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HEALTH CARE ECONOMICS AND MANAGEMENT

Economic modelling to assess the cost-utility of telehealth for chronic obstructive pulmonary disease

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ECONOMIC MODELLING TO ASSESS THE COST-UTILITY OF TELEHEALTH
FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Resumo

As tecnologias de telemedicina são particularmente relevantes na sociedade atual, em que o envelhecimento da população e as mudanças comportamentais contribuem para um aumento das doenças crónicas. Os esforços recentes das empresas de tecnologia em saúde têm-se concentrado no desenvolvimento de plataformas de telemedicina, enquanto as instituições de saúde têm procurado aplicar tecnologias que aumentem a eficiência do atendimento prestado. Por estes motivos, o Health Cluster Portugal (HCP) está a desenvolver uma Plataforma de Gestão de Doenças Crónicas (CDMP). Esta plataforma tem como objetivo monitorizar em casa os pacientes com diferentes patologias por meio de sensores que medem parâmetros fisiológicos e neuronais. Os objetivos do projeto proposto consistem no desenvolvimento de um modelo de Markov de análise económica de custo-efetividade para plataformas digitais aplicadas a pacientes com doença pulmonar obstrutiva crónica (DPOC) e apresentar um panorama atualizado dos trabalhos realizados nesta área. Para atingir as metas propostas, foram realizadas as seguintes etapas:

1. Foi realizada uma revisão do estado da arte para coletar dados relevantes para comparação com as intervenções existentes de telessaúde para DPOC. Foram analisados estudos semelhantes realizados em Portugal e no estrangeiro, as tecnologias de telemedicina implementadas e avaliados os resultados associados. Essas informações são usadas para prever os resultados esperados e melhorar as características da nova intervenção.
2. Foram identificados os dados clínicos e económicos que terão de ser definidos e recolhidos e definidos para se conduzir uma análise de custo-utilidade. Adicionalmente, são apresentadas sugestões para a recolha de dados ainda não disponíveis em Portugal ou ainda não recolhidos pelo HCP.
3. Foi desenvolvido um modelo de Markov em Excel que pode ser utilizado como plataforma para realizar a análise económica de plataformas de telemedicina como o CDMP.
4. O programa Excel desenvolvido foi testado com as melhores evidências bibliográficas e com dados fornecidos pelo HSJ.

Summary

Telehealth technologies are particularly relevant in our society as an ageing population and changes in societal behavior are contributing to a steady increase in chronic diseases. Recent efforts of healthcare technological companies have focused on the development of telemedicine platforms, while health institutions have sought to apply technologies that increase the efficiency of the provided care. For these reasons, Health Cluster Portugal (HCP) is developing the Chronic Diseases Management Platform (CDMP). This platform aims to monitor patients with different pathologies at home using sensors that measure physiological and neuronal parameters. The objectives of the proposed project consist of the development of a cost-effectiveness economic analysis through a Markov model for digital platforms applied to chronic obstructive pulmonary disease (COPD) patients and to present an updated overview on works conducted in this field. To achieve the milestones proposed, the following steps were carried out:

1. A state-of-the-art review was performed, to collect relevant data for comparison with existing COPD telehealth interventions. In this type of analysis, it is crucial to understand whether similar studies have already been carried out in Portugal and abroad, which telemedicine technologies have been implemented and the associated outcomes. This information is used to predict the expected outcomes and to improve the characteristics of the new intervention.
2. The clinical and economical inputs that need to be collected and defined to conduct a cost-utility analysis were identified. Furthermore, suggestions are made to collect the data that is still not available in Portugal or still has not been gathered by HCP.
3. A Markov Model was developed in Excel that can be used as a platform for carrying out the economic analysis of telemedicine platforms such as CDMP.
4. The developed Excel program was tested with the best available evidence and data available from the literature and requested from HSJ.

Index

List of figures.....	vi
List of tables	vii
Abbreviations.....	viii
1. Introduction.....	1
2. The role of Telemedicine in COPD.....	3
2.1. Telemedicine	3
2.1.1. Evolution of telemedicine.....	4
2.1.2. The role of Telemedicine in chronic diseases management	4
2.1.3. Chronic disease management platform.....	5
2.2. Chronic obstructive pulmonary disease	6
2.2.1. Definition, causes, symptoms, diagnostic and treatment	6
2.2.2. COPD prevalence in the world and in Portuguese Population.....	8
3. Economic evaluation of telehealth technologies	9
3.1. Types of economic evaluation.....	9
3.1.1. Cost-utility analysis	11
3.1.2. Markov model	12
3.2. Economic analysis of the implementation of telemedicine for COPD.....	16
4. Methodology.....	23
4.1. Model structure	23
4.2. Data inputs.....	24
4.2.2. Data collection request to Hospital São João	24
4.2.3. Data requested to Health Cluster Portugal	25
4.2.4. Data based on the state of the art	26

4.3. Markov Model program	34
4.3.2. Model parameters.....	34
4.3.3. Excel guide	38
5. Results and Discussion	42
5.1. Patients Baseline Characteristics	42
5.2. Deterministic analysis	42
5.3. Sensitivity Analysis	43
5.3.1. Base case study	43
5.3.2. Different scenarios	47
6. Conclusions and future perspectives	51
7. Appendices.....	64

List of figures

Figure 1. Utilization of telemedicine platform by patients and healthcare providers (from (Tuckson et al., 2017)).	3
Figure 2. ABCD assessment tool, adapted from (Lange et al., 2012).	7
Figure 3. Top 10 causes of death (A) worldwide (World Health Organization, 2020) and (B) in Portugal (Vos et al., 2020).	8
Figure 4. Example of Markov Model for Cost-Effectiveness Analysis (Hut, 2018).	13
Figure 5. Cost-effectiveness plane (NW: northwest , NE: northeast, SW: southwest , SE: southeast).	15
Figure 6. Cost-effectiveness plane and cost-effectiveness acceptability curve. Each dot from the ICER scatter plot represents the results from one sampling (Li et al., 2018).	16
Figure 7. Markov model structure for COPD.	23
Figure 8. Fletcher Curve; FEV1 (Fletcher & Peto, 1977).	32
Figure 9. Excel Menu for the cost-effectiveness analysis.	39
Figure 10. Excel sheet with Results Table (Press button to carry out the simulations).	41
Figure 11. ICER Scatter Plot of PSA for starting age group: 40-49y, time horizon: lifetime and healthcare costs of NHS+CDMP intervention (A) < NHS, (B) > NHS and (C) =NHS.	44
Figure 12. ICER Scatter plot of PSA for starting age: 40-49y, healthcare costs of NHS + CDMP > costs NHS and time horizon (A) 5 years, (B) 10 years, (C) 15 years and (D) for lifetime.	45
Figure 13. ICER scatter plot and CEA Curve of PSA, healthcare costs of NHS + CDMP > costs NHS. time horizon: lifetime and for starting age: (A) 40-49y, (B) 50-64y, (C) 65-69y and (D) $\geq 70y$.	46

List of tables

Table 1. Benefits and disadvantages of eHealth care for the management of chronic disease (information from (Medical News Today, 2020).	5
Table 2. Classification of the different stages of COPD and conventional therapies (Araujo, 2009), (Abordage, 2016).....	7
Table 3. Types of economic evaluation and their characteristics (Drummond & Stoddart, 2015),(Drummond, 1987).....	9
Table 4. Summary on studies that focus on the CUA of COPD. Research carried out in 2020 with the following keywords and search engines: obstructive pulmonary disease, telemedicine, economic analysis, cost-benefit, cost-effectiveness, cost-utility; Google Scholar, Science Direct (Elsevier), Scientific Electronic Library Online (SciELO), PubMed, b-on.	19
Table 5. Input parameters for the Markov model.	24
Table 6. Data used to calculate healthcare costs for the usual care.....	27
Table 7. Telemedicine costs of different published works, inflated costs to reflect 2020 costs, mean and standard deviation used for model simulation.	28
Table 8. Total healthcare costs, excluding telemedicine related expenses, reported in the literature.	29
Table 9. Quality of life of COPD Portuguese patients. Note: the published works present the quality of life according to SGRQ results. The SGRQ total scores were transformed to EQ-5D utilities using the algorithm developed by Starkie et al. (Starkie et al., 2011).	30
Table 10. Utility of GOLD I, II, IV, IV patients.	31
Table 11. Transition Matrix for the proposed Markov Model.....	32
Table 12. Transition probabilities included in the Markov model simulation.	33
Table 13. Input variables used to conduct simulation on the Markov Model.....	35
Table 14. HSJ Patients Characteristics (n=50).....	42
Table 15. Deterministic analysis assuming the telemedicine intervention to have a critical impact on outcomes.....	43
Table 16. Sensitivity analysis for the different starting age-groups considering different scenarios: base case scenario, with considering effects and costs discount and assuming a 20% cost reduction in the telemedicine solution (time horizon: lifetime, healthcare costs NHS + CDMP > healthcare costs NHS).	49

Abbreviations

CDMP – Chronic Diseases Management Platform

CE - Cost-effective analysis

CEAC - Cost-effectiveness acceptability curve

COPD - Chronic Obstructive Pulmonary Disease

HCP - Health Cluster Portugal

HSJ - Centro Hospitalar Universitário São João

ICER - Incremental cost-effectiveness ratio

NHS – National Health System

NMB- Net monetary benefit

PSA - Probabilistic sensitivity analysis

1. Introduction

Across the world, we are witnessing an inversion of the demographic pyramid, having an aging population means more chronic disease and increased health expenditure. In this context, healthcare technologies are currently an indispensable part of any health system. The introduction of new technologies has led, in many cases, to significant benefits, whether in terms of prevention, safety, improvements in health, quality of life and reduction of adverse effects. In particular, the delivery of health care services at a distance, also known as telemedicine, is revolutionizing healthcare (Pham et al., 2014),(Wade, Karnon, Elshaug, & Hiller, 2010) especially in the era of COVID 19 pandemic (Centers for Disease Control and Prevention, 2020).

However, in a framework where economic resources are limited, the correct incorporation and diffusion of technologies has proven to be a challenge for health systems worldwide and, in many cases, a serious problem. Thus, implementation of health assessment methodologies has increased in health systems all over the world over the last decade (Pham et al., 2014). Health economics intends to maximize “value for money” in healthcare, by optimizing not only clinical effectiveness, but also cost-effectiveness of medical interventions (Komorowski & Raffa, 2016).

There is a variety of approaches to perform an economic analysis, the suitability of any of which depends on the purpose of the assessment and the availability of data and other resources.

Among them, Markov models are stochastic processes that undergo transitions from one state to another, being used to account for the long-term consequences of healthcare strategies (Komorowski & Raffa, 2016).

In this paradigm, the Health Cluster Portugal (HCP) mission is to turn Portugal into a competitive player by focusing on the research, design, development, manufacturing and commercialization of health-related products and services (Health Cluster Portugal, 2021). To do so, HCP is developing the Chronic Diseases Management Platform (CDMP) for continuous disease management, for more quality of care with less effort and costs and with the ability to generate alerts for clinicians, patients and informal caregivers (Health Cluster Portugal, 2020b).

Hence, the aim of the present project was to develop a tool with practical utility for HCP and other entities that intend to implement telemedicine solutions. For this, a Markov

Model for chronic obstructive pulmonary disease (COPD) was developed. COPD was chosen as a base case due to its prevalence worldwide and as a result of the growing role of telemedicine in this pathology (World Health Organization, 2020),(Sociedade Portuguesa de Pneumologia, 2019).

Insights on the works carried out in this field, as well as the main results are also presented. In addition, the necessary inputs to perform the presented economic analysis are covered in detail in order to (1) collect data that is as close to reality as possible to test the model and also to (2) comprehend the data that needs to be gathered and the best way to collect it.

This dissertation is organized in 6 chapters. From chapter 1 to chapter 3, the state of the art and the theoretical foundations of the topics addressed are covered. Chapter 4 presents the methodology followed, which includes the description of the Markov model developed, the relevant variables and the input parameters considered. In chapter 5, the results are presented and discussed. Sensitivity analyses on key model parameters as well as a probabilistic analysis were conducted to assess the robustness of the model results. Finally, chapter 6 presents the main conclusions of this dissertation, the goals met, and limitations encountered. Furthermore, future perspectives are also addressed.

2. The role of Telemedicine in COPD

2.1. Telemedicine

According to the World Health Organization (WHO), telemedicine, also referred to as telehealth or e-medicine, consists on “the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities” (World Health Organization, 2012) (Figure 1).

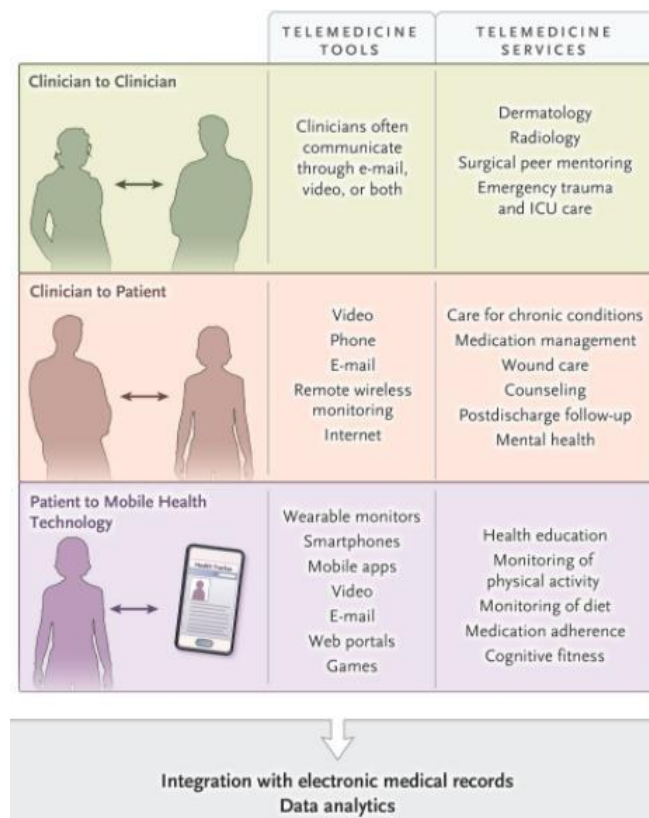


Figure 1. Utilization of telemedicine platform by patients and healthcare providers (from (Tuckson et al., 2017)).

This eHealth system can be classified according to different modalities in synchronous (real-time telephone or live audio-video interaction typically with a patient using a smartphone, tablet, or computer), asynchronous (when one healthcare provider can

share patient information with another healthcare provider) and remote patient monitoring (when there is direct transmission of a patient's clinical measurements from a distance, that may or may not be in real time, to their healthcare provider) (Tuckson, Edmunds & Hodgkins, 2017).

2.1.1. Evolution of telemedicine

Historically, telemedicine can be traced back to the mid to late 19th century, moment from which the radio has been used to give medical advice to clinics on ships. Modern telemedicine started in the 90s, when the military and space technology departments as well as private individuals started to acquire commercial equipment for its development. Examples of early technological milestones in telemedicine include the use of television to facilitate consultations between specialists at a psychiatric institute and general practitioners at a state mental hospital, and the provision of expert medical advice from a major teaching hospital to an airport medical center (Shirzadfar, 2017).

Recent advancements resulted from the rise of the Internet in the 1990s. It was easier and cheaper than ever to build a health care software application for exchanging and storing clinical data, using the existing tools and frameworks for web applications. In 2016, 79% of EU residents between 16 and 74 years old accessed the Internet using a mobile phone or smartphone. Innovations in artificial intelligence and connected wearables and health-related applications have allowed intermittent measurement processes for continuous monitoring and information and communication technologies applied to healthcare promise increasing efficiency, improvement of patients' health-related quality of life and contribution to new developments in health markets (Eurostat, 2016).

In the last decade, as diseases worldwide are increasing, costly health care needs are growing and the demand for health care services is increasing. New delivery models are emerging to address growing chronic care demands and according to the global market insights, telemedicine market size was valued at USD 45 billion in 2019 and is expected to witness 19.3% annual growth rate from 2020 to 2026 (Shirzadfar, 2017),(Ugalmugale & Swain, 2020).

2.1.2. The role of Telemedicine in chronic diseases management

Ageing population and lifestyle-related practices increase the incidence and costs of chronic and noncommunicable diseases, such as cancer, cardiovascular and respiratory

diseases. The need to face increasing citizen requests for welfare and, at the same time, to limit healthcare costs is one of the biggest challenges facing the healthcare systems. In 2019, data from the survey conducted by the National Institute of Health revealed that 3.9 million Portuguese reported having at least one chronic disease (Leonardo Negrão, 2019).

Telemedicine is increasingly seen as a key tool for the monitoring of chronic diseases. A team of researchers, led by Bashshur (Bashshur et al., 2014) from the University of Michigan Health System, reviewed a number of studies focused on the impact of telemedicine on chronic disease care to analyze its effectiveness and found that the majority of studies of telemonitoring for heart failure, stroke, and Chronic Obstructive Pulmonary Disease (COPD) reported lower hospital admissions and re-admissions, length of stay, and emergency department visits. Fewer episodes of health worsening, improved quality of life, and general improvement in clinical, functional, and quality of life status were also reported by some of the studies covered. Telemedicine has already been applied to other chronic diseases such as diabetes, Alzheimer's disease and chronic heart failure (Costanzo et al., 2020),(European Commission, 2018) (Table 1).

Table 1. Benefits and disadvantages of eHealth care for the management of chronic disease (information from (Medical News Today, 2020)).

	Benefits	Disadvantages
Patients	Lower costs	Insurance coverage
	Improved access to care	
	Preventive care	Protecting medical data
	Convenience	Care delays
	Eliminates the risk of picking up an infection at the doctor's office	
Healthcare providers	Reduced overhead expenses	Licensing issues
	Additional revenue stream	Technological concerns
	Less exposure to illness and infections	An inability to examine patients
	Patient satisfaction	

2.1.3. Chronic disease management platform

For the reasons covered in this chapter, Health Cluster Portugal is developing the Chronic Diseases Management Platform (CDMP) for continuous disease management, for more quality of care with less effort and costs and for the ability to generate alerts for clinicians, patients, and informal caregivers. This customizable platform will streamline person-

centered care with artificial intelligent chronic disease management workflows, data integration, broad-spectrum collaboration, patient engagement, and configurable analytics and reporting (Annex 1). Desired features include real-time monitoring of physical and neurologic parameters, medication management and compliance, eating management and diet compliance, neurologic stimulation and evaluation, patient educational materials and tools, data integration with a 360° patient view, data dashboard per patient, customizable alerts for clinicians, patients and caregivers, customizable analytics by patient and population (Health Cluster Portugal, 2020a). COPD is one of the chronic diseases that will be included in this platform.

2.2. Chronic obstructive pulmonary disease

2.2.1. Definition, causes, symptoms, diagnostic and treatment

COPD is characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change significantly over several months. Symptoms of COPD include breathing difficulty, cough, mucus (sputum) production, frequent respiratory infections, and wheezing. While COPD is mainly a chronic disease, a substantial number of patients suffer from exacerbations, which are defined as an acute worsening of respiratory symptoms requiring a change in treatment. Exacerbations are an important medical and healthcare problem, e.g. it is evident that severe exacerbations of COPD are related to a significantly worse survival outcome (Viniol & Vogelmeier, 2018). The disease is predominantly caused by smoking. In addition, frequent inhalation of polluting agents can also cause inflammation in the respiratory system, weakening the mucosa and contributing to the effectiveness of the disease (Johns, Walters, & Haydn Walters, 2014).

COPD diagnosis is confirmed by a simple test called spirometry, which assesses the integrated mechanical function of the lung, chest wall, respiratory muscles, and airways by measuring the total volume of air exhaled from a full lung (total lung capacity [TLC]) to maximal expiration (residual volume [RV]). The criterion for diagnosis defined in guidelines is based on the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC), the forced expiratory ratio (FER) and its severity is based on FEV1 from measurements obtained during maximal forced expiratory manoeuvres (Johns et al., 2014) (Table 2).

Table 2. Classification of the different stages of COPD and conventional therapies (Araujo, 2009), (Abordage, 2016).

Stages	Characteristics	Therapies			
I - Mild	VEF ₁ /CVF < 0.70 VEF ₁ ≥ 80%	Active reduction of risk factors	-	-	-
II- Moderate	VEF ₁ /CVF < 0.70 50% ≤ VEF ₁ < 80%		Add regular treatment with one or more long-acting bronchodilators (when necessary)	-	-
III - Severe	VEF ₁ /CVF < 0.70 30% ≤ VEF ₁ < 50			Add inhaled corticosteroids in case of repeated exacerbations	-
IV- Very severe	50% ≤ VEF ₁ < 0.70 VEF ₁ < 30% or VEF ₁ < 50% plus chronic respiratory failure				In case of respiratory failure add long-term oxygen and consider surgical treatments.

Nowadays, a combined COPD assessment tool is used to incorporate patient-reported outcomes and to highlight the importance of exacerbation prevention in the management of the chronic disease. Besides undergoing spirometry to determine the severity of airflow limitation, the number of exacerbations that the patient suffered in the last year are considered, and the dyspnea symptoms are assessed through Modified British Medical Research Council (mMRC) and a comprehensive assessment of other symptoms is conducted through COPD Assessment Test (CAT) (Global Initiative for Chronic Obstructive Lung Disease, 2017) (Figure 2).

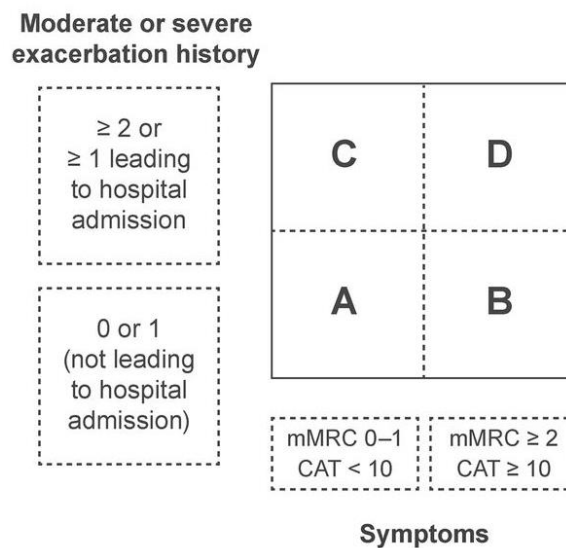


Figure 2. ABCD assessment tool, adapted from (Lange et al., 2012).

2.2.2. COPD prevalence in the world and in Portuguese Population

COPD has considerable impact on the quality of life of the patient, involving long term medical care, frequent hospital admissions for treatment of exacerbations and, often resulting in premature death (The National Collaborating Centre for Chronic Conditions, 1995).

In 2020, COPD was the third most common death cause worldwide (World Health Organization, 2020) (Figure 3A). According to the Portuguese Society of Pneumology, this disease affects around 800 thousand Portuguese and is the third leading cause of death in the world over the past years (Figure 3B). The prevalence of COPD in individuals over 40 years of age is around 14%, and for moderate, severe, and very severe COPD the prevalence is approximately 7% (Sociedade Portuguesa de Pneumologia, 2019),(Vos et al., 2020).

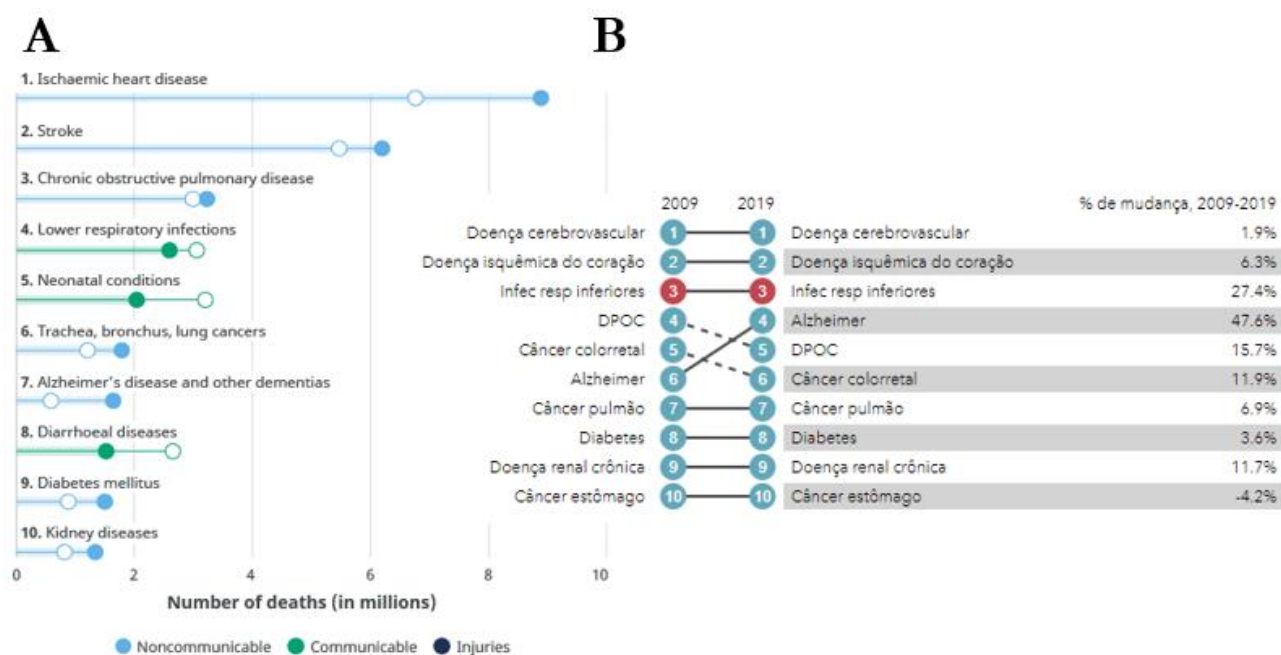


Figure 3. Top 10 causes of death (A) worldwide (World Health Organization, 2020) and (B) in Portugal (Vos et al., 2020).

3. Economic evaluation of telehealth technologies

As COPD is a major cause of morbidity and mortality worldwide, it results in an economic and social burden that is both substantial and increasing (Qureshi et al., 2014). Telemedicine has been suggested as a possible effective intervention to patients with COPD, especially in what concerns the quality of life and the reduction of hospital contacts (McLean et al., 2012). Hence, Health Economics has been applied to aid decision making in this field (Sonnenberg & Beck, 1993).

3.1. Types of economic evaluation

Health economists are concerned with evaluating choices about the best use of scarce healthcare resources. Economic evaluations provide decision-makers with structured, rigorous evidence for assessing the relative efficiency of competing healthcare interventions and can be divided in cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost benefit analysis (CBA), and cost utility analysis (CUA) (Klarenbach, Tonelli, Chui, & Manns, 2014) (Table 3).

Table 3. Types of economic evaluation and their characteristics (Drummond & Stoddart, 2015),(Drummond, 1987).

Type of Evaluation	Costs considered	Health considerations	Strengths	Important issues
CMA	All present and future health-care costs relevant to the patient and to the disease state are	No difference in health status attributable to disease or treatment strategies is assumed.	Requires minimal data (on costs only). Enables assessment of the technical efficiency of each strategy.	Assumption of identical outcomes of disease and the treatments compared should be robust.
CBA		The health benefits of an intervention is also expressed in monetary units.	Allows comparison between interventions with multiple effects / objectives (common or distinct) and allows	Monetary quantification of costs, and particularly of benefits, can be

	compared for each therapeutic strategy		comparison with the hypothesis of doing nothing (information is obtained about the absolute benefit of the Intervention).	extremely difficult.
CEA		Uses commonly evaluated health outcomes, including clinical or surrogate outcomes, such as blood pressure, renal function	Relates costs of treatment with therapeutic effectiveness based on health outcomes that are readily available from clinical trials	The “cost per unit of health” values can be difficult to interpret. Effectiveness outcome may not capture all relevant health outcomes.
CUA		Health status is transformed into a quality adjusted life year (QALY) score anchored between 0 (death) and 1 (perfect health). All aspects of disease and its treatment are captured in one metric.	The metric comprehensively measures health, enabling benchmarking and comparisons of outcomes among disparate populations and diseases.	Cost-utility analyses require the greatest amount of data of all the mentioned types of economical evaluation. Assumptions might be required when estimating health-related quality of life.

Regarding the costs considered to carry out an economical evaluation, different classifications have been used over the years. The first classification proposed by Drummond et al. (1987) included direct (mostly from the health sector and other governmental agencies or voluntary organizations), indirect (productivity losses), and intangible costs (Drummond, 1987). The most recent classification, from 2015, includes costs in the healthcare sector (medicines, equipment, hospitalizations, visits to doctors), costs in other sectors (for

example, programs for elderly or mentally ill patients and other public entities, such as social assistance) and patients and families related costs (expenses with trips to hospitals, co-payments, expenses at home and spent time) (Drummond & Stoddart, 2015).

Economic evaluations in healthcare can be conducted using different perspectives, which is the point of view adopted when deciding which types of costs and health benefits are to be included. Typical viewpoints include the typical health plan enrollee, the patient, the health plan manager, the provider, the technology manufacturer, the specialty society, the payer (public or private), or society as a whole (Byford & Raftery, 1998),(Garrison, Pauly, Willke, & Neumann, 2018).

3.1.1. Cost-utility analysis

When evaluating interventions aimed at reducing the burden of chronic diseases, the primary objective may not be improving survival but rather improving patient functioning in terms of mental state and physical abilities. Hence, CUA has been increasingly used. In the literature CUA analysis is sometimes referred to as cost-effectiveness evaluation (Fenwick, Marshall, Levy, & Nichol, 2006),(Cohen & Reynolds, 2008).

The value of a health outcome for an individual is calculated as the product of two factors: the increase in quality of life (utility) and the number of years in which this improvement occurs. This value corresponds to QALY (qualityadjustedlifecycleyears). The utility can be obtained through different methods (Dawoud & Baines, 2017):

1. Indirect methods (among which the EuroQoL - EQ5D and the SF-36 are the most used surveys and allow to evaluate different dimensions of quality of life that correspond to a state of health).
2. Direct methods (such as the visual analogue scale method, where the patient ranks his health status from 0 – that corresponds to the worst imaginable health state - to 100 – that corresponds to the best possible health state. Other direct methods include Standard Gamble (SG) or the Time Trade-Off and person trade-off.

To perform the cost-utility analysis, the cost-utility ratio is calculated: it corresponds to the ratio between the cost of an intervention and the utility of that intervention (QALYs). In the case of mutually exclusive alternatives and in order to compare the alternatives, the incremental cost-utility ratio (ICER) is calculated, thus obtaining the marginal increase (Walker, Sculpher, & Drummond, 2011) (equation 1).

$$ICER = \frac{\text{Costs A} - \text{Costs B}}{\text{Effects A} - \text{Effects B}} = \frac{\Delta \text{Costs}}{\Delta \text{Effects}} \quad (1)$$

Decision making about the alternative to adopt is dependent on the relationship between the ICER value and the maximum limit of willingness to pay per QALY earned (Dernovsek, Prevotnik-Rupel, & Tavcar, 2007). No single threshold exists for deciding whether or not a ICER ratio is acceptable. A variety of considerations including the prosperity of a nation NHS can determine the willingness to pay.

In Portugal, although INFARMED does not have a formally fixed amount, it considers 30,000 €/QALY as acceptable for reimbursement (Tribunal de Contas, 2011). However, according to the methodological guidelines of Portugal for economic evaluation studies of health technologies support contract negotiations, all analyses submitted by the company must calculate the opportunity costs using cost-effectiveness threshold ranges between 10,000€ per QALY and 100,000€ per QALY (Perelman et al., 2019),.

3.1.2. Markov model

Markov models are state transition models commonly used to estimate the cost-effectiveness of a new intervention. The model assumes that the patient is always in one of a finite number of states of health referred to as Markov states. All events of interest are modelled as transitions from one state to another. In Markov chain models, the probability to move to a new state (s_{t+1}) only depends on the current state (s_t), and not on any previous state, where t is the current time. This property can be expressed by equation 2 (Komorowski & Raffa, 2016).

$$P(s_{t+1} | s_1, s_2, \dots, s_t) = P(s_{t+1} | s_t), \quad (2)$$

Each state is assigned a utility and a cost, and the contribution of these parameters to the overall model depends on the length of time spent in the state (equation 3).

$$\text{Expected utility} = \sum_{s=1}^n t_s \times u_s, \text{ where } u_s \text{ and } t_s \text{ are the utility and time spent on state } s, \quad (3)$$

The time horizon of the analysis is divided into equal increments of time, referred to as Markov cycles. Throughout each cycle, the patient can make a transition from one

state to another, depending on the model structure (Sato & Zouain, 2010b),(Sonnenberg & Beck, 1993).

Cohort simulation models initiate at the moment 0 with a hypothetical population in an initial state. For each cycle of the model the transition probabilities are applied and the distribution of patients in each state is adjusted. For a Markov model of n states, there are n^2 possible transition probabilities (depending on the transitions between stages included in the model) that can be represented by an $n \times n$ matrix.

The execution of several cycles determines the profile of how many patients exist in each state of the model throughout time as demonstrated in (Figure 4) (Sonnenberg & Beck, 1993),(Sato & Zouain, 2010a).

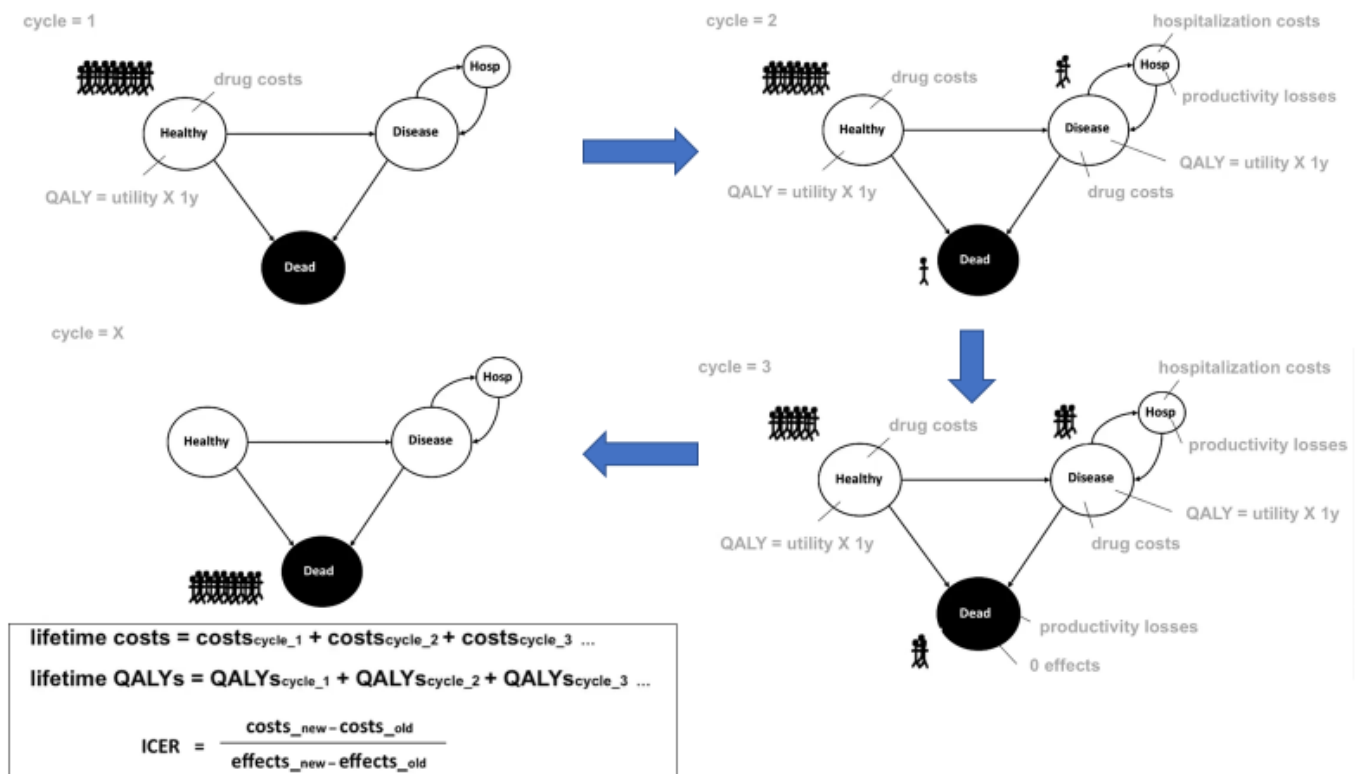


Figure 4. Example of Markov Model for Cost-Effectiveness Analysis (Hut, 2018).

Markov chains can include deterministic and probabilistic models. In deterministic models a single scenario is considered since every set of variable states is uniquely determined by parameters in the model and by sets of previous states of these variables (Navarro, Parker, & White, 1970).

On the contrary, probabilistic models incorporate quantitative information about uncertainty. Probabilistic analysis generates pseudorandom variables from a

continuous random variable, with probability density proportional to a known function (A. J. Hatswell, Bullement, Briggs, Paulden, & Stevenson, 2018), (Sato & Zouain, 2010b). Some distributions are more suitable for certain parameters because of their natural features, for example cost parameters are always positive, hence gamma distributions are a good fit. On the other hand, beta distributions values range from 0-1, thus being suitable for transition probability and utility values in the model (Graves et al., 2016).

The simplest way to perform probabilistic sensitivity analysis (PSA) is by Monte Carlo Simulation. This method is often used for healthcare economic studies to obtain a large number of representations of a stochastic process (Zhukova, 2019). Rather than start a whole cohort of patients through the model together, a large number of patients are followed through the model individually. PSA is required by many health technology assessment (HTA) agencies internationally, such the UK's National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) (Hatswell et al., 2018).

Each unique set of inputs results in a unique set of model outputs. Pondering the results of many interactions allows for estimation of the expected (mean) model outputs and the uncertainty around these outputs (Briggs & Gray, 1999).

Since PSA requires random sampling from distributions, the parameter inputs will differ each time the PSA is repeated (Baio & Dawid, 2015). Usually it is recommended to perform between 1,000 – 10,000 simulations for decision making, which gives suitably stable mean results without excessive computational burden (Hatswell, Bullement, Paulden, & Stevenson, 2017).

Model Validation for Cost-Effectiveness Analysis

The ICER scatterplot is a 2-dimensional graph used to visually demonstrate the cost-effectiveness of all the different ICERs generated from the iterations defined for the PSA (Figure 5). The new intervention under study will locate to the right or left of the origin if they are more or less effective than the current standard of care, and above or below the origin if they are more or less costly (Cohen & Reynolds, 2008).

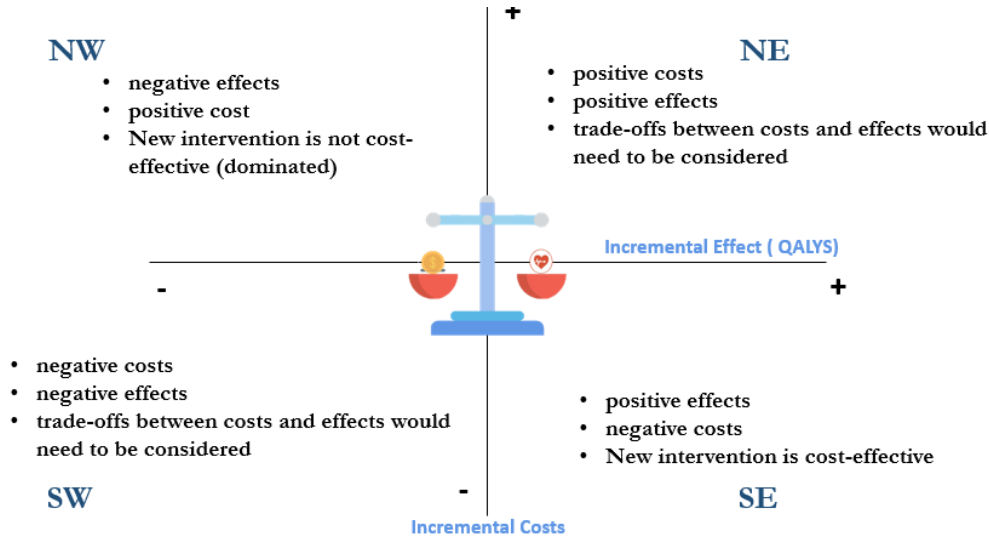


Figure 5. Cost-effectiveness plane (NW: northwest , NE: northeast, SW: southwest , SE: southeast).

Whether a strategy is cost-effective depends on the proportion of the point estimates generated by the Monte Carlo simulation that fall in the cost-effective part of the plane. A single-figure summary is usually expressed using the concept of net monetary benefit (NMB) which represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit is known. A new intervention is considered cost-effective if the NMB is superior to the NMB of the usual treatment (4).

$$\text{NMB} = (\Delta \text{ Effectiveness} \times \text{willingness to pay threshold}) - \Delta \text{ Costs} \quad (4)$$

The NMB is often used to construct cost-effectiveness acceptability curves (CEAC) which illustrate the probability that an intervention is cost-effective compared with the alternative for a range of thresholds that a decision-maker might be willing to pay for a particular unit of outcomes (Figure 6) (Charles & Edwards, 2016) (Baio & Dawid, 2015) (equation 5).

$$\text{Prob NMB}_{\text{new intervention}} > 0 \quad (5)$$

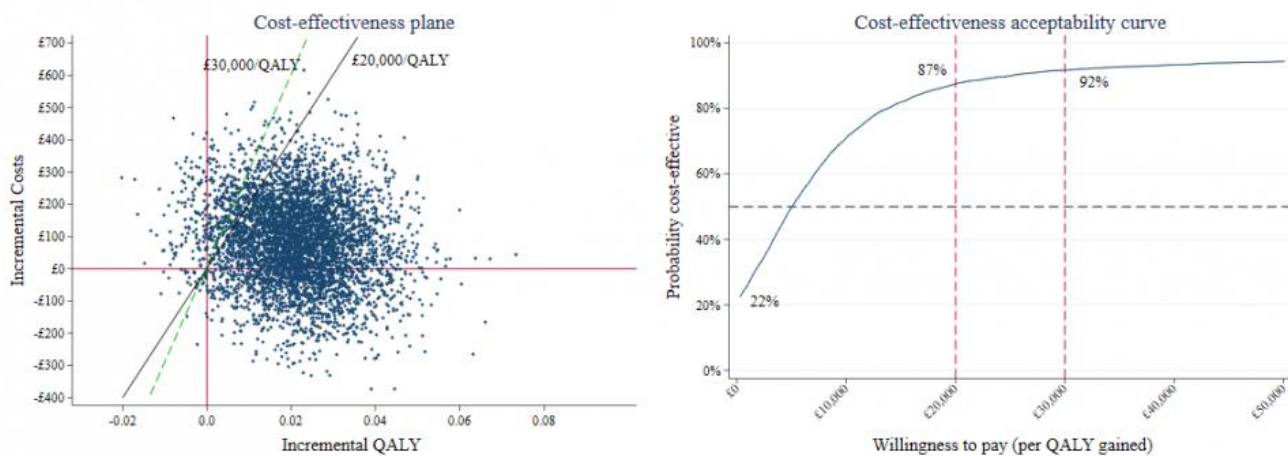


Figure 6. Cost-effectiveness plane and cost-effectiveness acceptability curve. Each dot from the ICER scatter plot represents the results from one sampling (Li et al., 2018).

3.2. Economic analysis of the implementation of telemedicine for COPD

Most published works that focuses on the economic analysis of COPD use cost-effectiveness methodology to compare the alternatives of 1) usual practice for treating, monitoring, and caring for patients, which involves the responsibility of the patient's general practitioner (treatment and monitoring) and that of the municipalities (practical help and nursing care) and 2) the application of a telehealth equipment. The results in terms of the adjusted mean difference in QALYS between telehealth care and usual care range from 0.003 to 0.08, while the cost per QALY gained ranges from 55 327 € to 227 323 € (Table 4). Thus, according to these studies the application of a technological based treatment for the monitoring of COPD is unlikely to be cost-effective for all patients with COPD. For this reason, the reported telemedicine solutions target COPD patients in more aggravated states (Table 4). When interpreting small differences in effectiveness, it is important to be aware that results can be highly sensitive to between-group differences in death. It is standard practice to assign an EQ5D summary score of 0 to deceased patients to calculate incremental QALYs. Furthermore, the calculated utility is intrinsically dependent on the used method. There are studies in which patients' utility has been calculated using the St George's Respiratory Questionnaire for COPD patients (SGRQ-C), in addition to the conventional EQ5D method. SGRQ-C comprises three domains encompassed in two parts: Part 1, which concerns the symptoms component, addresses the frequency of respiratory symptoms; and Part 2, which encompasses the Activity and Impact components, which

address the patient's current state. The activity component measures disturbances in daily physical activity, while the impact component covers disturbances in psychosocial function. Each answer has a “weight” that varies between 0 and 100 (Marlene, Barros, & Silva, 2012). EQ-5D utility values can be extrapolated using SGRQ results, through reported algorithms (Starkie, Briggs, Chambers, & Jones, 2011).

According to the revision conducted, the high cost of implementing a telehealth solution is mainly associated with the service costs (computer hardware and peripherals and monitoring of signs) (McDowell, McClean, FitzGibbon, & Tate, 2015). However, with technological development and increased access to the Internet by the population, the implementation of telemedicine solutions is becoming more profitable as cost of equipment continues to fall and network connections become cheaper (Schaafsma, Pantazi, Moehr, Anglin, & Grimm, 2007).

As already discussed, in addition to seeking to increase the patient's quality of life, telemedicine platforms also aims to reduce the costs associated with their care. However, it is sometimes challenging to detect a significant disparity in costs between the two interventions. This is mainly because the studies carried out are not prolonged enough to allow a significant difference in hospital contacts, and because as COPD patients usually suffer from other comorbidities it is difficult to limit hospital contacts to COPD-specific contacts (Table 4). In Portugal, a pilot study conducted from 2014 to 2015, showed that the telemonitoring of COPD patients reduced the number of hospitalizations by more than 70%, and the number of trips to the emergency department decreased by approximately 60%. Considering the costs of the platform service, total costs were reduced by 26% (Gonçalves, Castelo-Branco, & Campanella, 2013). A more recent study from 2019, performed a CBA and concluded that the benefits of telemonitoring by only one nurse, outweighs the costs in a sample of 61 users (saving 165.27 €/user/year) (Filipe, 2019).

One can also argue that disease integrated management programs encourage patients to assume greater responsibility for their own care, thus actively involving them in improving their health. The work of Bourbeau et al. (Bourbeau et al., 2006) showed that self-management interventions would be cost saving relative to usual care (cost saving of 1815.74€ per patient). Moreover, integrated care intervention based on shared care arrangements among different levels of the system with support of information technologies can effectively prevents hospitalizations for exacerbations in COPD (Craig & Patterson, 2005). Telehealth is a key component in future integrated care as clinical

pathways and service delivery processes are fully coordinated and patient data shared.

Thus, the literature does not seem to be consensual within the scope of the economic evaluation of telemonitoring for COPD. Different and new approaches to analyze the implementation of telemedicine solutions in patients with DCPO are needed.

As previously explained, other possible modelling methodology for cost-effectiveness analyses are the so-called Markov models (Einzinger, Leskovaar, & Wyrzens, 2012). To our knowledge, there is only one work in which a Markov model is applied to compare the usual care of COPD patients with an intervention with telemonitoring (Hofer, Achelrod, & Stargardt, 2016). Telemonitoring led to incremental costs (866€ per patient) and QALYs (0.05 per patient) (Hofer et al., 2016) (Table 4).

However, several works aim to compare the current treatment with other different medicines/therapies (Zafari et al., 2017). As the cycle duration is supposed to have a clinically meaningful significance, COPD models cycle usually have the duration of 1-3 months (van Boven et al., 2014),(NICE guideline, 2019) or 1 year (Hofer et al., 2016), which in Portugal is the normal period for repeating the spirometry test and subsequent reclassification in the GOLD states (Serviço Nacional de Saúde 2013).

Table 4. Summary on studies that focus on the CUA of COPD. Research carried out in 2020 with the following keywords and search engines: obstructive pulmonary disease, telemedicine, economic analysis, cost-benefit, cost-effectiveness, cost-utility; Google Scholar, Science Direct (Elsevier), Scientific Electronic Library Online (SciELO), PubMed, b-on.

Local where the study was conducted	Duration	Year	Telehealth solution	Equipment	COPD patients covered by telecare	Adjusted mean difference in QALYs gained	ICER (€/QALY)	Willingness to pay per QALY (€)	Sample	Perspective used	Ref.
Denmark	12 months	2017	- Patients were monitored asynchronously by a nurse daily. Measurements were classified with either a green, yellow, or red code (green code: no threshold values were exceeded; yellow code: one or more values exceeded the threshold values; red code: one or more values exceeded the threshold values and had not previously been recorded). The nurse had the option to contact the patient by telephone and/or the patient's general practitioner and/or dispatch an ambulance.	- Standard <u>tablet</u> (Samsung Galaxy) - The tablet can collect and wirelessly transmit data on blood pressure, pulse, blood oxygen saturation and weight via an attached <u>Fingertip Pulse Oximeter</u> , a <u>digital blood pressure monitor</u> , and a <u>scale</u> .	- applied to COPD patients classified as D (at least two exacerbations within the past 12 months, (mMRC)≥2 or mMRC≥3 and CAT Test≥10).	0.0132	55 327	the Danish Centre for Health Technology Assessment reports that there are no generally applicable limits concerning what can be considered a reasonable QALY price.	Ten out of 11 municipalities in the North Denmark Region are included in the study (1225 participants).	healthcare care and social sector perspective	(Flemming Witt Udsen, Lilholt, Hejlesen, & Ehlers, 2017), (Flemming W. Udsen, Lilholt, Hejlesen, & Ehlers, 2014)
England		2013	- Participants used telemonitoring equipment to collect and transmit vital signs data. These data were classified into risk related	- Patients were expected to have or to arrange for a telephone line, power points, and electricity. - Telehealth equipment	Participating practices were eligible for study inclusion if they were 18 years or	0.012	102 568		3230 participants		(Catherine Henderso n et al., 2013)

			alerts (for example, using a traffic light system), according to parameters that would be set initially based on clinical guidelines or by a clinician responsible for the patient's care.	included a <u>base unit</u> (freestanding or a television set top box) and peripherals such as <u>weigh scales</u> , <u>pulse oximeters</u> , <u>blood pressure cuff</u> , and <u>glucometers</u> .	older, with at least one of three long term index conditions (chronic obstructive pulmonary disease, heart failure, or diabetes).			22,000–33,000			
England		2015	The action taken was the responsibility of the monitoring clinician who normally knew the patient and was able to interpret the monitoring data in the light of the past history. Typically, this involved contacting the patient by telephone and undertaking a further clinical assessment to enable a decision about further management (e.g. rescue medication, a home visit, immediate admission, reviewing the following day).	- The equipment included a <u>touch-screen</u> interface with which participants were asked to complete a daily symptoms and medication use questionnaire from which a validated symptom score was generated. - This information and the <u>oxygen saturation</u> and <u>pulse</u> rate were transmitted by secure Internet connection to the clinical team.	- Patients were eligible for the trial if they had been admitted to hospital with an exacerbation of COPD in the previous year and were thus at risk of future admissions.	0.0033	153 046		256 patients	healthcare care sector perspective	(Stoddart et al., 2015)
Ireland	6 months	2015	The daily data were transmitted via the telephone line to a server and downloaded by Home Telehealth Ltd (HTL). A	Telehealth monitor uploaded to record vital signs (blood pressure, heart rate, SaO2) and answers to questions	- Diagnosis of moderate to severe COPD (GOLD stage 2 or 3), and at	0.08	227 323	45 000	110 patients		(McDowell et al., 2015)

			dedicated HTL nurse reviewed the daily data within 10 min of its arrival and compared it to the set normal limits. An alert indicated that one or more of the patient's clinical observations was outside the set normal limits or the patient had answered 'yes' to a question relating to their symptoms. Following an alert the HTL nurse contacted the patient to obtain additional information, advised the patient to sit down and relax for 30 min and to repeat the monitoring.	relating to symptoms.	least two of: emergency department admissions, hospital admissions or emergency GP contacts in the 12 months before the study.						
Spain	4 months	2014	The clinical response was the result of communication between the clinical call centre staff, the case manager and a specialist in respiratory medicine.	- Telehealth equipment includes a spirometer, a pulse oximeter, a heart rate and blood pressure monitor.	An adult patient with a diagnosis of COPD and chronic respiratory failure with long-term oxygen therapy indication according to international guidelines; at least one hospitalization for respiratory ill-	0.0053	223 726	21,000 -24,000	45 patient s		(Jódar-Sánchez et al., 2014)

					ness in the previous year; and being clinically stable during the previous three months.						
Germany	Cycle = 1 year Time horizon = 20 years	2016	Hypothetical solution based on the literature			0.05	17,410	8,580€ - 18,420€	46,924,000	German statutory sickness funds	(Hofer et al., 2016)

4. Methodology

4.1. Model structure

For this project, a Markov model was developed to conduct a cost-effectiveness study.

The model was used to simulate an economic analysis comparing the conventional treatment of COPD patients by the Portuguese NHS with an intervention in which the CDMP technology is implemented, from the perspective of the NHS. Both the model's structure and the practical usefulness of the project presented were improved and validated through the collection of feedback from professionals in the field (Annex 2).

The model structure is similar to that of a Markov cohort model, with five main health states: GOLD I , GOLD II , GOLD III and GOLD IV reflecting the severity of COPD (Norm nº 005/2019, (Serviço Nacional de Saúde, 2021b)) and a state for death (absorbing state, which is a state in the model from which it is technically impossible to move out). Each cycle will have the duration of one year since this is the normal period for the repetition of the spirometry test for COPD patients and subsequent reclassification. A schematic representation of the model structure is shown in Figure 7.

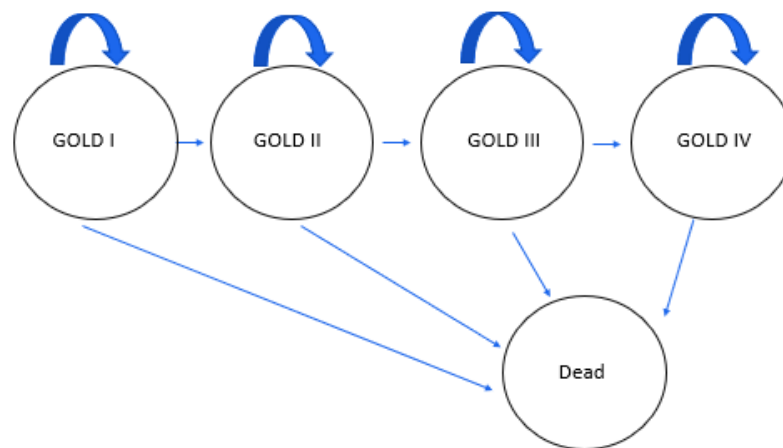


Figure 7. Markov model structure for COPD.

The program for the presented study design and intervention was achieved by using Microsoft Excel (Microsoft 365). A representation of the model structure in TreeAge software, tool for building decision trees, Markov models and event-based simulations, is also presented in Annex 3.

4.2. Data inputs

The data required for the model is summarized in Table 5. Regarding the costs of conventional treatment of COPD patients, those linked to external consultations and to the episodes of hospitalization and urgency were consulted in information provided by NHS integrated services (Annex 4). The quantity of hospital contacts, the patients general and clinical data was requested to the Ethics Committee of HSJ (3.2.1).

As regards to the costs of the telemedicine intervention, in addition to the costs of conventional treatment of COPD patients, hypothetical costs of implementing the CDMP were considered and additional data relevant for future analysis was provided to HCP (3.2.2).

The utility and transition probabilities of both NHS and NHS + CDMP interventions will be based on the reviewed works (3.2.3).

Table 5. Input parameters for the Markov model.

Conventional Intervention (NHS)			Incorporation of telemedicine platform (NHS + CDMP)		
Costs	Utility	Transition Probabilities	Costs	Utility	Transition Probabilities
- “Acordo modificativo ao contrato programa” (2020) for HSJ. - Request for Reuse of Clinical Records for Research and Development to HSJ.	- Request for Reuse of Clinical Records for Research and Development to HSJ - Expert opinion - Based on data available from the literature	Based on data available from the literature	- Conventional treatment costs. -Platform implementation costs (based on data from the literature).	Based on data available from the literature	

4.2.2. Data collection request to Hospital São João

For the collection of relevant data for the present work, it was necessary to fill in a “Request for Reuse of Clinical Records for Research and Development (I&D)” and a “Questionnaire for Research Submission” and submit it to the Ethic Committee of HSJ (Annex 5). The information’s requested included:

- Inpatient episodes for patients with COPD (ICD 10 coding - J44) during the period of January 2009 and December 2019 with the respective patient code (to be able to track patients over time, thus analyzing

changes in associated costs and other indicators related to clinical status and quality of care life).

- GDH associated with each hospitalization and severity of exacerbations.
- External consultations, hospitalizations, urgency episodes (to be obtained through codes of patients who were hospitalized) and exacerbation episodes without hospitalization.
- Gender, year of birth, marital status and city of residence.
- Date of diagnosis.
- Smoking status.
- Other comorbidities (diabetes ICD 10 - E11, lung cancer ICD 10 - C34, hypertension ICD 10 - I10, heart failure ICD 10 - I50, sleep apnea ICD 10 - G47.3 and depressive episodes ICD 10 - F32).
- GOLD classification (I-IV, A-D).
- Quality of life (St. George's Respiratory Questionnaire (SGRQ)).
- Bode Index.
- Physical activity (yes/no).
- BMI, weight, height.
- FEV1.

Before obtaining permission (Annex 6), a protocol for data collection had to be developed in collaboration with the director of the Pneumology Service (Dr. Venceslau Hespanhol), the Liaison Professional (Dr. Pedro Ferreira from the Pulmonology Service) and the Director of Clinical Coding Service of HSJ (Dra. Lucybell Moreira).

In a first phase, the ICD 10 codes of several patients with COPD (ICD10 – J44) (Serviço Nacional de Saúde, 2021a) were collected through the hospitalization episodes. Considering that most of these admissions are carried out in the Internal Medicine Service, the agreement of the Director of this Service was also requested (Dr. Jorge Almeida). Subsequently, together with the Dr. Pedro Ferreira a representative sample of 50 patients was selected. For these patients, the remaining data mentioned was collected using the SClínico information system, with the exception of the quality of life. Although there is a tendency to use the SGRQ questionnaire in consults, it is still not routinely applied.

4.2.3. Data requested to Health Cluster Portugal

In order to contribute to the value proposition of the CDMP, not yet in use, the theoretical telemedicine related parameter inputs were set to be as close as possible to its future implementation. To achieve these, several parameters must be defined by the HCP:

- To which groups of COPD patients, the telemedicine solution will be implemented.

- The business model in order to know how the CDMP will be sold to the NHS, the associated cost per patient and the availability of packages and maintenance and support costs (Annex 7).
- The equipment's and sensors to be used (usually a computer, mobile phone, blood pressure meter, scale and oximeter are used) in order to consider the lifespan.
- The type of data that will be collected and provided by the platform and instructions for its use (for example: daily data collection using sensors and surveys on the patient's health status). The information included in the platform (such as clinical data, curiosities, nutritional follow up, physical activity exercises, alerts, among other). Besides this information, the functioning of platform (interface with the patient / doctor / nurse / other health care providers, data storage and treatment) is also important to compare to previous implemented telemedicine solutions and to compare the results obtained.
- The professional work that would be needed (time that would be required for each monitored patient).

4.2.4. Data based on the state of the art

As previously stated, studies in which a Markov model is used to conduct an economic analysis to compare the conventional treatment of COPD patients with an alternative with telemedicine technology are still very scarce. Although there are few studies that perform a direct cost-utility analysis, in Portugal, there are still no published works in this area. In addition, there are essential parameters to the model that are not yet collected and treated in a systematic way. Thus, the available studies were used to gather information and attribute values to the input variables of the model.

Costs

The costs regarding the NHS were based on the data requested from HSJ and included the mean number of consultations, hospitalizations episodes, emergency episodes and exacerbations without hospitalization. Hence, for each GOLD stage, the total costs were calculated as follows (equation 5):

$$\begin{aligned} \text{Total Costs} = & \text{Mean n}^\circ \text{ of consultations} \times 75\text{€} + \text{Mean n}^\circ \text{ of hospitalizations} \times \\ & \text{Hospitalization costs} + \text{Mean n}^\circ \text{ of emergency episodes} \times 100\text{€} + \text{Mean n}^\circ \text{ of} \\ & \text{exacerbations without hospitalizations} \times 288.74 \text{ €} \quad (5) \end{aligned}$$

In the present work, it was considered that the NHS costs are the values defined in the “contracto-programa”. According to the HSJ “contrato-programa, 2020”, the cost per subsequent consultation is 75 € (the first referenced consultation is carried out in the year in which the patient is diagnosed, which will not be considered for analysis as it does not represent complete cost/year information). In the case of inpatient costs, the corresponding values were assumed to be those of the Diagnosis Related Group (DRG) used for COPD, corresponding to severity grades 1,2,3,4 (GOLD I: 1 070.07 €; GOLD II: 1 436.81 €; GOLD III: 2 144.08 €; GOLD IV: 4 258.78 €). It was also considered that the costs of exacerbations without hospitalization correspond to the outpatient price (288.74 €) (Ministério da Saúde, 2018). In the case of the emergency service, the cost of an episode was considered to be the price per episode in a polyvalent emergency service. In other words, knowing that the average expected volume of activity in this emergency department is 170,000 episodes and the value attributed for service availability is 17,000,000 € a price/cost per episode of 100 € is considered.

The data used from HSJ and the total costs consired from each GOLD stage are shown in Table 6.

Table 6. Data used to calculate healthcare costs for the usual care

HSJ data \ GOLD stage	GOLD I	GOLD II	GOLD III	GOLD IV
Mean of n° of external consultations	2	15.27	15.5	20.4
Standard deviation	0	8.91	7.41	4.71
Mean of n° of emergency episodes	13.5	6.72	7.37	8.7
Standard deviation	14.84	8.58	9.069	4.16
Mean of n° of hospitalizations	2	1.81	2.5	4
Standard deviation	2.82	1.43	2.22	2.67
Mean of exacerbations without hospitalization	0	5.45	4.81	8.3
Standard deviation	0	5.05	3.54	4.9
N	2	22	16	10
Total costs	3 640.14 €	5 991.51 €	8 573.54 €	21 831.66 €
Standard deviation	15.11	13.44	12.43	8.40

Regarding the costs of the telemedicine platform, as HCP is still developing their business model for CDMP, a review was made of the costs that these platforms normally

have for the NHS. However, costs associated with telehealth solutions greatly differ. In a work carried out in 2009 in Italy (Vitacca et al., 2008), total annual costs of telemedicine intervention (with equipment's and call center costs) were 948 € per COPD patient. In Ireland (McDowell et al., 2015), the cost of telemonitoring per patient was estimated at £10.12 per day, or £1 847 per patient over the 6-month study period (2015). In the same year, studied conducted in Scotland (Stoddart et al., 2015) and Germany (Haesum et al., 2012) stated that annual total telemonitoring service costs were £568.65 and 677 €, respectively. Other values have also been reported in the works of Jódar-Sánchez based in Spain (2014) (Jódar-Sánchez et al., 2014) and Henderson et al., (2013) based in England (Henderson et al., 2013) in which the average total costs for patients treated with telehealth was 2 300 € and £1 847, respectively. In Portugal, an economic analysis of a DPOC telemonitorization pilot project carried out in 2019 stated that the monthly cost per user is 93 € (Filipe, 2019).

Thus, the yearly value set for the simulation was based on the mean of the above studies. All prices/costs were inflated or deflated to reflect 2021 costs (Table 7) according to the inflation timelines in each country, using the formula (equation 6):

$$FV = PV (1 + i)^n \quad (6)$$

, where FV is the future value, PV is the present value, i is the interest rate (inflation) and n the number of times the interest is compounded (i.e. n° of years)

Table 7. Telemedicine costs of different published works, inflated costs to reflect 2020 costs, mean and standard deviation used for model simulation.

Source	Country	Year	Total costs/year	2021 costs	2021 costs in EUR	Mean	Standard deviation
(Vitacca et al., 2008)	Italy	2009	948 €		1 083.82 €		
(McDowell et al., 2015)	Northern Ireland	2015	£3693.8	£4 070.60	4752.42 €		
(Stoddart et al., 2015)	Scotland	2015	£568.65	£626.66	731.62 €		
(Catherine Henderson et al., 2013)	England	2013	£1847	£2 065.94	2 411.98 €		
(Haesum et al., 2012)	Germany	2015	677 €		735.76 €	1 893.36 €	1344.40
(Jódar-Sánchez et al., 2014)	Spain	2014	2 300 €		2 414.24 €		
(Filipe, 2019)	Portugal	2019	1 116 €		1 123.69 €		

Note: Pordata was used to obtain the inflation rate over the years (data available from 1997-2020) for the different countries. 2021 inflation rates were based on forecasts provided in Statistica Portal.

According to pooling results and published works, telemonitoring is estimated to significantly reduce the number of hospitalizations and emergency attendances due to an exacerbation (Hofer et al., 2016),(Udsen et al., 2014) (Annex 8). However, these savings could be offset by other costs such as more visits to general practitioners, community care, medicine consumption (Annex 8). In fact, telemedicine interventions are recurrently associated with an increase in the overall costs ($13.47\% \pm 1.92$). On the other hand, same authors registered a decrease of the healthcare costs when using a telemedicine approach (21.23%) (Table 8).

Table 8. Total healthcare costs, excluding telemedicine related expenses, reported in the literature.

Total healthcare costs / year			
Usual care	7 239.80 €	9 727.22 €	1 380.30€
Usual care + telemedicine	8 076.00 €	11 224.47 €	1 138.60€
Increase in costs with telemedicine (€)	836.20	1 497.25	- 241.70
Increase in costs with telemedicine (%)	11.55	15.39	-21.23
Source	(Flemming Witt (Stoddart et al., (C. Henderson Udsen et al., 2017) 2015) et al., 2013)		

Nevertheless, the study trials presented have a duration of 12 or less months, which may not be enough to register significant changes in healthcare costs. A study conducted in Portugal with 12 COPD patients for 3 years, showed a 50% reduction in hospitalizations and a 30% reduction in emergency episodes, compared to non-telemonitored patients (Sistema Nacional de Saúde, 2017).

Thus, three alternatives for the healthcare costs (excluding the telemedicine related expenses) were included in the model: 1) NHS + CDMP = NHS, 2) NHS + CDMP > NHS (increase of the overall costs with the platform of 13.47%), and 3) NHS + CDMP < NHS (reduction of the overall costs with the platform costs as a result of a reduction in emergency episodes and hospitalizations).

Utility

There are some works conducted in Portugal in which the quality of life of COPD patients was evaluated using the SGRQ (Table 9).

Table 9. Quality of life of COPD Portuguese patients. Note: the published works present the quality of life according to SGRQ results. The SGRQ total scores were transformed to EQ-5D utilities using the algorithm developed by Starkie et al. (Starkie et al., 2011).

Quality of life (SGRQ)	Quality of life (QALYs)	Sample Description	Reference
43.97+19.54	0.711	n=50 GOLD I: 2% GOLD II: 30% GOLD III: 32% GOLD IV: 36%	(Farias & Martins, 2015)
50.60	0.639	n= 45 patients GOLD I: 5.4% GOLD II: 21.6% GOLD III: 21.6% GOLD IV: 51.4%.	(R. Carneiro et al., 2010)
GOLD I: 30.33 GOLD II: 52.41 GOLD III: 58.59 GOLD IV: 64.85	GOLD I: 0.830 GOLD II: 0.619 GOLD III: 0.542 GOLD IV: 0.457	n=22 GOLD I:18.18% GOLD II: 59.09% GOLD III: 13.64% GOLD IV: 9.09%	(S. Carneiro, 2009)

However, the collection of data regarding the quality of life of patients with COPD is still not a systematic practice in Portugal. Thus, it was not possible to obtain this information from the HSJ clinical records. The values attributed to the utility of COPD patients at different stages were based on studies in which the Markov Model is applied to COPD patients to compare two interventions. Several works report similar utility values for the different stages of COPD. Thus, to conduct the simulation the mean values and standard deviation of the QALYs presented in Table 9 were used and further validated by Dr. Pedro Ferreira. The Portuguese study in which the quality of life of the different stages were analyzed was not included since the patient sample used is very low (Table 9). However, the values are comparable to those in Table 10.

Table 10. Utility of GOLD I, II, IV, IV patients.

	COPD stage				Country	n	Source
	GOLD I	GOLD II	GOLD III	GOLD IV			
(Utility /QALYS)	0.830	0.830	0.800	0.730	US	1235 (based on (Rutten-Van Mólken, Oostenbrink, Tashkin, Burkhart, & Monz, 2006) conducted in 13 countries(Mólken & Lee, 2006)	(Karabis, Mocarski, Eijgelshoven, & Bergman, 2014)
	0.897	0.755	0.748	0.549	Belgium	117 (based on (Menn, Weber, & Holle, 2010) conducted in Germany	(van Boven et al., 2014)
	0.897	0.755	0.748	0.549	US		(Rajagopalan, Bloudek, Marvel, Dembek, & Kavati, 2018)
	0.787	0.787	0.750	0.647	UK	604 (based on (Boutou et al., 2013)	(Ramos et al., 2019)
Mean	0.853	0.782	0.762	0.619	-	-	-
Standard deviation	0.05	0.03	0.02	0.08			

According to the literature review, it is expected that the quality of life will slight increase for patients who are followed by telemonitoring (Table 4). As the effect of this influence with the patient's age and GOLD stage has yet been reported, an increase was considered regardless of these factors. This parameter was based on cost-effectiveness studies of a telehealth solution compared with usual care with the duration of at least 12 months and with a sample of more than 1000 patients (mean = 0.013; standard deviation = 6.00×10^{-4}) (Udsen et al., 2014),(Udsen et al., 2017),(Catherine Henderson et al., 2013).

Transition probabilities

The transition probabilities matrix considered in the proposed Markov are represented in Table 11.

Table 11. Transition Matrix for the proposed Markov Model

GOLD I	GOLD II	GOLD III	GOLD IV	Dead	
I → I	-	-	-	-	GOLD I
I → II	II → II	-	-	-	GOLD II
-	II → III	III → III	-	-	GOLD III
-	-	III → IV	IV → IV	-	GOLD IV
1 → Dead	II → Dead	III → Dead	IV → Dead	-	Dead

For the simulation carried out, the transition probabilities between GOLD stages were based on the work of Hofer and co-authors (Hofer et al., 2016), which used data from patients with age > 40 years. Since the stage of the disease results essentially from FEV1, a parameter that declines with age, it is important to consider the variation in the probabilities with age. For this, an annual decline in the mean FEV1% predicted based on the Fletcher curve for patients which smoked regularly (Fletcher & Peto, 1977),(Rennard & Vestbo, 2008),(Dal Negro, Eandi, Pradelli, & Iannazzo, 2007) (Figure 8) (Table 12).

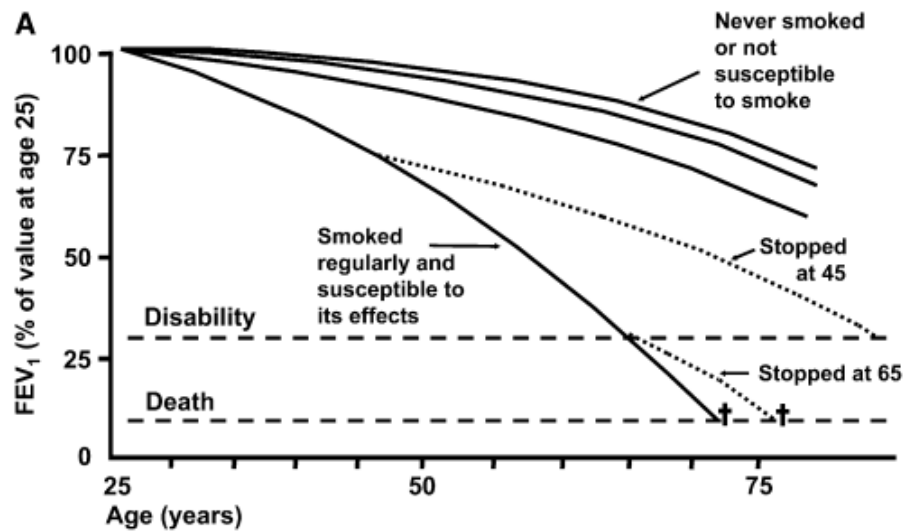


Figure 8. Fletcher Curve; FEV1 (Fletcher & Peto, 1977).

The transition probability to the death state were obtained by applying a stage-specific relative risk to the mortality rates of the general Portuguese population (Mortality tables in Portugal - Instituto Nacional de Estatística (INE)). The relative risks were based

in Kaplan–Meier survival curves after 4 years of follow-up in which GOLD III, II and I showed a 60%, 73% and 89% survival (Domingo-Salvany et al., 2002). As the mortality is closely related to FEV1, it was assumed that the survival rate of GOLD IV is inferior to GOLG III (50%).

Table 12. Transition probabilities included in the Markov model simulation.

40y-49y		50y-64y		65y-69y		≥70y	
GOLD I → GOLD II	0.020	GOLD I → GOLD II	0.024	GOLD I → GOLD II	0.030	GOLD I → GOLD II	0.031
GOLD II → GOLD III	0.020	GOLD II → GOLD III	0.024	GOLD II → GOLD III	0.030	GOLD II → GOLD III	0.031
GOLD III → GOLD IV	0.040	GOLD III → GOLD IV	0.049	GOLD III → GOLD IV	0.060	GOLD III → GOLD IV	0.062
GOLD I → Dead	0.002	GOLD I → Dead	0.006	GOLD I → Dead	0.012	GOLD I → Dead	0.189
GOLD II → Dead	0.002	GOLD II → Dead	0.007	GOLD II → Dead	0.014	GOLD II → Dead	0.216
GOLD III → Dead	0.003	GOLD III → Dead	0.008	GOLD III → Dead	0.015	GOLD III → Dead	0.238
Gold IV → Dead	0.003	Gold IV → Dead	0.008	Gold IV → Dead	0.016	Gold IV → Dead	0.255

COPD stages covered by the telemedicine interventions

In the reported study trials, the telemedicine intervention is applied according to the COPD stage. Usually, as the highest costs to the NHS are associated with exacerbation episodes and consequent hospitalization, GOLD III and IV patients are selected (Flemming W. Udsen et al., 2014),(Stoddart et al., 2015). However, in the work of McDowell et al. (McDowell et al., 2015) , GOLD II and GOLD III patients were chosen as the target population to test the cost-effectiveness of the new telehealth approach. In fact, according to feedback given by Professor Dr. Job van Boven (Annex 2), it is important to apply these interventions from an early stage in order to encourage the patient to adopt good practices from the beginning of the diagnosis, helping to reduce the deterioration of their health. On the other hand, patients on GOLD IV may no longer have the autonomy or capacity needed to start using a new intervention. Hence, in this

work it was assumed that CDMP will be used by GOLD II, III and IV patients.

4.3. Markov Model program

4.3.2. Model parameters

The parameters included in the Markov model are represented in Table 13. Each cycle corresponds to 1 year. In the interactive menu of the Excel program the user can select the age group (40y-49y; 50y-59y; 60y-69y; ≥ 70 y), time horizon (5 years, 10 years, 15years, lifetime), model type (deterministic, probabilistic) and healthcare costs considered for the NHS + CDMP intervention ($=$, $>$, $<$ NHS healthcare costs) before conducting a cost-effectiveness analysis. The health state distribution of the starting cohort population (cycle=0) was set so that 100% of GOLD patients are GOLD I. Furthermore, the perspective considered is from the NHS.

Table 13. Input variables used to conduct simulation on the Markov Model.

Variables Inputs	Baseline	Deterministic sensitivity analysis		Probabilistic sensitivity analysis	
Basic Population	Range	Mean	std	Low	High
Age	40y-49y	48.0	1.0	-	Normal
	50y-59y	54.5	2.3		
	60y-69y	62.9	2.2		
	≥70y	76.3	4.2		
Health state distribution (cycle=0)	Percentage				
GOLD I	100%				NA
GOLD II	0%				
GOLD III	0%				
GOLD IV	0%				
Health care costs per cycle (Usual Care)	Mean value	std			
GOLD I	3 656.61 €	15.11		-	gamma ($\alpha= 5.81\text{E}+04$; $\beta= 6.27\text{E}-02$)
GOLD II	5 991.51 €	13.44			gamma ($\alpha=1.99\text{E}+05$; $\beta= 3.01\text{E}-02$)
GOLD III	8 573.54 €	12.43			gamma ($\alpha=4.75\text{E}+05$; $\beta= 1.80\text{E}-02$)
GOLD IV	21 831.66 €	8.40			gamma ($\alpha= 6.75\text{E}+06$; $\beta= 3.24\text{E}-03$)
Healthcare costs per cycle (Usual Care + Telemedicine)					
	Cost Reduction			-	
GOLD II	4 489.60 €	13.44			gamma ($\alpha=1.12\text{E}+05$; $\beta= 4.02\text{E}-02$)
GOLD III	5 709.84 €	12.43			gamma ($\alpha= 2.11\text{E}+05$; $\beta= 2.71\text{E}-02$)

GOLD IV	13 053.10 €	8.40			gamma ($\alpha=2.41\text{E}+06$; $\beta= 5.41\text{E}-03$)
Cost Increase					
GOLD II	6 798.57 €	13.57			gamma ($\alpha= 2.51\text{E}+05$; $\beta= 2.71\text{E}-02$)
GOLD III	9 728.40 €	12.58			gamma ($\alpha= 5.98\text{E}+05$; $\beta= 1.63\text{E}-02$)
GOLD IV	24 772.39 €	8.62			gamma ($\alpha= 8.26\text{E}+06$; $\beta= 3.00\text{E}-03$)
Telemonitoring	Mean	std			
	1 893.36 €	1344.40	735.76 €	4 752.42 €	gamma ($\alpha=1.98$; $\beta= 954.61$)
Utilities (Usual Care)	Mean	std			
GOLD I		0.853 0.05	-		Beta ($\alpha=47.57$; $\beta= 8.20$)
GOLD II		0.782 0.03			Beta ($\alpha=137.94$; $\beta= 38.45$)
GOLD III		0.762 0.02			Beta ($\alpha=284.76$; $\beta= 88.94$)
GOLD IV		0.619 0.08			Beta ($\alpha=24.66$; $\beta= 15.18$)
Utilities (Telemedicine)					
GOLD II		0.7946 0.03	-		Beta ($\alpha=134.16$; $\beta= 34.68$)
GOLD III		0.7746 0.02			Beta ($\alpha=278.65$; $\beta= 81.08$)
GOLD IV		0.6316 0.08			Beta ($\alpha=24.81$; $\beta= 14.47$)
Discount rates					
costs		4%	-		
effects		4%			

Data relating to age groups (mean and standard deviation) were obtained from data provided by the HSJ.

Assessment of cost-effectiveness

An ICER was calculated as the ratio of the difference in cost and the difference in QALY gained with the intervention and presented as cost per QALY gained. Discounting was applied to costs and outcomes at a rate of 4% in line with “Portaria n.º 391/2019 (Diário da República Electrónico, 2019)” that states that as there is no official value in Portugal to support investment decisions with public funding, the practice of several European countries is considered”.

Sensitivity analysis

In order to test the uncertainties in the outcome and cost data, deterministic and probabilistic sensitivity analyses were conducted in order to generate robustness in the results that can be the basis for decision making.

For the deterministic one-way sensitivity analysis, it was assumed that the costs of the telemedicine intervention to have a critical impact on outcomes. In addition to the mean value obtained by meta-analysis, the highest (4 752.42 €) and lowest (735.76 €) values reported in the literature were also tested. After verifying the effect of this parameter on the outcomes, the analyzes performed were all probabilistic.

For probabilistic sensitivity analysis, a Monte Carlo simulation with 1000 simulations was performed. As listed in Table 13, input parameters were randomly drawn from either normal, beta or a gamma distribution. A gamma distribution was fitted for all cost parameters. A normal distribution was created for mean age values. Beta distributions were fitted for all utility estimates. β and α parameters were calculated according to formulas shown in equations 7 and 8. ICER scatter plots and CEAC were produced.

$$\text{For gamma distributions, } \beta = \frac{\sigma}{\mu} \text{ and } \alpha = \frac{\mu^2}{\sigma} = \frac{\mu^2}{\sqrt{\sigma^2}} \quad (7)$$

$$\text{For beta distributions, } \beta = \frac{(\sigma^2 + \mu^2 - \mu)}{\sigma^2} \text{ and } \alpha = \frac{(\sigma^2 + \mu^2 - \mu)(\mu - 1)}{\sigma^2}, \text{ where } \sigma \text{ is the variance and } \mu \text{ the mean (Privault, 2013)} \quad (8)$$

4.3.3. Excel guide

The developed Excel program is divided into several sheets where different contents were included as follows:

1. **Study Design:** Introductory sheet with the indication of the project developed and the representation of the Markov Model carried out.
2. **Input variables:** Identification of the input variables for the model, which represent the time independent parameters. In orange are the data that can be changed in the model, according to the collected data. (Table 13).
3. **Usual care costs:** Total healthcare costs of the standard care for each GOLD stage according to the data from the HSJ. The healthcare costs of the usual care + telemedicine considering an increase or a decrease (based on data available from the reviewed studies) is also presented. These data can be subject to modifications and are identified in orange.
4. **Menu:** In the drop-down menu are the parameters that can be selected before running the program. This sheet is the main program's user interface. As stated in 4.3.1, the type of model, the healthcare costs considered for the approach under evaluation, the age group, the time horizon are included. To perform the PSA, it is necessary to press the button with this indication. Furthermore, ICER scatter plot and CEAC curve of the resulting simulations are encompassed (Figure 9).

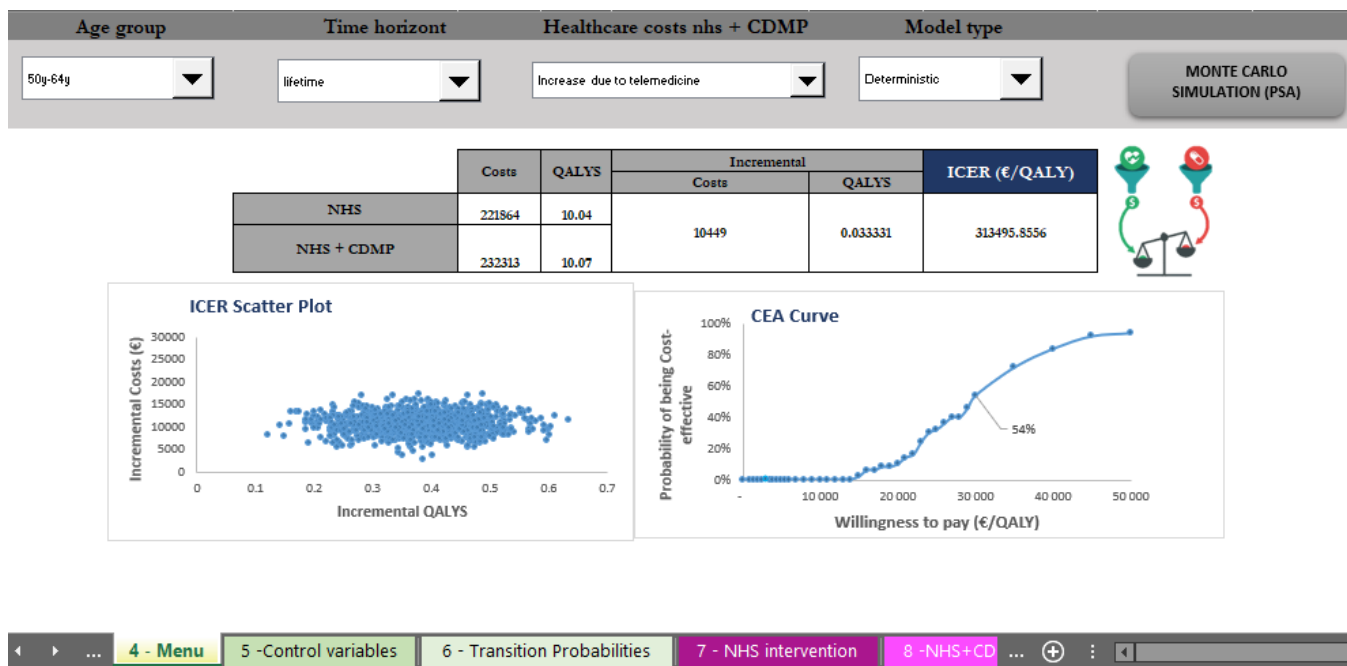


Figure 9. Excel Menu for the cost-effectiveness analysis.

5. **Control variables:** This sheet includes the variables that can be selected in the Menu. Both qualitative and quantitative variables are associated with a number that identifies the choice made on the menu.
6. **Transition probabilities:** On this sheet the tables of the transition probabilities included in the Markov model are represented. Considering that the transition probabilities from one stage to another essentially depend on the patient's age (time dependent variable), data for all considered ages are included. In the next sheet, the mortality tables of the Portuguese population taken from INE are included, which were used for the calculation of the transition probabilities (as explained in 4.2.4).
7. **NHS intervention:** On this page the Markov model itself is started. For this, relevant parameters for the conventional treatment of patients with COPD by the NHS are included, such as the cycle, the initial age, and the time dependent variables (which involve the possible transitions and the mortality risks that are on the transition probabilities sheet). The health state distribution, which corresponds to the percentage of patients in each stage (to simulate a population where all patients are the same), is also considered. The initial cohort is composed with 100% of the population in the GOLD I stage (cycle 0), with the percentage of the

population of the subsequent cycles being in accordance with the developed model (progressive disease, no regression in the disease stage). For each cycle n , the number of people in each stage results from the number of people in the same stage in cycle $n-1$, combined with the number of people who enter that stage (which come from the previous stage) and without the number of people who leave that stage (those who progress to a more severe stage or that they die) (Annex 9). The check column corresponds to the total percentage and must always correspond to 100%. It is possible to change the % of DPOC patients in each stage in this Excel sheet.

The cost and QALYs for each health state are also included. The costs for each COPD stage are calculated as the percentage of people in that stage $\times$ costs associated with that stage (Usual Care Costs Excel sheet). As each cycle corresponds to one year, the cost discount rate is also considered. The same logic is applied for the QALY data (9).

$$\text{Total outcomes} = \text{Population in } \frac{\text{Population GOLD}_n \times \text{utility}_n}{(1 + \text{discount rate})^{\text{cycle}}}, n = \text{I, II, III, IV (9)}$$

At the end of each cycle, the total costs are dependent on the time horizon selected in the menu (for example, if the selected time horizon corresponds to 10 years, the total costs correspond to the sum of the total costs of the first 10 cycles).

- 8. NHS + CDMP intervention:** This sheet has the same information as the previous, but with data relevant for the intervention that we want to compare to the NHS (NHS with CDMP). While the cycle and starting age are the same as for the NHS, the utility and costs differ.
- 9. Monte Carlo Simulation:** In this sheet the content used to perform the PSA is organized. In a first phase, the costs, effects (QALYS) of each intervention as well as the incremental costs and effects resulting from 1000 simulations are calculated. ICER scatter plot results from these data. Subsequently, for each simulation, the net monetary benefit (NMB) is calculated. When $\text{NMB}_{\text{NHS with CDMP}} > \text{NMB}_{\text{NHS}}$, the new intervention is considered cost-effective, otherwise it is not the approach with better approach according to the economic analysis. Once the

number of cost-effective simulations is determined the probability of the intervention being cost-effective is obtained and the CEAC curve is plotted. The VBA Macro used for the mentioned steps is further explained in Annex 10.

10. Tables Result: in the table on this sheet, the results of the simulations carried out for the different age groups are compiled after selecting the parameters in the Menu and pressing the “Update Results Table” button (Figure 10). In addition to the base case studies, alternative scenarios were also discussed, namely the use of a discount over time, for both effects and costs, of 1.5% and of a scenario where the telemedicine platform has a price reduction of 20%. These values can be changed in order to perform different sensitivity analyses. The VBA Macro used for this segment of the work is in Annex 11.



Base case	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness at willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00	30 000.00	100 000.00
40y-49y	NHS	11189.61	13.158	9835.48	0.041	241263.75	0%	86%	100%
	NHS + CDMP	121025.09	13.199						
50y-59y	NHS	83480.79	11.305	6093.88	0.031	197131.92	0%	98%	100%
	NHS + CDMP	89574.67	11.336						
60y-69y	NHS	49575.68	8.053	2574.85	0.017	153119.19	18%	100%	100%
	NHS + CDMP	52150.52	8.070						
≥70y	NHS	15953.34	3.016	624.75	0.005	130635.30	40%	100%	100%
	NHS + CDMP	16578.10	3.020						
1.5% discount rate	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness at willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00	30 000.00	100 000.00
40y-49y	NHS	11189.61	20.431	9835.48	0.078	125871.81	40%	100%	100%
	NHS + CDMP	121025.09	20.509						
50y-59y	NHS	83480.79	16.051	6093.88	0.052	116464.39	50%	100%	100%
	NHS + CDMP	89574.67	16.103						
60y-69y	NHS	49575.68	10.097	2574.85	0.024	105385.04	76%	100%	100%
	NHS + CDMP	52150.52	10.122						
≥70y	NHS	15953.34	3.363	624.75	0.006	100945.25	76%	100%	100%
	NHS + CDMP	16578.10	3.369						
20% reduction in telemedicine expenses	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness at willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00	30 000.00	100 000.00
40y-49y	NHS	11189.61	13.158	5981.00	0.041	146713.58	12%	98%	100%
	NHS + CDMP	117170.61	13.199						
50y-59y	NHS	83480.79	11.305	3864.63	0.031	125017.74	36%	100%	100%
	NHS + CDMP	87345.43	11.336						
60y-69y	NHS	49575.68	8.053	1738.54	0.017	103386.46	74%	100%	100%
	NHS + CDMP	51314.22	8.070						
≥70y	NHS	15953.34	3.016	434.98	0.005	90954.49	94%	100%	100%
	NHS + CDMP	16388.33	3.020						

Figure 10. Excel sheet with Results Table (Press button to carry out the simulations).

In the Excel file, information concerning the content of each sheet, as well as the sources used and the cells that can be modified are included.

5. Results and Discussion

5.1. Patients Baseline Characteristics

Due to the prolonged data collection process, for this project it was only possible to use data from 50 patients diagnosed in 2015. The data used to calculate healthcare costs were based on the year 2016 as this was the first year in which all clinical episodes were recorded for patients. The general characteristics of the sample population are described in Table 14.

Table 14. HSJ Patients Characteristics (n=50).

Population Characteristics	
Male	76%
Single	86%
Smoker	72%
Ex-Smoker	16%
Other comorbidities	
Diabetes (ICD 10 - E11)	24%
Lung cancer (ICD 10 - C34)	12%
Depressive episodes (ICD 10 - F32)	40%
Heart Failure (ICD 10 - I50)	22%
Sleep apnea (ICD 10 - G47.3)	16%
Hypertension (ICD 10 - I10)	58%

5.2. Deterministic analysis

Considering that the costs of the telemedicine platform are dependent on its characteristics and on the business model adopted by the developing company, reported values adopt a high range of values. Thus, to determine the effect of this variable on the final outcomes, a first deterministic evaluation was carried out to assess the resulting ICER. The starting age group and time horizon were fixed at 40-49y and for lifetime, respectively (Table 15).

Table 15. Deterministic analysis assuming the telemedicine intervention to have a critical impact on outcomes.

Telemedicine cost	Scenario 1 - ICER (for healthcare costs of NHS + CDMP < Healthcare costs of NHS)	Scenario 2 - ICER (for healthcare costs of NHS + CDMP > Healthcare costs of NHS)	Scenario 3 - ICER (for healthcare costs of NHS + CDMP = Healthcare costs of NHS)
735.76 €	-277 086.98	183 455.79	36 742.21
1 893.36 €	-219 279.02	241 263.75	94 500.15
4 752.42 €	-76 503.94	384 038.82	23 7325.25

According to the deterministic one-way sensitivity analysis, when the healthcare costs of the new telemedicine intervention are lower than the NHS costs (scenario 1), the solution is cost effective (negative ICER due to increased effects and reduced costs, which means that the usual intervention is dominated). On the other hand, when NHS + CDMP healthcare costs are higher or equal to usual care, ICER>0 (scenarios 2,3). The ICER is lower when the healthcare costs of the two interventions are equal (scenario 3), which means that the probability of being cost-effective is higher.

Regarding scenario 2, where the healthcare costs of the new intervention are higher (scenario 2), for a telemedicine cost of 735.76 € and 1 893.36 €, the resulting ICER is inferior to the payment threshold assumed in Portugal (30 000 €/QALY) (Table 15). Contrastingly, for the highest telemedicine cost tested (4 752.42 €), the ICER is 384 038.82, which means that the intervention would not be cost-effective in Portugal.

For the PSA, the mean cost of 1 893.36 € was considered as it better represents the reviewed works. However, it should be noted that the standard deviation is high (1344.40) (Table 7), which means that when applying a probabilistic model, the resulting ICER values will incorporate this variability.

5.3. Sensitivity Analysis

5.3.1. Base case study

NHS + CDMP Healthcare costs

Markov model simulations were carried out for the three healthcare costs of the NHS+CDMP interventions included in the interactive menu of the Excel program. As the incremental benefit in QALYs is low, the results are driven by cost.

For healthcare costs of NHS + CDMP < healthcare costs of NHS, the resulting ICERs from the different iterations performed lie in the NE and in the SE quadrant of the ICER scatter plot. The highest percentage of the observed points are situated in SE, which is characteristic of a approach with higher effects at lower costs (Figure 11A). Regarding the other scenarios (healthcare costs of NHS + CDMP > or = healthcare costs of NHS), results from the PSA showed all 1,000 simulated points were clustered in the NE quadrant, representing cases where systematic case-finding are more expensive and more effective than routine practice plot (Figure 11B). Thus, a trade-off between costs and effects needs to be considered. At a willingness to pay of 30 000 €/QALY, the probability of being CE is 80%. In the intermediate scenario (equal healthcare costs) the probability of CE increases to 96% (Figure 11C).

Logically, the impacts generated in terms of hospital contacts, by using the telemedicine platform can determine the efficiency of this new intervention. As demonstrated, lower costs (that usually result from the reduction in hospitalizations and emergency episodes) is key in this type of approach. However, for the remaining simulations it was considered that the overall healthcare costs of the new intervention are higher, since it is the hypothesis with the strongest literature support (Annex 8).

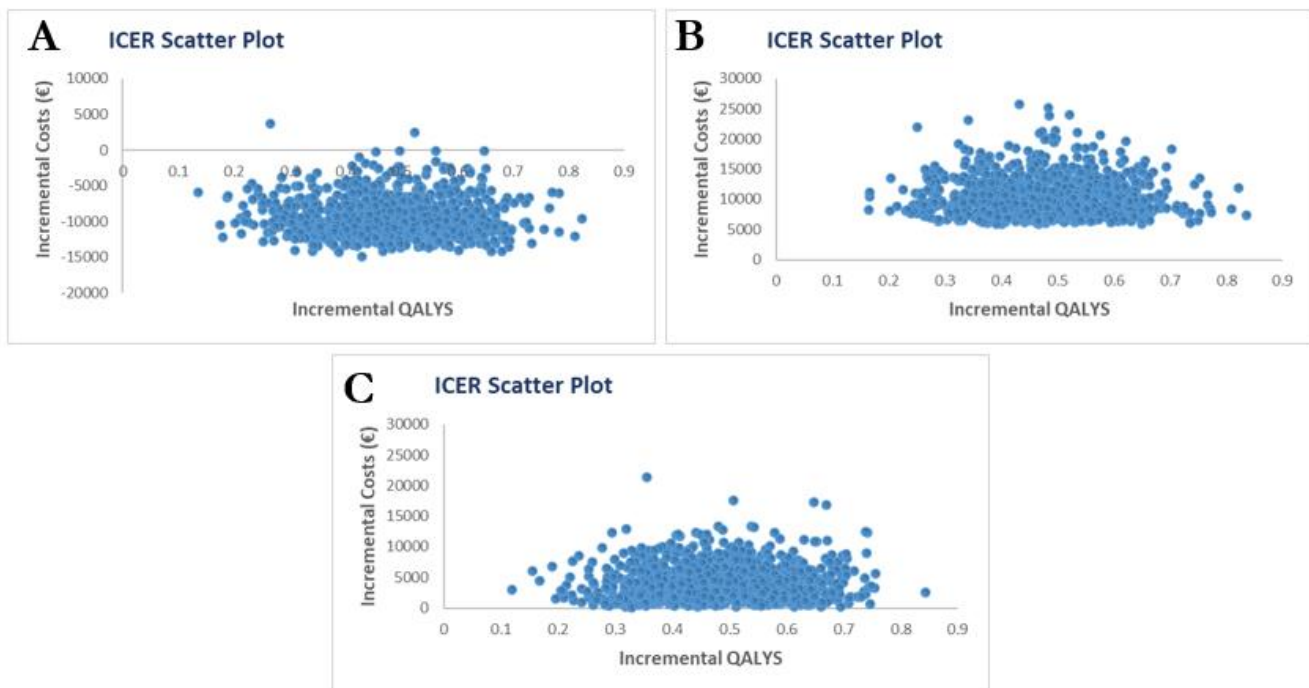


Figure 11. ICER Scatter Plot of PSA for starting age group: 40-49y, time horizon: lifetime and healthcare costs of NHS+CDMP intervention (A) < NHS, (B) > NHS and (C) =NHS.

Time horizon

Regarding the time horizon, it is possible to observe that as this parameter increases from 5 years to lifetime (60 years, which is sufficient to guarantee that all cohort is in the Dead state) the dispersion of the data increases, going from an ellipse to a more rounded distribution (Figure 12). This is because, as the cohort starts population is in GOLD I, it takes at least 4 cycles for there to be a percentage of the population in each stage, leading to more variability in the data. Furthermore, GOLD I is not covered by the telemedicine intervention, meaning that while the population is all practically in the first stage of COPD, the two interventions considered are very similar. Therefore, for short time horizons, the ICERs of the simulations performed are very close (≈ 0).

The time horizon should be long enough to include all the important differences of the technologies under comparison, in terms of costs and effects. Thus, to conduct a meaningful cost-effective analysis using the current model design, the lifetime should be considered.

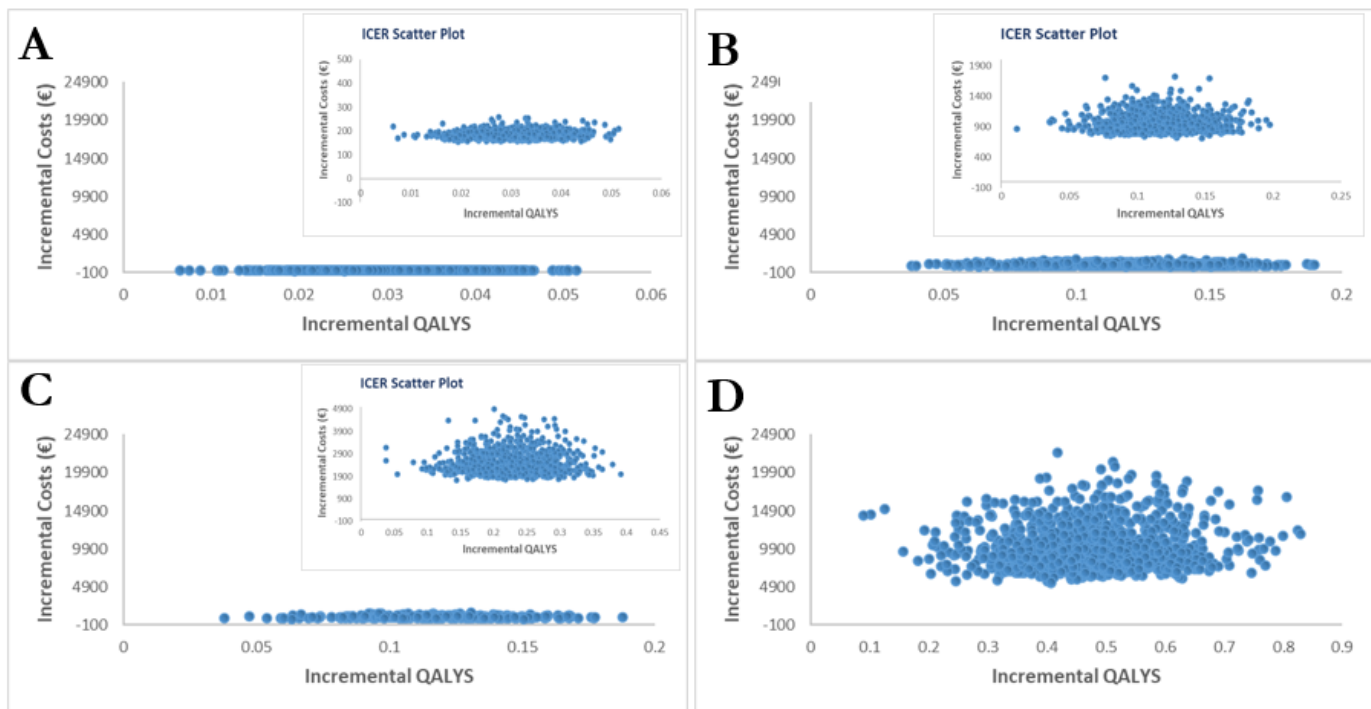


Figure 12. ICER Scatter plot of PSA for starting age: 40-49y, healthcare costs of NHS + CDMP > costs NHS and time horizon (A) 5 years, (B) 10 years, (C) 15 years and (D) for lifetime.

Start age range

Varying the age for starting screening slightly altered the probability of being CE (94-100%). The scatter of points for a cohort aged ≥ 70 years are more concentrated. This occurs since for this age group, the transition probability is higher. Unlike for a starting age of 40-49y, fewer cycles are needed for the entire population to be in the "Dead" stage. Thus, in this case a shorter time horizon could be used to generate the same results.

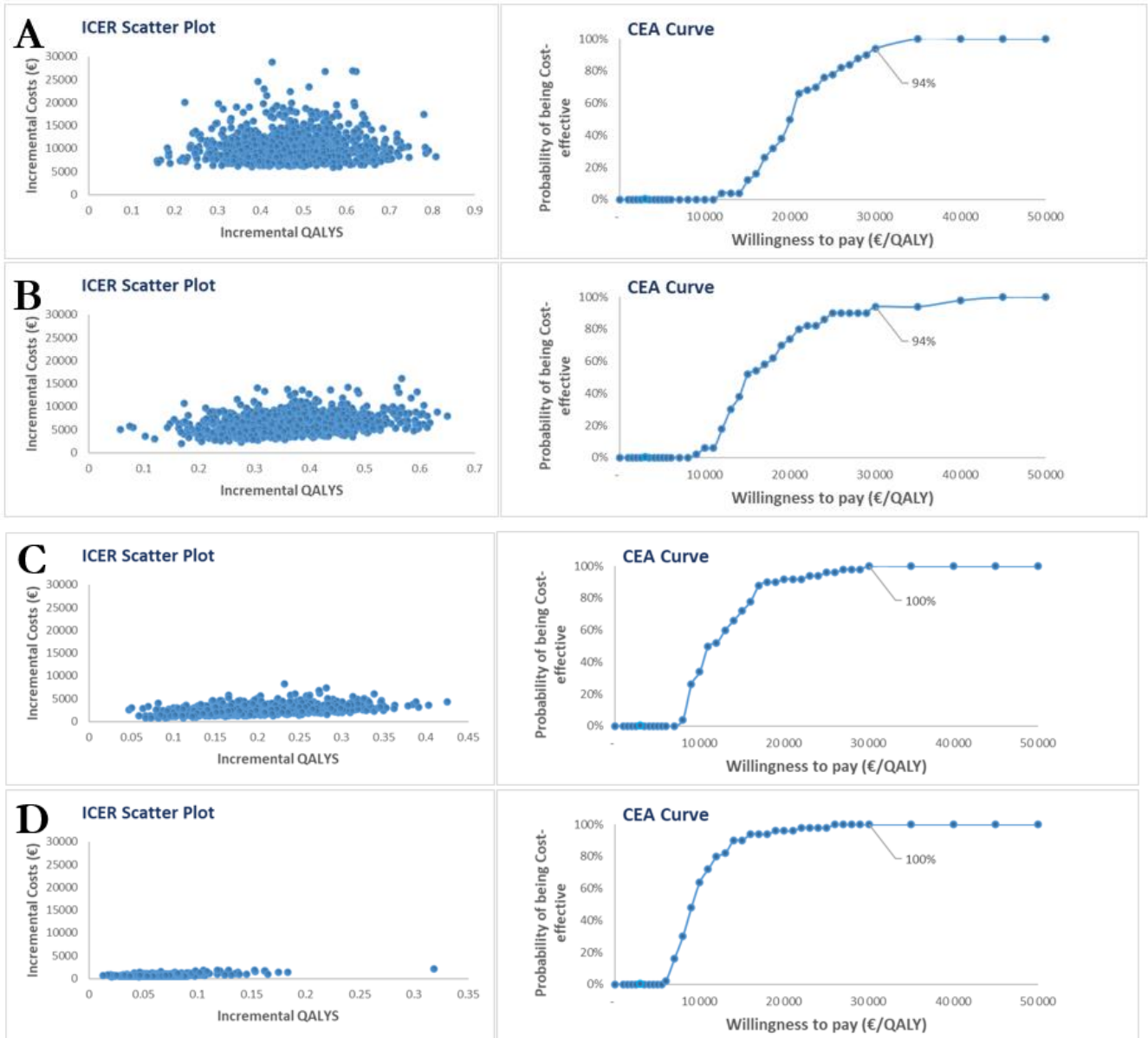


Figure 13. ICER scatter plot and CEA Curve of PSA, healthcare costs of NHS + CDMP > costs NHS. time horizon: lifetime and for starting age: (A) 40-49y, (B) 50-64y, (C) 65-69y and (D) ≥ 70 y.

5.3.2. Different scenarios

Other scenarios were also considered. In Table 15, in addition to the base case, 1.5% discount rates in costs and effects and a 20% in the CDMP platform were tested (Table 16).

Regarding the base case scenario and based on the input variables and model used, the telemedicine platform increases the quality of life by 0.005 - 0.0041 QALYS for an increase in costs between 624.75€ – 9 835.48 €. According to the PSA, the probability of being CE in Portugal is 86 - 100% depending on the age of onset. Portugal's willingness-to-pay value is not supported by any previous study or by budgetary constraints and there are studies that question whether this value may be promoting the adoption of little innovative and cost-effective health technologies (Tribunal de Contas, 2011). For a willingness-to-pay of 100 000 € per QALY the probability of being CE becomes 100%.

Discounting can also be quite influential on the outcomes of economic evaluations. The most prominent controversies regarding discounting consider whether costs and effects should be discounted at the same rate, and whether discount rates should decline or stay constant over time (Attema, Brouwer, & Claxton, 2018). According to the Centre for Guidelines Process and Methods Manual, sensitivity analyses using the same annual discount rate of 1.5% as an alternative rate for both costs and health effects may be presented alongside the reference-case analysis, particularly for public health guidance (National Institute for Health and Care Excellence, 2014). Thus, this scenario was considered in the present work, showing that incremental QALYs range from 0.006 - 0.0578 and incremental costs between 624.75€ – 9 835.48 €. Thus, in this scenario the resulting ICER values are lower.

The effects of a 20% reduction in CDMP costs were also tested, showing that this would make the platform CE at the standard considered willing to pay. However, the relevance of this estimation is limited mainly due to the lack of real-based data.

The modeling approach used is largely in line with previously published models in COPD (Karabis et al., 2014),(Dal Negro et al., 2007),(Ramos et al., 2019) although some differences should be noted. Most of the reported models have used patient level trial data as source data. In the current model, the use of aggregated level data was forced by the lack of comparative trial data. Hence, comparative data were generated by means of indirect treatment comparison techniques. This increases the number of assumptions and

complication of the model. Furthermore, inconsistencies in the reported data and the lack of reported data presented a challenge in parameterizing the model.

However, to our knowledge this is the first work in which a Markov model is developed to compare the conventional treatment of COPD patients with a telemedicine platform. Furthermore, the contents covered in this project can provide as a simple guide to conducting cost-effectiveness analyses and can be summarized in the following steps:

- Identification of interventions to be compared and contextualization of the proposed technology
- Define the perspective for which the analysis will be carried out
- State of the art review - identify the solutions already used, what distinguishes the new intervention from those already reported in order to identify the expected results
- Design the model to be used and the methodology to be followed. In the case of Markov models, the structure must represent relevant clinical pathways (define states and allowable transitions, the cycle length, initial distribution of the population and time horizon must be defined).
- Collect the necessary data. In the case of a prospective study, make a data request to the ethics committee of the hospital to be analyzed as described in 4.2.2; request the necessary data from the company which developed the new health technology as described in 4.2.3; complement the missing information with data from the literature which are as close as possible to the case under study as described in 4.2.4. In the case of an empirical study, design a clinical trial to systematically collect all the necessary inputs to the model (e.g., costs, quality of life (QALYs), transition probabilities, characteristics of the persons using the two interventions being compared - make sure they are comparable).
- Test the developed program with the selected input variables. Conduct sensitivity analysis.
- Interpret and discuss the results obtained

Table 16. Sensitivity analysis for the different starting age-groups considering different scenarios: base case scenario, with considering effects and costs discount and assuming a 20% cost reduction in the telemedicine solution (time horizon: lifetime, healthcare costs NHS + CDMP > healthcare costs NHS).

Base case	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness ar willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00 €	30 000.00 €	100 000.00 €
40y-49y	NHS	111189.61	13.158	9835.48	0.041	241263.75	0%	86%	100%
	NHS + CDMP	121025.09	13.199						
50y-59y	NHS	83480.79	11.305	6093.88	0.031	197131.92	8%	96%	100%
	NHS + CDMP	89574.67	11.336						
60y-69y	NHS	49575.68	8.053	2574.85	0.017	153119.19	20%	98%	100%
	NHS + CDMP	52150.52	8.070						
≥70y	NHS	15953.34	3.016	624.75	0.005	130635.30	48%	100%	100%
	NHS + CDMP	16578.10	3.020						
1.5% discount rate	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness ar willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00 €	30 000.00 €	100 000.00 €
40y-49y	NHS	111189.61	20.431	9835.48	0.078	125871.81	44%	100%	100%
	NHS + CDMP	121025.09	20.509						
50y-59y	NHS	83480.79	16.051	6093.88	0.052	116464.39	46%	98%	100%
	NHS + CDMP	89574.67	16.103						
60y-69y	NHS	49575.68	10.097	2574.85	0.024	105385.04	78%	100%	100%
	NHS + CDMP	52150.52	10.122						
≥70y	NHS	15953.34	3.363	624.75	0.006	100945.25	70%	100%	100%
	NHS + CDMP	16578.10	3.369						

20% reduction in telemedicine expenses	Intervention	Costs	QALYS	Incremental		ICER (€/QALY)	Probability of cost-effectiveness ar willingness to pay (€/QALY)		
				Costs	QALYS		10 000.00 €	30 000.00 €	100 000.00 €
40y-49y	NHS	111189.61	13.158	5981.00	0.041	146713.58	12%	100%	100%
	NHS + CDMP	117170.61	13.199						
50y-59y	NHS	83480.79	11.305	3864.63	0.031	125017.74	38%	100%	100%
	NHS + CDMP	87345.43	11.336						
60y-69y	NHS	49575.68	8.053	1738.54	0.017	103386.46	74%	100%	100%
	NHS + CDMP	51314.22	8.070						
≥70y	NHS	15953.34	3.016	434.98	0.005	90954.49	90%	100%	100%
	NHS + CDMP	16388.33	3.020						

6. Conclusions and future perspectives

Traditionally, chronic disease has been managed through an episodic office-based model rather than a care management model, which uses frequent patient contact and regular physiologic measurement. However, the use of telemedicine technologies for COPD management has been associated with reductions in hospitalizations, readmissions, lengths of stay, and costs; improvement in some physiologic measures; high rates of satisfaction; and better adherence to medication.

The importance of eHealth-based alternative treatment methods is reinforced by the pandemic times in which we live. Telemedicine can be leveraged by physicians to provide healthcare services to chronic patients, thereby promoting social distancing and lowering the risk of SARS-CoV-2 infection. Furthermore, the applications of new technologies that aid the health sector can help to address contemporary global health problems such as access, equity, and quality.

Despite the growing economic burden associated with COPD, little quantitative economic information is available to guide decision-making and treatment. The state-of-the-art revision conducted in this report shows there is no consensus opinion on the adoption of telemedicine for COPD. Thus, the development of an economic model to assess the cost effectiveness of eHealth for COPD represents a major contribution to this field. Decision-analytical modelling such as Markov models have been increasingly used to estimate the cost effectiveness of healthcare interventions and to assist in complex decision-making.

In the present project dissertation, in addition to a vast state of the art revision, the detailed description of the information needed for this type of study and the development of a Markov Model are included. These steps constitute a crucial phase for health technology assessment that is based on conceptual development and preparation. Moreover, simulations were carried out by incorporating data from different clinical trials and other data sources, and also with real data provided to HSJ. Thus, this is the first work in which a Markov Model is applied for COPD in the Portuguese context based on best available evidence.

Once data resulting from the use of the CDMP is collected, it can easily be placed as inputs into the model to obtain more accurate results. It is expected that in that phase

the results will be more optimistic since, while the published works use simple telemedicine platforms, the CDMP is a platform that uses artificial intelligence allowing a more personalized care and monitoring. In addition, this platform is expected to include the involvement of several health professionals (such as nutritionists) and related areas (physical education technicians). Early economic evaluation is essential to assess the value of emerging technologies, but empirical data to inform the current practice of early evaluation is limited.

Future perspectives include the implementation of a controlled clinical trial to gather high quality scientific evidence to support clinical and health policy choices. For this it would be important to first standardize the methods of collecting and recording information (regarding the effects and costs to be considered). The collected data could also be used for estimation of survival probabilities (Williams, Lewsey, Mackay, & Briggs, 2017).

The inclusion of other perspectives to conduct the cost-effectiveness study would also be interesting. For instances, the social perspective could be included in the model. To achieve this (1) data of the social fees in Portugal (the contributions are due on the employee's gross remuneration at rates of 11% and 23.75% by the employee and the employer, respectively) (Worldwide Tax Summaries, 2021); (2) the mean income (including income from employment and business and excluding pensions, sick leaves and other transfers that are taxable but not producible); (3) and the consumption (education, social, public expenses, and other private consumption) with age should be gathered. With this information, tables for the productivity losses $((1 + \text{social fees}) * \text{mean annual wage})$ and consumption could be included in the Excel file developed. For consumption, if using data collected in previous years it would be necessary to consider the inflation rate to carry out a current analysis.

The comparison of the perspective of the HSJ with the one of NHS would also be of interest. In Portugal, payments to health care institutions by the NHS are done prospectively. The value is based on DRG (which is a classification system that groups patients into clinically coherent and similar groups from the perspective of resource consumption) and is calculated using the Index Case Mix. The problem is that the Index Case Mix has not been updated since 2015, which means that there are probably great disparities between what is paid by the national health system and what is actually spent by hospitals (Acordo modificativo ao contrato programa, 2020).

A budget impact analysis (BIA) could also be added to the economic analysis to estimate the financial consequences on the decision-maker's budgets of adopting a new intervention. According to NICE guidelines, a BIA of 5 years is sufficient for a basic level economic analysis. This analysis only considers costs and benefits which are monetized (National Institute for Health and Care Excellence, 2019).

The model could also be improved by considering the effects of individual patient's characteristics on the outcomes. In the work of Udsen and co-authors (Udsen et al., 2017) two linear mixed effect models were developed to calculate incremental costs and QALYS. A deterministic ICER estimate was calculated using the treatment beta-coefficients from these two models. The possibility of including an initial cohort with different age groups would also be an advantage and would allow a closer representation of reality.

In addition, although most papers present the unit costs per patient, it would also be important to distinguish between fixed and variable costs. Henderson suggested that 90% of costs related to installers (and their associated administrative and capital overheads, plus costs of equipment support in terms of transport and storage) are fixed and spread over five years (Henderson et al., 2013).

The proposed model can also serve as a platform to develop a general model that allows the cost-utility analysis of telemedicine interventions for different pathologies.

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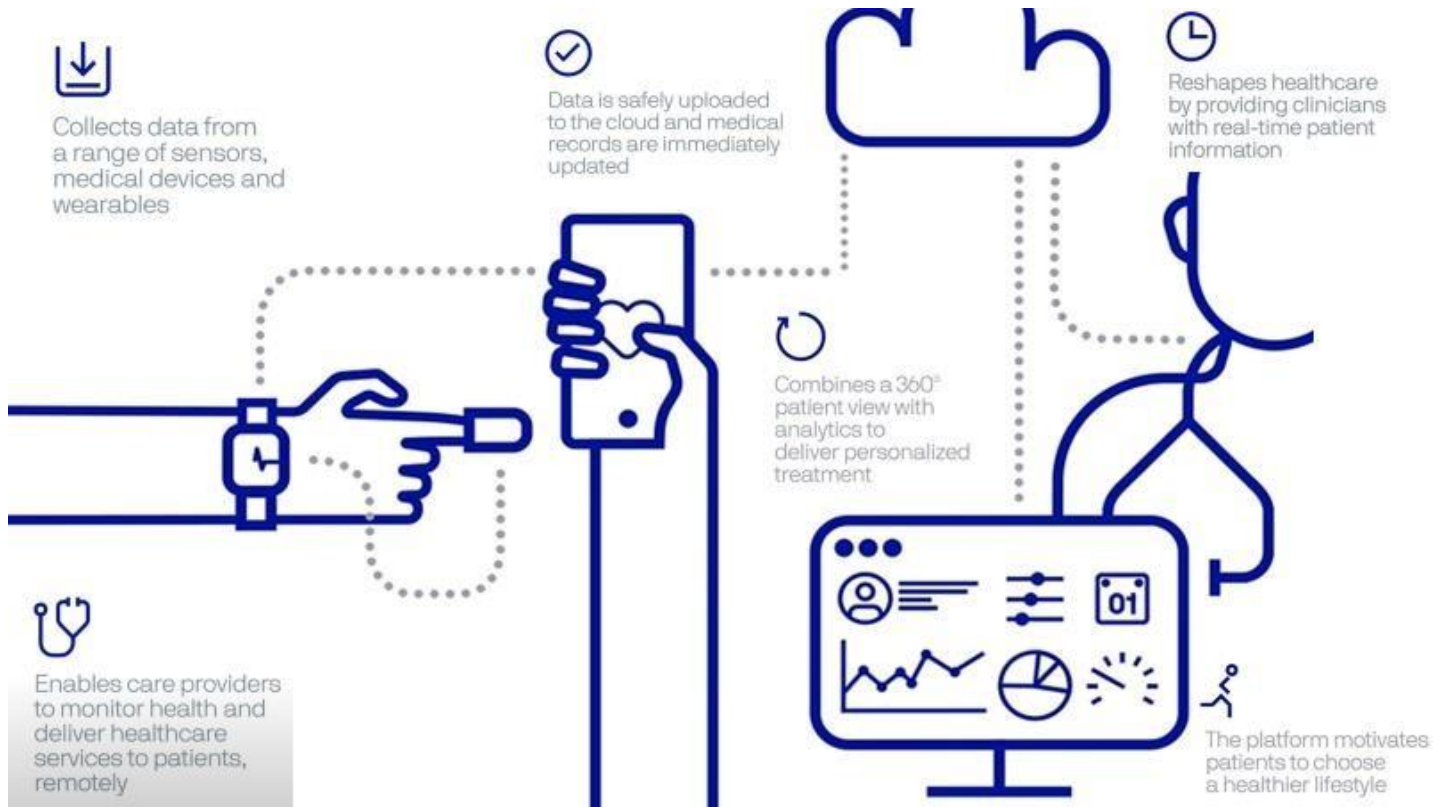
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7. Appendices

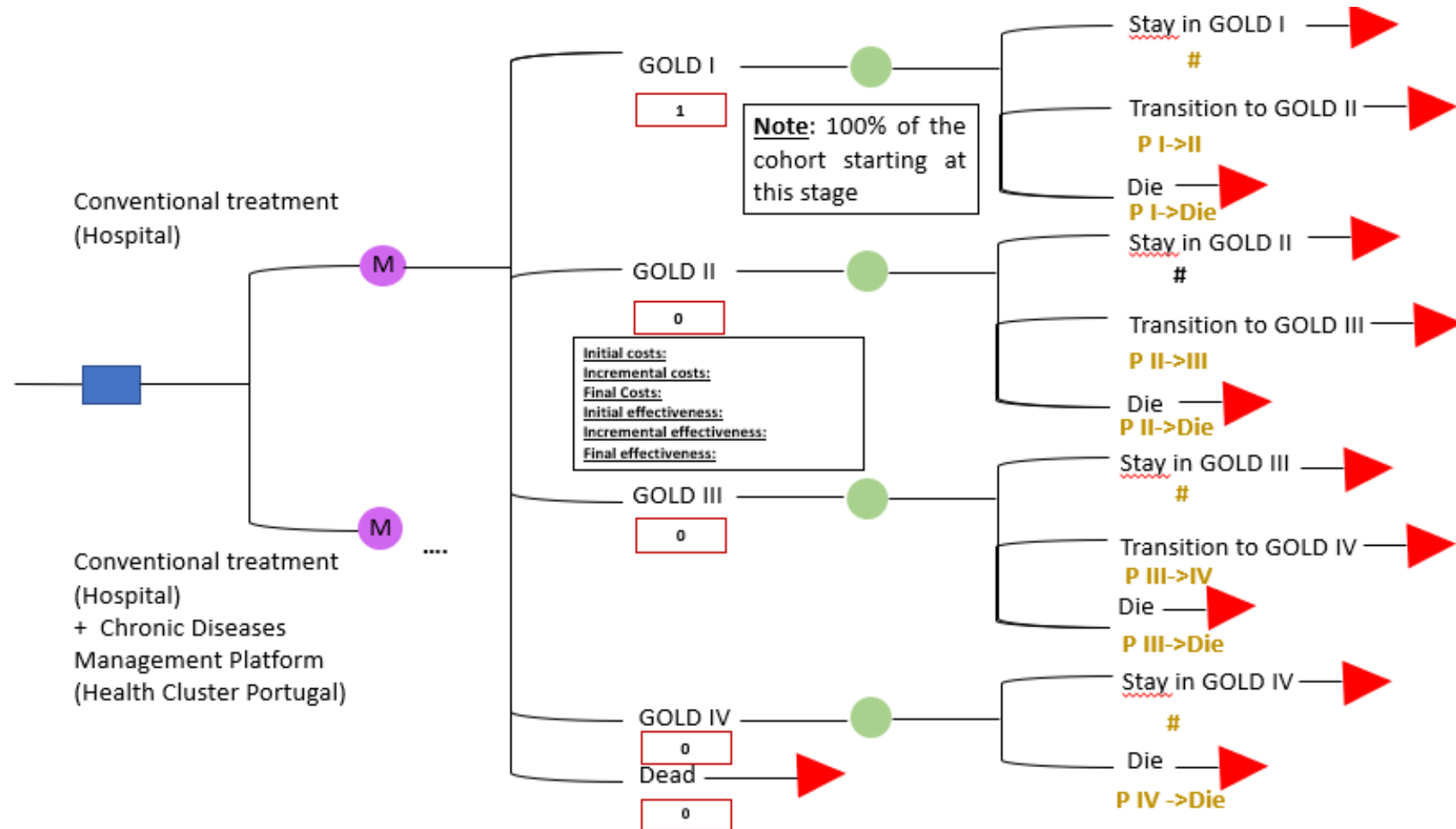
Appendix 1. Chronic diseases management platform description.



Appendix 2. External feedbacks on the presented Project.

Professional	Field	Highlights
Professor Dr. Job van Boven	- Health economics and real-world drug outcomes expert specialized in lung diseases.	- Participation on the Value-Added Medicines Online Summit, event in which I had the opportunity to attend. - Whether or not a telemedicine platform is cost-effective can depend on the Markov Model design used, the input parameters included, and data used. Thus, it is crucial that all these parameters are well thought out and accurately represent the interventions to be compared. - The biggest problem of cost reduction for COPD patients is non adherence, which is characterized by the lack of adoption of correct practices by the patients themselves (such as the correct taking of medication). Thus, new technologies try to promote patient involvement (e.g., smart inhalers). This is an important insight information for HCP to develop CDMP.
Dr. João Fonseca	- Head of the Department of Community Medicine, Information and Health Decision Sciences. - Principal investigator of the PaCeIT research group of CINTESIS.	- The main interest of the developed projected is not the concrete results obtained from the cost-utility analysis itself (since much data is not available), but rather the elaboration of a model where all the variables were described, as well as the best way to collect them. - In addition, the description of the data required for the model that is missing in Portugal is an asset in carrying out future work. - The model, in addition to being of interest to the HCP, can also be applied in several projects, such as the AIRDOC financed by Norte2020.

Appendix 3. Decision Tree structure of the proposed Markov Model in TreeAge Software.



Appendix 4. National Health System costs of hospital contacts for COPD patients in Hospital São João. Source: “Acordo modificativo ao contrato programa 2020” and “Portaria n.º 254/2018”.

Instituição:

Centro Hospitalar Universitário do Porto, EPE

Contratualização 2020

		Doentes Equivalentes				
	ICM	N.º	%	Preço Unitário (€)	Quantidade	Valor (€)
1. Consultas Externas:						
Nº de 1ªs consultas médicas (s/ majoração)				75,00 €	112.356	8.426.700,00 €
Nº de 1ªs consultas referenciadas (CTH)				83,00 €	48.379	4.015.457,00 €
Nº de 1ªs consultas (Telemedicina)				83,00 €	3.800	315.400,00 €
Nº de 1ªs consultas na comunidade (Saúde mental)				83,00 €	719	59.677,00 €
Nº de 1ªs consultas descentralizadas				83,00 €	0	0,00 €
Nº de 1ªs consultas Cuidados Paliativos				83,00 €	57	4.731,00 €
Nº de 1ªs consultas CRe				83,00 €	2.000	166.000,00 €
Nº de 1ªs consultas CRI				83,00 €	0	0,00 €
Nº de consultas subsequentes médicas (s/majoração)				75,00 €	464.489	34.836.675,00 €
Nº de consultas subsequentes (Telemedicina)				83,00 €	0	0,00 €
Nº de consultas subsequentes na comunidade (Saúde mental)				83,00 €	4.357	361.631,00 €
Nº de consultas subsequentes descentralizadas				83,00 €	0	0,00 €
Nº de consultas subsequentes Cuidados Paliativos				83,00 €	234	19.422,00 €
Nº de consultas subsequentes CRe				83,00 €	16.000	1.328.000,00 €
Nº de consultas subsequentes CRI				83,00 €	0	0,00 €
Valor Total das Consultas						49.533.693,00 €

GDH	Designação	Nível de severidade	Tipo de GDH	Peso Relativo (INT)	Preço de Internamento	Peso Relativo (AMB)	Preço em ambatório	Diária de Internamento	GDH Cirúrgicos 1º Dia de Internamento	Limiar Inferior	Limiar Superior	Limiar Máximo	Demora Média Pura
140	DPOC	1	M	0.4683	1.070.07 €	0.1264	288.74 €	390.66 €	-	1	21	31	6.85
		2		0.6288	1.436.81 €			574.03 €			22	32	8.29
		3		0.9252	2.114.08 €	-	-	704.69 €		2	27	40	10.66
		4		1.8638	4.258.78 €			1.419.59 €			36	53	12.74

4. Urgências:						
Atendimentos (SU - Polivalente)					17ME/170.000 ep.	223.696
Atendimentos (SU - Médico-Cirúrgica)					5ME/100.000 ep.	

Appendix 5. Request for Reuse of Clinical Records for Research and Development (I&D) submitted to the Ethics Committee of HSJ.

 SÃO JOÃO	 U. PORTO FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO	Comissão de Ética Centro Hospitalar São João / / Faculdade de Medicina da Universidade do Porto n.º _____ / _____
Questionário para submissão de Investigação		
Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto, Pretendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.		
IDENTIFICAÇÃO DO ESTUDO		
Título da investigação: Economic Modelling to assess the cost-utility of telehealth for chronic obstructive pulmonary disease		
Nome do investigador: Anabela Alves Veiga		
Endereço eletrónico: up201502682@fep.up.pt		Contacto telefónico: 915850781
Caracterização da investigação:		
☒ Estudo retrospectivo	☒ Estudo observacional	☐ Estudo prospetivo
☐ Inquérito	☐ Outro. Qual? _____	
Tipo de investigação:		
☐ Com intervenção	☒ Sem intervenção	
Formação do investigador em boas práticas clínicas (GCP): ☐ Sim ☐ Não		
Promotor (se aplicável): _____		
Nome do orientador de dissertação/tese (se aplicável): Professora Doutora Susana Maria Sampaio Pacheco Pereira de Oliveira		
Endereço eletrónico: soliveira@fep.up.pt		
Local/locais onde se realiza a investigação: Serviço de Pneumologia do Centro Hospitalar Universitário de São João (CHUSJ)		
Data prevista para início: 1 / 02 / 2021		Data prevista para o término: 31 / 12 / 2021
PROTOCOLO DO ESTUDO		
Síntese dos objetivos:		
O objetivo deste trabalho, a desenvolver no âmbito do Mestrado em Gestão e Economia de Serviços de Saúde pela Faculdade de Economia da Universidade do Porto é desenvolver um modelo para a análise custo-utilidade do tratamento convencional de pacientes com Doença Pulmonar Obstrutiva Crónica (DPOC) comparativamente com uma solução de tratamento que envolve a aplicação de telemedicina.		
Fundamentação ética (ganhos em conhecimento/ inovação; ponderação benefícios/riscos):		
O envelhecimento da população e as práticas relacionadas com o estilo de vida da sociedade atual aumentam a incidência e os custos de doenças crónicas. A necessidade de fazer face às crescentes solicitações por bem-estar e, ao mesmo tempo, de limitar os custos de saúde é um dos maiores desafios dos sistemas de saúde. Os sistemas de telemedicina permitem que os profissionais de saúde forneçam cuidados agudos, crónicos, primários e especializados a pacientes de forma remota. Os objetivos deste trabalho consistem no desenvolvimento de um modelo de Markov para efectuar a análise económica de uma plataforma de telemedicina aplicada à DPOC. Esta plataforma vai ser baseada na "Chronic Diseases Management Platform" (Health Cluster Portugal). Os resultados pretendem contribuir para a elaboração de uma proposta de valor, para o setor público e privado, bem como para consciencializar os decisores políticos sobre as vantagens da digitalização da saúde e da plataforma em questão. Os dados requisitados são essenciais para analisar os custos e a utilidade do tratamento convencional de pacientes com DPOC. Em Portugal ainda não existe nenhum trabalho que incida sobre a análise custo-utilidade de uma solução de telemedicina para a DPOC. Para além disso, na literatura não existem trabalhos publicados sobre a elaboração de um modelo de Markov para este efeito. De salientar que não existem riscos associados à realização deste trabalho.		

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

- O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não
- Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não
- Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTIMENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

- ☒ Investigador ☐ Promotor ☐ Ambos ☐ Serviço onde é realizado
- ☐ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Os participantes não terão benefícios imediatos previsíveis. No entanto, a longo prazo o modelo proposto pode auxiliar a analisar qual a melhor intervenção para pacientes com DPOC (em termos de custos e utilidade).

Riscos/incómodos previsíveis:

Não há riscos nem incómodos para os intervenientes.

São dadas contrapartidas aos participantes:

- pela participação ☐ Sim ☐ Não ☒ Não aplicável
- pelas deslocações ☐ Sim ☐ Não ☒ Não aplicável
- pelas faltas ao emprego ☐ Sim ☐ Não ☒ Não aplicável
- por outras perdas e danos ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

- ☐ Investigador ☐ Promotor ☐ Serviço onde é realizado
- ☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- ☒ Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João (se aplicável)
- ☐ Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto (se aplicável)
- ☒ Protocolo do estudo
- ☒ Declaração do Diretor de Serviço onde decorre o estudo
(sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- ☒ Profissional de ligação
- ☒ Informação dos orientadores
- ☐ Informação ao participante
- ☐ Modelo de consentimento
- ☐ Instrumentos a utilizar (inquéritos, questionários, escalas, p.ex.): _____
- ☒ Curriculum Vitae abreviado (máx. 3 páginas)
- ☐ Protocolo financeiro
- ☐ Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 29 de janeiro de 2021

Nome legível:

Amabela Alves Veiga

Amabela Veiga
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/FMUP

Emitido na reunião plenária da CE de 19 / 02 / 2021

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.

[Assinatura]
Prof. Doutor João Almeida
Presidente da Comissão de Ética



Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9º da Lei n.º 26/2016, de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

Número do Pedido

(A preencher pelo Credente de Apoio ao PAF)

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal No caso de haver mais do que um investigador mencionar nas observações

Nome **Anabela Alves Veiga**

[illegible]Endereço eletrónico **up201502682** @fep.up.pt

1.2. Investigador(es) Asociado(s)

Número Total: 3

Nome Joana Feijó

[illegible]

Endereço eletrónico jfeijo @ healthportugal.com

Nome Adriana Camargo

[illegible]

Endereço eletrónico adriana.camargo @ ps.pt

Nome Tiago Silva Costa

Contacto telefónico _____

Endereço eletrónico tcosta @ virtualcare.pt

1.3. Afiliação Institucional do Investigador Principal

1.3.1. Grupo Profesional

☐ Médico(a)☐ Enfermeiro(a)

Docente

☐ Estudiante☐ Outro. Qual?

1.3.2. Documento de identificação pessoal ou profissional

☐ Cartão de Cidadão☐ Bilhete de Identidade☐ Cédula Profesional☐ Cartão de Docente☐ Cartão de Estudante☐ Outro. Qual?

Número de Documento 1 4 5 9 4 4 0 8 5 z w 3

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento Preenchimento Obrigatório

2.1. Enquadramento da investigação

☐ Projeto ou trabalho académico de investigação e desenvolvimento:

☐ Não conferidor de grau

☐ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento

2.2. Entidade(s) que tutela(m) a investigação

☐ Centro Hospitalar de São João

Serviço:

☒ Universidade do Porto

Faculdade / Instituto: **Faculdade de Economia**

☐ Outra Instituição. Qual?

Há alguma parceria entre instituições?

☒ Não ☐ Sim. Qual(is)?

2.3. Orientador Se Aplicável

Contacto telefónico **917538645**

Endereço eletrónico **soliveira** @ **fep.up.pt**

2.4. Título provisório

Modelling to assess the cost-utility of telehealth for chronic obstructive pulmonary disease

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI - Data REuse Certificate for Research - DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

☒ Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

Episódios de internamento para doentes com DPOC (com respetivo código) durante 10 anos (2009-2019); severidade das exacerbações; datas de admissão e alta;

GDH associado a cada internamento; nº de consultas de pneumologia e episódios de urgência; sexo; ano de nascimento; estado civil; distrito

de residência; data do diagnóstico; classificação GOLD; outras comorbilidades; questionário SGRQ; índice BODE; IMC, peso, altura, FEV1; Atividade física

☒ Consulta de processos clínicos em ambiente papel:

☐ Bloco

☒ Consulta Externa

☐ Hospital de Dia

☒ Internamento

☒ MCDT

☒ Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro(s) ao ato de envio

→ Ainda não tem esta informação (explicação no protocolo)

☒ Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:

SClínico

Data previsível de fim de utilização das credenciais de acesso **2021 - 08 - 30**

☒ Outro Acesso. Qual?

Acesso às variáveis descritas em Excel.

2.3. Pareceres e Autorizações

☐ Autorização da Hierarquia

☐ Protocolo Científico Aprovado¹

☐ Parecer da Comissão de Ética para a Saúde (CES)¹

☐ Parecer do Centro de Epidemiologia Hospitalar¹

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro(s) ao ato de envio

¹ Ou, quando aplicável, da autoridade

3. Observações Preenchimento Facultativo

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada (n.º 2 e 3 do art.º 21 e o n.º 1 e 2 do art.º 12, ambos da Lei n.º 26/2016, de 22 de Agosto) ao submeter o presente pedido concordo e fico ainda vinculado, juridicamente, aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a Lei 26/2016, de 22 de agosto, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudo anonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Além do presente pedido para reutilizar registos clínicos, dirigido ao RAI, comprometo-me a obter os necessários pareceres quer do Encarregado da Proteção de Dados, quer da Comissão de Ética do Hospital, quer ainda do Centro de Epidemiologia Hospitalar;
- Comprometo-me a citar as fontes, sempre que publicitar o trabalho de investigação, independentemente de requerer a Certidão de Reutilização (**DA**t**A** **RE**use **C**ertificate for **R**esearch – **DARE**).
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a **DA**t**A** **RE**use **C**ertificate for **R**esearch – **DARE** Preenchimento Obrigatório

☒ Pretendo desde já requerer a Certidão de Reutilização (**DARE**) cujo sentido, valor e significado consultei em <http://portal-chsj.min-saude.pt/pages/710>.

☐ Não pretendo requerer a Certidão de Reutilização (**DARE**) cujo sentido, valor e significado consultei em <http://portal-chsj.min-saude.pt/pages/710>.

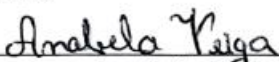
Na circunstância do requerente não indicar nenhuma opção, presumimos que pretende requerer o **DARE**.

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada, ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal; ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.

Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

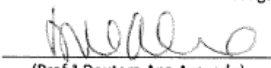
Data | 2 | 0 | 2 | 1 | - | 0 | 1 | - | 2 | 7 |


Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt ou ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 ou 918 880 299

SUBMETTER

Attachment 6. Approval by the HSJ Ethics Committee

Unidade de Investigação
Tomei conhecimento. Nada a opor. À DC.
20 de Abril de 2021
A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)



n.º 45, 2021

DIREÇÃO CLÍNICA
2021 4/20

PEDIDO DE AUTORIZAÇÃO Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

24.4.21

Nome do Investigador Principal:
Anabela Alves Veiga

Título da Investigação:

**Economic Modelling to assess the cost-utility of telehealth for
chronic obstructive pulmonary disease**

CONSELHO DE ADMINISTRAÇÃO - REUNIÃO DE
Presidente do Conselho de Administração

(Prof. Doutor Fernando Araújo)
Direção Clínica:    
Vogal Executiva:  
Vogal Executiva:  

Pretendendo realizar no(s) Serviço(s) de:

Pneumologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/Promotor

Porto, 21 de janeiro de 2021.

Anabela Veiga
assinatura

•Centro Hospitalar São João•
Centro de Epidemiologia Hospitalar

7,4,2021



SÃO JOÃO

Encarregado
de Proteção de Dados
Data Protection Officer

Entrada 10/03/2021

CES-IM005-0

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do projeto: *Economic modelling to assess the cost-utility of telehealth for chronic obstructive pulmonary disease.*

Nome da investigadora principal: Eng.ª Anabela Alves Veiga.

Onde decorre o estudo: No Serviço de Pneumologia do CHUSJ. Apresentou declaração do Prof. Doutor Venceslau Hespanhol. O profissional de ligação será o Dr. Pedro Magalhães Ferreira.

Objetivos do estudo: Desenvolver um modelo para a análise custo-utilidade do tratamento convencional de pacientes com Doença Pulmonar Obstrutiva Crónica (DPOC) comparativamente com uma solução de tratamento que envolve a aplicação de telemedicina. Estudo realizado no âmbito do Mestrado em Gestão e Economia de Serviços de Saúde da Faculdade de Economia da Universidade do Porto, sob orientação da Prof.ª Doutora Susana Maria Sampaio Pacheco Pereira de Oliveira.

Conceção e pertinência do estudo: O envelhecimento da população e as práticas relacionadas com o estilo de vida da sociedade atual aumentam a incidência e os custos de doenças crónicas. A necessidade de fazer face às crescentes solicitações por bem-estar e, ao mesmo tempo, de limitar os custos de saúde é um dos maiores desafios dos sistemas de saúde. Os sistemas de telemedicina permitem que os profissionais de saúde forneçam cuidados agudos, crónicos, primários e especializados a pacientes de forma remota. Os objetivos deste estudo consistem no desenvolvimento de um modelo de Markov para efetuar a análise económica de uma plataforma de telemedicina aplicada à DPOC. Esta plataforma vai ser baseada na "*Chronic Diseases Management Platform*" (*Health Cluster Portugal*). Os resultados pretendem contribuir para a elaboração de uma proposta de valor, para o setor público e privado, bem como para consciencializar os decisores políticos sobre as vantagens da digitalização da saúde e da plataforma em questão. Os dados requisitados são essenciais para analisar os custos e a utilidade do tratamento convencional de pacientes com DPOC. Em Portugal ainda não existe nenhum trabalho que incida sobre a análise custo-utilidade de uma solução de telemedicina para a DPOC. Para além disso, na literatura não existem trabalhos publicados sobre a elaboração de um modelo de Markov para este efeito. Estudo retrospectivo. Estão definidas as variáveis a recolher, e o período da amostra.

Benefício/risco: Benefício potencial para a sociedade através da evolução do conhecimento científico neste domínio.

Confidencialidade dos dados: Apresentou um pedido de reutilização de registos clínicos para investigação e desenvolvimento ao RAI. De notar que a investigadora principal não deve ter acesso direto a registos de saúde exceto se anonimizados, devendo o profissional de ligação, Dr. Pedro Magalhães Ferreira, assegurar a absoluta privacidade dos doentes e a confidencialidade dos dados.

Respeito pela liberdade e autonomia do sujeito de ensaio: Assegurado.

Curriculum da investigadora: Adequado à investigação.

Data previsível da conclusão do estudo: dezembro de 2021

Conclusão: Proponho um parecer favorável à realização do estudo tendo em atenção as considerações efetuadas sobre a confidencialidade de dados.

Porto, 19 de fevereiro de 2021

O Relator da CE, Prof. Doutor Rui Nunes

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética



ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE

Paulo Alexandre Mota da Silva

Encarregado de Proteção de Dados do CHUSJ

epd@chsj.min-saude.pt

Ref.º CES CHUSJ: 45 / 2021

Título do Projeto	Economic Modelling to assess the cost-utility of telehealth for chronic obstructive pulmonary disease		
Responsável pelo tratamento	Anabela Alves Veiga		
Instituição	Faculdade de Economia da Universidade do Porto (FEP)		
Investigador	☐ Interno	☒ Externo	
Contacto telefónico	915850781	Endereço Electrónico	up201502682@fep.up.pt
Profissional de Ligação	Pedro Magalhães Ferreira (Médico)		
Amostra	Entre 100 - 200		
Análise de Risco	☐ Tolerável	☒ Baixo	☐ Elevado ☐ Muito Elevado

Finalidade: desenvolvimento de um modelo de Markov para realizar uma análise económica de custo-utilidade para comparar (em termos de custo e de qualidade de vida) o tratamento convencional de doentes com doença pulmonar obstrutiva crónica (DPOC) pelo Hospital São João com uma intervenção que inclui a utilização de uma plataforma de telemedicina (baseada na desenvolvida pelo HCP). Este é o primeiro modelo desta natureza a ser desenvolvido em Portugal e poderá contribuir para determinar quais os parâmetros que tornam uma plataforma digital custo-efetiva.

Licitude: fundamento previsto no artigo 9(2)(j), com as garantias do artigo 89(1) do RGPD, e artigo 31(1) da LERGD.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 25/03/2021, ponto 13, tendo presente o princípio da minimização dos dados.

Conservação: os dados serão alvo de **pseudonimização**, armazenados numa **USB Flash Drive (pen)** do Investigador Principal com acesso protegido por palavra-passe, ficheiros protegidos por palavra-passe, efetuando-se a conservação até ao tempo estritamente necessário para terminar a tese de mestrado, nomeadamente até **setembro de 2021**. Os dados recolhidos **serão destruídos** após a finalização da investigação.

Comunicação de Dados: **não há partilha** de dados pessoais.

Face ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o **tratamento é realizado em conformidade com o RGPD**.

Recomendações:

1. Garantir medidas de segurança adicionais para o envio da informação por correio eletrónico, nomeadamente através de medidas de encriptação / codificação dos dados a tratar;
2. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (USB Flash Drive), nomeadamente através de medidas de cifragem e autenticação;
3. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Recomendações:

1. Garantir medidas de segurança adicionais para o envio da informação por correio eletrónico, nomeadamente através de medidas de encriptação / codificação dos dados a tratar;
2. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (USB Flash Drive), nomeadamente através de medidas de cifragem e autenticação;
3. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão: ____/____/____

☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 45/2021
2. Parecer CES (19/02/2021)
3. AIPD (25/03/2021)

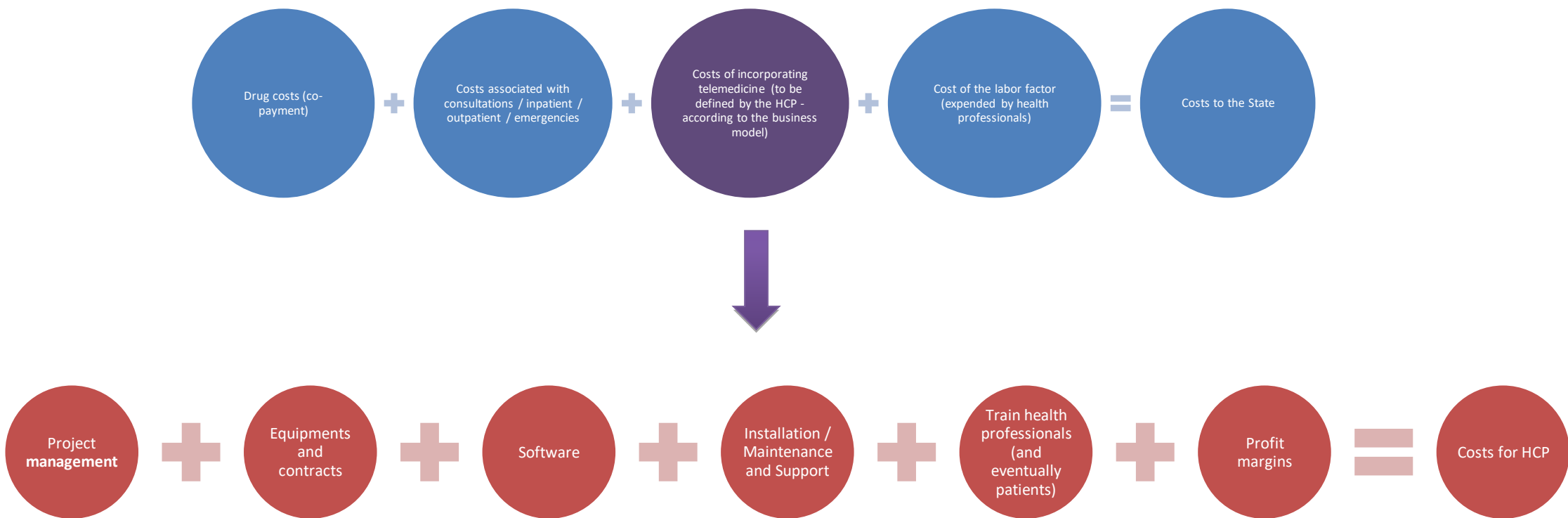
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**

Num. de Identificação: B1120610043

Data: 2021.04.06 17:13:41+01'00'



Appendix 7. Parameters to be considered by the NHS when purchasing a telemedicine platform and to be defined by the HCP in its business plan.



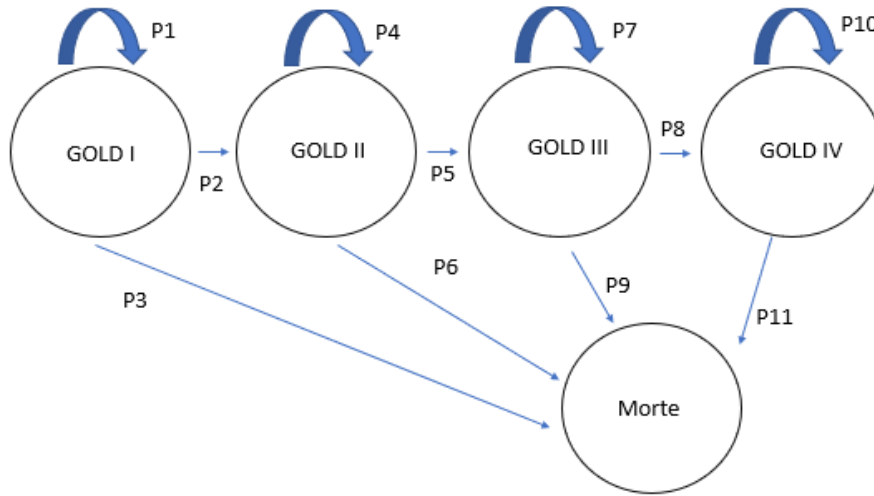
Appendix 8. Costs considered for telemedicine intervention and conventional intervention (health sector perspective) and comparison of the hospital contacts.

Telemedicine costs considered	Hospital costs considered	Hospital contacts with Telehealth / Usual care (per contact)	Trial duration	Overall reduction using telemedicine	Ref.
• Project management (valued as mean yearly salary for an administrative officer including all standardly available pensions and pay supplements). • Computer hardware and peripherals - Per person costs of the 'package' of telecare equipment - the same for all patients. • Installation/deinstallation/ swapping any defects in the equipment (negotiated with an external supplier prior to the trial and valued as prices paid) • Maintenance and support - software licenses and data charges, technical support to patients and healthcare professionals as well as IT infrastructure and application maintenance (not dependent on the number of patients in the trial but the software and hardware configuration employed by the telehealth- care solution which in principle could include all patients with COPD) • Training healthcare professionals (planned time spent conducting education workshops in COPD disease awareness and the telecare solution and the average hourly wage for a community district nurse) • Patient-specific training (planned time and valued based on a mean hourly wage for a community district nurse) • Monitoring vital signs	• Admissions • Outpatient/emergency department visits • Primary care	• Admissions – 0.5 / 0.45 • Inpatient bed days – 2.69 / 2.60 • Outpatient/emergency department visits: 0.87/0.74	12 months	Inexistent	(Flemming W. Udsen et al., 2014),(Flemming Witt Udsen et al., 2017)
• Equipment costs - Computer hardware and peripherals • Computer software Installation • Contract costs/fees to other organizations • Inhouse staff - Telehealth support costs included personnel involved in monitoring and responding to telehealth “triggers,” • Supervision of monitoring staff	• Hospital Costs • Primary care costs • Medication	• Emergency department – 0.23/0.38 • Inpatient bed days – 0.98/1.23		• Emergency department – 39.47% reduction • Inpatient bed days – 20.3 %	(Henderson et al., 2013)

• Back-office functions, project management (planning, contract supervision, monitoring) • Staff training.		• Day hospital and other day attendances – 0.39/0.51 • Outpatient attendances – 1.07/1.26		• reduction • Day hospital and other day attendances – 23.53% reduction • Outpatient attendances – 15 %reduction	
• Equipment (four-year lifespan) • Installation and maintenance - based on costs for contracted services • Initial patient training • Broadband contract • Weekly monitoring of telemonitoring and alert handling (Priced at min/patient/week of time of respective grade of staff undertaking monitoring)	• Primary care – Practice nurse surgery consultations • Medication costs • Secondary care costs - length of stay, the number of intensive care and high dependency unit days and	• Consultations: 1.44/1.92 • Telephone consultations: 1.30/1.34 • home consultations: 1.59/ 1.18 • Practice nurse - Surgery consultations: 1.13/1.37 - Telephone consultations: 0.11/00.15 -Home consultations: 0.11/ 0.52 • District nurse - Surgery consultations: 0.04/0.31 - Telephone consultations: 0.11 /0.31 - Home consultations: 1.88/ 0.89 • Accident and emergency visits: 0.73/0.77	3 months	• Consultations – 25% reduction • telephone consultations – 2.98% reduction • Practice nurse - Surgery consultations – 17% reduction - Telephone consultations – 26.6% reduction -Home consultations – 78.84% reduction • Accident and emergency visits -5.19 % reduction	(Stoddart et al., 2015)
• Equipment costs • Contracts	• Hospital Costs • Primary care costs	• Emergency department visits:	6 months	• Emergency department	(McDowell et al., 2015)

		0.60 / 0.79 • COPD total hospitalizations: 0.50/ 0.65 • COPD total length of stay, days: 3.4 / 4.3 • Community Respiratory Team total contacts: 10.1 / 6.9 • Total exacerbations: 2.35 / 2.81		visits – 24% reduction • COPD total hospitalizations – 23% reduction • COPD total length of stay, days - 20.9% reduction • Total exacerbations – 16.3% reduction	
• The average healthcare utilization (A&E department visits, specialized care consultations and hospital admissions) visit • Specialized care (first visit) • Specialized care (following visit) • Hospitalizations related to COPD • Hospitalizations related to other chronic diseases • Clinical call center (hour) • Technical staff (hour) • Medical parameters monitoring (unit) • Receiving station (unit) • Hosting (month) • Equipment (Blood pressure monitor, Spirometer, pulse oximeter and heart rate (unit), Hub tele-modem (unit), Mobile phone (unit)) - The lifetime of the equipment and software was set at 5 years and the discount rate at 3% • Installation. • Home visits.		• Accident and emergency (A&E) department total (SD): 0.50/ 0.57 • A&E department related to COPD (SD): 0.29 / 0.43 • A&E department related to other chronic disease: 0.21/0.14 • Specialized care total (SD): 0.54/0.29 • Specialized care related to COPD (SD): 0.25/ 0.05 • Specialized care related to other chronic diseases (SD): 0.29/0.24 • Hospitalizations total (SD): 0.54/0.24 • Hospitalizations related to COPD (SD): 0.38/0.14 • Hospitalizations related other chronic diseases (SD): 0.17/ 0.10	4 months	• Accident and emergency (A&E) department total (SD) – 12.8% reduction • A&E department related to COPD (SD) – 32.6% reduction	(Jódar-Sánchez et al., 2014)

Appendix 9. Health state distributions used the Excel file (from cycle = n to n+1).



Cycle	GOLD I	GOLD II	GOLD III	GOLD IV	Dead	check
0	100%	-	-	-	-	
1	$100\% - 100\% \cdot (P2 + P3) = A$	$100\% \cdot P2 = B$	-	-	$100\% \cdot P3 = C$	
2	$A - A \cdot (P2 + P3) = D$	$B + A \cdot P2 - B \cdot (P5 + P6) = E$	$B \cdot P5 = F$	-	$C + A \cdot P3 + B \cdot P6 = G$	
3	$D - D \cdot (P2 + P3) = H$	$E + D \cdot P2 - E \cdot (P5 + P6) = I$	$F + E \cdot P5 - F \cdot (P8 + P9) = J$	$F \cdot P8 = K$	$G + D \cdot P3 + E \cdot P6 + F \cdot P9 = L$	100%
4 + n cycles, n=1,2...n+1	$H - H \cdot (P2 + P3)$	$I + H \cdot P2 - I \cdot (P5 + P6)$	$J + I \cdot P5 - J \cdot (P8 + P9)$	$K + J \cdot P8 - J \cdot P11$	$L + H \cdot P3 + I \cdot P6 + J \cdot P9 + K \cdot P11$	

Appendix 10. VBA Macro used for Monte Carlo simulation.

```

DPOC_VR_4_testes2.xlsm - Module1 (Code)
[General] MonteCarlo_PSA

Sub MonteCarlo_PSA()
|
| ' 1 - Identify and declare variables
| ' NHS
Dim TOTAL_C(1000) As Double
'Double is for real numbers (i.e. which have decimal points)
Dim TOTAL_Q(1000) As Double

| ' NHS + CDMP
Dim TOTAL_C_2(1000) As Double
Dim TOTAL_Q_2(1000) As Double

| 'Cost-effectiveness analysis (CEA)
Dim incremental_C(1000) As Double
Dim incremental_Q(1000) As Double

| 'Delete previous results
Application.ScreenUpdating = False 'used to turn ON/OFF screen updating

Sheets("9 - Monte Carlo Simulation").Select
Range("b4:g1003").Select
Selection.ClearContents

Range("w4:w122").Select
Selection.ClearContents

Sheets("4 - Menu").Select
Application.ScreenUpdating = True ' to visualize the different values of the different iterations in the Menu

| ' 2 - Use MACRO when probabilistic model is selected in the Menu
Range("Model_type") = 2

| ' 3 - n° of iterations = 1000
| ' the defined variables will adopt 1000 distinct values according to its distribution
For i = 1 To 1000
    'For i = 1 To 50 'for testing

| ' copy and paste results to sheet simulation

Calculate 'random sampling

TOTAL_C(i) = Range("Total_C") 'cell name in the Excel file
TOTAL_Q(i) = Range("Total_Q")
TOTAL_C_2(i) = Range("Total_C_2")
TOTAL_Q_2(i) = Range("Total_Q_2")

incremental_C(i) = TOTAL_C_2(i) - TOTAL_C(i)
incremental_Q(i) = TOTAL_Q_2(i) - TOTAL_Q(i)

    Next i

| ' 4 - Register the results

Application.ScreenUpdating = False

Sheets("9 - Monte Carlo Simulation").Select

    For i = 1 To 1000
        'For i = 1 To 50 'for testing

```

```

'NHS
Cells(3 + i, 2).Value = TOTAL_C(i)
'Row index: 3+i (4 is the first cell); Column index (identified in the Excel sheet)
Cells(3 + i, 3).Value = TOTAL_Q(i)

'NHS+CDMP
Cells(3 + i, 4).Value = TOTAL_C_2(i)
Cells(3 + i, 5).Value = TOTAL_Q_2(i)

'Incremental
Cells(3 + i, 6).Value = incremental_C(i)
Cells(3 + i, 7).Value = incremental_Q(i)

Next i

' ----- CEA Curve

'Identify new variables
Dim wtp As Double
Dim proba_CE As Double

Application.ScreenUpdating = False

Sheets("9 - Monte Carlo Simulation").Select

'loop
' to calculate the probability of being CE (proba_CE) for each value of wtp:
'each wtp value included in the table is placed in the wtp cell used for the NMB. The resulting CE_prob is included :
wtp = Cells(3 + i, 22) ' localização dos valores de wtp
Range("wtp").Value = wtp

proba_CE = Range("proba_CE")
Cells(3 + i, 23).Value = proba_CE 'insert the calculated values in the "probability of being CE" column

Next i

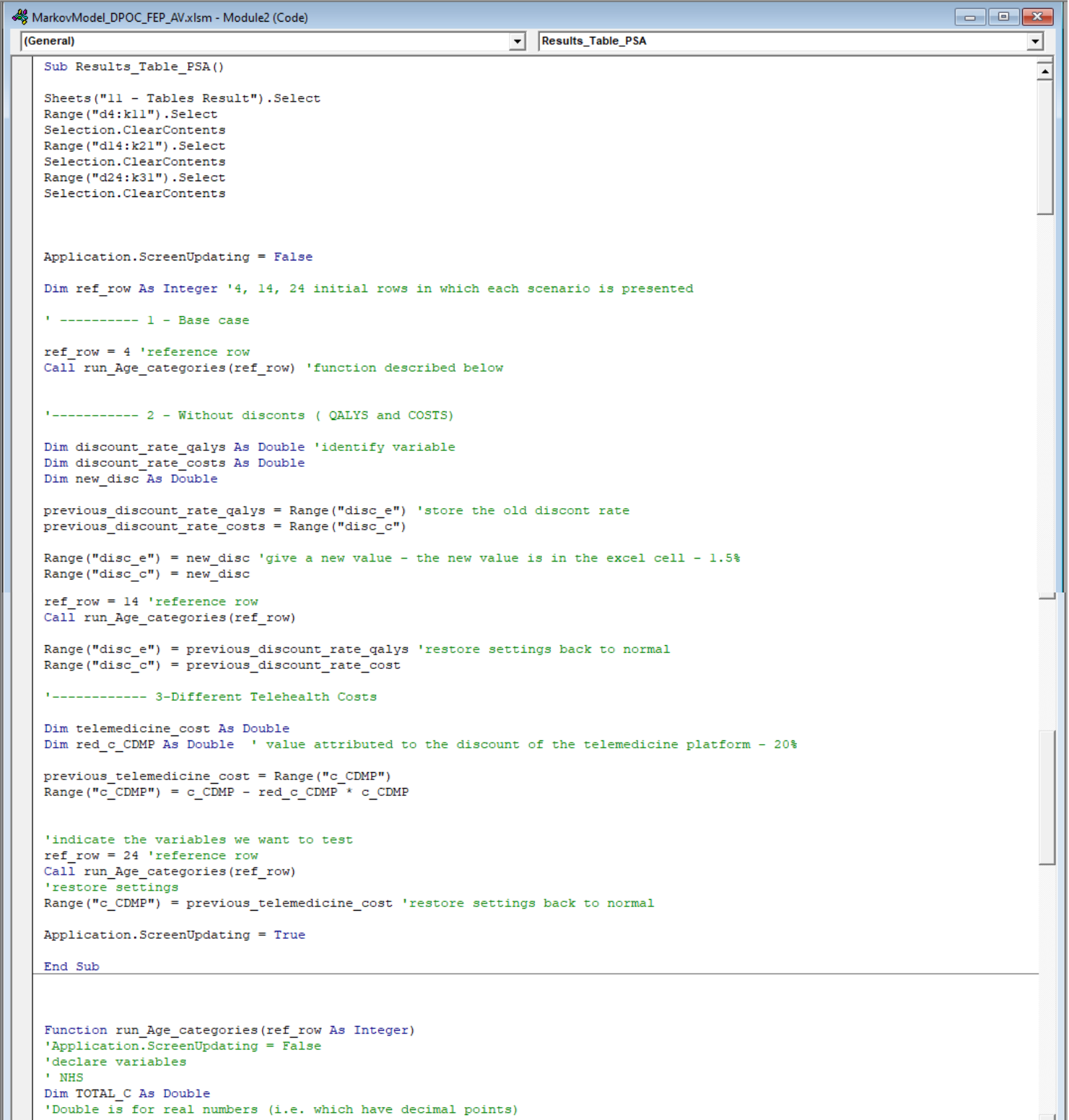
' Back to determinist model
Range("Model_type") = 1

Sheets("4 - Menu").Select 'return to the initial page

End Sub

```

Appendix 11. VBA Macro used for Tables Result.



```

MarkovModel_DPOC_FEP_AV.xlsm - Module2 (Code)
[General] Results_Table_PSA

Sub Results_Table_PSA()

    Sheets("11 - Tables Result").Select
    Range("d4:k11").Select
    Selection.ClearContents
    Range("d14:k21").Select
    Selection.ClearContents
    Range("d24:k31").Select
    Selection.ClearContents

    Application.ScreenUpdating = False

    Dim ref_row As Integer '4, 14, 24 initial rows in which each scenario is presented

    ' ----- 1 - Base case

    ref_row = 4 'reference row
    Call run_Age_categories(ref_row) 'function described below

    '----- 2 - Without discounts ( QALYS and COSTS)

    Dim discount_rate_qalys As Double 'identify variable
    Dim discount_rate_costs As Double
    Dim new_disc As Double

    previous_discount_rate_qalys = Range("disc_e") 'store the old discount rate
    previous_discount_rate_costs = Range("disc_c")

    Range("disc_e") = new_disc 'give a new value - the new value is in the excel cell - 1.5%
    Range("disc_c") = new_disc

    ref_row = 14 'reference row
    Call run_Age_categories(ref_row)

    Range("disc_e") = previous_discount_rate_qalys 'restore settings back to normal
    Range("disc_c") = previous_discount_rate_cost

    '----- 3-Different Telehealth Costs

    Dim telemedicine_cost As Double
    Dim red_c_CDMP As Double ' value attributed to the discount of the telemedicine platform - 20%

    previous_telemedicine_cost = Range("c_CDMP")
    Range("c_CDMP") = c_CDMP - red_c_CDMP * c_CDMP

    'indicate the variables we want to test
    ref_row = 24 'reference row
    Call run_Age_categories(ref_row)
    'restore settings
    Range("c_CDMP") = previous_telemedicine_cost 'restore settings back to normal

    Application.ScreenUpdating = True

End Sub

Function run_Age_categories(ref_row As Integer)
    'Application.ScreenUpdating = False
    'declare variables
    ' NHS
    Dim TOTAL_C As Double
    'Double is for real numbers (i.e. which have decimal points)

```

```

Dim TOTAL_Q As Double
' NHS + CDMF
Dim TOTAL_C_2 As Double
Dim TOTAL_Q_2 As Double
'Cost-effectiveness analysis (CEA)
Dim incremental_C As Double
Dim incremental_Q As Double
Dim ICER As Double
'a name was given to the cells corresponding to these values
'in sheet 9 monte carlo simulation (part related to the CEA curve)
Dim CEA_10000 As Double
Dim CEA_30000 As Double
Dim CEA_100000 As Double

Dim i As Integer

For i = 0 To 6 Step 2
'0 (1st age category), 2 (2nd age category), 4(4rd age category) ,6 (last age category)

If i = 0 Then Range("control_Age_group") = 1 '40y-49y
If i = 2 Then Range("control_Age_group") = 2 '50y-59y
If i = 4 Then Range("control_Age_group") = 3 '60y-69y
If i = 6 Then Range("control_Age_group") = 4 '>70y

'RUN Monte_Carlo_Simulation MACRO

Call MonteCarlo_PSA

'store the results
TOTAL_C = Range("TOTAL_C")
TOTAL_Q = Range("TOTAL_Q")
TOTAL_C_2 = Range("TOTAL_C_2")
TOTAL_Q_2 = Range("TOTAL_Q_2")

incremental_C = Range("INCR_C")
incremental_Q = Range("INCR_Q")
ICER = Range("ICER_")

CEA_10000 = Range("CEA_10000")
CEA_30000 = Range("CEA_30000")
CEA_100000 = Range("CEA_100000")
Application.ScreenUpdating = True

'Put the data on the Table of sheet 11 - for each age category:
Sheets("11 - Tables Result").Select

Cells(ref_row + i, 4).Value = TOTAL_C
Cells(ref_row + i + 1, 4).Value = TOTAL_C_2 'i+1 -to insert in the line below
Cells(ref_row + i, 5).Value = TOTAL_Q
Cells(ref_row + i + 1, 5).Value = TOTAL_Q_2
Cells(ref_row + i, 6).Value = incremental_C
Cells(ref_row + i, 7).Value = incremental_Q
Cells(ref_row + i, 8).Value = ICER
Cells(ref_row + i, 9).Value = CEA_10000
Cells(ref_row + i, 10).Value = CEA_30000
Cells(ref_row + i, 11).Value = CEA_100000

Next i

End Function

```