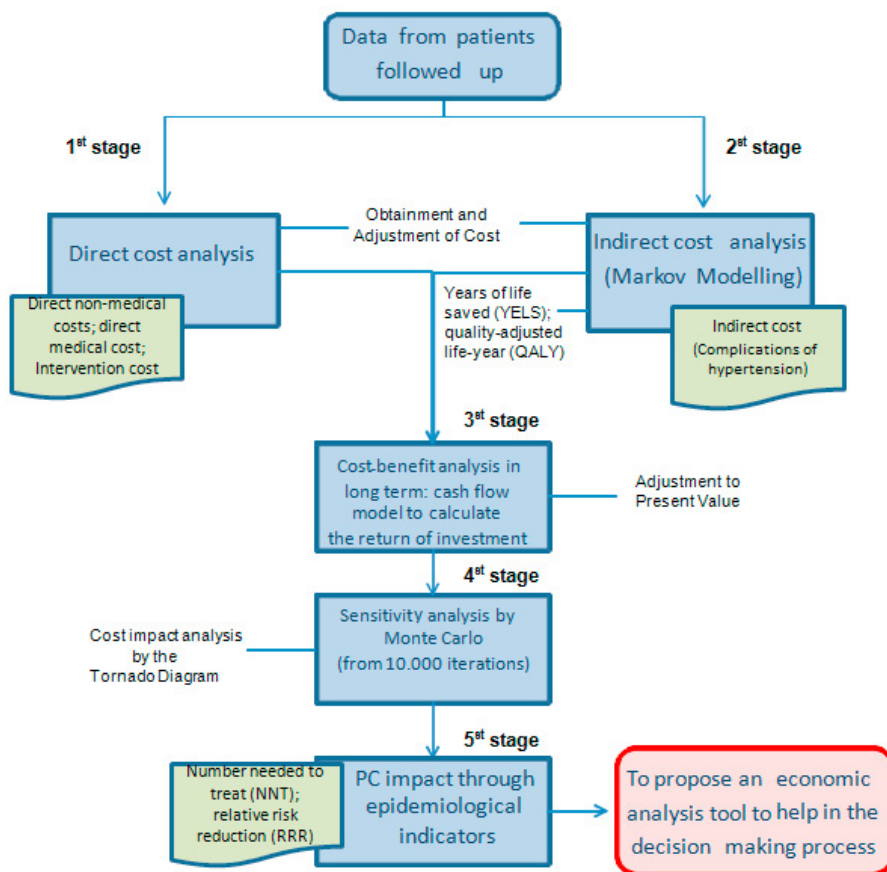


Fig. 1 Schematic diagram of the elaboration of the economic tool.

### 3.1. Programming and development of the pharmacoeconomic tool

The previously stages of the pharmacoeconomic study that had grounded the development of the tool were defined. The tool was designed with three fields: one static and two others to be filled by the user. The "accumulated inflation (base 2015)" is related to the accumulated inflation rate in years after 2015, because the estimated costs were based on that year. The "initial investment", in which the manager will put the intended amount of investment in structuring PC in a region or municipality. And finally, the "loss of resource", which will be filled automatically and will show how much of the value to be invested is obsolete, that is, the surplus of the investment. Thus, the manager can save or reallocate this resource, or make the decision to complement it and extend the scope of the PC in the municipality or region. The tool will then show financial and epidemiological impact estimations as well as its aid to health management

The core of the pharmacoeconomic tool is web-based following the model-view-controller (MVC) pattern<sup>31</sup>. The MVC architecture organizes the application into three interconnected parts. The first, the model, represents an object carrying data. The second, the view, represents the presentation layer, where it is possible to visualize the data that the model contains. Finally, the controller acts on both model and view controlling the data flow updating the view whenever data changes. This pattern enables a better organization of the code and allows the development of multiple views for a model.

The tool will provide interoperability by a web service application program interface (API) that adhere to the representational state transfer (REST) architecture<sup>32</sup>. REST is also a pattern to provide easy access to the logic of the application and facilitates the integration with other systems.

The API and the web tool will be implemented using the PHP framework CakePHP that makes building web applications using the MVC patterns and implementing REST services simpler, faster, while requiring less code<sup>33</sup>. The presentation layer will be developed using HTML5, CSS and JavaScript. Also, a mobile application will be developed and will uses the REST API.

The main interface of the tool is presented in Fig. 2.

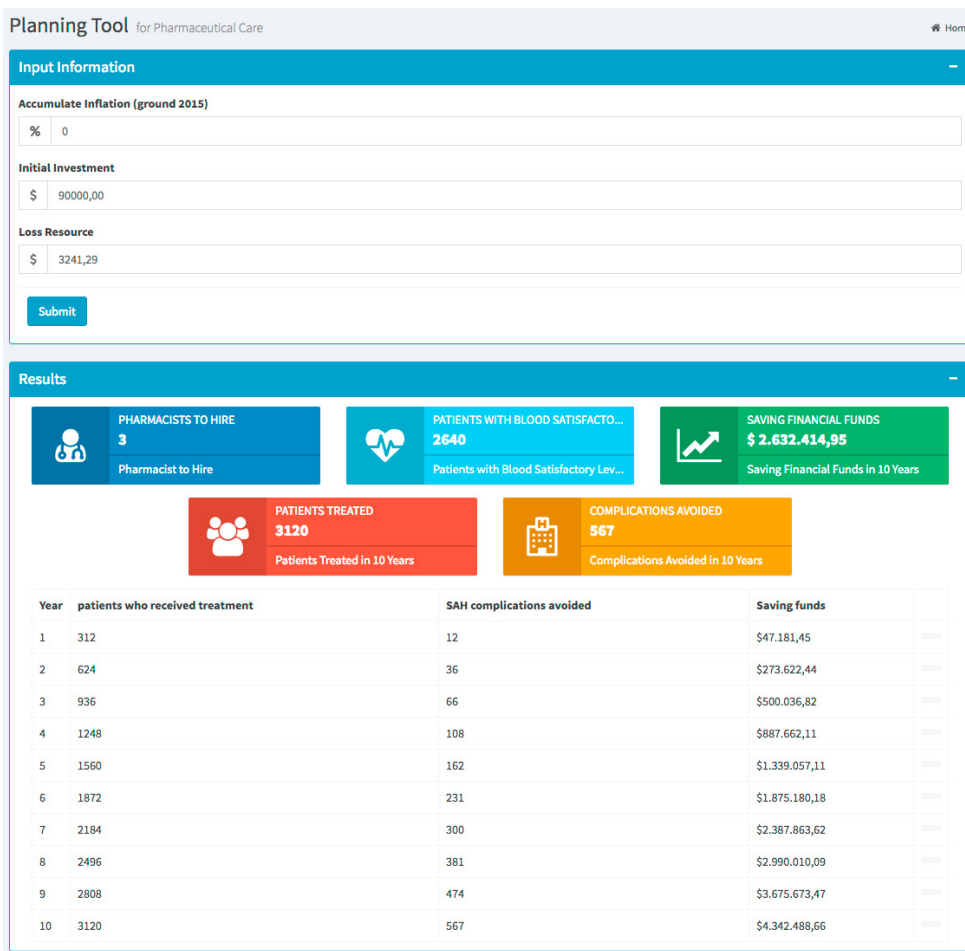


Fig. 2 Main layout of the pharmacoeconomic tool to aid decision making by health managers for the implementing the care of hypertensive patients by Pharmaceutical Care.

### 3.2. Systematic Review

The systematic review will address the question: "What are the clinical outcomes regarding blood pressure, cholesterol, HDL and cardiovascular risk reached by pharmaceutical care in patients diagnosed with essential systemic arterial hypertension in treatment at the primary care?". The objective is to know the existing models of pharmaceutical care for hypertensive patients, summarizing the clinical results achieved by this technology in health.

### 3.3. *Human Network Disease and projection of the diseases associated with the complications of SAH*

The projection of the morbidities associated with SAH and its complications will be performed by a hypothetical cohort in Markov modeling, which will be distinguished between health care without and with Pharmaceutical Care. Each group will have the peculiarity of the difference in the number of patients with SAH complications. The health states will be defined as: Stable (under treatment for HAS); Morbidity (in treatment of the complication of SAH); Death (state of absorption). Patients with SAH complications will be likely to remain stable, in treatment for the complication, to present the morbidity associated with the complication or to die due to the complication. Those who present the associated morbidity will be likely to remain stable in morbidity treatment or die due to the morbidity. Thus, patients will transit between the three Markov health states along ten Markov cycles, which represent ten years of projection, according to the methodology developed for the elaboration of the pharmacoeconomic tool<sup>23,24,25,34,35,36</sup>.

The probabilities will be acquired by the Delphi method, a systematic method of judging information, used to obtain the consensus opinion of experts on a given subject. This method was chosen because studies on Human Networks diseases are incipient and the literature is poor in epidemiological and statistical information for calculating probabilities. A form will be drawn up for collecting epidemiological information from the specialists and then the probabilities to be assigned to Markov modeling will be calculated. For this purpose, this study predicts collaboration on the knowledge of a group of experts in CVDs and SAH<sup>37</sup> that will judge the information. A Markov model will be structured for each known complication of SAH for the development of the pharmacoeconomic tool (Chronic Renal Disease, Heart Failure, Ischemic Heart Disease, Stroke and Peripheral Arterial Disease).

The diseases associated with the complications of hypertension will be listed according to the studies on Human Networks diseases. The cost of each morbidity associated with hypertension will be obtained by the SIH and SIASUS. These systems integrate the TabWin database of the Brazilian Department of Informatics, DATASUS<sup>38</sup>.

### 3.4. *Validation of the pharmacoeconomic tool*

A questionnaire with three domains will be elaborated to validate the tool, namely the applicability in the management practice; the layout and understanding of the information; and the contentment with the tool and its reliability<sup>39</sup>. This questionnaire will be appreciated by a group of ten judges, chosen as experts in management or in economics. The suggestions and observations of the experts will be discussed and the questionnaire will be reformulated until the instrument does not require further corrections by the specialists. It is noteworthy that for validation studies, there is no consensus for the determination of the sample number, and the researcher is empirical to judge with observance and aptitude regarding the method used<sup>40,41</sup>.

A tutorial will be prepared for the use of the tool after its restructuring. Therefore, a group of five public health managers will be invited to perform a previous training on the use of the tool and then test their use in a fictional case of public health management, to be elaborated specifically to this study. After using the tool and performing the situational case, managers will respond to the questionnaire previously validated on the pharmacoeconomic tool<sup>42</sup>.

According to the internal validity of the answers, it will be evaluated if the tool needs adjustments, which will be later reevaluated by the judges. With the tool validated for use, it is intended to disseminate it by scientific means and make it accessible to the practice of health management in Brazil. It should be noted that the elaborated pharmacoeconomic tool is in the process of patent application by the USP agency of innovation. Its disclosure and applicability will be made after registration of the copyright.

### 3.5. *Analysis of the results*

The analysis of the results will be through classic and Bayesian statistics. The Bayesian statistics will be used for the stage of the projection costs of diseases associated with HAS complications. The level of significance of 5% will be considered for both cases.

For the systematic review, the agreement between the two researchers will be analyzed by the coefficient of Kappa, being acceptable the value above 0.80, otherwise a new search strategy will be restructured. The Mann-Whitney test will be performed to test the difference between the quality scores of studies in which PC has favorable and

unfavorable clinical results. Finally, the software SPSS version 19 will be used for the classical inferential statistical analysis.

To design the morbidities associated with the complications of SAH, the software OpenBUGS version 3.2.3 will be used to perform the descriptive statistics from previous data, which correspond to the opinion of the experts obtained by the Delphi method. In this way, the prediction of the probability of SAH complications occurrence, as well as of the SAH associated diseases, will be measured to run the Markov model<sup>43</sup>. The sensitivity of the cost results will be analyzed using the software @Risk, considering the variation according to the distribution of probabilities of each cost variable to ten thousand iterations in the Monte Carlo simulation.

Through the Cronbach's alpha<sup>44</sup>, the internal consistency of the validation questionnaire of the pharmacoeconomic tool will be analyzed by measuring the correlation between the responses. This method of analysis was chosen because the questionnaire to be elaborated presents more than two options as a response and will be applied only once. The objective is to demonstrate the trust and applicability of the tool for public management.

#### 4. Conclusion

The proposed tool can enable the measurement of the epidemiological and economic impact of hypertension management by PC, but it should be emphasized that the tool is not 100% accurate, as well as many others that are used in management, because there may be variations in the economy capable of influencing health policies and access. These factors interfere in the quality of health care, which difficult the work of pharmacists and health professionals involved in the service, culminating in worse than expected clinical results. However, with the validation of this tool it will be possible to make it applicable to the management practice in health and, thus, to improve the pressure control index among hypertensive patients and the quality of life, as well as to reduce the morbidities associated with SAH, the complications associated with these morbidities, deaths, and overhead costs such as disability and death pension. In addition, the health planning promoted with the use of this tool will be able to optimize health resources, since the acquired savings can be reallocated in other assistance programs and in the care of more costly morbidities to SUS. Although the training of the pharmacist in Brazil is incipient for clinical practice, which may delay the implementation process of PC due to the lack of professional training to perform it, the development of this tool tends to assist in the process of change in the profession, in which it foresees the curricular change tending to the formation of more clinical character. In this sense, the use of the tool can subsidize decision making for the absorption of the pharmacist regarding the development of clinical practice in the labor market. In addition, it is hoped that this study will foster a possible subarea in pharmacoeconomics, the use of proteomics both for the incorporation of new technologies in SUS and for prevention planning and disease aggravations. In this context, the intention of this project is to contribute to the research, innovation of studies in the field and to the advances of science.

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