ASSESSING THE FEASIBILITY OF CONDUCTING AND USING HEALTH TECHNOLOGY ASSESSMENT IN COLOMBIA

-The case of severe haemophilia A-

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I, Hector E. Castro, confirm that the work presented this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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INTEGRATING STATEMENT

Introduction

When pursuing senior development in the field of Public Health, I decided to follow the Public Health and Policy Doctorate (DrPH) course because my main academic and career interests are in understanding how to bridge the gap between evidence and evidence-based health policy and practice. The aims of the DrPH – to equip its graduates with the skills required by managers and leaders in this field and to provide experience of dealing with the challenges of understanding and adapting scientific knowledge in order to achieve public health gains - seemed to be a "tailor made" opportunity for me.

The following paragraphs summarise the academic knowledge I have accumulated over four years of studies; they also highlight the links between each academic component. My final remarks offer some insights into how the DrPH has undoubtedly enhanced my career prospects in public health over a relatively short period of time.

The taught component

The taught component comprises two academic modules: Evidence Based Public Health Practice (EBPHP) and Leadership Management and Personal Development (LM&PD), now renamed as Understanding Leadership, Management & Organisations. I undertook both during October and December 2010.

The aim of EBPHP is to help students to identify, assess, synthesise, present and use research-based information to improve public health. One of the tasks I was assigned was to provide evidence-based health policy on tobacco warnings targeting adolescent population to a Ministry of Health (MoH). This task was more challenging for me than I expected since my previous background as a medical doctor and senior organisational manager had given me the skills to be a decision-maker, rather than a rigorous academic researcher or technical advisor. By conducting the assigned task I learnt how to conduct systematic searches of the literature, appraise and synthesise the evidence. It was the first time I had to produce a policy brief for a policy maker myself.

The second assignment for EBPHP was to design an 'influencing and knowledge transfer strategy' to put a research-based issue onto the policy agenda. At that stage of my career I was involved with a policy project supported by the Colombian MoH. The idea of institutionalising Health Technology Assessment (HTA) had recently seized the attention of policymakers; hence my project consisted of designing strategies for such a policy solution to reach the policy agenda and be implemented in this country.

I conducted a policy analysis on the topic of interest using John Kingdon´s model of agenda setting to depict the problem, policy and politics streams that created a window of opportunity for policy action. I also conducted a stakeholder analysis and suggested some prospective strategies that should be considered to help successfully implement an HTA agency in this country. I did not envision at that moment that those were the first steps of what is today the Health Technology Assessment Institute of Colombia- IETS, the institution that I currently lead.

The objective of the LM&PD is to provide students with the opportunities to explore a range of issues and theories relating to management, leadership, organisation, and to develop an understanding of what is required to become a future leader and manager in public health. At the time, the module had two compulsory assessed components. The first was an organisational management case study where I used my previous experience as senior health manager at a health insurance organization. Strengths, weaknesses, opportunities and threat analysis (SWOT) and Deming cycle were all familiar management tools to me, but whenever I used them to retrospectively analyse an organisational strategy, the *do´s* and *don'ts* emerged more clearly than ever before.

The second task was to develop a personal development plan and produce a reflective commentary. In all honesty, I was initially very sceptical about the value of this module. However, it turned out to be something of watershed moment in my career. Through the LM&PD I learnt to design a career plan, to reflect on my own personality and limitations, and to develop strategies and short-term goals to pursue a final objective: "to become a senior and effective health policymaker in Colombia". I realized that by aligning my personal values: contribution, recognition, fairness and achievement with a career plan, I could achieve this final goal.

The OPA fieldwork and report

I had the immense opportunity to conduct my organisational placement and policy analysis (OPA) at the National Institute for Health & Care Excellence - NICE, at its international branch (NICE International, NI) in the UK. At that time the Inter-American Development Bank sponsored a consultancy project with NI aimed at advising the Colombian MoH on how to set up a local HTA agency. My supervisor was of great help to me in liaising with and meeting the right people in order to secure the position; additional networking with the Colombian counterpart was very important to be admitted for this placement.

The OPA started in early 2011 and lasted 5 months; it consisted of supporting the NI team in locating and summarising the available information about how four western countries of interest for Colombia had established their own HTA institutions. My work also included advising on the most appropriate institutional arrangement for establishing a "NICE-like" institution in this setting. As part of the OPA, I conducted primary research, focus groups with relevant stakeholders in Colombia, and presented preliminary results to senior policymakers within the MoH.

Once the fieldwork was finalised I produced two different pieces of research, one for the host organisation (NI) and an OPA report for my academic institution (the LSHTM). This was probably the most challenging task of all. Besides being part of the team, I had to produce at the same time a consultancy report for NI and a rigorous academic essay for LSHTM. After six months of writing up I developed a framework for NI aimed at attracting project funding, and an OPA report for the academic faculty. I used all the skills acquired during this first year of studies and was challenged throughout the organisational placement; this period also provided me with valuable networks of co-operation within the UK and Colombia.

The thesis

The overall purpose of the DrPH research project is to help the student to learn about the role of research in public health practice. However, the specific aim of my thesis was to assess the feasibility of conducting and using HTA to inform decision-making in Colombia, using severe haemophilia A as the main case study. To fulfil the aims of this research work, I used a mixed methods approach.

The project was developed in Bogotá, Colombia and London. The issues around previous HTA work in this country were identified through a qualitative approach using semi-structured interviews. To assess whether primary prophylaxis should be a funding priority compared to a number of other (selected) health care technologies and to document potential difficulties in establishing formal HTA methods and procedures in Colombia a number of steps were undertaken. The main ones were conducting a de novo economic evaluation of primary prophylaxis with FVIII for people with severe haemophilia A, and using the Evidence and Value: Impact on Decision-Making (EVIDEM) framework to establish whether it should be a priority to fund, and establishing whether it is a credible / acceptable framework with which to make resource allocation decisions.

The economic evaluation was undertaken using standard decision modelling techniques. The use of EVIDEM as a decision making framework was applied and tested in a focus group emulating decision-making with participants who compared four mini HTA reports of public resource-competing health care technologies.

Final remarks

The DrPH has been an extremely rewarding journey, but at the same time, the most challenging one. It has a dual focus on developing the expertise to conduct and evaluate research and also on acquiring the skills crucial for leadership roles in public health policy and practice; I hope I have acquired both. It is worth mentioning that in order to expedite "travelling" throughout this academic programme, it is advisable that every new step should be interconnected with the previous and next one. EBPHP, LM&PD, the OPA and thesis in my case were all interconnected.

Currently I am the CEO of the first HTA agency in Spanish speaking America. I have no doubt that without the expertise, skills and exposure provided through the DrPH curriculum it would not have been possible to reconcile the aims of producing incremental public health and policy gains while achieving a personal goal of becoming a senior and effective health policymaker in my home country.

Abstract

Health Technology Assessment (HTA) examines the consequences of the application of health technologies. HTA is aimed at better informing decision-makers. In November 2012 Colombia established its own HTA agency (IETS). Up until the establishment of IETS, HTA had had a limited role in providing information to set priorities. Severe haemophilia A (SHA), an infrequent disorder of blood coagulation, serves as a good example of how the adoption of new technologies can change the course of a disease while challenging the financial sustainability of health systems.

The aim of this study was to assess the feasibility of conducting and using HTA to inform decision-making in Colombia. To fulfil these aims a mixed methods approach was used. Because decision-making is a task embedded in a complex and highly customised context, the case study method was considered as appropriate.

Through a qualitative approach using semi- structured interviews ten "drivers" emerged with the ability to help or hinder HTA: availability and quality of data, implementation strategy, cultural aspects, local capacity, financial support, policy/political support, globalisation, stakeholder pressure, health system context and usefulness perception.

A CUA from the Colombian health system perspective was developed to assess the cost-effectiveness of primary prophylaxis (PP) versus on-demand (OD) provision of FVIII for SHA. The ICER of PP with FVIII compared to OD was COL\$105,081,022 (USD\$55,204) per QALY gained. This is not considered cost-effective using a hypothetical threshold of up to three times the GDP per-capita.

Two approaches were used to assist decision-making for PP in Colombia, including EVIDEM. The final reimbursement decision about PP in Colombia would be "it would not be prioritised". Nonetheless, the final valuation of technologies was sensitive to the methods and criteria used to assist decision-making.

The combined results of the research appear to suggest that HTA development and use in Colombia is feasible, even for technologies that are difficult to evaluate. Results of this research work could be of significant value to the field of public health and policy since resource-allocation decisions in many settings similar to Colombia have often been made without enough evidence-based information. Further research in the field of priority-setting is still required.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

ANVISA   National Agency for Health Surveillance-Brazil

APCC   Activated Prothrombin Complex Concentrate

CETS   *Conseil d'évaluation des technologies de la santé*-Canada

CINETS   *Centro Nacional de investigación en Evidencia y Evaluación de Tecnologías en Salud* (National Centre for Research on Evidence and Health Technology Assessment)

CLH   Colombian League for Heamophilia (*Liga Colombiana de hemofílicos y otras deficiencias sanguíneas*)

COLCIENCIAS   National Administrative Department for Science, Technology and Innovation

CPGs   Clinical Practice Guidelines

CRES   Regulatory Commission for Health-Colombia

CTCs   Technical Scientific Committees-Colombia

DALY   Disability Adjusted Life Year

DECIT   Department of Science and Technology-Brazil

DERP   US Oregon State Drug Effectiveness Review Project

EBM   Evidence-Based Medicine

EPS   *Entidades Promotoras de Salud* (Health Insurers- Colombia)

EuroScan   International Information Network on New and Emerging Health Technologies

EVIDEM   Evidence and Value: Impact on DEcision-Making

FEIBA   Factor VIII Inhibitor Bypassing Activity

FVIIa   Activated Factor VII.

FVIII   Clotting Factor Eight

GDP   Gross Domestic Product

HICs   High Income Countries

HiTAP   Health Intervention and Technology Assessment Program-Thailand

HIV   Human Immunodeficiency Syndrome

HJHS   Haemophilia Joint Health Score

HR-QoL   Health Related Quality of Life

HSR   Health Sector Reform

HTA   Health Technology Assessment

HTAi   Health Technology Assessment International

IADB   Inter-American Development Bank

ICER   Incremental Cost-Effectiveness Ratio

IECS   *Instituto de Efectividad Clinica y Sanitaria* (Clinical Effectiveness and Health Institute)-Argentina

IETS   *Instituto de Evaluación Tecnologica en Salud* (Health Technology Assessment Institute-Colombia)

INAHTA   International Network of Agencies for Health Technology Assessment

INVIMA   National Institute for Food and Drug Surveillance-Colombia

IQWiG   Institute for Quality and Efficiency in Health care-Germany

ISPOR   International Society for Pharmacoeconomics and Outcomes Research

ISS   Instituto de Seguro Social- Institute of Social Security

IU   International Units

LMICs   Low and Middle Income Countries

MCDA	Multi Criteria Decision Analysis
MoHSP	Ministry of Health and Social Protection-Colombia
NICE	National Institute for Health and Clinical Excellence
OTA	Office for Technology Assessment
PAHO	Pan American Health Organisation
PBAC	Pharmaceutical Benefits Advisory Committee-Australia
PCORI	Patient Centered Outcomes Research Institute-USA
POS	Statutory Health Package-Colombia
QALY	Quality Adjusted Life Year
RCTs	Randomised Controlled Trials
RedETSA	*Red de Evaluacion de Tecnologias Sanitarias de las Americas* (Regional HTA network of the Americas)
rFVIII	Recombinant Clotting Factor Eight
SBU	*Statens beredning för medicinsk utvärdering*-Sweden
SHA	Severe haemophilia A
SISMED	National registry of prices for medicines-Colombia
SNS	National Superintendence for Health-Colombia
Tutelas	Judiciary mandates to protect fundamental rights-Colombia
VAS	Visual Analogue Scale
vCJD	Variant Creutzfeldt-Jakob disease
WFH	World Federation of Haemophilia
WHO	World Health Organisation
WTP	Willingness to Pay
WW2	World War II

I. INTRODUCTION

1. Health Technology Assessment supporting decision-making around the globe

Health Technology Assessment (HTA) examines the consequences of the application of health technologies and is closely related to evidence-based medicine (EBM)[1]. Both HTA and EBM are aimed at better informing decision-makers. As such, HTA has become an issue of great interest, although it has also attracted controversy. Advocates of HTA argue that it helps to promote efficiency of resource-allocation, whilst critics state HTA is simply a means to restrict access to new and costly technologies (O´Donnell et al, 2009).

Over the past decades different countries have established specialised HTA organisations aimed at better informing health care policies and clinical practice. The first technology assessment institution, although not exclusively health related, was the Office for Technology Assessment (OTA), established in the United States (US) public sector in 1972 with the aim of informing the US congress of the advantages and disadvantages of newly developed technologies. This early initiative became attractive to other western countries that were similarly dealing with imperfect and asymmetric information to make decisions. Soon after Austria, Denmark, France, Germany, the United Kingdom, Netherlands, and Sweden created similar institutions.

Early models of specialised HTA institutions[2] were established in 1987 in Sweden (*Statens beredning för medicinsk utvärdering*-SBU) and in Canada (*Conseil d'évaluation des technologies de la santé* (CETS) and Australia (Pharmaceutical Benefits Advisory Committee-PBAC) in 1988. This latter is recognised as the first HTA committee with binding power over drug reimbursement policies in a public health system; it is considered to be one of the earliest versions of an HTA agency[3]. SBU is recognised as one of the co-founders of the International Network of Agencies for Health Technology Assessment-INAHTA in 1993[4].

In 1999 the United Kingdom introduced the National Institute for Clinical Excellence, renamed later as the National Institute for Health and Clinical Excellence, and more recently as the National Institute for Health and Care Excellence (NICE). NICE perhaps remains the most well-known HTA organisation worldwide according to Morrison et al, 2009. Its clear ability to establish a transparent review process to determine the clinical and cost effectiveness of health care interventions for the NHS[5] continues to attract interest across the world.

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[1] The systematic collection and analysis of clinical evidence
[2] Also known as HTA agencies.
[3] When in 1992 it published its first formal guidelines for pharmaceutical reimbursement
[4] INAHTA (International Network of Agencies for Health Technology Assessment) a non-profit organization established in 1993 and has now grown to 57member agencies from 32 countries including North and Latin America, Europe, Africa, Asia, Australia, and New Zealand. All members are non-profit making organizations producing HTA and are linked to regional or national government.
[5] NHS National Health System England and Wales

HTA agencies have gained space in taxation-based and social health insurance systems. This is evidenced by the development of these agencies in different settings. For example, in 2004, the Institute for Quality and Efficiency in Health care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* -IQWiG) was established in Germany. The US Oregon State Drug Effectiveness Review Project (DERP) has applied principles of EBM to formulary decision-making in the public sector since 2000 and in 2010 the PCORI (Patient Centered Outcomes Research Institute), an independent organisation aimed at helping patients, clinicians, purchasers and policymakers to make informed health decisions, was created. In fact, most HICs[6] utilise some form of HTA process or agency to facilitate decision-making and priority-setting within their health systems (Bulfone et al, 2009 and Castro, 2011 and 2012).

Recent examples of HTA agencies in the developing world are: the National Agency for Health Surveillance (ANVISA) established in 1999 and the Department of Science and Technology (DECIT) (both in Brazil and conducting HTA since the mid-2000s), as well as the Health Intervention and Technology Assessment Program (HiTAP) in Thailand, created in 2007. In 2011 at the HTAi[7] global meeting in Rio de Janeiro, Latin America established a regional HTA network (RedETSA) initially comprising twelve countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, México, Paraguay, Peru, Uruguay); more recently countries like Canada have been incorporated. In September 2012 Colombia established its Health Technology Assessment Institute (IETS) which started operations soon after. That same month the Pan-American Health Organisation (PAHO) member states enacted a Resolution of commitment to introduce the use of HTA to inform decision-making in the Americas[8]. Currently, Chile and Costa Rica, among others, are planning to establish their own HTA organisations.

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[6] High Income Countries

[7] HTAi: Health Technology Assessment International is a global scientific and professional society for all those who produce, use, or encounter HTA. HTAi embraces all stakeholders, including researchers, agencies, policymakers, industry, academia, health service providers, and patients/consumers, and acts as a neutral forum for collaboration and the sharing of information and expertise. With members from 59 countries and six continents, HTAi is a thriving global network. Source HTAi web page http://www.htai.org/index.php?id=428 as per July 13th 2013.

[8] Evaluación e Incorporación de tecnologías sanitarias en los sistemas de salud. CSP28.R9. 19 de Septiembre del 2012. OPS/OMS

2. Methodological considerations in conducting HTA and the process of decision-making

It is often assumed that policies and decisions are made and implemented in a rational way (Simon, 1957). However, the real world is clearly more complex than this linear process, meaning that designing and implementing a successful policy change is unlikely to be this simple (Buse et al, 2010). Indeed authors like Lindblom (1959) have proposed that decision-makers take incremental steps for policy solutions by comparing only a small number of possible alternatives which are not substantially different form the *status quo.* Accordingly, decision-makers will test the political waters in deciding whether or not to pursue a given course of action (Buse et al, 2010), these representing a contested and dynamic policy process.

Resource allocation decision-making is a complex policy process that takes place along a continuum that moves from evidence generation to deliberation and communication of the decision made (Goetghebeur et al, 2008). HTA is only a part of this intricate process whereby the best available evidence is assessed with the aim of informing decision-makers about the most efficient use of resources under conditions of uncertainty. Although country-specific HTA health organizations and processes vary according to setting, some procedural principles (such as transparency, robust and appropriate methods for combining costs and benefits, explicit characterization of uncertainty and active engagement with stakeholders) have been associated with the robust operation of HTA programmes and institutions (Drummond et al, 2008 and Chalkidou et al, 2009). Nonetheless, according to Pichon-Riviere et al (2010) in Latin America, including Colombia where this project was developed, "the current level of application [of these principles] is considered uniformly poor".

Problems with quantity, quality, usability and accessibility of evidence have been identified as hindrances to informed policy-making (Jewell and Bero, 2008). Randomised clinical trials (RCTs) traditionally considered as a reliable source of evidence-based information are extremely valuable, but not always feasible due to cost or ethical considerations. Whenever conducted, RCTs operate under experimental circumstances, with rigid protocols that often differ from "real-world" conditions. HTA is a technique with the ability to bring together evidence and data from a variety of sources; whenever it is used alongside economic modelling, HTA is able to simulate "real world" conditions (Hjelmgren et al, 2001).

HTA reports usually draw on evidence from a broad array of sources and types of data, including clinical, use of resources, unit costs and health-related quality of life information. Broadly speaking, a comprehensive HTA report usually consists of a description of technologies, a summary of the evidence on safety, efficacy and clinical effectiveness and sometimes incorporates economic modelling and budget impact. Sources are likely to include RCTs, but also observational studies, and in some circumstances, even poorer quality evidence, such as expert opinion. Data could also be gathered from sources close to where such a decision needs to be made or from elsewhere.

Decision analytic models provide a means of bringing evidence altogether in order to generate estimates of cost-effectiveness (Drummond et al, 2005). Nonetheless, economic evaluation results are conditional on the data and structural assumptions they incorporate. If relying on modelling, a good analytic model should be able to simulate reality, capture relevant costs and outcomes, and be transparent and explicit about assumptions and limitations.

Authors such as Box and Draper (1987) state that all models are wrong, but some are useful. Recent methods guidelines for economic modelling have produced recommendations for good practice (Phillips et al, 2004 and Eddy et al, 2012). Currently there is reasonable consistency about what is considered good practice. According to Sculpher et al, 2000, there are "good and bad" decision models which thus need careful review and evaluation to ensure the value of their input into decision-making (Drummond el al, 2005).

One of the implications of making comparisons across different health care interventions through analytic modelling is that in order to help decision-making, costs and outcomes should be measured in comparable units across interventions, and a decision rule needs to be set. Whenever conducting cost-benefit analysis this problem is potentially solved since both costs and outcomes are measured in monetary value, and for a health technology to be considered "worth doing" total benefits must outweigh total costs.

In the case of cost-effectiveness (cost-utility) analyses this decision rule is less straightforward. Costs are measured and expressed in monetary terms, but outcomes are stated in either "natural" or combined units capable of capturing morbidity and mortality to allow cross comparison (e.g. Quality Adjusted Life Year- QALY). Hence, a threshold or ceiling ratio is required to assist decision-making. Ideally, this ceiling ratio represents the opportunity costs of any forgone programme within the system or elsewhere or the willingness to pay (WTP) of decision-makers; thus this threshold serves as a decision rule for a technology to be deemed cost-effective or not.

Some countries have proposed or implemented ceiling ratios (cost-effectiveness thresholds) as decision rules (Eichler et al, 2004). Many examples have been historically or arbitrarily set, such as the "rule of thumb" in the US of $50,000 per QALY gained (Weinstein, 1995 and Hirth et al, 2000), in Canada of CAN$20,000 per QALY gained (Laupacis et al, 1992) or the UK (where the CE ceiling ratio used by NICE ranges from £20,000 to £30,000 per QALY gained (Hutton et al, Loomes, Littlejohns, Towse and Pritchard, 2002). However, this latter figure has been refined by recently collected empirical data and now the central estimate seems to be nearer £13,000 per QALY gained (Claxton et al, 2013).

The use of cost-effectiveness ratios has been criticised by different authors (Birch and Gafni 1992, 1993 and 2002; Johannesson and Weinstein, 1993 and Donaldson et al 2002) who suggest that thresholds may not be able to capture all the relevant benefits of health care programmes, there might be issues about the transferability of data incorporated, and they may well represent an aggregated Willingness to Pay (WTP) per QALY gained instead of the real shadow prices of the programme under consideration. However, it is unlikely that decision-makers will be fully aware of the costs and benefits of every competing alternative (within and outside the health care sector) each time a decision needs to be made. Further concerns arise when considering the implementation of cost-effectiveness thresholds in contexts severely constrained by scarcity of data, as these preclude the possibility of reliably estimating forgone opportunity costs should a new technology be incorporated into their health systems.

Methodological considerations aside, neither HTA reports nor the results of economic models or cost-effectiveness thresholds should be blindly used in decision-making. Beyond scientific evidence and thresholds, decision-making also requires value judgements to be made (Eddy, 1990 and Tunis, 2007). "Decision-making can be regarded as the cognitive process resulting in the selection of a course of action among several alternative scenarios. Every decision-making process produces a final choice" (Reason, 1990).

According to Goetghebeur et al (2008), decision-making can be broadly subdivided into scientific and value judgment components. Scientific judgment relies on globally accepted standards defining the quality of evidence, this is not highly dependent on the evaluator and in principle could be standardised across jurisdictions. Value judgments, on the other hand, are subject to evaluator preferences and would be difficult to standardise. This value consideration also requires for well-organised decision-making processes, according to Rawlins (2004) those responsible for formulating NICE's advice have to make judgments both about what is good and bad in the available science (scientific value judgments) and about what is good for society (social value judgments).

It is worth mentioning that any viewpoint assumed during the analysis has an influence both on measurement and on the final decision made (Drummond, 2005). Decision-makers often represent a broad scope of individuals with different roles within the health and health care sector, ranging from clinical practitioners (micro level decision-makers) to those in charge of coverage and reimbursement policies for health care technologies (macro level decision-makers). According to Garrison et al (2007) decision-makers are increasingly seeking evidence on costs and outcomes on which to base their conclusions.

Health care resource-allocation decisions are complex and involve the assessment and appraisal of available evidence, while bearing in mind societal values and ethical considerations (Miot et al, 2012). Most of the published literature on priority-setting and decision-making has focused primarily on the technical aspects of quantifying the burden of disease or assessing the cost-effectiveness of different interventions. Although these are relevant inputs into the process, priority-setting as a whole is a wider political process because it involves the distribution of benefits and responsibilities among society (Glassman et al, 2012).

In many developing countries priority-setting and resource-allocation decision-making has been inconsistent and unstructured. Important criteria such as budget impact, equity, and disease severity have not always been taken into consideration, and if they have, it has often been in an ad-hoc manner with limited acknowledgement as to how they have impacted a final decision (Baltussen et al, 2006). In these cases the lack of coherence between limitless promise and limited resources leads to implicit and covert rationing through waiting lines, low quality, inequities, and other mechanisms (Glassman et al, 2012).

In recent years Multi Criteria Decision Analysis (MCDA) has emerged as a tool to support complex decision-making in health care, moving beyond the evidence generation phase. Multi- criteria methods are designed to help people make 'better' choices when facing complex decisions involving several dimensions. "MCDA are especially helpful when there is a need to combine "hard data" with subjective preferences or make trade- offs that involve multiple decision-makers" (Dolan, 2010). In theory, MCDA allows a structured and objective consideration of the factors that are both measurable and value-based in an open and transparent manner (Baltussen et al, 2006).

In 2008 Goetghebeur et al conducted extensive analyses of the literature and documented decision-making processes worldwide. They explored the steps used to make decisions (from evidence generation to communication of decisions) with the aim of constructing a MCDA framework able to capture the quantifiable components of decision-making into a matrix, thus the Evidence and Value: Impact on Decision-Making (EVIDEM) was developed. It includes core quantifiable components alongside a methodology to synthesise the evidence needed to assess each component.

EVIDEM (according to the original authors), promotes transparent and efficient health care decision-making through the systematic assessment and dissemination of the evidence and values on which each decision is based. Modified versions of the EVIDEM framework have incorporated additional criteria and been tested for clinical and resource-allocation decision-making in developed and developing countries including Canada, US, Nepal and recently in South Africa (Goetghebeur et al, 2010 and 2012, Tony et al, 2011, and Miot et al, 2012).

In the case of countries where no cost-effectiveness thresholds have been discussed or accepted, MCDA may have space to incorporate cost implications and societal values to rank health care interventions, departing from the "hard" methodological constraints imposed by unmeasured opportunity costs. Indeed, it has been stated that MCDA can be an important step toward rational priority-setting in developing countries (Baltussen et al, 2007, Miot, 2012).

3. <u>Colombia´s current problems prioritising and allocating resources for health care, and its recent interest in priority-setting and HTA</u>

Since the 1993 health sector reform (HSR), access to health care in Colombia has been facilitated by the issue of statutory health insurance which covers an explicit list of health care benefits (POS)[9]. As part of this reform, coverage is guaranteed and financed from contributions of employers and employees in the formal sector, and poor and unemployed citizens are subsidised by the Government via earmarked taxes. According to figures published by the Colombian Ministry of Health and Social Protection (MoHSP), Colombia invests 6.5-7.4% of the country´s GDP in health and POS now covers nearly 96% of the country´s population[10]. Many macro performance indicators have improved since the HSR was introduced (The World Health Organisation-WHO/ PAHO health indicators and Escobar, 2005), nonetheless the country struggles to set priorities and allocate resources for health care in an efficient manner.

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[9] POS: Mandatory Health Plan, Spanish acronym
[10] 46 million inhabitants by 2011

The first list of health care benefits, established in 1994, was thought to be inequitable (less comprehensive for those covered by the subsidiary scheme) and not regularly updated to reflect the growing availability of newly developed technologies. As such, the explicit benefits package was often challenged by patients who, via exceptional requests and judiciary claims (CTCs and *tutelas*) [11], were granted access to services that had not been initially budgeted for. Between 1999 and 2012 *tutelas* regarding health and health care services increased from 21,301 to 114,343 per-year respectively (Caballero- Uribe, 2012 and *Defensoría del Pueblo*, 2013). Unsurprisingly this has caused a strain on the public budget for health.

Figures from the MoHSP estimated that up to 25% of total health spending was used to reimburse services not originally listed in POS. Most beneficiaries of these exceptional health services are wealthy and well-educated individuals, and just a few belong to the poorest quintile of the population. At the peak of the crisis, the constitutional court mandated the government to amend any structural factors leading to inequitable coverage, and to update and equalise POS content for the entire population as soon as possible, all of which caused an additional financial burden to the system.

In late 2009 the then president of Colombia announced a COL$2 billion (USD$ 1.045 billion)[12] deficit in the health budget. The country is in epidemiological transition, and the strain has been exacerbated by soft entry criteria for new technological developments. The current government, elected in late 2010, pushed by the financial crisis has attempted two major HSRs and taken incremental steps to control costs and strengthen its institutional capacity. In December 2011, in compliance with the constitutional court´s mandate, POS content was updated by the Regulatory Commission for Health (CRES). However, it received considerable criticism from the media[13] and the academic community due to the inadequate use of evidence and weakness of methods, but also the lack of transparency within the decision-making process. As part of the government´s efforts to set priorities for health, it created IETS in September 2012, disbanded CRES in December 2012, and re-assumed its role of resource-allocation decision-maker; nonetheless the process of incorporating HTA in a more systematic fashion is still under construction.

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[11] CTCs (Technical Scientific Committees) and Tutelas (Judiciary challenges and verdicts from the courts) are the exceptional mechanisms of citizens to access non POS services in Colombia.

[12] Currency exchange rate on July 12th 2013 at www.oanda.com. Notice a language difference on definition of billion. For billions measured in Spanish subtract 000 (divide by 1000).

[13] From press releases on POS update, see editorials from *el colombiano* and *el tiempo* on reference section

Up until the establishment of IETS, HTA had played a limited role in Colombia in terms of providing information to set priorities, allocate resources or formulate evidence-based policies for health and health care. However, a limited number of Colombian universities, out of academic interest from the late 1990s onwards have been involved in producing HTA reports. Moreover, in recent years the Colombian pharmaceutical industry and international organisations like PAHO have requested HTA information to these institutions to inform their market access strategies or vaccination policies respectively.

During the last decade the MoHSP, regional secretariats for health, former CRES and pharmaceutical companies have been the predominant users of HTA in Colombia, and a limited number of academic institutions the producers. A preliminary exploratory research on the feasibility to institutionalise HTA in Colombia conducted by the main researcher (Castro, 2011) found a positive social mood on the need to have rigorous HTA information to support decision-making; especially the central government and health care insurers are prompt to use it, however the level of support on HTA policies varied among stakeholders, being the pharmaceutical industry and the healthcare professionals the most reluctant to its implementation.

The government's interest in relying on scientific evidence to better inform health policies began in the mid-2000s (IDB project 2011) but it has only been in the last two or three years that the methods and processes for assessing health technologies akin to those used by NICE in the UK or PBAC in Australia have attracted the attention of policymakers. Periodic meetings and technical support, especially from the international branch of NICE, have been influential.

Technical aspects such as economic modelling and the use of the Quality Adjusted Life Year (QALY) as a relevant outcome unit have recently been used in constructing a set of 24 clinical practice guidelines commissioned by the MoHSP and the National Administrative Department for Science, Technology and Innovation (COLCIENCIAS) and released in July 2013[14]. In Colombia there is no systematic process in place to set priorities, there is no "reference case" to standardise methods or methodologies to produce HTA, nor is there a transparent or active engagement process with stakeholders for coverage decision-making.

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[14] See the ToR of CPGs at http://www.COLCIENCIAS.gov.co/convocatoria/convocatoria-para-la-elaboraci-n-de-una-gu-metodol-gica-para-el-desarrollo-de-gu-de-pr-

Despite current efforts, the system´s allocation of health care resources is still far from efficient and equitable. For example, up to late 2011 POS did not cover mammography testing for diagnosing breast cancer in women in the lowest socio-economic quintile of the population, whilst access to newly developed Monoclonal Anti-Bodies (MAB) for advanced cases of disease was granted via "*tutelas*" (De Charry et al, 2008). Further, effective coverage was not guaranteed for the poorest the population[15] (Florez and Soto, 2007) and the level of catastrophic health expenditure for households remained significant (Xu et al, 2003).

A further example is the case of Fabry[16] disease, a rare condition that affects a total of 31 to 37 citizens; opportunity costs of treatment for this health condition are equivalent to enrolling 664,000 additional people in the subsidised scheme (cited by Glassman et al, 2012). Some non-POS health care services prescribed and reimbursed via exceptional mechanisms are considered either as luxury goods or experimental interventions with no robust evidence whatsoever (e.g aesthetic procedures, fertility treatments, and equine or bird therapy for cerebral palsy)[17]. Off-label prescribed medicines were reimbursed by the system without any control. For example, *bevacizumab* was registered by the local authority, INVIMA,[18] for use in the treatment of metastatic colorectal, lung and kidney cancer, and glioblastoma, but it was prescribed, used and reimbursed for age-related macular degeneration via *tutelas*.

It seems from these findings that decision-making in Colombia has been ad-hoc and has not considered the best available evidence or the opportunity costs of decisions made. It may also not have explicitly considered good HTA practice or societal values or preferences. In this somewhat chaotic scenario, many health conditions and technologies are competing for public funding without a systematic and transparent process of resource-allocation in place.

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[15] Source: "Así vamos en salud 2007"- Equity comparison by gender, location and income. Universidad de los Andes. Fundación Corona at http://www.asivamosensalud.org/descargas/Presentacion_Equidad_Corona_DNP.pdf

[16] Fabry disease (also Anderson-Fabry disease, angiokeratoma corporis diffusum and alpha-galactosidase A deficiency). Rare X-linked (inherited) lysosomal storage disease, causes a wide range of systemic symptoms. The disease is named after Johannes Fabry. Source: James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. P 538

[17] According to datasets of FOSYGA (national funding pool) and the MoHSP years 2008 onwards

[18] INVIMA National Agency for Surveillance of Medicines and Food of Colombia

4. Severe haemophilia A and the availability of evidence on the clinical and cost-effectiveness of primary prophylaxis

Haemophilia A is an infrequent inherited disorder of blood coagulation, characterized by a permanent tendency to haemorrhage. Classic haemophilia (also known as type A), results from a deficiency of clotting factor VIII (FVIII) as an X-linked inherited disorder (Stachnik, 2010). Patients usually remain asymptomatic until the haemostatic system is stressed by a surgery or trauma. Nonetheless, severe haemophilic patients can also bleed spontaneously. Haemophilia A is rare, but is the most common type of haemophilia and affects 1 in every 5,000-10,000 male births.

Debuting age, location and frequency of bleeding are all dependent on the severity of the disease, which is categorised by the Level of Activity (LoA) of FVIII. Disease is classified as mild (LoA from 5-40% [0.05- 0.4 IU/ml]), moderate (LoA from 1-5% [0.01- 0.05 IU/ml]) and severe (LoA less than 1% [<0.01 IU/ml]) (White et al, 2001). Around 70-80% of all bleeding episodes occur in the joints (most frequently the knee), which leads to haemarthrosis (joint haemorrhage with pain and swelling) (Stachnik, 2010, Wong and Vdovin et al, 2011 and Kempton et al, 2012).

Cumulative chronic bleeding episodes in the joints leads to progressive and chronic damage and scarring (haemophilic arthropathy); this is the most important long-term complication of recurrent bleeding (Wong et al, 2011). The development of clotting factor inhibitors (a neutralizing immunoglobulin which acts directly against FVIII) is also a serious and frequent complication associated with chronic exposure to exogenous clotting factor that may occur in up 30% of all cases of disease (Collowick et al, 2000 and Farrugia et al, 2013). Different therapeutic options for inhibitors have been trialled in recent years with different levels of success [high doses of FVIII or FEIBA[19] (rFVIIa or APCC)].

There are two predominant approaches to treating severe haemophilia A. The first is on-demand (OD) administration of exogenous clotting factor either plasma derived (FVIII) or recombinant (rFVIII[20]) whenever joint or extra-articular bleeding occurs. The second approach provides exogenous clotting factor to prevent patients from bleeding (prophylaxis) in this first instance and thus, developing arthropathy. There are two forms of prophylaxis: primary and secondary. Primary prophylaxis (PP) provides frequent (typically at least three times a week) administration of missing clotting factor at early stages of life or once the first bleeding episode has occurred. Secondary prophylaxis on the other hand refers to the use of clotting factor after joint damage has already occurred, but prior to elective surgery or expected joint stress in order to reduce further joint injury.

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[19] FEIBA- Factor VIII Inhibitor Bypassing Activity [FVIIa- Activated Factor VII or APCC- Activated Prothrombin Complex Concentrate]
[20] rFVIII refers to the recombinant (synthetic) form of clotting FVIII.

PP has proven more effective in reducing joint *sequelae* than OD, and is currently considered the gold standard of care, especially for younger patients in HICs[21] (Biss et al, 2008). In spite of this, OD treatment is still the prevailing approach in many affluent settings and more so in resource constrained contexts because PP is usually more costly to provide (Giangrande, 2004).

In 2012 Castro et al conducted a search of the literature about the history and evolution of the clinical effectiveness of treatment for haemophilia type A. According to a number of studies, in the 1930s average life expectancy of haemophiliacs was less than 11 years, treatment was merely 'supportive', and death was commonly associated with severe intracranial or joint haemorrhage.

In the 1940s, whole blood transfusion was introduced which enabled swifter access to treatment; as a result, life expectancy reached 39.7 years for American haemophiliacs in the post-World War II era (Lee, 2009). After 1964, when Pool discovered that *cryoprecipitates*[22] were able to restore clotting function to normal, life expectancy of haemophiliacs who received this treatment reached 60 years. Nonetheless disability rates remained high due to cumulative joint damage associated with each new bleeding episode (Wong et al, 2011).

During the late 1970s Nilsson and Ahlberg in Sweden pioneered a prophylactic scheme in which FVIII was regularly administered in order to prevent bleeding and avoid subsequent joint damage. Life expectancy for these patients reached an average of 68 years (Larsson, 1985). Currently in HICs life expectancy of mild and moderate haemophiliacs is around 70 years (close to that of the general population), whilst severe cases are still expected to live at least 15 years less than general population (Darby et al, 2007). Prophylaxis has been associated with the consumption of additional resources; these could be at least twice the average cost per-patient, when compared with OD treatment (Daliri et al, 2009).

Regardless of this progress, in 1982 the first US haemophilic patient that had been infused with plasma derived FVIII infected with HIV[23] was diagnosed as positive. By the early 1990s HIV reached a prevalence of 60 cases per million in the USA, and 1 in every 7 haemophilic patients in the UK was infected (Evatt, 2006). In the same decade HIV/AIDS was the cause of at least a quarter of all deaths among haemophiliacs in the Netherlands (Ragni et al, 1986, Chorba et al, 1994, and Triemstra et al, 1995). In 1992 an estimated 60% of all haemophiliacs, and 80% of all patients ever treated in the US with plasma-derived products had also become infected with hepatitis C (Makris et al, 1993 and Van Der Poel et al, 1991). It was only after the introduction of antiretroviral therapy (ARVT) that mortality from HIV in haemophilic patients decreased (Mocroft et al and Porter et al, 2003).

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[21] HICs- High Income Countries
[22] The cryoprecipitate fraction of plasma contains proportionally greater quantities of FVIII.
[23] HIV- Human Immunodeficiency Virus

Viral attenuation processes against the transmission of HIV and HCV[24] were introduced in the manufacture of FVIII concentrates in 1985 (Oldenburg et al, 2009). New technological developments led to the first successful treatment with recombinant (synthetic) factor VIII- rFVIII reported in the literature in 1987 (Mannucci et al, 2001). rFVIII concentrates have, over the years, practically eliminated the risk of blood-borne infections through human or animal plasma products (Oldenburg et al, 2009). Indeed, there has been no reported HIV transmission linked to the use of rFVIII in the developed world since 1985, and virally safe products for hepatitis C have been available since the early 1990s (Van Der Poel et al, 1991).

Current methods of viral inactivation, such as improved viral-depleting processes, nano-filtration and donor screening practices, have resulted in safer plasma-derived clotting products and greatly reduced the risk of transmission of HIV, hepatitis B and C viruses, amongst others (Mannucci et al, 2001). According to Farrugia et al (2013) "we are currently facing an era of safe FVIII concentrates". Nevertheless there are no screening tests available for the detection of prions, including the presumed causative agent of variant Creutzfeldt-Jakob disease (vCJD). Precautions are largely based on donor exclusion, and although no cases of the classic or variant form of CJD have been reported in haemophiliacs anywhere in the world or after long periods of observation in the UK, uncertainty still remains particularly over the threat of as yet unknown 'future' pathogens (Giangrande, 2002; Darby et al, 2007).

The evidence base on the effectiveness of haemophilia A treatment has grown exponentially in recent decades, and although controlled studies remain the exception, a main concern of researchers now relate to the cost-effectiveness of PP and treatments for clotting factor inhibitors, especially in settings affected by the global economic downturn, and with competing demands on health care budgets (Castro et al, 2012). Long-term allocation concerns are expected to grow in the near future as longer acting exogenous clotting factors are in development by pharmaceutical companies, and will soon enter the market. According to O´Mahony (2011) and Farrugia et al (2012) all these factors are leading both advisory bodies and payers to explore HTA to obtain recommendations for reimbursement policies.

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[24] Hepatitis C Virus

In contrast with this increasing stock of knowledge on the clinical effectiveness of the prophylactic administration of exogenous clotting factors, published economic evaluations of haemophilia care remain very limited and their results are inconclusive For example, a recent review of the literature by Miners (2013) found that while a number of economic evaluations of prophylaxis with FVIII have been undertaken, their results vary enormously from it being "dominant" to costing over €1 million per QALY gained.

According to this review, only 11 published studies had conducted some form of full economic evaluation[25]. All studies have adopted different perspectives, made different structural assumptions, used different time horizons, discount rates and sources of data. A salient finding from this review was that "all the reviewed studies contained methodological weaknesses, but some were considered weaker than others" (Miners, 2013); and nearly all costs of treatment were attributable to clotting factor provision.

From this wide range of published results it is still unclear if this intervention (either with FVIII or rFVIII) has reached the point of being considered "good value for money". It is worth mentioning that even if prophylaxis is "worth-doing" in HICs, it might not be the case for all countries (Geraghty et al, 2006 and De Moerloose et al, 2008). Most of the published evidence on the clinical effectiveness and cost-effectiveness of prophylaxis comes from affluent settings. According to Giangrande (2004), the prognosis for haemophiliacs is still bleak in many parts of the world. The World Federation of Haemophilia (WFH) estimates that two thirds of haemophiliacs worldwide receive little or no treatment for their condition. For instance 45% of the world´s population lives in India, Bangladesh, China and Indonesia: while 10% of diagnosed patients with haemophilia are located in these countries, their consumption of clotting products available in the global market for treatment is only 2%.

5. The current context of severe haemophilia A in Colombia

In Colombia, haemophilia A care represents an important financial burden to the health system. Costs associated with clotting factor replacement for this condition were COL$140,164,400,000 (USD$73.72 million) in 2010[26] or 0.46%[27] of the country's annual spending on health with the aim of treating approximately 2,000-2,600 patients, 800-1,040 of whom are classified as severe cases (Colombian League for Haemophilia (CLH), 2011).

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[25] Those considering the costs and health outcomes associated with treatment and complications
[26] Figures published by the Colombian Medical Federation- FMC in October 2010. See http://www.observamed.org/
[27] These costs do not include inpatient or ambulatory care arising from bleeding episodes or their complications, or the costs arising from the use of rFVIIa for patients with inhibitors

Primary prophylaxis (PP) and on-demand (OD) approaches to treat haemophilia A co-exist in Colombia with OD treatment based on plasma-derived products predominating clinical practice (National registry for medicines, SISMED, 2010) [28]. Nevertheless, the use of prophylaxis and recombinant therapy has steadily grown over the past seven years.

There are no evidence-based clinical practice guidelines in place for this health condition. Half of the haemophilic population in Colombia is under 18 years of age, and although mandatory insurance coverage for haemophiliacs has risen from 65% to 85% in the past five years, and death rates associated with bleeding episodes have decreased, long-term clinical outcomes are still far from optimal. Haemophilic arthopathy with its subsequent impact on health related quality of life (HR-QoL) and long-term disability is still a frequent finding (CLH, 2011).

There are eight or nine registered centres for haemophilia care with heterogeneous levels of quality in Colombia according to the National Superintendence for Health (SNS). Haemophilia care while competing with other priorities has raised the awareness of the general public and seized the attention of the media and local Government in recent years. This is not only because, of all the orphan[29] conditions, haemophilia accounts for the biggest proportion of the population, but also because not even in the upcoming new HSR has the issue of sustainable funding for orphan conditions been solved.

In 2010, law 1392 stated that patients with orphan diseases should be granted access to quality health care and reimbursed via exceptional mechanisms. This law created confusion because it defined orphan diseases as those with a prevalence of less than 1 case per 2,000 people and categorised them in a similar way to neglected diseases. This frequency definition, which is higher than global standards, raised considerable criticism from the media and expectations of full coverage[30] from patients. The local confusion over the definition of "neglected" versus "orphan" diseases was resolved in further legislation enacted in January 2011 (Law 1438) and a new, more evidence-based definition of less than 1 case in every 5,000 people for orphan conditions was issued.

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[28] According to internal data from the Colombian League for Haemophilia in 2010 nearly 34,000,000 IU of FVIII were sold in Colombia compared with 26,685,000 IU of rFVIII.

[29] Orphan means a rare disease. According to US criteria, an orphan disease is one that affects fewer than 200,000 people. The EU definition is less than 5 cases in 10,000. WHO suggest a frequency of less than 6.5- 10 in 10,000. In Colombia law 1438 defined orphan diseases as those affecting less than 1 person in every 5000 people. There are more than 5,000 such rare disorders. Source: /http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1885017

[30] See press releases at http://www.elespectador.com/columna-211633-ley-sobre-enfermedades-huerfanas and http://www.prismatv.unal.edu.co/nc/detalle-serie/detalle-programa/article/enfermedades-huerfanas.html

The fifth international "rare disease day" on 29th February 2012 served as a focusing event for pressure groups. The former Colombian Minister of Health released a public statement backing the system´s commitment to provide and reimburse health care outside POS content in all cases of orphan diseases[31] (including haemophilia). The (SNS) was commissioned to collect and update the list of queries and claims arising from faulty health care for patients suffering from orphan diseases. Although the commitment to exceptional mechanisms to grant unrestricted access to health care for this population was maintained, such access has not yet been accomplished since prophylaxis has not been explicitly included in POS.

According to Rawlins (1999), "clinical care given to patients frequently departs from best practice; the fast adoption of new technologies without certainty about its clinical and cost-effectiveness, but also the slow adoption of those proven to be effective and "good value for money", leads to inefficiency". The case of severe haemophilia A, serves as a good example of how the progressive adoption of newly developed health care technologies can dramatically change the natural course of a historically fatal disease while challenging the financial sustainability of health systems. Haemophilia A has become a chronic and 'manageable' condition nowadays. Although this represents a remarkable achievement for science, it creates an additional burden for health systems due to longer survival rates and costly lifetime replacement therapy (Castro et al, 2014), Colombia is no exception.

Colombia has faced in recent years a financial and "lack of trust" crisis within its health care system that has threatened its sustainability. After two attempted reforms (Laws 1122 of 2007 and 1438 of 2011) the country still struggles to set priorities in a systematic and transparent manner. Yet there is a global trend to use or institutionalise HTA to inform coverage decision-making in many parts of the world that has seized the attention of local policy makers. Just recently this country established its own HTA agency, however the contextual aspects that may facilitate or hinder successful HTA implementation have not been yet explored. Since resource allocation decision-making is an intricate process that goes beyond HTA methods and institutions, the relevance of this work for Colombia may be of value for both producers and users of HTA.

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[31] Public declaration from the Minister of Health source official web page of the MoHSP on Feb 29 2011
http://www.minproteccionsocial.gov.co/Paginas/Super%20Salud%20deber%C3%A1%20tener%20registro%20de%20quejas%20y%20recla
mos%20de%20pacientes%20con%20enfermedades%20huerfanas.aspx

II.   AIMS, OBJECTIVES, METHODS AND TIMEFRAME OVERVIEW

The overall aim of this thesis was to assess the feasibility of conducting and using HTA to inform decision-making in Colombia, using primary prophylaxis (PP) for the treatment of severe haemophilia A as the main example. To achieve this, a mixed methods approach was used and is presented in three empirical chapters. In the first chapter qualitative methods are used to further explore past and future issues with respect to establishing formal HTA processes and methods in Colombia. The second chapter contains a cost-utility analysis of PP, as an example of how an economic evaluation for a challenging disease could be undertaken. The third chapter consists of a quantitative report of an attempt to use EVIDEM, as a framework for producing evidence-based guidance on four brief HTA reports, one of which is the expansion of the CUA of PP from Chapter 2 which was complemented with a "full" HTA report. In summary, the main questions that are addressed in the thesis chapters are as follows:

- **What are the main aspects that may help or hinder HTA development and use in Colombia?**

- **What is the incremental cost-effectiveness of primary prophylaxis compared to on- demand treatment in Colombia?**

- **Can EVIDEM be used in Colombia to assist resource-allocation decision-making, and should the use of primary prophylaxis be prioritised over three other non-haemophilia health care technologies?**

The dynamic process of using the available evidence to inform decision-making creates a continuum that favours the use of a case study. Case studies have been used to analyse health services elsewhere (Keen, 2007) and gained renewed interest in recent decades. The project was undertaken in London and Bogotá, Colombia, where relevant stakeholder interviews and meetings were held.

A timeline is shown in Figure 1 to explain the evolution of HTA in Colombia, my role as main researcher within it and the relation of these changes impact on and relate to this thesis. In an overall period of less than three years, the main researcher´s roles ranged from being a consultant at NICE international to becoming the Chief Executive Director of the Colombian HTA agency (IETS). This timeline analysis also served to support reflexivity of findings as it is presented in the overall discussion session. The triangulation of results from interviews, observation and focus group improved their validity. This comparison of findings is presented in the section titled convergent, divergent and contradictory findings.

Figure 1. Timeline, HTA evolution in Colombia and roles played by researcher throughout the project

	2011		2012		2013		2014	
	I	II	I	II	I	II	I	II
Research stage	First literature searches on HTA globally and primary prophylaxis for severe haemophilia		Semi-structured interviews conducted Chapter 1	Literature searches on PP for SHA updated Chapter 2	Economic model for SHA developed Chapter 2	MCDA- EVIDEM pilot with decision-makers Chapter 3	Thesis writing up	Thesis submission and viva
HTA evolution in Colombia	Law 1438 is enacted giving space to establish an HTA agency	IETS formulation stage, project funded by IDB and supported by NICE international aimed at producing a blueprint for the MoHSP		IETS established , CRES selected decision-making criteria, later disbanded	IETS works with the MoHSP on updating POS content using comparative safety and effectiveness methods and prospective budget impact analysis		IETS works on producing a reference case for economic evaluation and supporting the MoHSP on developing a more systematic and transparent decision-making process	
Roles played by researcher	DrPH student- placement at NICE international	DrPH student- Colombian MoHSP consultant		DrPH student- appointed as Chief Executive Director of IETS	DrPH student- current Chief Executive Director of IETS			

The issues around previous HTA work in Colombia were identified through qualitative enquiry methods using semi- structured interviews, which are reported in Chapter 1. The qualitative enquiry methods were used to assess the feasibility of conducting HTA as well as its potential future role in Colombia. A series of semi-structured interviews helped to explore previous experiences of academics devoted to HTA over the past years, and also to explore their perception of the potential use HTA may have in the near future.

The treatment for SHA was chosen as a case study to develop an economic evaluation in Colombia, since no local HTA for this health condition has been developed so far, it has captured substantial media attention in recent times and there is still the political promise of limitless health care coverage for orphan diseases. To do this, a *de novo* Cost-Utility Analysis (CUA) comparing PP versus OD treatment for severe cases of disease was conducted. This also served to identify methodological aspects that may make HTA and economic modelling difficult in Colombia.

Finally, to assess the feasibility of HTA as a tool to assist decision-making, the MCDA framework known as EVIDEM was tested in a focus group resembling decision-makers comparing four mini HTA reports (including the expanded CUA form chapter 2). This also explored the needs and expectations of participants regarding HTA and the use of broader decision-making criteria; findings are presented in chapter 3. Participants in the focus group appraised HTA results of PP with FVIII for SHA with three other non-haemophilia health care technologies (zinc supply for diarrhoea prevention, anastrozole for breast cancer and ticagrelor for acute coronary syndrome). These were chosen for convenience by the researcher, since all three have recently had Colombian HTA summaries published, and are on the waiting list of technologies to be incorporated into POS. This focus group also acted as a pilot to advise the Colombian MoHSP on how to design a more systematic and transparent process to update the publicly reimbursed benefits package (POS) and incorporate the use of budget impact analysis into the process.

A detailed description of methods and findings is presented in each one of the empirical chapters, as follows:

1) CHAPTER 1: Exploring the issues of previous experiences of conducting HTA, and academics' perception of its role and future use in Colombia.

2) CHAPTER 2: Cost-utility analysis of primary prophylaxis for the treatment of severe haemophilia A in Colombia.

3) CHAPTER 3: Testing the MCDA-EVIDEM and the use of HTA for resource-allocation decision-making in Colombia.

III.   EMPIRICAL CHAPTERS

1.   <u>CHAPTER 1</u>- Exploring the issues of previous experiences of conducting HTA, and academics' perception of its role and future use in Colombia:

INTRODUCTION:

The aim of this chapter is to identify and assess the various factors that may facilitate or hinder HTA production, and use, as a source of evidence-based information for decision-making in Colombia. As previously mentioned, common motivations for establishing HTA processes and agencies across the globe are the growing costs of health care, uncertainty about the cost or effectiveness of new and existing technologies, and the variability of clinical practice. HTA has become a focal point for the support of priority-setting in many countries which are dealing with budget constraints, expanding expenditure for health care, and market pressure for the entry of newly developed technologies.

Increasing interest from different countries in developing or improving more systematic and transparent processes to set priorities and allocate resources has created a propitious trend for HTA and EBM to emerge and grow. According to Drummond et al (2000) country specific variables such as history, culture, politics, health-care systems organisation and rationale for undertaking HTA should be considered before implementing its use. HTA also seems to be surrounded by political and social values that need to be borne in mind alongside good methodological practice. Colombia is no exception and there is an opportunity through this research to identify those aspects that may help or hinder HTA development and use in this country.

Colombia itself poses a challenge to conduct HTA because necessary data about disease incidence, prevalence, use of health care resources, and costs may be scarce or not available for many health conditions. Therefore, it is important to explore the needs and expectations of those devoted to HTA work in this interest. Authors such as Drummond et al, 2008 and Chalkidou et al, 2009 have identified some procedural principles associated with the robust operation of HTA programmes and institutions. Nonetheless, according to Pichon-Riviere et al (2010) in Latin America including Colombia, "the current level of application [of these principles] was considered uniformly poor". All these aspects are explored in this chapter through qualitative enquiry methods with the aim of answering the research question of interest.

METHODS:

To answer the empirical research question: What are the main aspects that may help or hinder HTA development and use in a setting such as Colombia? The in-depth semi- structured interview approach was selected as a means to collect data, and thematic content analysis was used to analyse it. As with many other forms of qualitative methods of data collection, the interviews aimed to collect data from a small sample of participants, since the size of sample was not determined by the need to ensure generalizability, but by the desire to fully investigate the topic of interest and gather information-rich data (Grbich, 1999). Another reason for selecting this frequently used approach (Green & Thorogood, 2009) was its usefulness for answering questions about salient issues among particular groups of participants.

"The most basic way of characterising qualitative studies is to describe their aims as seeking answers to questions about the "what", "how" or "why" of a phenomenon" (Green and Thorogood 2009). These studies are usually conducted to understand more about phenomena, rather than measuring them. For the purpose of this chapter, qualitative enquiry methods were used to explore the issues of previous experience of conducting HTA in Colombia from the perspective of local academics involved in HTA research over the past decade, and to examine their views of the potential use of HTA in this context.

Qualitative research methods are designed to test or build theories, but many others are designed to address empirical questions without any explicit theoretical aims (Green & Thorogood, 2009). Analysis of qualitative data has largely focused on three methodological approaches: grounded theory, phenomenology and ethnography. Nonetheless, authors like Murphy et al (1998) recognise many other forms of qualitative enquiry (Awoko, 2001).

All three classic approaches of qualitative enquiry were considered before selecting the most suitable approach for this study. In the grounded theory approach explicit data receives analytic treatment through constant comparison to produce a theoretical foundation. The Glaser and Strauss (1965, 1967) methodological strategy of theory generation was not followed in this part of the research since the aim was to explore and describe issues of previous experiences of conducting HTA in Colombia and not to build up new theory; neither there was an intention to move beyond description into conceptualization or theorizing Glaser (1992) and Kendall (1999).

Phenomenological inquiry was also considered. This interpretative approach focuses on interviewing and gaining understanding of the meaning of the participant´s experiences (Van Manen, 2001). This approach is concerned with individual experience, and aims to making the unspoken "audible and visible" (Awoko, 2001). In this particular case phenomenology was not used because the aim of the study was not to understand the "essence" of HTA as a phenomenon, but to understand the overall HTA context in Colombia; hence the "life- world" (the everyday world experienced and taken for granted and constituted by members within that world [Schutz, 1964 and 1970]) was not explored in this case study.

Finally, ethnography which refers to methods of participant observation, but also to the product of the ethnographic investigation (Green and Thorogood, 2009) is aimed at understanding how beliefs are embedded in local cultures through living and working with the community. In the case of this study there was no intention to live or work with the HTA research community in Colombia to identify enablers or barriers, mainly because of time and budget constraints.

Thematic content analysis, on the other hand, was selected over the above-described options of analysis, because it is an analysis of the content of collected data that allows researchers to look at data from interview transcripts to categorise participants´ accounts in a way that can be summarised. In this type of approach themes that recur or are common are classified, compared and categorised.

Sampling

Purposive sampling was used in this part of the research, and concurring with Crookes and Davis (1998), sampling was judgemental and involved the conscious selection of participants to be included in the study. In this case individuals with similar characteristics were considered eligible (local academics with at least five years' experience of leading research groups working on HTA in Colombia). Relevant variables were established before sampling started (reputed academics, leaders of research groups, with relevant MSc or PhD degrees in topics related to HTA). A total of eight senior researchers throughout the country were identified as potential target participants. All names were extracted from a list of research groups registered and publicly available on the COLCIENCIAS web page and currently conducting HTA.[32]

During January and February 2013 five out of these senior eligible researchers were invited to participate in a set of semi-structured interviews, the remaining three senior researchers were not invited because they belonged to institutions already represented by the first five eligible participants.

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[32] Look for GrupLAC y CvLAC at: http://www.colciencias.gov.co/scienti

The sample strategy was homogeneous in nature; nonetheless in order to capture maximum variation within settings (different institutions and regions), participants were selected from research groups representing different regions and institutions within the country (North- Caribbean, North-West and Central Colombia). No prominent research groups or academics fulfilling eligibility criteria were identified throughout sampling in South Colombia. All individuals received an information sheet and consent form in Spanish which explained the objectives of the study, and stressed that their participation in the study was completely voluntary (Appendix 9). Participants were asked to consent to being audio-recorded during the interviews. All forms complied with the London School of Hygiene and Tropical Medicine (LSHTM) ethics approval requirements for non- interventional studies). All participants gave consent to participate in the study and to be recorded.

Interview procedure

Each semi-structured interview was planned to last between 30- 40 minutes which was considered enough time to capture the salient findings. The interview guide followed a pre-determined set of topics that included the individual´s knowledge and experience of conducting HTA, quantity and skill mix of the teams to which they belonged, availability of resources devoted to HTA, and possible barriers, facilitators and challenges to conducting HTA in Colombia.

The first question about previous individual experience of conducting HTA served to validate the expertise considered in the eligibility criteria. The potential role of HTA in the near future and its feasibility to be used in decision-making were also explored in the interviews. Interviews were open-ended to allow the participants to guide the discussion as much as possible, and to diverge if necessary in order to address ideas and concepts not anticipated by the interviewer (Britten, 1995).

The main researcher (a Colombian medical doctor and doctoral candidate in public health and policy at the London School of Hygiene & Tropical Medicine who was recently appointed as the Chief Executive Officer of the new HTA agency in Colombia- IETS) personally conducted the interviews in Spanish, which was his and the participants' native language. During the interviews the main researcher summarised comments from each participant and encapsulated those considered as potential barriers or facilitators for HTA in Colombia. Interviews took place in quiet, private environments, two at the workplace of participants, two at a neutral venue selected by the main researcher, and one at the home of the participant. All interviews were audio recorded.

<u>Analysis</u>

Once finished, each interview was transcribed *verbatim* by an independent transcriber. Each interview was then uploaded to ATLAS- ti7 as a new hermeneutic unit. No preliminary hypothesis was considered, and the researcher aimed to interpret data instead of simply describing it (Braun and Clarke, 2006).

Before starting coding, a panel comprising of the main researcher and two independent advisors (a psychologist and an engineer, both professors of qualitative methods at *Pontificia Universidad Javeriana* in Bogotá, Colombia) was set up to decide on a pre-selected labelling scheme of potentially emerging codes. This scheme took into consideration the guide of pre-selected topics discussed during the interviews, and later added labels to account for changes in time and their perceived level of importance as potential barriers and facilitators not only for the development, but also for the use of HTA to inform decision-making in Colombia.

The first coding stage was independently performed by the main researcher and carried out in parallel by each one of the advisors. Instead of using the "scissors and paste" method described by Krueger and Casey (2002), all data were coded using ATLAS- ti7 based on memos and quotes selected by the research panel. Combined quotations considered as relevant were pre-selected for further analysis by the panel after this first round of coding.

To enhance the rigour of research, a second panel meeting was held in April 2013 to analyse emerging data and decide on a potential taxonomy of codes. After this meeting, the term "drivers" for conducting and/or using HTA in Colombia emerged instead of "barriers and facilitators". A second round of coding was then started, this time performed solely by the main researcher. At this stage coding was open and looked at previously depurated quotations (controlling for coinciding coded quotes) looking for emergent "drivers".

A third and final panel session was held in June 2013 to refine the final taxonomy of codes selected as "drivers" by the main researcher, and also to analyse the potential relationship among codes and to control for the accuracy of translated quotes from Spanish to English. The detailed description of the context of interest, participants´ profiles and the emergence of "drivers" and their relationship are given in the findings section of this chapter.

RESULTS:

Background of participants

It emerged from the interviews that all participants were physicians; four were male and one female. Four were affiliated to academic institutions and one to a public hospital; all except one belonged to public organisations such as universities or hospitals. Four were active academics and one a research leader at a public hospital. All except one had an MSc in Clinical Epidemiology; the other had a PhD in Health Economics. Most of the academics (three out of five) are located in central Colombia. Figure 2 provides a detailed profile of participants. Figure 2 provides a detailed profile of participants.

Figure 2. Profile of participants

	PARTICIPANT 1	**PARTICIPANT 2**	**PARTICIPANT 3**	**PARTICIPANT 4**	**PARTICIPANT 5**
Gender	Female	Male	Male	Male	Male
Profession	Medical Doctor	Medical Doctor	Medical Doctor	Medical Doctor	Medical Doctor
Affiliation	Public University	Public Hospital	Public University	Private University	Public University
Region	Northwest Colombia	Central Colombia	Central Colombia	Central Colombia	North Caribbean Colombia
Postgraduate studies	Physical Medicine & Rehabilitation, MSc in Clinical Epidemiology	MSc in Public Health, MSc in Clinical Epidemiology	Gynaecologist & Obstetrician, MSc in Clinical Epidemiology	Psychiatrist, MSc in Clinical Epidemiology	MSc in Public Health, PhD in Health Economics
Years of experience	> 5 years	5 years	> 5 years	> 5 years	> 5 years

Depth and breadth of knowledge about HTA varied among participants. Most of them were familiar with EBM methods, especially with systematic reviews of evidence, meta-analysis and clinical effectiveness. Recently HTA methods such as economic modelling have been incorporated into their research. Only one of the participants was formally trained in health economics and economic evaluation for health care. Their experience of the methods for producing HTA reports was heterogeneous.

Evolution of HTA and local capacity for HTA in Colombia

It emerged from the interviewees´ responses that HTA was first practiced in Colombia during the early 1990s when a limited number of academics who had studied overseas returned to the country and started producing isolated pieces of research using methods related to those of evidence-based medicine (EBM) and health technology assessment (HTA).

In 1994, the first school of Clinical Epidemiology was established in Colombia (at *Pontificia Universidad Javeriana*) further influencing the establishment of another three schools[33] around the country in the early 2000s. Over the past decade these institutions have promoted the use of evidence-based medicine (EBM) to inform clinical decision-making.

From the "emic"[34] experience of participants it seems clinical effectiveness was the dominant topic of research up to the mid-2000s, when economic evaluation, burden of disease and budget impact analyses were incrementally incorporated into HTA reports and research agendas. The continuity of work and stability of research groups have steadily grown over the past 4 or 5 years. Each of the research groups (currently led by participants) has an average of 20 full time equivalent committed researchers. All groups are mainly project-based funded institutions with modest infrastructures.

By 2009 at least five research groups were involved in conducting HTA in Colombia, all commissioned by the MoHSP and COLCIENCIAS. These groups developed 24 Clinical Practice Guidelines (CPGs) that included HTA and economic modelling aimed at informing both macro and micro decision-making. Over the past four years there has been an increasing academic drive to develop HTA to inform decision-making.

The local capacity to produce HTA is limited. Participants estimated there are around 150 clinical epidemiologists in the country capable of conducting HTA. Nonetheless it is estimated that the total number of health economists or bio-statisticians suitable for this task is ten times lower. The early academic interest in producing HTA has evolved and HTA is seen as a potential aid for resource-allocation decision-making and health care planning. Current users of HTA reports in the country are: the MoHSP, regional secretariats of health, hospitals and clinics, pharmaceutical industry and medical device developers, health care insurers, National Institute for Health, and the former Health Regulatory Commission (CRES).

Besides the academic interest of research groups to develop HTA in Colombia, at the end of 2010 the government commissioned a project funded by the Inter-American Development Bank (IADB) which was technically supported by the international team of the National Institute for Health and Care Excellence, NICE, to inform a blueprint for the establishment of a local specialised HTA institution. In November 2012 this local HTA agency (IETS) started operations in Colombia, initially at the piloting stage.

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[33] Universidad de Antioquia (2002), Universidad de Cartagena (2003) and Universidad Nacional de Colombia (2006)
[34] "The emic approach investigates how local people think" (Kottak, 2006): How they perceive and categorize the world, their rules for behavior, what has meaning for them, and how they imagine and explain things.

At the time of writing (November 2013) no academic institution in Colombia had formally established a postgraduate HTA specialised Master's degree, although basic HTA training is provided as short courses in postgraduate Masters Degrees in Science (MSc). The current MoHSP commissioned IETS in 2013 to assess 105 health care technologies to update POS before the end of that year.

During the first round of coding knowledge and previous experience regarding HTA, availability of resources devoted to the development of HTA, the perceived barriers and facilitators to developing HTA, and the possible future role of HTA in Colombia were used as static labels to code participants´ quotations. Nonetheless it emerged soon, after a deeper round of coding, that a sub-set of codes accounting for changes in time and their perceived level of importance were relevant when considering the aspects that may help or hinder HTA development and use.

The emergence of "drivers"

After the first round of coding a total of 684 combined quotations emerged from the interviews; these were pre-selected for further analysis by the research panel. After the panel meeting in April 2013, the advisors agreed with the main researchers´ view that the terms "barriers" and "facilitators" considered before were rather static whilst the aspects that may help or hinder HTA seemed more dynamic and interconnected, hence the term "driver" for conducting and/or using HTA in Colombia emerged from discussion.

A "driver" was defined as a factor that could potentially have an impact on the development or use of HTA (or both) in Colombia. The potential impact of a "driver" implied directionality, as either being positive (facilitator) or negative (barrier); the potential impact of a "driver" could be perceived as being high or low (levelled) at specific moments of time. A current positive "driver" could become negative and vice-versa depending on the context and its dynamic evolution over time.

A new round of coding performed by the main researcher alone looked at 367 previously depurated quotations looking for "drivers". Ten possible "drivers" emerged as codes for the development and/or use of HTA in Colombia. A third meeting of the research panel in June 2013 refined the names of two of the emergent "drivers" and also described the possible inter-connections and relationships between all of them. Figure 3 depicts the taxonomy and interaction of these "drivers" on the development and/or use of HTA in Colombia.

The list of emergent "drivers" includes the following: availability and quality of data, cultural aspects, financial support, globalisation, health system context, implementation strategy, local capacity, policy and political support, stakeholder pressure, and usefulness perception. Each driver is described below.

Figure 3. Emergent drivers for the development and/or use of HTA in Colombia
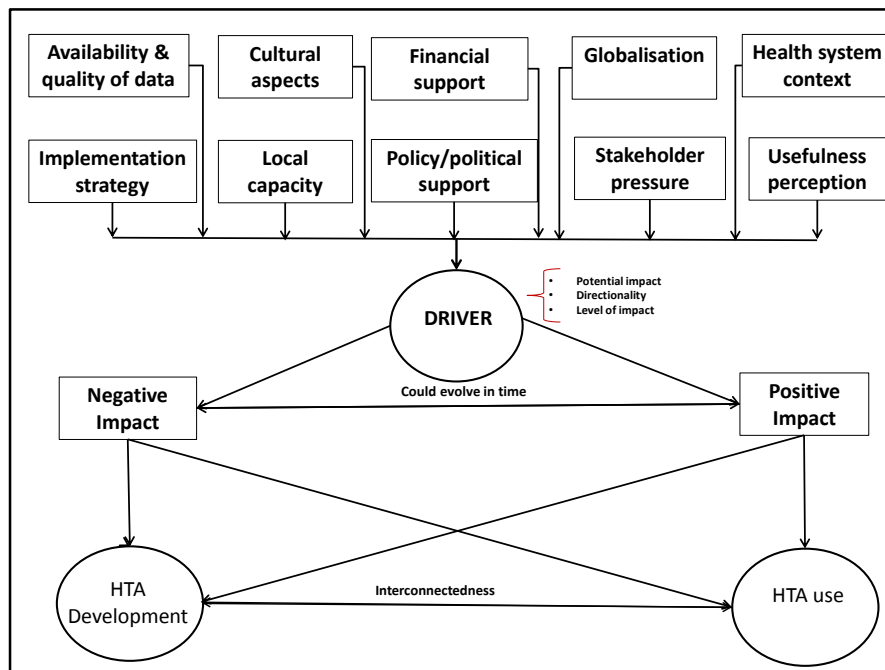
All "drivers" have a potential (positive or negative) impact on HTA in the years to come, but also harbour the dynamic potential to switch the directionality of their impact over time. Some "drivers" were considered capable of operating in association or interdependently; for instance, implementation strategy could be associated with installed capacity, and installed capacity with resources devoted to HTA, but availability and quality of data could have a potential impact with no interconnection with any other "driver".

a) **Availability and quality of data**: availability of data refers to the concerns of participants about the amount and quality of local data available to support the development of HTA. This may have an impact on the internal validity of HTA results, extrapolation or generalisation of the findings.

"[…] as far as I am concerned, one of the limitations when you are evaluating [HTA], uhm is related to costs information […] so you need to rely on experts' estimations […] what is becoming necessary, absolutely necessary is to have our own parameters, local data […]"P2

This driver accounts for the limitations of local information about the clinical effectiveness of interventions, probabilities, costs, and health state preferences, all necessary to populate robust decision-making models. The uncertainty of results had a potential negative impact that may prevent the use of HTA as a reliable source of information for resource-allocation decision-making:

"[…] the complexity of the Colombian Health System implies high levels of uncertainty […] probably in Germany, Holland or England their systems carry less uncertainty than we have here, this could be a point to start with [...]" P3

"[…] the sources of data, so I think this is a big weakness […] economic models and in general studies [HTA] are as good as the quality of data one has available, and that is a big limitation for us and the system, I mean we need to know about costs, frequencies of use of resources, distribution of variables that one may use to populate the models […]" P2

b)   **Cultural aspects:** emerged as a "driver" related to context-specific conduct or behaviours that may have an impact on HTA. This refers also to social conceptions determined by local custom, meanings and beliefs with the potential to influence the development or use of HTA. Most emerging cultural aspects were identified as having a potential negative impact, for instance the lack of tradition of priority setting or relying on the best available evidence to inform decision-making or a lack of long-term planning:

"[...] well, as far as I know people are not willing to prioritise […]" P3

"[...] there is a resistance to accepting technocracy in this country […]" P4

"Decision-makers are able to make decisions without considering it [HTA] and as a matter of fact they have done this all the time [...]"P5

"Self-criticism [...] uhm it is hard for us to ask for help, am I right? Or to envision long-term plans […]" P2

A cultural reluctance of health care professionals to follow evidence to harmonise clinical practice and promote self- regulation also emerged from participants' remarks:

"[...] I think is a hurdle too […] uhm collective imagination […]this topic [HTA] becomes […] a pressure – being told how to do things [...] they [health care professionals] feel like it [HTA]is an imposition on their practice, one of them may say: "are you telling me how to do things? […] and what to prescribe or not? […] that part is a barrier and could hinder further [HTA] development […]" P1

Although corruption is not a country specific phenomenon, it emerged as a source of concern for the successful implementation of HTA in Colombia, this representing the lack of trust among stakeholders within the current context in this country:

"[...] corruption is worse now than ever, here it is very complicated […] I think the development of HTA in contexts with much lesser corruption must be easier […]" P3

c)   **Financial support:** this "driver" refers to the potential sources of funding that could promote the development of new and on-going HTA projects. It emerged that most of the funding for research centres is project based and envisioned as short-term, nonetheless the availability of financial resources for HTA projects has increased in recent years:

"[…] so all funding is project based […]" P1

"[...] and also that now we count with budget for that [HTA] so, so we have funding […]" P4

"[…] I think everything has happened for good […] uhm and nowadays […] we that work in this area have gained a reputation and […] that has been evident through the existence of budgets to conduct HTA[…]" P5

It also emerged that financial support was usually associated with another "driver", policy and political support. Participants believe funding within academic institutions and government agencies is associated with policy commitment to support long-term research.

"[…] at Antioquia University there are a number of annual calls for research proposals […] and there are also other resources, for instance there is one […] named sustainability funding[…] which allows us to have more or less stable staff and basic resources for the research groups to operate […]" P1

"So far the Clinical Practice Guidelines programme [...]has money each year [...] this budget is not permanent, so it means it is environmentally dependent [political context][...] and they provide us with [...] people trained in epidemiology to focus on the CPGs development and some support for logistics[...]" P2

"Yes, we have CINETS[35] which is supported [policy and financial support] from three universities […] now we have financial support for a year […]" P3

The policy implementation of establishing an HTA agency in the country is seen as a new opportunity for financial support and institutional strengthening:

"[...]the establishment of new institutions [IETS], the existence of budgets, so I mean before there was no way to finance projects [HTA] it was more the interest of a group, I think that has strengthened over time […]" P2

"[…] on the other hand, counting on resources to guarantee sustainability for us [research group] apparently that is an achievement with the establishment of the institute [IETS] […]" P3

d) **Globalisation:** emerged as a "driver" that has influenced the development and use of HTA in Colombia. It refers to a perceived global and social trend to produce and use HTA to inform decision-making in different countries.

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[35] CINETS- *Centro Nacional de investigación en Evidencia y Evaluación de Tecnologías en Salud* (National Centre for Research on Evidence and Health Technology Assessment) is a national think tank created by *Universidad Nacional de Colombia*, *Universidad de Antioquia* and *Pontificia Universidad Javeriana*.

"[...] I also think the international context, the way this topic has evolved in different countries and how those countries that valued HTA […] have attained good health outcomes […]" P1

"[...] right now there is a trend about that [HTA] and that is a key, good or bad trend, but there is a trend to conduct this assessment [HTA], we live in an economists era […] an era of evidence and evidence-based medicine that started a long time ago, but right now has gained influence at government level, I think that is key […]" P4

"[...]if it is used [HTA] as happens in developed countries to inform decision-making through evidence generation it may be able to contribute in a huge manner[…]" P5

Globalisation has influenced academics who returned to Colombia to implement HTA research agendas after studying overseas. Most of the participants´ remarks regarding globalisation were considered as having a potentially positive impact.

"[...]a professor that studied HTA, a Master's degree overseas and came back; precisely his first research project at the University was an HTA proposal […]in US at John Hopkins we have some of them, there is a young professor studying evidence-based health policies at the University of McMaster, also in England […]" P1

Also the concept of an international "peer pressure" to get involved in HTA or an opportunity to work with international organisations in co-operative networks regarding HTA projects emerged. Globalisation may also have an influence on the social perception or "mood" about HTA´s potential usefulness, and also on the possibility of international co-operation for research:

"[...] the constant international peer pressure has made researchers do it [HTA], with or without resources; many researchers are members of HTAi […] INAHTA […] members of ISPOR […] so this has created a peer pressure […]" P2

"[…] the mood at the social level […] after the government has noticed this trend [HTA], let´s say economist reaching health trend […]" P4

"[...] we are a centre of excellence regarding HTA development for vaccines for PAHO have worked in co-operation with Albert Sabin Institute from Washington DC [...] because it is a research network." P5

According to participants' remarks, globalisation may carry a negative impact if skilled researchers leave the country to work overseas, this potential 'brain drain' may have a negative impact on the stability of research groups:

"[…] with health economists there is a […] bizarre story of people that have studied this topic [HTA] […]this staff is the most volatile of all […] and the other one in Canada; actually there were five because another one was hired by IADB […] and the last one was appointed as the Chief Officer at IETS." P4

Globalisation also raised concerns about the possibility of generalising HTA reports across borders without the careful consideration of its methodological limitations. This arose from the current limited perception about its usefulness. Potential caveats of extrapolation of results, and a lack of confidence in HTA work produced by international think tanks also emerged:

"[...]if it works in US you could assume it also works in Colombia, so to conduct economic evaluation usually parameters of efficacy and effectiveness are extrapolated from other countries, what becomes necessary, absolutely necessary is to have our own parameters, local data [...]" P5

"[...] from other countries clearly they have a vested interest to sell their products [HTA related] and sometimes they are not the best, but foreigners anyway [...]" P4

e)   **Health system context:** the health system structure, the current context of financial crisis and the macro performance indicators emerged as a "driver" for potential HTA development and use in Colombia; this was labelled as health system context. The need to regularly update POS content, making use of the best available evidence, emerged as having a potential positive impact on HTA development:

"[...] need, I feel right now the system which for a while has experienced complicated issues from all points of view [...] has been overwhelmed and this [HTA] could be like an institutional solution to improve governance [...]" P1

"[...] the current limitations to decide on the explicit basket of health care benefits of health insurers." P3

"[...] the pressing need to update POS content." P5

Currently the health system is facing a financial crisis and "lack of trust" that has threatened sustainability. This financial strain also emerged as an important factor, which may have a potential impact on HTA, to be incorporated into resource-allocation decision-making:

"[...] probably a key factor is the fact that the health system has exploded, so when something explodes, well one starts thinking, one must do something and this leads to policy alternatives such as HTA [...]" P4

"[...] cost increases of health technologies, and an important fact in Colombia was exceptional reimbursement of health care services [...] and of course on the other hand the need to incorporate newly developed technologies within the benefits´ basket that for nearly 20 years was not properly updated, so let´s say these two issues, uhm pressured [...] the development of HTA in Colombia." P5

"[…] the current pressure, I think this will facilitate this field [HTA] […] and I think the current crisis within the health system is fundamental because, this pushes for exits, and this crisis well, needs an exit […]" P1

The Government has taken major steps to control costs and strengthen its institutional capacity. Nonetheless, political instability after two attempted and failed HSRs in such a short period of time (2011 and 2013) is envisioned as a factor able to produce further institutional instability that may also have negative implications for the future development or use of HTA:

"[...] obstacles associated with coordination within the system ought to influence IETS too, this crisis has affected EPS [health care insurers], IPS [health care providers] due to the financial strain, this uncertainty we have about the future of the Colombian health system […]" P1

"[...] when in crisis, you cannot plan mid or long-term to reduce the burden of disease […] this has made the whole system blow up […]" P3

f)   **Implementation strategy**: the need for an organised and well-planned HTA implementation strategy emerged as a "driver". This "driver" groups not only the challenges regarding the use of evidence-based recommendations to inform policy, but also the expected systematic process of institutional (HTA related) strengthening in Colombia. This involves dissemination of results, capacity building, institutional strengthening, and introduction of incentives, amongst others. Regarding dissemination of HTA results and knowledge transfer, academics expect a systematic and well-organised process bearing in mind the target audiences of information.

"[...] it should have a process of communication, socialisation, call it implementation? […] well organised alongside each one of these products [HTA reports] […] so if these processes, HTA reports or Clinical Practice Guidelines have an organised implementation plan in Colombia, they will succeed […]" P1

"I think firstly, it is important to present them [HTA results] to users in their own words, usually an HTA report comes out as a brick [hard to understand], and apologies for saying this, but it is intended for a restricted audience, so a closer communication with users […]may be hard but surely will induce their further use […]"P2

Capacity building needs to consider strengthening the skills of researchers devoted to HTA, but also of those in charge of using HTA as a source of information to make decisions and policies. Implementation strategy, in contrast to some other "drivers", emerged more as a challenge that needs to be borne in mind during the operationalization of HTA policies. Its potential impact may be bi-directional depending on a successful or unsuccessful implementation plan.

"[...] I believe the main thing [challenge] is going to be the local technical capacity being able to cope with demand, but let´s think it could be implemented with strategic planning and grow incrementally [...]" P2

"[...] I think that if it is possible to sensitise decision-makers [...] there won´t be much trouble on the perceived value of it [HTA] by society [...]" P3

A well-planned implementation strategy is expected to be incremental and step-by-step regarding the development of methods. HTA reports are expected to be available and "digestible" to a broad audience:

"[...] and the other important aspects are methods [...] they could be step by step and if necessary adapted to our reality, so it would require awareness of our available resources and the making of some concessions, but to adapt our own standards for HTA [...] CGPs as well." P2

"[...] if it [HTA reports] becomes unintelligible to many people it will become very complicated aspect [...]" P4

The recent settlement of IETS represents, according to participants' remarks, a new opportunity to improve the rigour of independent HTA work and the possibility to strengthen local capacity. It raised great expectations; there is the expectation of hiring skilled staff which implies challenges throughout its implementation stage:

"[...] the organisation created by the Government should facilitate transparency, independence of HTA reports on behalf of the whole society´s instead of serving some interest groups [...]" P3

"[...] the institute [IETS] is the institutional space aimed at promoting and implementing HTA techniques to support evidence-based decision-making regarding technologies for health [...] second [key success factor] to hire competent and experienced staff [...]" P5

g)   **Local capacity**: Local capacity emerged as a "driver" which refers to the existence or absence of human technical and installed capacity, infrastructure, tools, resources, and academic institutions in place to promote the development and use of HTA in Colombia. Local capacity had two different levels of interpretation: individual and institutional. Organisational capacity referred to the establishment of postgraduate schools dedicated to EBM, especially of clinical epidemiology; these have increased the supply of skilled professionals over the last two decades:

"[...] we provide a Master's degree in clinical sciences, we have graduated nearly 45 clinical epidemiologists and within the Masters we have also introduced short courses on economic evaluation [...] this has been going on since 2006." P1

"[…] I think in Colombia the development of clinical epidemiology has been very important […]in total we are three leading institutions building up capacities in the country, on the one hand Universidad Javeriana, and on the other Universidad Nacional and Universidad de Antioquia […] between the three of us easily we have graduated 200 people […]" P1

Organisational capacity referred also to the recent establishment of research groups, think tanks and institutions in charge of developing HTA work commissioned by the Government:

"[…] generation of new institutions, and availability of financial resources, I mean in the past there was no way to fund them [HTA projects] […] I believe this has strengthened […]" P2

At the individual level the number of HTA specialised professionals is still insufficient to cope with local demand; according to participants, Colombia has 150 clinical epidemiologist capable of conducting HTA (mainly clinical effectiveness requests), but the estimated number of skilled health economists and bio-statisticians able to conduct economic modelling and evaluation was ten times lower. The recent development of HTA related projects has strengthened local capacity:

"The group of clinical research amounts to 25 people, uhm exclusively working on CPGs or HTA around 15." P2

"[…] graduated people from Javeriana we estimate 90 people, from Nacional may be 20 or 40 […]" P4

According to participants´ remarks, skilled human resources are still scarce in some knowledge fields and are mostly concentrated in big urban areas:

"Well, I haven´t mentioned the disparity of development between big cities and rural areas, we could be sure of technical capacity in big cities like Barranquilla, Cali, Medellin, Bogotá, but there are so many places where this issue [HTA] is underdeveloped […]" P1

"The production of a critical mass of researchers is not really big, it is partially concentrated in cities […]" P3

A perceived challenge for the stability of research groups and think tanks is the competitive local market for scarce HTA professionals, so far in Colombia there is no formal specialised postgraduate training in health economics or HTA.

"[…] we have no-one with formal training in HTA, but just courses, short courses […]" P2

"[…] with health economists there is a […] let´s call it bizarre story […] so I was about to say this staff is the most volatile of all […]" P4

Infrastructure of research groups tends to be modest, more related to software and hardware and the availability of resources is limited and highly dependent on financial and policy support:

"[...] regarding infrastructure, it has always been linked to projects, it has been projects that have pulled out development [...] and each thing [resources] has arrived associated with projects [...] infrastructure is more related to software and hardware [...]" P2

According to participants, the need to build up local capacity goes beyond researchers' and academics' needs, and also requires raising awareness and strengthening theoretical foundations of local policy and decision-makers:

"The limited stock of knowledge they have at the Ministry of Health [regarding HTA]" P4

h)   **Policy and political support**: policy support refers to the local social acceptance of HTA by the academic community and different stakeholders, and political support to the politicians' support to include HTA into policy agendas. This "driver" is represented by the enactment of laws, explicit policies within the government or any other funding bodies regarding HTA production or use. It emerged from participants´ quotations, usually associated with funding. Although previous studies (Castro, 2011) have tracked the policy interest of Colombia to use HTA back to the early 2000s, it is only in the last 5 years that major policy changes have boosted HTA development and use in this context.

"[...] it has been continuous [...] since 2008 with the work of CPGs [...] with stable groups working in HTA specific projects [...] just recently an institution has been set up with support from the Ministry of Health, able to pull this out [HTA] [...], and this [IETS] needs to cohere different actors around an institutional policy [...]" P1

Local policy support from governmental institutions such as COLCIENCIAS, the MoHSP or public hospitals have granted funding for HTA work and capacity building in recent times:

"[...] our client has always been the state, our number one client of HTA [...] the Ministry of Social Protection, uhm [...] COLCIENCIAS obviously, throughout the CPGs programme [...] the Regulatory Commission for Health- CRES [...]"P2

"The Ministry of Health, the National Institute for Cancer [...] COLCIENCIAS, some of them have been ad hoc requirements and some others after tendering [...]" P3

Policy and political support may have a bidirectional impact on the production or use of HTA, negative if it is lacking and positive if it is present. According to participants this policy/political support is still unstable and heavily reliant on the political environment:

"[...] well, provide resources that assure our sustainability, hopefully an upcoming Minister does not come and say "that stuff [HTA] is not relevant for me" regarding IETS resources, in that case we have to be sure that decision is not dependent only on Ministerial will [...]" P3

"[...] I mean it is very volatile [funding], we need a policy, hopefully scholarships from COLCIENCIAS to train more people on that [HTA], it would be an opportunity, because I believe that is a major weakness in this country [...]" P4

"[...] but, it will massively depend on how it is perceived by the Ministry of Health, from those leading it, those who should decide on its real role [HTA] [...]" P5

Policy and political support are expected to have a broad remit that goes beyond the health sector, for instance to assure HTA development, policies within the Ministry of Education may enhance capacity building within the country.

"[...] a political decision is missing at the Ministry of Education, as well as at the Ministry of Health to promote formal education and continuous training in this field [HTA] [...]" P5

i) **Stakeholder pressure**: the contested pressure among relevant actors with vested interests in Colombia came up as an important "driver". This "driver" incorporates market and stakeholder pressure to either use or prevent the use of HTA that may, in the end, induce regulation. Among the stakeholders mentioned by interviewees are patients´ associations, providers, insurers, professional bodies, manufacturers, academics, and government bodies. Stakeholder pressure was perceived as mainly having a potential negative impact on both the development and use of HTA in Colombia:

"[...] it could be a barrier again, sectional groups, physicians´ and health professionals' associations, and of course the industry would be a limitation [...] the neo-liberal character of Colombia [...] favours particular interests of certain groups [...]" P1

"[...] pressure groups will try to influence HTA processes [...] we all know that pharmaceutical labs and innovation tanks have huge interest, the others are patients´ groups that have tight links with labs [...] and on the other hand insurers [...]" P3

"[...] so let´s say there is a permanent pressure [...] when we refer to interest groups we are talking about those who advocate for a narrower benefits package, like health care insurers and those who advocate for a wider benefits plan, especially pharmaceutical and medical devices industry [...]" P5

j) **Usefulness perception**: usefulness perception came up as a "driver" that refers to the meaning and values that academics, decision and policymakers, and the whole society put into HTA methods as a tool to help inform health and health care decisions. An incremental shift from pure academic interest to a more pragmatic use of HTA as an aid to inform decision-making emerged from participants:

"[...] I think it [HTA] should have a clear impact on benefits planning, service organization [...] I really think its impact [HTA] must go beyond the academic field, definitely [...]" P2

"[...] basically many of them [HTA projects] were made out of academic interest, right? But many others were assessed aimed at informing decision-makers, which is the right thing to do, do you agree?" P3

According to participants' remarks HTA is perceived as having a role to support regulation, improve transparency, allocative efficiency and equity:

"So, I think that [HTA] regulates in a rational and conscious manner the use of resources, it also favours equity [...] for resource-allocation and priority-setting [...]it [HTA] allows [...] the foundations and further construction of a more equitable, efficient, effective and safe system for Colombians." P1

"I think the main role [of HTA] is to inform decision-making, and to allow better planning [...] speed of research is very fast, so this requires drawing a line, there is always a limit to set up [...] this is much better if done through a rational and reasoned process [HTA] [...] this is much better understood by the people on one side or the other of that drawn line [...]" P2

"It [HTA] is an alternative available for governments aimed at improving evidence generation to inform more efficient decisions under current pressures for incorporating new and some times better health technologies [...]"P5

This "driver" also refers to the awareness of HTA limitations and the need to incorporate additional values into decision-making that goes beyond HTA itself. Nonetheless, the lack of usefulness perception, especially among clinicians, policy and decision-makers may have a negative impact on the future development and use of HTA in Colombia:

"[...] there is still a lack of knowledge about the benefits and how physicians could own this knowledge [HTA] to improve professional performance [...]"P1

"[...] it would be necessary to raise awareness among decision-makers about the importance of taking HTA reports into consideration [...] among decision-makers' knowledge about these methodologies is weak "[...] we have to educate them and sensitise them, obviously they are not interested in being trained in systematic reviews, but they are willing to understand what a systematic review is [...]" P3

"The hardest [...] for the development of HTA is the lack of knowledge among decision-makers of these tools, there is a big gap of information and knowledge [...] many times they mix up terms, study types, potential usefulness of these studies, so if there were more information on decision-makers side the development of HTA would have a clearer pathway in the near future [...]"P5

DISCUSSION

Qualitative enquiry was used in this chapter to "reach the parts other methods can´t reach" (Green and Thorogood, 2009). Thus semi-structured interviews with local academics devoted to HTA and thematic content analysis were performed as a means to answering **what are the main aspects that may help or hinder HTA development and use in Colombia?**. Although there are no mechanical solutions to assess the likelihood of errors in this qualitative part of the research, clear exposition of methods and data collection, and analysis, reflexivity and triangulation were considered by the main researcher for improving validity. The triangulation analysis of results is presented in a separate section after the empirical chapters.

In response to the research question, ten drivers: local capacity, policy and political support, perceptions of its usefulness, globalisation, financial support, availability and quality of data, cultural aspects, implementation strategy, stakeholders´ pressure and the health system´s context emerged as "drivers" with the ability to prevent or induce HTA development and use in this country.

Recent development of local capacity may have had a positive impact on HTA development, but human resources are still scarce in some knowledge fields such as health economics and bio- statistics and are mostly concentrated in big urban areas. The infrastructure of research groups is modest and available resources for HTA are limited and highly dependent on financial and policy and political support. According to participants, the need to build up local capacity extends beyond the needs of researchers and academics and also includes raising awareness and strengthening the theoretical foundations of local health care professionals and policy and decision-makers. The recent establishment of IETS represents a new opportunity to improve the rigour of HTA and the possibility of strengthening institutional capacity. This has encouraged optimism coupled with awareness of the challenges faced at its implementation stage.

Policy and political support was usually associated with funding, this may also have a positive impact on promoting the use of HTA in Colombia. A shift from pure academic interest to a more pragmatic use of HTA (as an aid to inform decision-making) also emerged from participants´ remarks. This shifted perception of the potential usefulness of HTA was seen as a positive "driver". However, perceived lack of usefulness, especially among clinicians, policy and decision-makers, may have a negative impact on the future development and use of HTA.

Most participants thought globalisation had a potential positive impact on the use of HTA, but it also had an impact on HTA development, especially regarding those academics who had returned after studying overseas to implement HTA research agendas.

Participants perceived international "peer pressure" to get involved in HTA. Globalisation emerged as an opportunity for such co-operative work and involvement in international HTA networks. It may also have a positive impact on both development and use of HTA. Nevertheless globalisation could also have a negative impact, due to the influence and interconnectedness of countries: for instance on the stability of research groups. Concerns were also raised about the current asymmetry of information among HTA users and possible generalisation of HTA reports across borders, which would prevent *de novo* development of HTA in Colombia. A lack of confidence in HTA-related international think tanks emerged from the interviewees, since some participants believed that these groups have commercial interests and not real concerns about quality improvement or local capacity building.

Financial support was usually associated with another "driver", policy and political support. Financial support or the lack of it could have an impact on both use and development of HTA. A lack of funding may have a potential negative impact on the stability and continuity of research groups. The recent development of CPGs funded by COLCIENCIAs and the MoHSP as a policy solution to homogenise clinical practice has recently created some stability for HTA projects and research groups. The recent policy implementation of IETS is also expected to attract funding and enhance local capacity building.

Stakeholder pressure was perceived as mainly having a potential negative impact on both the development and use of HTA. For instance, the contested policy pressure between those who advocate for a narrower benefits package (government and health care insurers), and those who advocate for a wider benefits plan, (pharmaceutical and medical devices industry) represents a challenge for HTA institutional strengthening. On the other hand, stakeholder pressure associated with the current context of the financial and "lack of trust" crisis within the health system could have a positive impact on HTA development and also on its future use, for example the Government´s interest in using the best available evidence for quality improvement and resource-allocation decision-making in a transparent and systematic fashion.

The importance of a well-planned HTA implementation strategy emerged from participant interviews. Also the existence of such a strategy may have an impact on the development of HTA. This "driver" could simultaneously have a potential impact on both development and use of HTA. According to participants, implementation refers to communication, dissemination of HTA evidence, as well as individual and institutional capacity building.

The health system context has pushed HTA as a possible policy solution to inform resource decision-making in Colombia. It emerged that the current context may have an influence merely on the development of HTA, but also this "driver" may have an impact on its use. The current crisis within the system has created institutional instability that may have negative implications if instability extends to HTA specialised organisations and research groups.

Cultural aspects such as resistance to change, lack of transparency for decision-making and recent tradition and interest of professionals´ self-regulation were identified as mostly having a potential negative impact on both use and development of HTA. Health care professionals in Colombia do not want to be told how to provide health care, and there are no clear rules from professional bodies on how to incorporate evidence-based information into practice.

Finally, problems with availability and quality of data emerged as always having a potential negative influence, mostly on development. This may reduce the internal validity of HTA reports, with its subsequent negative impact on HTA as a reliable source of information which could cause doubt among decision-makers. However, in recent years the government has invested in improving the availability and quality of data essential to conduct HTA.

All "drivers" could potentially have a positive or negative impact at specific moments in time. They could shift according to the dynamics of the policy process of implementing HTA in Colombia. Some "drivers" that in the last decade were considered as main barriers (local capacity, policy support, usefulness perception, globalisation and financial support), according to participant´s views have changed in recent years. For instance, local training and the entry of new specialists in the field in the last couple of years have eased HTA production, this arose from the establishment of new research think tanks and institutions. According to participants, the growing reputation of HTA research groups has gained policy, political and financial support from the government and many other funding bodies.

Awareness of HTA usefulness and its limitations has increased over the past four to five years, boosted by a favourable international trend and a social mood to rely on EBM, and to prioritise and use HTA to inform health and health care decision-making. The establishment of CINETS, formed by three top ranking Universities in 2011, and the establishment of the IETS in late 2012 are tangible facilitators that may ease HTA in Colombia. The former was closely involved in using EBM and HTA methodologies in developing 24 CPGs aimed at homogenising clinical practice and improving quality of care. The latter is perceived by participants as a "great thing" and has given rise to expectation for methods development, capacity building and institutional strengthening.

According to participants, some "drivers" such as the financial crisis within the health system, and resultant lack of resources, as well as corruption and the perceived lack of transparency [cultural driver] have become problematic in recent years. A well-organised implementation strategy needs to surmount cultural aspects that resist technocratic methodologies and transparency, and the lack of available and valid data to populate economic models. Short-term challenges to be borne in mind to enhance HTA development and use in Colombia also include, insufficient local capacity, the need for sustained financial support, and the standardisation of HTA methods which started in 2008-2009 when the first methodological guidance to produce CPGs was released by COLCIENCIAS.

According to participants, if researchers could explain the possible benefits of incorporating HTA into decision-making, as well as disseminating HTA results in a "digestible" manner, HTA use would succeed at both the individual and institutional level. They also believed that implementation strategies should be well planned and incentives ought to be incorporated if HTA is intended to have a bigger impact on policy and decision-making in Colombia.

In recent years qualitative methods have become more commonplace in areas such as health services research and HTA. The status of qualitative research, like many other forms of research, depends on the quality of methods used (Mays and Pope, 2000). Authors like Kirk and Miller (1986) and Hammersley (1992) argue that there is an underlying reality which can be studied; hence the aim of researchers should be one of "subtle realism", an attempt to represent that reality rather than to attain "the truth". It is from this position that authors like Mays and Pope (2000) agree that it is possible to assess qualitative research according to two broad criteria: validity and relevance.

Strengths and limitations

In carrying out the research described in this chapter, the researcher sought to preserve key principles of qualitative research methods. Respondent validation, clear exposition of methods, reflexivity, attention to negative cases and fair dealing were considered to improve the validity of results. Due to the commitment to naturalism, in-depth semi-structured interviews were used to explore the experience and expectations of Colombian researchers in their natural context and in their own language. Perhaps a more participatory approach could have provided a different perspective of such a topic of interest, but time and budget constraints made the researcher opt for a thematic content analysis instead.

Consistent with Morse and Field (1996) the sample approach chosen was considered appropriate and adequate to provide the researcher with in-depth information about the topic of interest. The purposive (homogeneous) sample fitted the aim of this part of the research - to help understand HTA development and use in Colombia. It also generated relevant information and quality data.

The total number of HTA specialists is limited in Colombia, and although qualitative enquiry usually relies on small sample sizes; the sample size and eligibility criteria were perhaps the biggest limitations of this part of the research. The strict eligibility criteria of inviting to participate only those leading researchers with 5 or more years in the field led to a sample size of only eight potential participants, which were restricted to five in order to avoid context duplication. Using a bigger sample and with a more heterogeneous composition, the results might have been different.

The main researcher has experience of, and is familiar with, HTA methods and processes. This enabled him to explore and validate the level of expertise of participants throughout the interviews. It was also an advantage when assessing their seniority and previous exposure to HTA work. This served to depict that senior experts on HTA in Colombia were more familiar and had formal training in comparative clinical effectiveness research than with economic evaluation methods. Nonetheless, being familiar with the context of interest may have shaped the process of data collection or analysis. For example, there was a prior assumption before data collection that barriers and facilitators for HTA in Colombia already existed. Although the initial assumption of the researcher was that these aspects could be considered as "barriers and facilitators", participant interviews suggested these aspects were dynamic and highly interconnected, and more appropriately called "drivers".

Although the main researcher was close to the academic community, he was not as close to the participants as to jeopardise independence. According to Green and Thorogood (2009), "it is impossible to have a field for study that is untainted by values and impossible for the researcher to stand outside those values and subjectivities". Nonetheless, the researcher strived to minimise personal values and assumptions that may "bias" findings. For instance he used a pre-determined interview guide to allow the exploration of the issues of interest, and maintained a non-judgemental attitude with flexibility to allow for any deviant cases.

A flexible research strategy was adopted. It began with a review of the literature aimed at selecting the qualitative methods that best suited the research question, under time and budget constraints. The interview guide resulted helpful to shape discussion but also to look up for emerging themes and changes overtime. Purposive sampling and semi-structured interviews were selected to generate and collect value-rich data. As early data analysis suggested that thematic content analysis was suitable to allow the researcher to look at data from interview transcripts and categorise participants´ accounts in a way that could be summarised, this method was selected.

This whole process provided the researcher with an in-depth conceptual description of the context, conditions, and processes regarding the feasibility of producing or using HTA in Colombia. According to participant responses, ten factors emerged as "drivers" with the potential to help or hinder HTA in Colombia. The research approach provided relevant information that moves beyond the initially assumed list of "barriers and facilitators".

The emergence of "drivers" for HTA in other contexts

Findings from this part of research coincided with Rajan et al (2011), through an observational design the authors used a questionnaire aimed at analysing the motives, enablers, and barriers to promote or initiate HTA in different contexts. They surveyed HTA agencies of HICs and those LMICs with HTA agencies that were members of International Network of Agencies for Health Technology Assessment (INAHTA), International Information Network on New and Emerging Health Technologies (EuroScan), or European network for Health Technology Assessment (EUnetHTA), or belonged to the interest subgroup for LMICs at the Health Technology Assessment International (HTAi) which aimed to initiate HTA activities.

According to this study, the top three motives for HTA initiation were the same for both HICs and LMICs: to support decision-making in health care and promote appropriate resource-allocation; to strengthen credibility, transparency and accountability of different decision-making levels; and to achieve better quality of health services. These motives coincided with the role or usefulness perceived of HTA in Colombia described in this chapter.

The top five enablers published by Rajan were also similar in both settings and coincided with some of the "drivers" mentioned herein: availability of human resources to develop HTA [local capacity]; availability of financial resources to perform/run HTA [financial support]; existing good practices and examples from other countries [globalisation]; existing international networking, support and collaboration [globalisation]; and understanding the local needs and setting priorities [health system context and stakeholder pressure].

The top five barriers described by these authors were more context specific, but also coincided with some of the identified "drivers": lack of financial resources to perform/run HTA [financial support], resistance to change from existing practice routines and culture [cultural aspects], lack of knowledge about EBM and/or HTA [local capacity and usefulness perception], lack of human resources to perform/run HTA [local capacity]; and lack of interest in EBM and/or HTA [usefulness perception].

In 2011 Varela-Lema et al explored the perceptions of the use of HTA in the Galician public health system, identified opinions on the usefulness of the products and services developed by the regional Health Technology Assessment Agency (avalia-t), and determined the barriers and facilitators to the transfer of results to clinical practice. Through a qualitative study, based on in-depth semi-structured interviews with experts, some of their findings were similar to those explored in this thesis, interest in HTA activities was high, but participants considered these activities to be underused as a tool to aid decision-making in clinical practice.

Also a series of key factors identified by these authors to enhance HTA use were similar to the emergent "drivers" described in this chapter. For instance, greater dissemination of HTA activities and availability of the results, increased involvement and communication among health care professionals in the selection and prioritization of relevant research, contextualization and adaptation of results to the local context, were similar to the implementation strategy "driver". Increased organizational support and greater financial resources resembled the "drivers" policy and financial support.

In 2010 Silva et al conducted a systematic review which looked at the use of economic evaluation in decision-making at the macro-level and observed that the main facilitator to using economic evaluation in decision-making was governmental/institutional incentive (UK and Australia) which also resembled the "driver" policy/political support. According to Silva, barriers remain without apparent variation over time or between countries, mostly related to the accessibility and acceptability of economic evaluation [usefulness perception and cultural aspects].

Pichon-Riviere et al (2009) ran a web-based auto-administered survey designed by INAHTA in collaboration with PAHO/WHO and mailed 242 contacts in Latin American countries. 78 complete surveys from nine Latin American countries were received (response rate 32%). Government support for HTA activities emerged as a main "driver" for HTA promotion [policy/ political support], as well as the use of HTA evidence [usefulness perception] and the availability of resources to develop HTA [financial support and local capacity]. Support from the pharmaceutical industry was considered to be low which coincides with the "driver" stakeholder pressure and the perceived position of participants regarding this interest group and HTA use as described before.

According to Hyder et al, 2011 barriers to evidence-based policy-making included poor communication and dissemination, lack of technical capacity in policy processes, as well as the influence of the political context. All three aspects coincided with the "drivers" implementation strategy, local capacity, health system context and policy/political support.

Hyder´s study also accounts for policymakers´ recommendations for facilitating the uptake of research into policy. These included improving the technical capacity of policymakers, better packaging of research results, use of social networks, and establishment of fora and clearinghouse functions to help assist in evidence-based policy-making. Many of these comments emerged when coding the "driver" implementation strategy.

This facet of research was considered as relevant and important since it is an attempt to add to the knowledge about the aspects that may enable or stifle HTA development and use in a context like Colombia. This country, as noted previously, is currently struggling to set priorities for health and health care in a more systematic and transparent manner (Castro, 2011; Caballero-Uribe, 2012 and *Defensoría del Pueblo*, 2013).

Of worth mentioning that "drivers" such as policy/political and financial support, as well as usefulness perception were considered as useful information for the strategic planning of IETS during its first years of operation. The incremental implementation strategy of IETS has also borne in mind aspects like in-house and external capacity building, established links with the international academic community and set up a consultative committee with representatives from senior experts of HTA agencies around the globe, incorporated good practices of vested interest declaration and stakeholder engagement in order to deal with their pressure and attain legitimacy, IETS is also currently working on the development of guidance and manuals to improve the quality or reports and reduce uncertainty of estimates; all these after considering some of the emerged themes and "drivers" of this thesis.

The attempt of the current government to strengthen institutional capacity has led to the establishment of the first HTA agency in Spanish speaking America with the purpose of informing resource-allocation decision-making. Hence of special interest for the government and the main researcher, is the uncovering of those dynamic aspects, reported as "drivers" that should be considered for the successful implementation of HTA in the context of interest. Although it has been said that the main purpose of qualitative research is not to assure external validity (generalizability or extrapolation), this research chapter is intended to be as detailed as possible so that readers can judge the applicability of its findings to similar settings.

SUMMARY

This part of the research used qualitative methods to explore previous experiences of conducting HTA, and the perception of its role and future use in Colombia; ten potential 'drivers' were identified. The methods were chosen to pay close attention to evidence, critically approach subjective and analytic accounts of participants, and offer careful and rigorous analysis. After purposive homogeneous sampling, semi-structured interviews, rigorous transcription, and thematic content analysis, those aspects that may help or hinder HTA development and use in Colombia were identified. However, it is worth emphasising that the analysis was relatively 'basic' and departs from approaches of qualitative enquiry aimed at generating new theory such as grounded theory, phenomenology or ethnography. Further qualitative analyses may serve to explore in much more detail HTA development and use as a phenomenon in Colombia.

Although HTA has become a tool to inform decision-making around the world, those aspects that may help or hinder HTA development and use in Colombia may not be generalizable to other countries. Nonetheless, the conceptual transferability of concepts like "drivers" with caveats may be of interest for similar settings trying to incorporate HTA processes and institutions into decision-making.

2. <u>CHAPTER 2</u>- A cost-utility analysis of primary prophylaxis for the treatment of severe haemophilia A in Colombia

INTRODUCTION:

Haemophilia A is a rare inherited disorder affecting the blood coagulation system, which is characterized by a permanent tendency to haemorrhage. Bleeding into the joints (such as knees, ankles and elbows) leads to articular damage (haemophilic arthropathy) which is the most frequent long-term complication of the disease. The mainstay of treatment is replacement therapy with exogenous clotting factor VIII (FVIII). However, in some circumstances the chronic exposure to exogenous clotting factor leads to the onset of antibodies (inhibitors) against therapy, this is a serious and frequent complication of treatment.

People with haemophilia A are categorised depending on their endogenous level of FVIII activity (LoA) as being either mild (LoA from 5-40% [0.05- 0.4 IU/ml]), moderate (LoA from 1-5% [0.01- 0.05 IU/ml]) or severe (LoA less than 1% [<0.01 IU/ml]) (White et al, 2001). For people with severe haemophilia A (SHA) bleeding can be spontaneous or traumatic and sometimes life threating. Of all the orphan conditions, haemophilia accounts for the biggest proportion of the population (approximately 1 case in every 5,000 people)[36].

In Colombia, haemophilia A care represents an important financial burden to the health system. The costs associated with clotting factor replacement for this condition were COL$140,164,400,000 (USD$73.72 million) in 2010[37] or 0.46%[38] of the total annual spending on health while treating approximately 2,000-2,600 patients, 800-1,040 of whom are classified as severe cases (Colombian League for Haemophilia- CLH, 2011). Indeed, health care coverage for this disease has attracted much media attention in recent times, but not even in the upcoming new health sector reform (HSR) has the issue of sustainable funding for orphan conditions been solved.

There are two main types of FVIII treatment for people with SHA. On-demand (OD), following a bleed, to stop it. Or prophylaxis, when treatment is given prior to bleeding with the aim of preventing joint damage. 'Primary prophylaxis' (PP) represents treatment prior to the onset of repetitive bleeding, whereas 'secondary' prophylaxis refers to initiation of treatment sometime after this process has begun.

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[36] Orphan disease definition as per Colombia Law 1438 2011
[37] Figures published by the Colombian Medical Federation- FMC in October 2010. See http://www.observamed.org/
[38] These costs do not include inpatient or ambulatory care arising from bleeding episodes, or their complications or the costs arising from the use of rFVIIa for patients with inhibitors

Although the prophylactic replacement of clotting factor has been recommended as the gold standard of care by institutions such as the World Federation of Haemophilia (WFH) and the WHO (Giangrande 2004), in Colombia, as in many other countries, PP is provided to less than 50% of all severe haemophilic patients (CLH, 2011), largely because it is considered to be much more expensive than treatment OD. Indeed, in Colombia, there are no evidence-based clinical practice guidelines in place for this health condition, and haemophilic arthopathy with its subsequent negative impact on HR-QoL is still a frequent finding (CLH, 2011).

Knowledge about the clinical effectiveness of haemophilia A has exponentially grown in recent decades. For example, a number of observational studies have shown that clinically observable signs of haemophilic arthropathy can be almost entirely prevented over prolonged periods (20 years) if exogenous replacement factor is provided early and frequently (Nilsson et al, 1992, Aznar et al, 2000, Coppola et al, 2008 and Berntorp 2009). However, the cost-effectiveness of PP remains a particular concern (Castro et al, 2012). The number of published economic evaluations for prophylaxis is very limited and their results are confusing. For example, while nearly a dozen studies have been published since 1996, they have reported results ranging from prophylaxis being "dominant" to it costing over €1 million per QALY gained (Miners, 2013).

From this wide range of published results it is still unclear if this intervention has reached the point of being considered "good value for money", or cost-effective. This statement is also true for Colombia, but no primary haemophilia-specific HTA or economic evaluation has been published in this context. Thus in Colombia, where the health system is facing severe financial strain, the research question of this chapter "what is the incremental cost-effectiveness of PP throughout life with exogenous FVIII compared with OD treatment for severe haemophilia A?" becomes particularly relevant.

There are many types of economic evaluation (Drummond et al, 2005) , but in order to allow cross comparison of interventions a cost utility analysis (CUA) where costs are measured and expressed in monetary terms and outcomes stated in combined units capable of capturing morbidity and mortality (e.g. Quality Adjusted Life Year-QALY) was developed. This chapter presents a CUA comparing PP to OD treatment for severe haemophilia A. Methodological issues relating to conducting HTA through this economic study in Colombia are described at the end of it. A full HTA report of PP was also developed and presented to decision-makers in order to test the MCDA-EVIDEM in this context; this is described in the next thesis chapter.

METHODS:

<u>The decision problem</u>

The decision problem for the analysis was the choice between PP versus OD for people with SHA, from the health system perspective and over a lifetime horizon. This perspective was adopted because up to 95% of costs of long-term treatment for SHA may be associated with FVIII provision (Daliri, 2009 and Miners, 2009). A lifetime horizon was considered as clinically relevant since SHA is a lifelong disease, and the long-term benefits, costs and complications of treatment are expected to occur throughout the life span of patients. The analysis considered the use of plasma-derived FVIII and OD as current practice in Colombia. The cost of exogenous factor replacement using recombinant FVIII (rFVIII) is expected to be higher than for plasma-derived products, and since its use has increased in recent years, this was considered as an alternative in a scenario analysis.

For the purposes of this evaluation PP is defined as treatment by intravenous injection of exogenous clotting factor in order to prevent bleeding in the first instance. It is assumed to begin in infancy and continue into adulthood. On the other hand, OD treatment was defined as FVIII administration whenever joint or extra-articular bleeding occurs.

<u>The rationale for modelling</u>

SHA is a chronic condition where patients are at risk of recurrent bleeding for many years, and joint damage is expected to develop after cumulative stress and injury within the joints. This clinical spectrum presented the researcher with "an unavoidable fact of life", in order to emulate "real world" conditions and conduct rigorous economic evaluation it was necessary to use a modelling approach (Buxton et al, 1997 and Hjelmgren et al, 2001). After reviewing the available evidence, a previous framework developed by Drummond et al (2009) to assess the feasibility of developing or transferring economic evaluations across jurisdictions was used to decide if it would be necessary to conduct *de novo* modelling or to 'adjust' previous cost-effectiveness information.

Coinciding with the findings of Miners (2013), economic evaluations for haemophilia A are still very limited, especially CUAs. Moreover, the existing studies have adopted different perspectives, made different structural assumptions, used different time horizons, discount rates and sources of data. Figure 4 presents a modified version of the steps outlined by Drummond for determining appropriate methods for adjusting cost-effectiveness information, red circles account for the answers in the case of PP for SHA in Colombia.

There was limited cost-effectiveness (cost-utility) information available that adopted a broad variety of structural approaches and compared results of different treatment patterns. The most relevant studies considered the cost of rFVIII as common practice instead of FVIII which is the current case in Colombia, also showed model structures and results that were not transferable or adjustable to this setting since they analysed different prophylactic schemes, made different assumptions, adopted different infusion schedules and reported non-comparable treatment patterns, all these represented "general knock-out criteria" for transferring results. Further, since no cost-effectiveness multi-location trial data had included Colombia, the starting point of published economic studies was considered as irrelevant to the decision problem of interest.

When considering the methodological soundness of these studies there were considerable limitations. Of special interest for this thesis work was the analysis of the structure, parameters and quality of the Miners (2009) and Colombo (2011) studies. In 2009, Miners et al updated a previous version of the first published CUA. In their model the prophylactic regimen treatment was not dose or time specific, but was set as a clinical target trough *in vivo* clotting factor level of 1 IU/dl, and doses required to reach it were calculated using pharmacokinetic principles. There was no linkage between bleeding and major surgery joint-related clinical status. The base case model was run from the period of treatment initiation (1 year of age) for 70 cycles. In their updated version costs and benefits were discounted at 3.5%.

A number of criticisms can be levied at this model, the sole structure could be challenged from a clinical standpoint since up to 10% of severe haemophiliacs with FVIII concentration of < 1IU/dl may not experience frequent bleeding or express the full clinical spectrum of disease (Royal et al, 2002). This study also uses four health states "no specific problems", "year prior to major surgery", "major surgery" and "dead" which, from a clinical perspective, are not self-explanatory.

As mentioned by Olivieri et al (2012) who reported MRI-positive findings of joint damage in up to 19% of SHA patients, there is evidence of subclinical joint deterioration and the health state "no specific problems" may not be entirely realistic, since it is expected that the baseline disease may carriage morbidity for patients.

Also not all patients would require "major surgery" throughout life and a large number of cycles need to be experienced for patients to move from having no problems after bleeding to the year before major surgery and surgery itself, especially in those with PP. Another limitation of Miners (2009) is that the values used to estimate outcomes OD were derived from a cross-sectional study of HCV[39] infected haemophiliacs; this may have overestimated the impact on health of PP.

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[39] HCV Hepatitis C Virus

Figure 4. Modified version of the steps for determining appropriate methods for adjusting cost-effectiveness information
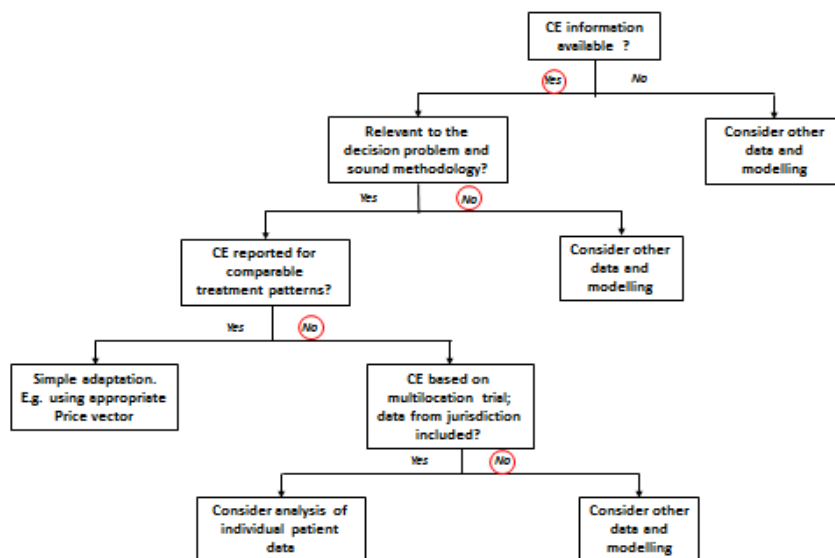
In 2011, Colombo et al replicated Miners et al work (and perhaps some of its limitations). The authors used a similar model with health states: "alive", "require major surgery", "surgery" and "dead", but in this case patients entered the model at birth. This may represent a limitation of the study since, as mentioned by Kurnik et al (2010), the highest risk of developing inhibitors is during the first 20 exposure days, and it might be preferable to delay the first exposure to exogenous factors for at least one or two years. The model was run for 100 cycles. A 6% discount rate was used for both costs and outcomes. Life expectancy of severe haemophiliacs was assumed to be similar to that of the general North European male population (similar to Miners, 2009); this latter assumption departs from evidence supporting the expectation that severe cases of haemophilia may well live 15 years less than general population (Darby et al, 2007). The authors estimated the probability of dying after the first year of surgery to be equal to that of the general population, based on an Italian male life-table by adding a 1% that is not further explained in the publication.

Another limitation of the Colombo study is that the utilities for the health states "alive" and "surgery" were derived from the Miners et al study (2009) without considering the transferability of results. The utility for the health state "require major surgery" was obtained from Laupacis et al (1993) who assumed that HR-QoL of living in such health state was equivalent to individuals with osteoarthritis. Another limitation is that the HR-QoL of severe patients in PP is equivalent to people with mild/moderate cases; this also may depart from the clinical profile of this population, since as mentioned before SHA patients tend to bleed even spontaneously. The Colombo study did not incorporate any costs other than those of clotting factor, inpatient care and surgery.

Context issues such as lack of local rules for conducting HTA in Colombia and the aspects of the published analyses that would have to be addressed before considering transfer of estimates fulfilled the so-called "specific knock-out criteria", and left no other option for the researcher than considering other data and modelling.

The model type and structure

In order to compare the long-term costs and effects of OD and PP for SHA it was necessary to move beyond the relatively short term results of the observational and RCTs studies, and since decision analytic models provide the means of bringing evidence and data together in order to generate estimates of cost-effectiveness, it was necessary to consider the type and structure of such a new model. A decision tree in this case would have become very "bushy", with many recurring pathways given the long time horizon of the disease, and the recurrent nature of bleeding episodes, thus a Markov model was considered the most suitable structure to simulate movements between relevant health states over time.

The *de novo* Markov model was designed and populated making use of the best available evidence; this was collected and gathered through two literature searches, and supplemented with 'local' evidence when necessary. Three physicians (two haematologists and a public health specialist) familiar with SHA participated as local clinical experts to validate, refine or estimate some of the model input parameters. Three third-party payer senior managers of health insurers also participated as experts on local costs and tariffs. This panel of experts was virtually allocated and requested to consent in at least two rounds of enquiry about unit consumption and costs whenever needed, participants were anonymous to each other.

The model was constructed using TreeAge Pro 2013 software. The basic model logic was that fewer bleeding episodes leads to lower rates of joint-related complications, which in turn is assumed to lead to better HR-QoL. This assumption is supported by Nilsson et al (1992) who followed up 60 severe haemophiliacs A and B aged 3–32 years whose treatment was started at 1–2 years of age. The study suggested the possibility of preventing haemophilic arthropathy by giving effective continuous prophylaxis from an early age, by preventing clotting factor concentrations from falling below 1% of normal. Lalezari et al (2011) and Kempton et al (2012) have also reported similar findings.

The model consisted of a simplified version of the natural course of the disease and considered three health states for each treatment branch: "Alive-no arthropathy", "Alive-with arthropathy" and "Dead".

The health state "Alive-no arthropathy" represented those patients with SHA without active bleeding that have not developed joint damage. The health state "Alive-with arthropathy" represented those patients with SHA without active bleeding that have already developed joint damage. Patients in the model could either experience active spontaneous or traumatic bleeding located within the joints (articular) or not into the joints (extra-articular) and the difference between the two treatments being the annual rate at which this occurs. In the model once bleeding has occurred, patients could die or recover (i.e. stop bleeding and stabilise).

For a pictorial representation of the decision node and health states for each decision branch see figure 5, where the circles represent the three possible health states. All patients entered in the model in the health state "Alive-no arthropathy". This initial health state coincides with the clinical spectrum of disease, in which patients are asymptomatic until the haemostatic system is stressed by a surgery or trauma, and by the fact that without joint bleeding, joint damage does not occur (White et al, 2001). Supporting this assumption, in 2010 Capaci et al used the radiographic Gilbert score to asses joint status of patients and found that in severe haemophiliacs that received prophylaxis bleeding was prevented and results were almost as good as those of mild cases (p <0.05).

The primary assumption was that all severe haemophiliacs bleed at some point in life (regardless of the treatment option allocated), this is supported by Olivieri et al (2012) who reported MRI-positive findings of joint damage in 19% of asymptomatic haemophilic patients in a 10-year period of follow up, suggesting the substantial impact of sub-clinical bleeding within the joints and also that MRI-positive findings may not always be clinically expressed.

Every cycle, patients in the health state "alive-no arthropathy" bleed at a mean annual specified rate per-treatment option. A proportion of these bleeds are articular, with the remainder being extra-articular. At this point, individuals can either die from bleeding, or recover (i.e. stay alive). A proportion of patients who have experienced intra-articular bleeding and recover, develop arthrosis and enter the heath state "alive-with arthropathy" with the remaining proportion staying in the health state "alive-no arthropathy".

The annual probability of developing arthropathy was assumed to be constant and independent of the number of bleeds per cycle as this relationship is complex and not well understood. For example, no published evidence documenting the cumulative probability of developing joint damage after repetitive bleeding within the same joint could be identified. In the base case model it was further assumed that once people had entered the health state "alive-with arthropathy", they continued to experience an annual rate of bleeding, but that individual joints do not further degenerate.

It was also assumed that patients remained in the health state "alive-with arthropathy" irrespective of treatment, since once arthropathy has occurred it does not regress, as observed by Hilberg and Czepa´s 2009 in their physio-pathological description of the disease. Eventually, throughout their life span, all patients without any previous joint damage who present with additional articular bleed would either develop arthropathy or die.

Dying from bleeding is expected to be similar for each treatment branch; chances of dying in the model were considered to be associated with the promptness of access to health care, and not with the total number of bleeds per-cycle or the severity of haemorrhage. Although the annual probability of dying from bleeding of any type was likely to be relatively low, was considered as important by the local clinical experts thus it was incorporated in the base case model making use of the data reported by Darby et al (2007).

Figure 5. The Markov model for SHA
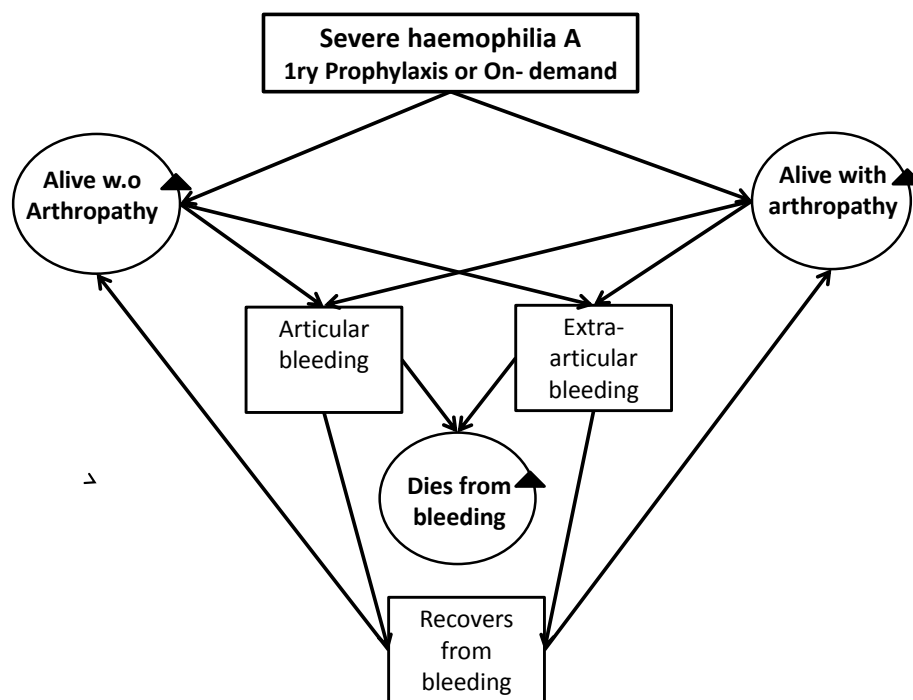
In Colombia the probability to die from bleeding is still expected to be significant. The relevance of the mortality form bleeding in this context was reported by Bernal and Suarez in 2008 who estimated the potential years of life lost (PYLL) from haemorrhage in haemophiliacs in Colombia as 21.8 per-patient, the authors calculated the years lost by subtracting from life expectancy the years lost derived from disability and severity of disease. Nor did this source or any other account for the frequency of deaths associated to bleeding in SHA patients in this country.

In Colombia there are still barriers to access to prompt treatment whenever bleeding occurs, also logistic and cultural limitations that may prevent home-based provision of FVIII such as lack of electricity or lack of cold-chain quality assurance, literacy, and a black market of costly medicines (CLH, 2001 and *Noticiero del llano*, 2013).

The costs and outcomes associated with each health state were expected to be different and associated with the treatment allocated, hence they were estimated separately. Patients entered the model at two years of age, taking into consideration the international recommendation deemed as gold standard[40] (Nilsson et al, 1992, Manco-Johnson et al and Petrini et al, 2007), doses per-year were adjusted for weight dependence as is normal when treating with FVIII. The base case model ran for 70 yearly cycles accounting for the life expectancy of non-HIV-positive severe type A haemophiliacs (Darby et al, 2007), which is expected to be 15 years less than the general population.

In the model it was assumed that once treatment was allocated (PP or OD) patients fully complied with it and would not switch during their lifetime; clinical effectiveness and safety from treatment with either FVIII or rFVIII were expected to be similar (Mingot et al, 2009 and Gouw et al, 2013). Although the development of inhibitors is expected to be substantial and, according to some authors, may reach up to 30% of cases (Collowick et al, 2000 and Farrugia et al, 2013), there is still controversy in the current published evidence about the differential rates of inhibitor development among those receiving replacement therapy via OD versus those with prophylactic schemes (Lusher, 2000 and Scharrer et al, 1999 vs. Kurnik et al, 2010), hence this frequent complication was not considered in the model.

Other complications from clotting factor application were assumed to be equal for PP and OD treatment. The number of hospitalisations whenever bleeding occurred and blood tests for diagnosis and inhibitor screening were expected to be similar between two groups, hence not considered, this is similar to the findings reported by Manco-Johnson et al in 2007.

The probability of dying from other causes was considered similar for haemophiliacs and the general population for individuals borne in 2014 onwards in Colombia (5.29 per 1000 people as per DANE, 2014), and thus not incorporated in the model. Blood-borne infections were expected to be non-existent if proper viral attenuation methods were used or if recombinant exogenous factor was used, and were therefore not considered (Gringeri et al, 2011 and Darby et al, 2007).

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[40] Malmö protocol: treatment is started when boys are 1–2 years of age but later than 18 months of age, the regimens used being 20–40 IU F VIII kg three times weekly in haemophilia-A cases (i.e. > 2000 IU kg^{-1} annually).

<u>Model Inputs</u>

In order to inform the decision problem of interest and gather information to populate the model, two literature searches were performed in 2013 to update effectiveness and cost-effectiveness information for PP retrieved through a preliminary search conducted by the main researcher in 2011 (Castro et al, 2012).

The first search assessed the clinical effectiveness of PP compared to OD treatment for SHA, and the second reviewed whether any previous economic model had modelled the same decision problem, used comparable treatment patterns or adopted a structural design that could potentially be used or adapted in this case study. Studies published in English and Spanish were sought from specialized electronic databases in medicine, health economics and health technology assessment. For details of the literature searches and main findings see Appendices 1 and 2.

The first search update was performed on May 8th 2013, and aimed to identify the relevant clinical literature. Using OVID browser, Journals@Ovid, LSHTM Journals@ovid, ACP Journal Club (ACP), CCTR (formerly Cochrane Controlled Trials Register), the Cochrane Database of Systematic Reviews (COCH), CAB abstracts, Econlit, Embase and Scielo were searched from their date of inception up to the above mentioned date. The search terms used were: [haemophilia A], [haemophilia A], [coagulation ADJ3 disorder], [clot* ADJ3 disorder*], [clot* ADJ3 deficiency], [prophylaxis], [primary ADJ3 prophyl*], [on demand], [on- demand], [arthropath*], [arthrosis], [joint damage*]. These were used taking into account headings and sub-headings and their correspondent wording in Spanish. Boolean operators OR and AND were used as follows: (OR) to combine synonyms, headings and sub-headings and (AND) to combine different concepts.

The inclusion criteria were: complete articles published in English or Spanish from 1970 onwards including systematic reviews, meta-analyses, randomized controlled trials, cohorts, case and control studies, case studies, full economic evaluations and review articles. 1970 was set as the start date, being the time when the first reports about the inception of plasma-derived clotting factors and the start of prophylaxis were published.

Information on patients of all ages and from all kind of studies was sought, since SHA is a rare condition looking only for RCTs could severely constrained the number of studies retrieved. Only publications considering the clinical effectiveness of different treatment options for SHA (regardless of complications, age of diagnosis or time of treatment initiation) were eligible. Publications that described and/or compared OD versus PP for SHA were also included. Outcomes including at least one of the following: frequency of bleeding episodes, mortality, potential complications, quality of life and joint damage were considered.

The exclusion criteria were: publications considering patients with any coagulation disorder other than haemophilia A, and any stage other than severe cases (level of activity of clotting factor > 1%); publications addressing patients with acquired haemophilia A, clotting factor inhibitors or HIV co-infection (due to the differences of clinical presentation, natural course of disease, co-morbidities, and therapeutic response to usual treatment).

Quality control and assessment of data included extraction and a synthesis of published evidence. PRISMA work flow was used to systematically assess papers retrieved, control for duplication and assess eligibility criteria. A total of 166 articles were retrieved from the search and identified as potential relevant references; 25 records were added to the total number of possible articles to be analysed. 147 publications were recognized after controlling for duplicates, and 110 abstracts were screened searching for relevant data.

After abstract screening, 41 articles were excluded because they did not specifically address the main topic of research; 69 full text articles that described and/or compared different treatment options for hemophilia A were scoped for eligibility. 13 full text articles were excluded with reasons, and finally 56 publications were included in the analysis. Due to the heterogeneity of studies and outcomes reported, no studies were included in a quantitative synthesis of evidence (meta-analysis). See Appendix 2.1 for a detailed graphic of the PRISMA flow.

The second search aimed to identify previously developed economic studies for SHA that compared the two interventions of interest. A preliminary search of the literature carried out by Miners in 2012 and published in 2013 was extended and updated on May 15th 2013. The following databases were searched: The Health Technology Assessment database, The NHS Economic Evaluation Database-HEED, and Ovid Medline.

Combinations in English of the terms [haemophilia], [hemophilia], [cost], [economic-analysis], [economic-evaluation], [economic-study], [cost-effectiveness], [cost-benefit], [cost-utility] were used. These were used taking into account headings and sub-headings. Boolean operators OR and AND were used as follows: (OR) to combine synonyms, headings and sub-headings and (AND) to combine different concepts together (see Appendix 1 for the detailed search history of both searches).

Inclusion criteria were: complete articles published in English from their date of inception. Systematic reviews and full economic evaluations (i.e. those that focused on the costs and health outcomes associated with treatment and cost-minimization analyses) were considered. Only publications comparing PP versus OD treatment for SHA were eligible. Exclusion criteria were similar to those of the first search on the clinical effectiveness of PP.

Quality control and assessment of data included extraction and a narrative synthesis of published studies. PRISMA work flow was used to systematically assess papers retrieved, control for duplication and assess eligibility criteria. A total of 178 articles were retrieved from the search and identified as potential relevant references; no records were added to the total number of possible articles to be analyzed. 113 publications were recognized after controlling for duplicates; after a title search, 23 abstracts of full economic evaluations or reviews were considered relevant and screened for information.

After abstract screening, six articles were excluded because they did not specifically address the main topic of the research; 17 full text articles that specifically described findings of PP versus OD for severe hemophilia A were scoped for eligibility. Four full text articles were excluded with reasons, and finally a total of 13 publications were included in the qualitative analysis. (See Appendix 2.2 for a detailed graphic of the PRISMA flow).

Most of the model inputs were derived from the published literature. Besides the cost of exogenous replacement therapy, other costs associated with the long-term treatment of severe haemophiliacs included were: general practitioners and specialist visits, central venous catheters and catheter infection treatment, conventional radiology, ultrasonography and MRI, as well as minor and major orthopaedic surgery, orthopaedic equipment, and physiotherapy (See Table 1 for a list of input parameters used for the economic model).

<u>FVIII dosing schedule</u>

The dose of PP was set based on the clinical trial of Manco-Johnson et al, (2007). The primary outcome of this study was the incidence of bone or cartilage damage as detected in index joints (ankles, knees, and elbows) by radiography or magnetic resonance imaging (MRI). Boys under 30 months of age were randomly assigned to PP (n=32) or to enhanced episodic therapy (n=33). PP dosage in the model was set at 25 IU/Kg three times per week for a minimum of 46 weeks per-year (3450 IU/Kg year); this dosing schedule represents the typical clinical approach to PP provision in Colombia. When bleeding occurred during prophylaxis in Manco-Johnson's study, patients received 40 IU/Kg of FVIII and the assigned prophylaxis scheme was resumed the next day; this approach was also incorporated in the model.

TABLE 1. Input parameters used for the economic model

	Description	Source	Root Definition
	Probability to develop an articular bleeding	Stachnik, 2010, Wong, 2011; Vdovin, et al, 2011 and Kempton et al, 2012	0.8
	Probability to develop extraarticular bleeding	Stachnik, 2010, Wong, 2011; Vdovin, et al, 2011 and Kempton et al, 2012	1-p_articular_bleeding
	Probability to die from bleeding of any type	Darby et al, 2007	0.00525
	Probability to develop arthropathy PP	Manco- Johnson et al, 2007	0.0188
	Probability to develop arthropathy OD	Manco- Johnson et al, 2007	0.145
V	Probability of needing a central catheter PP	Manco- Johnson et al, 2007	0.5659
A	Probability of needing a central catheter OD	Manco- Johnson et al, 2007	0.3420
R	Probability of infection from central venous access	Manco- Johnson et al, 2007	0.0615
I	Utility of alive without arthopathy PP	Secondary local source 31 patients	0.937
A	Utility of alive with arthropathy under PP	Secondary local source 31 patients	0.739
B	Utility of alive without arthopathy OD	Secondary local source 31 patients	0.937
L	Utility of alive with arthropathy OD	Secondary local source 31 patients	0.739
E	Dosage per Kg per year PP	Manco- Johnson et al, 2007	3450
S	Dosage per Kg per joint bleeding episode OD	Manco- Johnson et al, 2007 modified	200
	Dosage per Kg infuse on PP when joint bleed	Manco- Johnson et al, 2007	40
	Dosage per Kg OD any other bleeding	Smith et al, 1996 & Mannucci et al, 2009	100
	Number of all bleeds OD	Manco- Johnson et al, 2007	17
	Number of all bleeds PP	Manco- Johnson et al, 2007	3
	Discounting rates costs	NICE Guidance 2011 & Farruigia et al, 2013	0.035
	Discounting rate effects	NICE Guidance 2011 & Farruigia et al, 2013	0.015
	Number of cycles-Life expectancy of severe haemophilics 60 years	Darby et al, 2007, Larsson 1985	70
	Table of weights boys 50 percentile	Center for Disease Control- CDC, 2000	Age specific

On the other hand, OD dosage in the base case departed from the enhanced episodic treatment presented by Manco-Johnson. In their study children were treated at the time of clinically recognised joint haemorrhage and received 40 IU/Kg at the time of haemorrhage, 20 IU/Kg at 24 hours and 20 IU/Kg 72 hours after the first dose. Treatment was continued at 20 IU/Kg every other day until symptoms resolved, which in this study was expected to happen after week four. According to local experts[41] (through informal consensus) recovery was assumed to happen in Colombia after two weeks of treatment instead of four, thus this regimen was incorporated in the model to make it more realistic. This equated to a total of 200 IU/Kg of FVIII per articular bleeding episode OD (form onset to resolution).

Any other kind of extra-articular bleeding OD dosage (soft tissue, intra-abdominal or intra-cranial or post-surgery [form onset to resolution]) was estimated in 100 IU/Kg of clotting factor per-episode, this was transferred from Smith et al (1996) and Mannucci (2006) and validated with the local experts who considered it as plausible.

The annual rate of bleeding

There are numerous studies reporting the yearly bleeding frequency associated with PP. For example, Vdovin et al (2011) evaluated three different prophylactic regimes of FVIII: 70 IU once-a-week, 30 IU + 40 IU in different days per week, and 25 IU three-times-a-week (all per-Kg). It measured all bleeds and joint status in 32 paediatric patients, and reported that the median number of bleeds per-year in patients on prophylaxis ranged from 1.5-3.

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[41] Local clinical experts in haemophilia A care: two haematologists, one specialized in children and one in adult population currently working at two centres of excellence in central and northwest Colombia, one public health specialist familiar with heamophilia care from central Colombia.

In 2006, a study by Feldman et al compared a tailored prophylactic scheme for SHA, and showed that after a median follow-up time of 4.1 years 36% of patients developed target joints[42]. The median time to escalate from once to twice-weekly therapy was 3.42 years. There was an average of 1.2 joint bleeds per person-year. Ten subjects (40%) required central venous catheters.

The mean estimates of bleeding episodes of Manco-Johnson et al (2007) were also considered. This study reported results of treatment branches PP and OD, and median values of 1.15 and 17.13 (p<0,001) respectively. Whilst a mean value of 17.69 (CI +/-9.25) for bleeding episodes OD was very close to the median, a higher mean value and wider interval was presented for prophylaxis 3.27 (CI +/- 6.24). After looking at the mean values reported by Fischer and Van Den Berg (2003), Coppola et al (2008) and Vdovin (2011) in their observational studies, three bleeding episodes per-year with PP and 17 bleeding episodes per-year OD were selected as the input parameters for the base case model (close to mean estimates of Manco-Johnson et al in 2007). These seemed more realistic to clinical experts than more conservative estimates in the context of interest.

Transition probabilities

Input probabilities incorporated in the decision model included the annual probability of articular bleeding, the probability of extra-articular bleeding, the probability of dying from bleeding of any type, and the probability of developing arthropathy under each treatment branch.

Whenever bleed occurs, the probability of it being articular was extracted from the published literature taking into consideration the data reported by Stachnik (2010), Wong and Vdovin et al (2011) and Kempton et al (2012). These authors estimated the probability a bleeding to be located in the joints as around 80% of all bleeding episodes, this figure was derived and validated by the panel of clinical experts who considered it as plausible in this context, thus incorporated in the model. The probability of presenting with extra-articular bleeding was calculated as the complement of the probability of articular bleeding.

Data of poor quality from 2011 from the CLH was reviewed before considering other jurisdictions. Since in Colombia there is no available, updated and reliable data about the mortality rates and causes of death among SHA patients, henceforth the probability of dying from bleeding of any type was extracted from Darby et al (2007) which reported the life expectancy and causes of death of people with haemophilia A or B (non-HIV infected) in the UK from 1977 to 1999. This study reported that 145 deaths from bleeding occurred during this 22 year period of observation.

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[42] Target joint- CDC definition MRI-positive findings after 3 bleeding episodes in the same joint over a period of 3 months

The study followed up 1320 severe haemophilic patients (type A and B) and reported that 81% of them were severe type A haemophiliacs (1069); by assuming a similar distribution among those who died from bleeding over the period of observation, a total of 117 deaths would have occurred from bleeding of any type among SHA patients (145 x 0.81). Hence the cumulative incidence over the 22 year period of observation was calculated as 0.109 (117/1069). This period hazard rate of dying from bleeding was annualized making use of the formula:

$$\mu = \frac{-\ln[1-P(t)]}{t}$$

As presented by Kuntz and Weinstein (in Drummond et al, 2001), where μ is the annual rate, *P(t)* the cumulative rate (0.109) and *t* the period of observation (22), it was estimated as 0.00526. By assuming that the annual hazard rate μ was constant over the study time horizon, the annual transition probability of dying from bleeding of any type was estimated as 0.00525 making use of the formula:

P(1)= 1- $exp\,(-\mu t)$

Where P(1) is the annual probability and μt is the annual rate. The issue of the time difference between the publication of Darby´s study and this thesis was further considered before incorporating this data into the model; however, it was not perceived by experts as a major source of concern in the Colombian context.

Similarly, the overall probability of developing arthropathy was estimated and extrapolated from the published evidence. No publications have reported the specific risk of developing arthropathy within each new bleeding episode and only two recent RCTs reported the risk rates of developing joint damage with PP and OD after a period of observation (Manco-Johnson et al, 2007 and Gringeri et al, 2011). The characteristics of the dosing scheme and profile of participants in the Gringeri study limited extrapolation of results and left the former as the most reliable source of evidence for the model.

Manco-Johnson et al reported that after a mean follow-up period of 49 months, 2 out of 27 patients (7.4%) with PP developed joint damage and for those OD, 13 out of 29 patients (44.8%) developed it (p=0.002). Joint damage in this study was defined as at least one joint with positive MRI findings. Using Miller and Homan´s (1994) approach, the monthly hazard rates of developing arthropathy with PP and OD were converted to monthly transition probabilities using the formula:

1-(1-P(t))^(1/t)

Where P*(t)* is the period rate and *t* the period of observation, hence monthly transition probabilities of 0.0120 for OD and 0.00157 for PP were calculated. Since the decision model was expected to run yearly cycles, these monthly transition probabilities of developing arthropathy OD and PP were annualized in 0.145 and 0.0188 respectively by multiplying the monthly transition probabilities by 12 and incorporated in the base case model.

Other probabilities such as the annual probability of requiring a central venous access device (CVAD) with PP or OD and the probability of CVAD infection were not incorporated in the model. However, these were used to refine (weight) the annual consumption of resources to estimate "other medical costs". These were also gathered from the Manco-Johnson study. Over the follow-up period 29 (90.62%) out of 32 patients in PP required CVAD, compared with 25 (75.75%) out of 33 OD. Among patients requiring a CVAD, infection occurred in 20.69% of PP cases, and 24% of OD patients. Using the method described before by Miller and Homan, these hazard rates were used to estimate the annual transition probabilities of requiring a CVAD and acquiring CVAD-associated infection among sub-groups. The annual probabilities of CVAD OD and PP were estimated as 0.3420 and 0.5659 respectively; and of having CVAD infection 0.056 for OD and 0.067 for PP. However the panel of experts expected the chances of CVAD infection to be similar regardless of the treatment allocated in Colombia, hence an average annual probability of 0.0615 was estimated to weight the annual costs of CVAD infection.

Costs

All relevant costs associated with replacement therapy with FVIII, follow up, bleeding episodes, and treatment of complications from chronic bleeding or joint damage were gathered from local sources. Costing considered the quantities of resources used per-patient per-year, as well as the local unit cost of health services consumed from the health system´s perspective. Besides exogenous factor consumption, it also calculated additional medical costs, taking into account the natural course of disease and local clinical standards. (See Table 2 for a detailed description of estimated costs and units used to populate the economic model; for the full table of input parameters see Appendix 3).

The base case model assumed FVIII was administered at 3450 IU/Kg per-year for PP and 40 IU/Kg when bleeding occurred during prophylaxis, and for OD a total of 200 IU/Kg per articular bleeding and 100 IU/Kg for any other kind of bleeding. Doses per-cycle in the model were adjusted using a table accounting for age-dependant weight variation of boys in the 50th percentile[43]; when patients reached adulthood all subjects were given a weight of 70 Kg in the base case model.

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[43] 2 to 20 years boys chart- stature weight-for-age percentiles. Source http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf as per September 30th 2013.

The cost per IU of FVIII was estimated as COL$900 (USD$0.47)[44] and the cost per IU of rFVIII COL$1450 (USD$0.76). Prices in Colombia of FVIII and rFVIII had not been regulated or publically available at the time of writing up; hence a market reference of average costs per IU/Kg paid by health care insurers (EPS) was used to populate the model. Since the difference in costs between FVIII and rFVIII were substantial, a variant of the base case model was run considering the costs of rFVIII.

Exogenous replacement therapy represented the biggest burden of resources consumed. Other medical costs such as number of units consumed per-year of general practitioner, haematologist and orthopaedist visits for both regimes, as well as MRI and radiology tests and physiotherapist sessions after bleeding were considered to have an annual frequency of use of more than one. Cost of services such as arthrocentesis, sinovectomy, arthroplasty, orthopaedic surgery devices and the use of walking aids OD were also included in the category of other medical cost, these were not as frequent as those described above, but seemed important for the accuracy of costing. For these services, unit consumption was expected to be less than one per-year, hence the annual frequency of use was proportionally adjusted making use of frequency weights informed by published data and experts´ input.

Most of the data used to assign weights was gathered from cross-sectional population surveys, presented to the local experts who provided additional estimates used to populate the model. For instance, to estimate the number of ultrasonography tests and arthrocentesis (joint aspiration) OD per-cycle, the data reported by Manco-Johnson et al (2007) were used to inform local experts about the expected number of life-threatening haemorrhages among patients per-year (0.0222). Also a study published by Rodriguez et al in 2011 reported that in up to 50% of all cases of massive haemorrhage within the joints it was necessary to aspirate the blood and use ultrasonography to minimise scarring and injury, hence the panel agreed on using 0.0111 (0.0222 x 0.5) as a frequency weight to refine the annual number of units for these two interventions.

According to Hilgartner (2002) and Windiga, et al (2005), it was estimated that up to 25% of all patients would require sinovectomy over their life span (65 years), hence a 0.0038 (0.25/65) frequency weight per-year was considered to estimate the cost of this intervention per cycle. Costs of arthroplasty and orthopaedic prosthesis and material needed to perform the intervention were refined in accordance with Windyga et al (2005), Gorina et al (2002) and Aznar et al (2000) who estimated that OD patients would require two major orthopaedic surgeries throughout life, by estimating an annual frequency weight of 0.0307 (2/65).

TABLE 2. Estimated costs, units and probabilities used for the economic model

	Description	Unit cost COL$2013	Total units	Frequency p.y	Total costs p.y COL$2013
C O S T S	Average cost recombinant Factor VIII per IU	1450	3450 IU/Kg 46 wks	1	5,002,500
	Average cost plasma derived Factor VIII per IU	900	3450 IU/Kg 46 wks	1	3,105,000
	Number of GP visits per year PP	20,000	12	1	240,000
	Number of GP visits per bleeding OD	20,000	2	1	40,000
	Number of haematologist visits per year PP	120,000	4	1	480,000
	Number of haematologist visits per year OD	120,000	9	1	1,080,000
	Number of orthopaedist visits per year PP	47,500	2	1	95,000
	Number of orthopaedist visits per year OD 50% of times they bleed	47,500	2.5	1	118,750
	Catheter + procedure PP	1,502,681	1	0.5659	850,367.18
	Catheter + procedure OD	1,502,681	1	0.342	513,916.90
	Antibiotic (Piperacillin+Tazobactam 56 vials)+catheter removal	1,448,327	1	0.0615	89,072.11
	Magnetic resonance imaging follow up OD or PP	257,183	1	1	257,183
	X Ray of any 6 target joints per year OD or PP	24,817	1	1	24,817
	Utrasonography when massive joint bleeding (50%) OD	36,550	1	0.0111	405.71
	Arthrocentesis when massive joint bleeding (50%) OD	33,020	1	0.0111	366.52
	Sinovectomies throughout life OD/65 cycles OD	983,118	1	0.0038	3,735.85
	Knee arthroplasty at 25 y.o and at 35 y.o OD	320,200	1	0.0307	9,830.14
	Physiotherapy after major joint bleed per session	10,121	5	1	50,605
	Orthopaedic surgical devices (wires, nails,plates, prosthesis, etc) OD	8,857,172	1	0,0307	271,915.18
	Walking aids (crutches, sticks, troley, weel chair, splints) OD	123,325	1	0.006	739.95
	SAID for hemarthroses, arthropaty or haematuria	43.28	15	0.013	8.44
O T H E R	**Medical cost p.y OD no arthropathy**				3,566,195.23
	Medical cost p.y OD with arthropathy				3,852,416.35
	Medical cost p.y PP no arthropathy				2,088,386.52
	Medical cost p.y PP with arthropathy				2,374,607.64

The same situation was assumed for those patients requiring walking aids OD at an expected frequency over a lifetime of up to 40% (Windyga et al, 2005), an annual average frequency weight of 0.006 (0.40/65) was used to refine this cost in the model. In the case of medication, steroidal anti-inflammatory drugs costs were based on Gorina et al's (2002) estimations that 85% of haemophiliac adults had been offered medication to control swelling or haematuria at least once in their lifetime, hence the panel considered it adequate to multiply annual cost of medication by weighting it at a factor of 0.013 (0.85/65). To estimate annual weights for other medical costs the panel assumed a uniform distribution of resources consumed over the period of observation. All presented data were considered plausible in the setting of interest.

Unit costs of central venous implantation, MRI, radiology, ultrasonography, physiotherapy sessions, arthrocentesis, sinovectomy, and arthroplasty per joint were estimated using the reference tariff manual ISS 2001 (*Manual del Instituto de Seguro Social* year 2001), which is widely used by insurers and health care providers to purchase health care services in Colombia. Unit costs of visits to general practitioners, haematologists and orthopaedists were also estimated using this manual. The global tariff was refined by informal consensus with local experts (purchasers) adding a 30% factor to control for inflation and regional variability of prices.

The costs of osteo-synthesis material for major orthopaedic surgery, central venous catheter and walking aids were gathered from local market reference prices collected by the researcher from a small sample of local retailers; cost of antibiotics to treat central catheter infection or prednisone to treat severe joint swelling or haematuria were gathered from SISMED 2013 (the official site of prices for medicines in Colombia). Finally "other medical costs" per-cycle incorporated into the model were, COL$3,566,195.23 for OD no arthropathy, COL$3,852,416.35 for OD with arthropathy, COL$2,088,386.52 for PP no arthropathy, and COL$2,374,607.64 for PP with arthropathy. Costs are presented in Colombian Pesos (COL$) and corrected for inflation if not gathered for the year 2013.

Utilities

The further impact of chronic arthropathy, the most frequent complication of bleeds, is expected to have a deleterious impact on the overall HR-QoL. Collecting and gathering utilities for the health states incorporated into the model represented a major challenge for the researcher since no general instruments to assess preferences for health states have been formally applied in Colombia (either to patients or general population). Under these circumstances the first option to estimate utilities to populate the model was to look at published references. The Tufts cost-effectiveness analysis registry (CEA) was searched for this purpose.

The CEA search suggested that lower utility values may be reasonable for patients with haemophilia who develop further complications versus those who do not, e.g. HIV co-infection 0.680 vs. 0.710 (Lippert et al, 2005) or inhibitors 0.660 vs. 0.850 (Knight et al, 2003). Risebrough et al (2008) reported differential utility values for those with and without complications irrespective of the treatment allocated (0.920 for PP without port complications and 0.875 PP with port complications, the same for those OD who did not meet the target joint bleeding criteria (0.905) and those who did (0.875)), thus making feasible the assumption that those patients who developed further joint damage may experience lower HR-QoL than those who did not.

This search also supported the preliminary aim of giving differential utility values according to the treatment allocated. For instance, Miners in 2002 and Colombo in 2011 reported higher utility values for 30-year-old HIV-negative individuals with PP compared to OD (0.87 versus 0.66 respectively). In 2009 Miners again used differential utility values of 0.50 for OD and 0.71 for PP. In 2005 Lippert et al reported utility values of 0.760 for severe haemophilic patients A and B (age less than 30) on prophylaxis and 0.730 for those OD (age less than 30). Nonetheless, no utility values have been published in the literature to account for the health states described in the base case model "Alive PP and no arthropathy", "Alive OD and no arthropathy", "Alive PP and arthropathy" and "Alive OD and arthropathy".

CEA registry findings were discussed with the panel of experts who believed the utility value of being treated with PP could be expected to be higher than for those OD because the positive impact of prophylaxis on the frequency of bleeds bears the potential of making severe cases comparable to the clinical profile of moderate cases of disease (Miners, 2009 and Farrugia, 2013). This view coincided with Risebrough´s (2008) report of 0.950 and 0.920 for those in PP (without port and with port) and those OD 0.905 (without target joints). Nonetheless, Risebrough´s values did not specifically address severe patients as was the aim of the base case model. Similarly, Lipperts´s study reported utility values for type A and B haemophiliacs of 0.760 for those on prophylaxis (secondary) and 0.730 for those OD, and also lower values (0.680 and 0.660 respectively) for older populations, which might represent an age-dependent disutility factor that was not considered in the base case model.

Tufts CEA registry was also searched for utilities associated with chronic joint damage, arising from health conditions other than haemophilia (e.g. rheumatoid arthritis, osteo-arthritis). This latter option was discarded by clinical experts since the clinical spectrum and comorbidities of other diseases that can also lead to joint damage may clearly differ from the utility values related to haemophilia and haemophilic arthropathy.

With such a shortage of published data, the second best option was to use primary or secondary sources of local data to populate the model. A cohort of 48 Colombian patients that had been followed up since 2009 served as a secondary local source to be inserted into the model. A total of 31 severe haemophilic A patients (18 treated OD and 13 with PP) and their clinicians (5) participated in a recent survey that used the Haemophilia Joint Health Score (HJHS) questionnaire and a Spanish version of the EQ-5D to elicit their preferences about health states associated with haemophilia and joint damage.

The HJHS (Feldman, et al 2011) is a multidimensional clinic-metric tool that is reported to be more sensitive than the WFH questionnaire to diagnose early joint damage among the haemophiliac population. HJHS evaluates 6 "index joints" (elbows, knees and ankles) using a quantitative scale from 0 to 124 points to capture joint damage progression by a trained physiotherapist. The scale evaluates swelling, duration of swelling, muscle atrophy, axial alignment, and crepitus of motion, flexion loss, extension loss, instability, joint pain, strength and gait. HJHS also relies on a physician's global score of joint health consisting of a series of six 10 cm visual analogue scales (VAS), one for each index joint, whereby 1 equals "no complaints, no findings" and 0 equals "continuous pain, severe limitations, worst damage", and one VAS for the overall assessment of arthropathy on HR- QoL whereby 1 equals "no impact on life" and 0 equals "most severe impact on life". Each yields an individual score and the average of the 6 joints yields the total physician's score.

During February and May 2012 five clinicians in charge of the cohort were asked to complete the HJHS questionnaire per-patient and assess the overall impact of arthopathy on HR-QoL in the sub-groups treated with PP and OD. Patients were also asked to self-assess their overall HR-QoL associated with arthropathy using the same 10 cm VAS anchored by 1 which equals "no impact on life" and 0 equals "most severe impact on life". They were also asked to answer the Spanish version of the EQ-5D. Thus the potential options to estimate health state preferences from this cohort were the VAS scores from patients and physicians and EQ-5D scores from patients.

Various methodological limitations of VAS scores restricted its use in the base case model. For instance, the rating scale scores are not an interval scale of preferences (Torrance 1976, Torrance et al 1982, 1996 and 2001; and Robinson et al 2001), or the "end of scale" bias in which subjects tend to resist using the extremes of the scale, and "context" bias in which respondents tend to spread outcomes over the scale regardless of how good or bad those states are (Bleichrodt and Johanesson, 1997, and Torrance et al in 2001).

Despite its limitations, however, EQ-5D scores represent preferences gathered using a multi-attribute generic questionnaire where pain/discomfort and mobility are scored as separate dimensions. These two dimensions seemed potentially useful to populate the model since they could be relevant whenever assessing joint damage. Thus, the local EQ-5D scores from patients were chosen as the best available source of data to estimate QALYs.

It should be noted that in Colombia the EQ-5D 3 level questionnaire has not been formally applied to a random sample of population, hence the scoring function has not been measured using time trade off (TTO) or standard gamble (SG) techniques. Utility values for each of the four possible health states of interest were therefore calculated making use of the UK tariffs (Dolan et al, 1995), these were chosen because of the rigorous method of elicitation followed by the authors. However, from the above-mentioned dimensions and after further consideration, pain/discomfort was not considered as a reliable source to estimate utilities, since these symptoms may be unspecific and not necessarily joint damage-related in SHA patients according to the panel of experts´ perception. Therefore health states related to chronic arthropathy were assumed to be those reported in the EQ-5D 3L with a score of 2 or more in the mobility dimension of the questionnaire. This assumed that the main differences in quality of life among sub-groups were associated with joint damage and not derived from any other variable or comorbidity.

Basic statistics were performed to calculate score of tariffs per-patient, and the mean utility value for each one of the model health states. The utility of "Alive-no arthropathy" PP was initially calculated as 0.942 which was close to Noone et al´s 2011 estimates (0.930 for the Swedish population on prophylaxis) and Risebrough et al in 2008 (0.950); the utility of "Alive-no arthropathy" OD was 0.925 which was close to that reported by Risebrough et al in 2008 (0.905); the utility of "Alive-with arthropathy" PP was 0.756, similar to that reported by Lippert el al in 2005 (0.760) for severe type A and B patients aged under 30; and the utility of "Alive-with arthropathy" OD was 0.679, similar to that reported by Lippert el al in 2005 (0.660) for severe type A and B patients.

However, after further consideration, the uncertainty of parameters in such a small sample and evidence of age heterogeneity among sub-groups limited the possibility of using differential utility values for the before mentioned four health states of interest. For instance, of sub-groups PP versus OD (mean age = 8.3 versus 25.4 years respectively) and those who had developed joint damage and those who had not (PP mean age without arthropathy 8.0 versus 9.3 years with arthropathy; and OD mean age without arthropathy 14.5 versus 28.5 years with arthropathy).

Therefore a more conservative approach was advised for the base case model in which the same average utility scores were to be used, irrespective of the treatment allocated. However, since joint damage is expected to have a further negative impact on the overall quality of life of those who develop it, a lower utility value was considered for those with a score of 2 or more in the mobility dimension of the EQ-5D questionnaire. Making use of basic statistics an aggregated mean score of tariffs was estimated for those with PP and OD without joint damage and with it (scores of less than 2 or 2 or more respectively, in the mobility dimension). The utility value was estimated as 0.937 for those without joint damage and as 0.639 for those with joint damage irrespective of the treatment allocated. The previously published utility values for haemophilia A and the VAS scores from physicians and patients were set as parameters to be used in the sensitivity analyses. For all variables and health states half cycle correction was incorporated in the base case model.

Table 3 shows the demographic, clinical and HR- QoL characteristics of the local sample of patients. There were 13 patients with PP and 18 OD, the table shows the number of patients OD and with PP who developed joint damage, VAS average scores gathered form examiners and patients and also the EQ-5D average tariffs by sub-groups, mean age and number of bleeds per-year by sub-group. The utility values highlighted are those used in the base case model. (See Appendix 4 for further details of patient scores and demographics).

TABLE 3. Demographic, clinical and HR-QoL characteristics of local sample of severe haemophiliac A patients

Demographic, clinical and HR-QoL characteristics of local sample of patients with severe haemophilia A											
Number of patients	Type of treatment	VAS examiner	C.I	VAS patient	C.I	EQ-5D patient	C.I	Mean age	C.I	Mean n bleeds py	C.I
13	Primary prophylaxis	0.911	0.740-1.000	0.923	0.600-1.000	0.899	0.691-1.000	8.3	2-18	2.5	1-9
18	On-demand	0.678	0.200-1.000	0.818	0.600-1.000	0.734	-0.077-1.000	25.4	4-53	2.7	0-8
31	Total number of patients										
Number of patients	Type of treatment/ Onset of arthropathy	VAS examiner	C.I	VAS patient	C.I	EQ-5D patient	C.I	Mean age	C.I	Mean n bleeds py	C.I
10	Primary prophylaxis/ No	0.920	0.740-1.000	0.935	0.600-1.000	0.942	0.692-1.000	8	2-17	2.5	1-9
3	Primary prophylaxis/ Yes	0.880	0.760-0.980	0.883	0.800-0.950	0.756	0.691-0.850	9.3	4-18	2.7	1-5
4	On-demand/ No	0.858	0.633-1.000	0.925	0.700-1.000	0.925	0.815-1.000	14.5	4-33	2.3	0-6
14	On-demand/ Yes	0.627	0.200-1.000	0.787	0.600-1.000	0.679	-0.077-0.850	28.5	11-53	2.9	0-8
31	Total number of patients										
Number of patients	Onset of arthropathy	VAS examiner	C.I	VAS patient	C.I	EQ-5D patient	C.I	Mean age	C.I	Mean n bleeds py	C.I
14	No	0.902	0.633-1.000	0.932	0.600-1.000	0.937	0.692-1.000	9.9	2-33	2.4	0-9
17	Yes	0.672	0.200-0.980	0.804	0.600-1.000	0.693	-0.077-0.850	25.1	4-53	2.8	0-8
31	Total number of patients										

To account for time preference within the model, discounting rates for costs and outcomes were incorporated. In Colombia there is no "reference case" in place to control for structural uncertainty of economic evaluations, only preliminary HTA work, and a local clinical practice guidelines (CPGs) manual from 2010 (*Ministerio de la Proteccion Social*) that incorporates economic modelling suggest discounting both costs and outcomes at rates ranging between 0 and 5%. Recent HTA work in Colombia for the development of 24 CPGs published in 2013, discounted costs and effects at an arbitrary rate of 3% (no empirical data were used to support this figure). Since no empirical work has been undertaken in Colombia to estimate discounting rates, it was necessary to look at current policies of a relevant HTA authority such as the NICE in the UK (NICE Guidance, 2011). NICE guidance states that where a treatment's effects are both substantial in restoring health and sustained over a very long period of time (at least 30 years) it should be applied at a rate of 1.5% for health effects and 3.5% for costs, thus these discounting rates were incorporated in the base case model, bearing in mind local guidance, the range 0 - 5% for health effects and costs was used in the sensitivity analyses.

Analysis

A theoretical cost-effectiveness threshold of one to three times the current Colombian gross domestic product (GDP) per-capita was set as the WTP decision rule, although WHO recommendations use this threshold as WTP for DALYs averted[45], it could serve as a point of reference to inform decision-makers in Colombia.

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[45] Source WHO at http://www.who.int/choice/costs/CER_thresholds/en/index.html. DALYs Disability Adjusted Life Years. The Commission on Macroeconomics and Health-CHOICE uses GDP as an indicator to derive three categories of cost-effectiveness: highly cost-effective (< 1 GDP per-capita); cost-effective (1-3 times GDP per-capita); and not cost-effective (> 3 times GDP per-capita).

The Colombian GDP per-capita for the year 2012 was USD$8,127 (COL$15,528,700)[46] [47]and when corrected for inflation for the year 2013 it reached COL$16,152,954[48] (USD$8,445). Hence, if the ICER is up to three times the Colombian GDP per-capita 2013 (USD$25,335 or COL$48,458,861), the intervention is considered cost-effective

To control for methodological, structural and parametric uncertainty, statistical methods for economic evaluation alongside deterministic and probabilistic sensitivity analyses were used. One-way and two-way sensitivity analyses (SA) were conducted to check for the impact of variables considered crucial in the model. The variables chosen were cost of FVIII and rFVIII, utilities, probability of having an articular bleeding episode and of developing arthropathy, discount rates for costs and QALYs, and number of bleeding episodes per-year OD and with PP.

The deterministic sensitivity analyses of costs of FVIII and rFVIII varied, assuming a hypothetical 50% increase and a 90% decrease in costs. Discount rate for costs and QALYs was varied according to NICE and local guidelines[49] from 0% to a rate of 5%. The ranges for one-way sensitivity analyses were obtained from the literature. The number of bleeds OD varied from 8 to an upper value of 27 and for PP from 0 to 9 as reported by Manco-Johnson et al, 2007.   The utility values for both OD and PP were deterministically ranged taking in to consideration the lowest values reported by Miners in 2009 (0.500 OD and 0.710 PP) and the highest values obtained from the local sample of patients (0.883 OD and 0.942 PP). The probability of articular bleeding was ranged according to Stachnik et al, 2010 and Kempton et al, 2012 published values (0.5-1.0). The probabilities of developing arthropathy or dying from bleeding were given a 50% range variation from the base case model accounting for the uncertainty regarding joint damage development and severity of bleeding events between the country of interest and the origin of data.

Probabilistic Sensitivity Analysis (PSA) was conducted to take into consideration the uncertainty of parameters and structural assumptions of the model. PSA was conducted on variables such as the number of bleeds, utilities and the probabilities of articular bleeding, dying from bleeding, and of developing arthropathy with both treatment options simulating 1000 iterations. To deal with parameter uncertainty, distributions for the PSA were chosen according to the characteristics of each of the random variables. (See Table 4 for deterministic and probabilities distributions used for the sensitivity analyses; see Appendix 5 for a detailed description of means, standard errors, probabilities and other parameters used to calculate probabilities distributions for PSA).

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[46] Report of selected countries and subjects. International Monetary Fund. Source As per 16 of May 2013
http://www.imf.org/external/pubs/ft/weo/2012/01/weodata/weorept.aspx?
[47] Currency exchange rate as per July 12th 2013. Source http://www.oanda.com/ . All calculations from COL$ to USD$ used the same rate
[48] 2013 correction inflation in Colombia 4,02%
[49] Source: http://www.pos.gov.co/Documents/GUIA%20METODOL%C3%93GICA%2023%2011%2009-1.pdf

TABLE 4. Sensitivity analysis of the key variables in the Markov model

Parameter	Ranges for 1- way SA	Probability distribution
Number of bleeding episodes OD	8.0-27.0	~ Poisson (17)
Number of bleeding episodes PP	0.0-9.0	~ Poisson (3)
Cost of FVIII	$90- $1350	Not applied
Cost of rFVIII	$145- $2175	Not applied
Utility PP or OD without arthropathy	0.500- 0.942	Beta $\beta \sim$ (4.426, 0.298)
Utility PP or OD with arthropathy	0.500- 0.883	Beta $\beta \sim$ (3.011, 1.334)
Discount rate costs	0- 5%	Not applied
Discount rate benefits	0- 5%	Not applied
Probability of articular bleeding	0.5- 1.0	Beta $\beta \sim$ (80, 20)
Probability of arthropathy after bleeding OD	0.0725- 0.2175	Beta $\beta \sim$ (4.205, 24.795)
Probability of arthropathy after bleeding PP	0.0094- 0.0282	Beta $\beta \sim$ (0.508, 26.492)
Probability of dying from bleeding	0,0026- 0.0079	Beta $\beta \sim$ (5.618, 1064.383)

The number of bleeding episodes per-year with PP and OD were considered as discrete variables (3 and 17 respectively) in the model, and since bleeding episodes occur in the model within an interval of one year per-cycle and always adopt values from 0 upwards, a Poisson distribution was considered as adequate for this purpose. Each year a "rare" event - bleeding - occurs with a probability that rapidly decreases over the period of observation. The distribution parameter Lambda (λ) represents the expected average number of events in the relevant period of time. In this case λ was 3 for PP and 17 for OD.

A beta distribution was selected for the utilities and probabilities of bleeding, arthropathy development and dying; these are all continuous variables with values lying in an interval between 0 and 1 in a distribution with beta (β) parameters (alpha, beta). The mean probabilities and number of patients reported in the published sources were used to estimate α and β; in the case of utilities of health states, the secondary data from the local cohort of patients was used and mean utility scores and standard deviations were used to estimate α and β parameters.

RESULTS:

Once the base case model had been rolled back, the ICER calculated for PP versus OD treatment for SHA using FVIII throughout life was COL$105,081,022 (USD$55,204) per QALY gained, and thus not considered cost-effective according to the threshold of up to three times the current Colombian GDP per-capita (USD$25.335 or COL$48.458.861). When PP was provided throughout life using rFVIII, which is much costlier than FVIII, this ICER reached COL$174,159,553 (USD$91,494) per QALY gained. (Table 5 shows the ICER with these two different therapeutic strategies).

Table 5. Results of the Cost Utility Analysis and ICERs per therapeutic approach

Therapeutic Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Incremental Cost- Effectiveness
Primary prophylaxis throughout life FVIII					
On- demand	$ 3,231,064,672		27.71		
Primary prophylaxis	$ 3,716,401,052	$ 485,336,380	32.33	4.62	$ 105,081,022
Primary prophylaxis throughout life rFVIII					
On- demand	$ 5,151,022,220		27.7		
Primary prophylaxis	$ 5,956,345,834	$ 805,323,614	32.33	4.62	$ 174,159,553

One-way sensitivity analyses were performed to the perceived most relevant variables. Ranging the probabilities of developing arthropathy with both treatment approaches at 50% intervals, did not show a significant impact on the final ICER, neither did ranging discount rates for QALYs and costs, from 0 to 5%. Only with a discounting rate of the effects very close to 0 was PP considered to be cost-effective.

The ICER results are sensitive to cost of FVIII, a reduction of 50% or more on the cost of FVIII would make PP cost-effective in Colombia (see Figure 6 for details). In the case of rFVIII only a 75% or more price discount would make PP cost-effective in this context.

Figure 6. Sensitivity analysis of average (unit) cost of FVIII
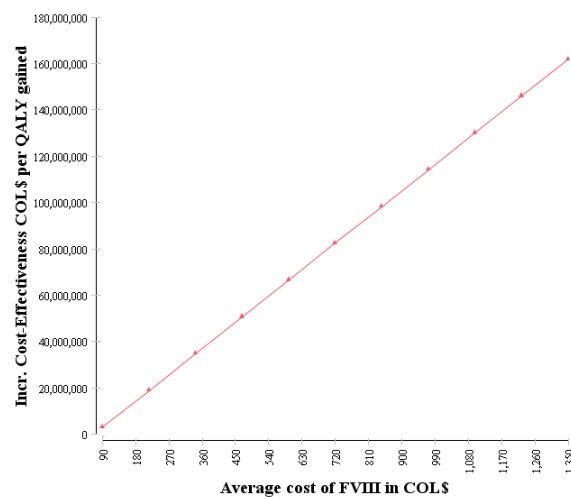
The model results are also sensitive to the utility values of living without arthropathy OD, varying the utility range of being alive without arthropathy OD from 0.5 to 0.942 does not reduce the ICER of PP up to a point of being considered cost-effective, this only happens with a utility of 0.2 or less in this health state (see figure 7). The opposite occurs with the utility of being alive with arthropathy PP, the higher the value of this health state the lower the ICER of PP, but not even when the utility value of this health state is closer to 1, PP becomes cost-effective.

Figure 7. Sensitivity analysis of utility OD without arthropathy
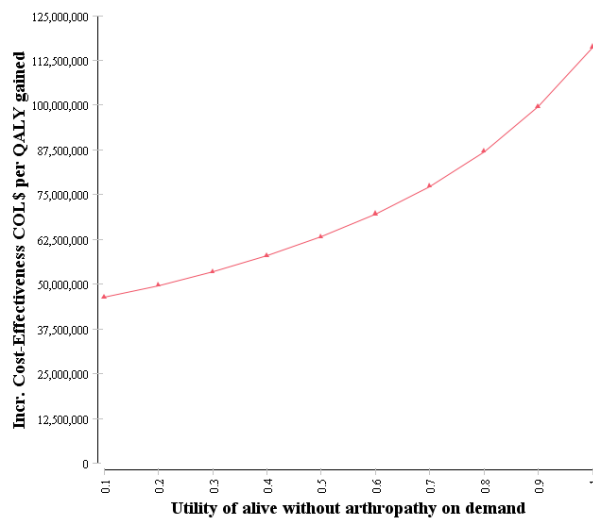
Performing a sensitivity analysis on the number of bleeds, showed that if the number of annual bleeds OD reaches more than 19 episodes, PP dominates (more effective and less costly) OD treatment (see Figure 8); the opposite did not happen even if PP was able to reduce bleeding frequency up to 0.

Figure 8. Sensitivity analysis of number of all bleeds OD
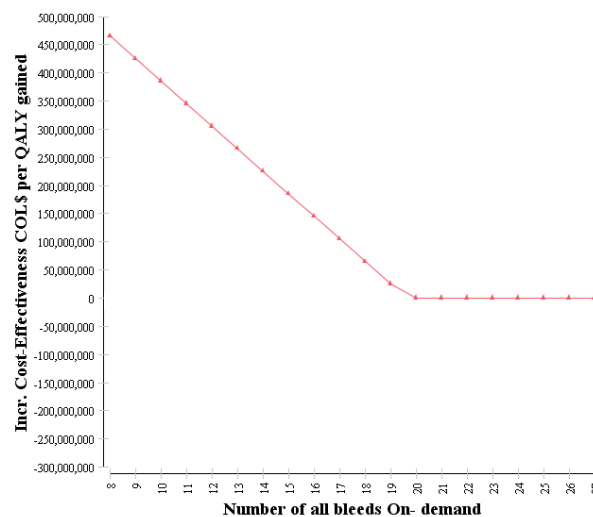
The model results show sensitivity to the location of bleeding episode. Ranging the probability of having an articular bleed from 0.5 up to 1.0 shows that the higher the chance of bleeding within the joints, the lower the ICER of PP, making it cost-effective only above 0.95 (see Figure 9).

Figure 9. Sensitivity analysis of probability of articular bleeding
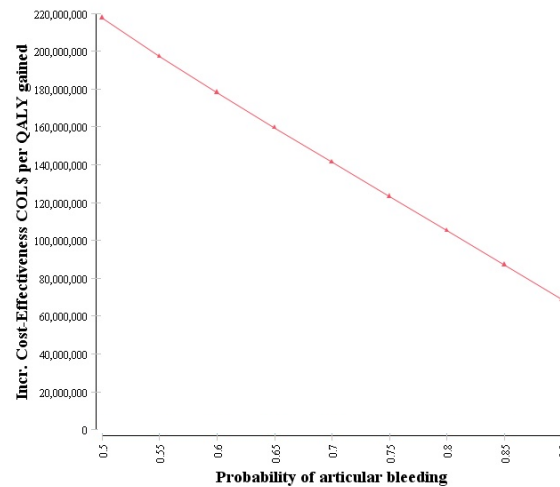
A two-way sensitivity analysis was performed to assess the impact of total number of bleeding episodes on the final ICER. The total number of bleeding episodes OD had the biggest impact. PP becomes cost-effective if patients OD experience more than 17 episodes per-year and if it is able to reduce bleeding episodes to 0. This also happens when the number of episodes per-year OD is higher than 19 and the bleeding pattern of patients in PP equals 9 episodes per-year (Figure 10).

Figure 10. Two-way sensitivity analysis of number of bleeding episodes per-year OD vs. PP
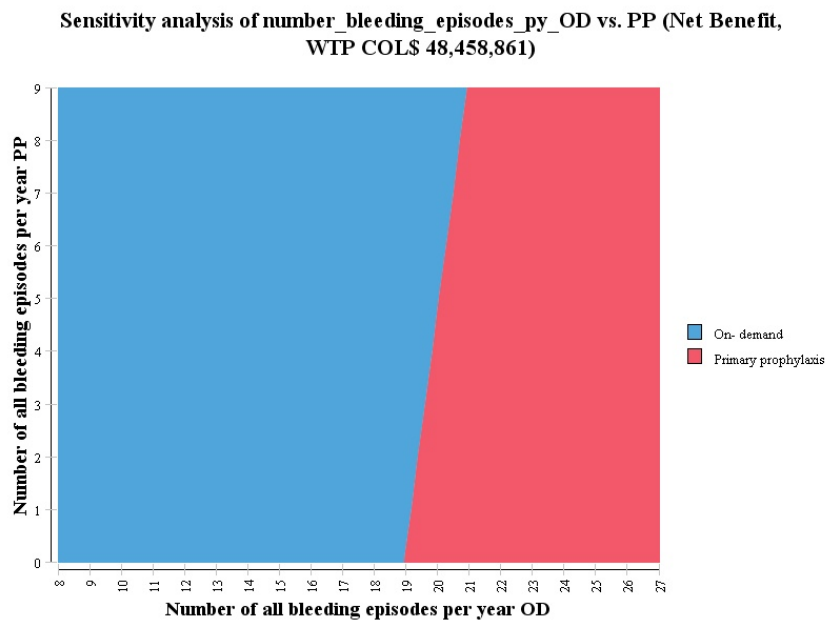
The Tornado diagram shows that the discounting rates for costs, cost of FVIII, number of bleeding episodes OD, probability of presenting with an articular bleeding, dosage/Kg per joint bleeding OD, probability to die from bleeding and dosage/Kg per any other bleeding OD had the biggest impact on the final reported ICER (Figure 11).

Figure 11. Tornado Diagram ICER Primary prophylaxis vs. on- demand

Tornado Analysis (Net Benefits), WTP COL$ 48,458,861
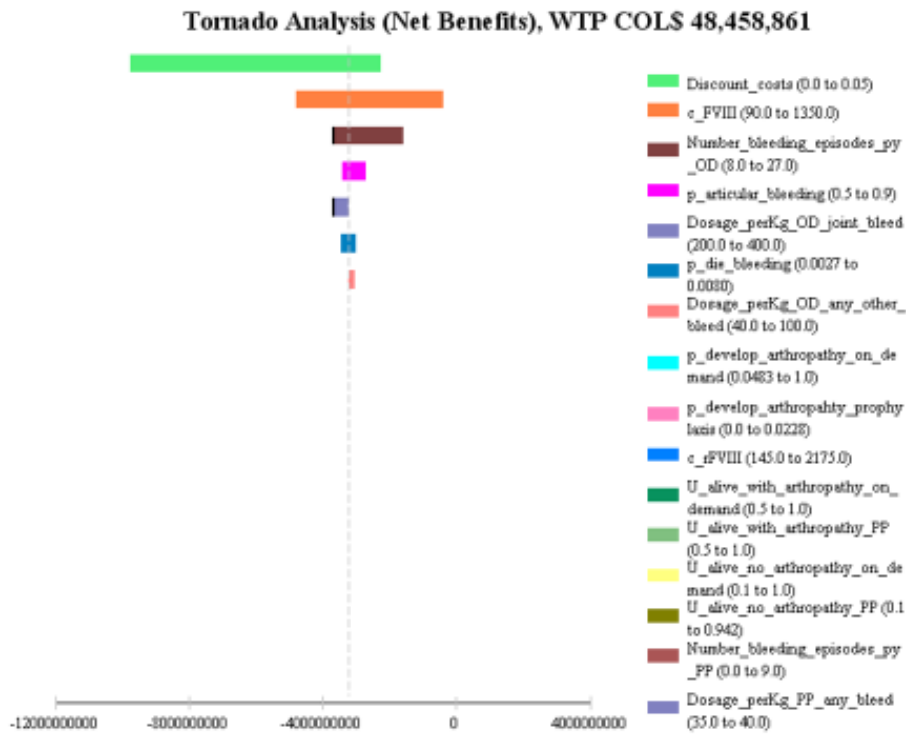
The cost-effectiveness scatterplot (Figure 12) shows that PP is more effective, but also more costly than OD in almost all iterations, irrespective of the WTP.

Figure 12. Probabilistic Sensitivity Analysis PP vs. OD CE scatterplot

Cost Effectiveness Scatterplot PP vs. OD
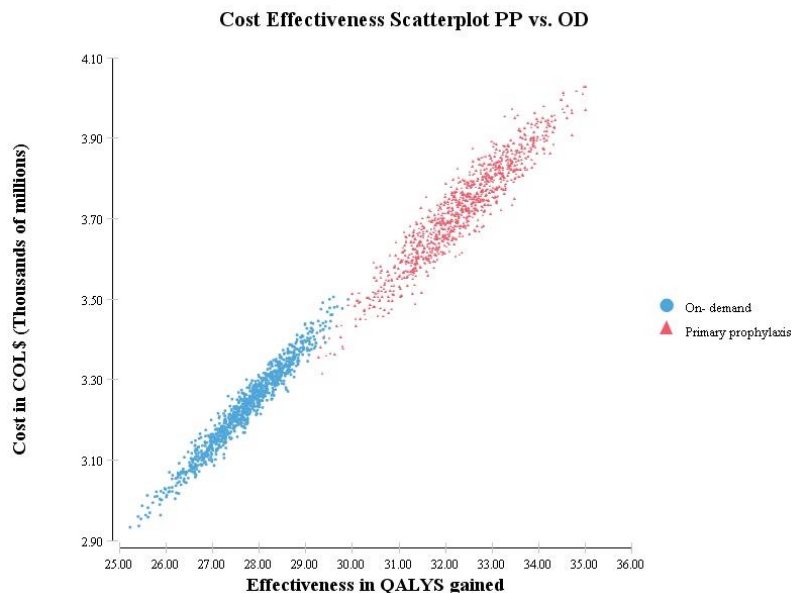
At a WTP of COL$48,458,861 (USD$25,335) the incremental cost-effectiveness scatterplot (Figure 13) shows PP is not considered cost-effective in any iteration when compared to OD.

Figure 13. Probabilistic Sensitivity Analysis PP vs. OD ICER scatterplot (WTP COL$48,458,861)

Incremental Cost-Effectiveness, PPvs. OD, WTP COL$ 48,458,861
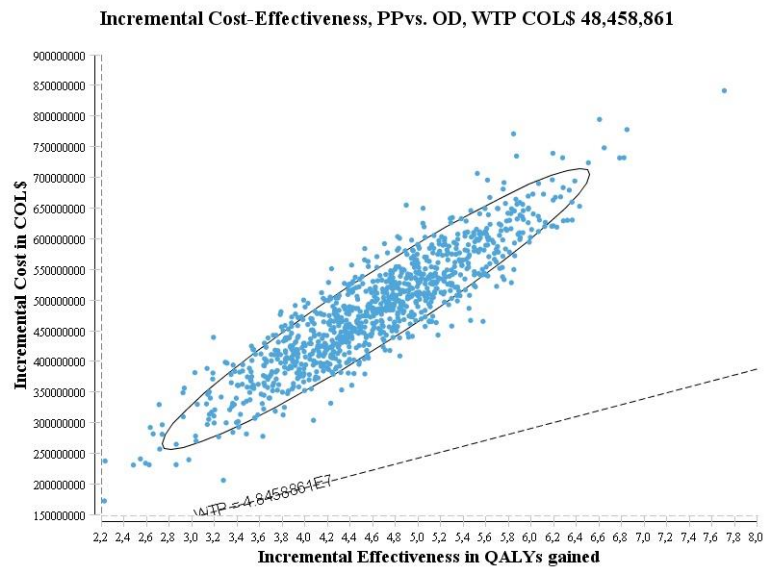
The cost-effectiveness acceptability curve (Figure 14) shows that PP would only be considered as cost-effective if the Colombian threshold were higher than COL$95,000,000 (USD$49,908). PP would be cost-effective at a range between COL$95,000,000 and COL$120,000,000 (USD$63,041). A formal willingness to pay for an additional QALY threshold does not currently exist in Colombia, but using WHO recommendations in all model iterations, PP was found not to be cost-effective at such a WTP.

Figure 14. Probabilistic Sensitivity Analysis PP vs. OD- cost-effectiveness acceptability curve

CE Acceptability Curve
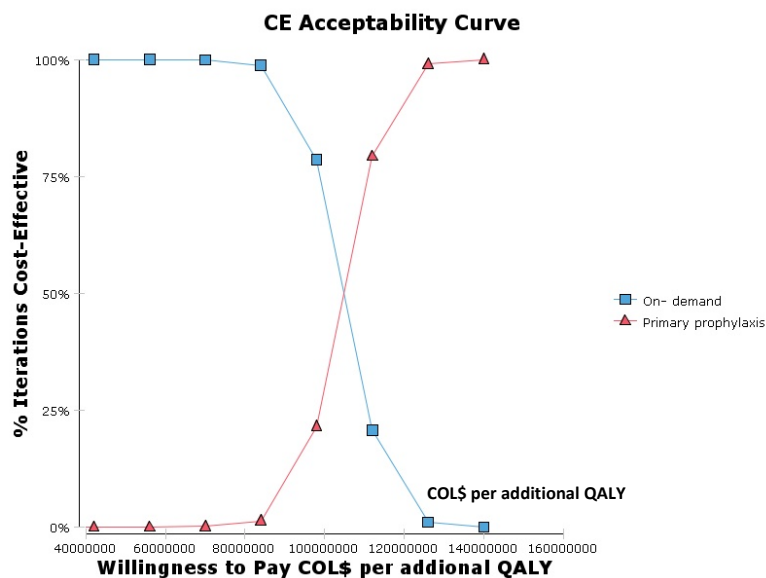
DISCUSSION

Severe haemophilia A is a life-long disease that can be highly costly to treat. Therefore, the aim of this chapter was to perform a CUA of primary prophylaxis (PP) with FVIII versus treatment on-demand (OD) for people with severe haemophilia A in the context of interest. In answer to the research question: **"what is the incremental cost-effectiveness of PP compared to OD treatment in Colombia?"** the base case model showed an ICER of COL$105,081,022 (USD$55,204) per QALY gained whenever PP using FVIII is provided throughout life. When PP was provided throughout life using rFVIII (recombinant), which is much costlier than FVIII the ICER reached COL$174,159,553 (USD$91,494) per QALY gained. Sensitivity analysis showed that PP is more effective, but also more costly than OD in almost all iterations. PP would only be considered as potentially cost-effective if the Colombian threshold were higher than COL$95,000,000 (USD$49,908). A formal threshold does not currently exist in in this context, but using WHO recommendations of a threshold of up to three times the current Colombian GDP per-capita (USD$25.335 or COL$48.458.861) in all model iterations, PP was found not to be cost-effective at such a WTP.

Only Miners has published a model structure that explicitly considered the decision problem of interest for this thesis, this model was later replicated by Colombo in 2011. Arguably, the structure of the *de novo* model presented in this thesis is an attempt to model in a more "clinically driven" manner the complexity of a long-term orphan condition, since it links joint damage with HR-QoL. For more than three decades the early initiation of PP in children has proven to be beneficial in preventing haemophilic arthropathy. However, in Colombia PP is still not usual practice and no previous HTA report has been produced for this health condition, the results from this CUA could perhaps be used to assist decision-making in this country.

Strengths and limitations

This economic study has attempted to add to the stock of economic evaluations for PP. Up until the present only one economic evaluation has been published for LMICs (Daliri et al, 2009) and no CUA has been published in these contexts. According to Miners (2013), studies that might be of use for this condition should collect utility data derived from discrete patient cohorts, link intermediate outcomes such as bleeds with longer term likelihood of developing arthropathy and, if necessary, gather expert opinion using formal elicitation methods to fill data gaps for insertion into appropriately designed decision models. Controvertibly, some of these methodological recommendations were considered in the model.

The main limitations of this CUA arose from the structural assumptions, methods and parameters used to populate the model. For instance the assumption that all severe haemophiliacs bleed at some point in life (spontaneously or traumatically), may not be completely accurate since according to Royal et al (2002), up to 10% of severe haemophiliacs have a milder bleeding pattern. The model developed included much uncertainty about the ability to detect subclinical spontaneous bleeding and subsequent joint damage, although MRI seems to be the gold standard for detecting both, the model did not incorporate the accuracy of diagnostics in its base case.

The overall annual probability of developing arthropathy was adjusted in the base case after considering the probability of bleedings being articular (into the joints), this may have led to different ICER results. In the model whenever bleed occurs, the probability of it being articular was estimated as around 80% after looking at published observational data, although this figure was validated by the panel of experts, it departed form Manco-Johnson´s baseline estimations of a 48% joint bleeds rate per-patient per-year. This limitation was addressed by using one way sensitivity analysis, ranging the probability of articular bleeding up to 1.

Haemophilic arthropathy in the model is assumed to develop at a constant pace, this assumed that transition probabilities did not change regardless of the cumulative effect that each new bleeding episode within the same joint would bring to future risk of bleeding. Instead it extrapolated the overall probability of developing joint damage after a 49 month period of follow up from a small RCT published in 2007 by Manco-Johnson. The lack of data limited the possibility of controlling for this "memoryless" limitation of the model by including differential transition probabilities to account for time dependence; this could have been attempted though, but not without introducing other sources of uncertainty into the model.

In the base case, it was assumed that those patients who had recovered (stopped bleeding and stabilised) after having an extra-articular bleeding episode without previously having joint damage would always remained alive and without sequelae, this may not always be the case in real life since extra-articular bleeding may occur in different locations, i.e. soft tissue, intra-abdominal, intra-cranial or post-surgery, all these carrying important leverage in the overall quality of life. The utility of health states of individuals that developed joint damage remained the same throughout each cycle, this might not be realistic since incremental joint damage is expected to have a further deleterious impact on overall quality of life.

Complications from clotting factor application were assumed to be equal for PP and OD. Inhibitor development, another major complication is expected to be substantial, nonetheless chances to develop inhibitors were expected to be similar in both regimes and were not considered in the base case model, despite recent evidence that may support the effectiveness of prophylaxis in decreasing inhibitor incidence (Kurnik et al, 2010 and Gouw, 2013, Farrugia et al, 2013).

The probability of dying from other causes was considered similar for haemophiliacs and the general population, and thus not incorporated in the model. This structural assumption may have led to different ICER estimations, however a scenario analysis considering a probability of dying from other causes as of 0.00529 accounting for local estimations of the probability to die from all causes in general Colombian population resulted in an ICER per QALY gained of USD$74 lower than the one reported in the base case. Using a 0.0106 probability of dying from all causes as suggested by Darby in 2007 for SHA resulted in an ICER per QALY gained of USD$190 lower than the one reported in the base case scenario.

The assumption that once treatment was commenced, patients in the model would fully comply and not switch between schemes throughout life may not be entirely realistic in a context like Colombia, or perhaps anywhere. According to Fischer et al 2008, up to 66% of patients suspend PP when they reach adulthood for different reasons; this was not incorporated in the base case scenario. This assumption coincides with the mechanistic approach of Miners´ (2009) model in that people are implicitly assumed to be fully adherent to treatment. Like Miners approach, the model assumes that people are efficient when they administer the exact dose of treatment, and no more or less than this amount is consumed.

All patients entered the model at 2 years of age, although more customised protocols, depending on bleeding patterns and the onset of the first bleed may produce different findings. Radiological and follow-up costs were considered for the two treatment approaches, but additional costs of surgical correction of long-term joint impairment were only incorporated for OD treatment. All bleeding episodes were assumed to be of the same average severity (no life-threatening or minor events), and chronic joint damage was modelled as average clinical cases (not the mildest or the most severe). These assumptions may depart from the natural course of disease.

It was assumed that up to 95% of costs of treatment were associated with exogenous factor replacement and although other medical cost were incorporated in the model, no further statistical analysis was considered to account for the uncertainty of costing. Costs were assumed to be uniformly distributed and non-variant over the lifespan of patients.

Blood-borne infections were expected to be non-existent if proper viral attenuation methods were used or if recombinant exogenous factor was supplied, hence they were not considered in the base case model, even though proper viral attenuation or recombinant FVII may not be available in all regions in a country like Colombia. Even if used or incorporated in a "current safe era", uncertainty remains about prions or yet-to-be discovered pathogens.

Another limitation of this study is the use of international rates for discounting costs and outcomes after the lack of methodological standards in Colombia. Although NICE guidance was followed in the analyses, the economic evaluation results should be interpreted cautiously, since applying a discount rate of 1.5% to the effectiveness and 3.5% to the costs may not be appropriate for the Colombian setting. This absence of standards leads to methodological and parametric uncertainties regarding any HTA results.

To estimate utilities a Spanish version of the EQ-5D was used and health states related to chronic arthropathy were assumed to be those reported with a score of 2 or more in the mobility dimension of the questionnaire by assuming that the main differences in quality of life among sub-groups were associated with joint damage and not derived from any other variable or comorbidity. The average age among sub-groups was very different in each cohort (9.9 years PP vs. 25.1 OD), this heterogeneity carries uncertainty on how age difference or age-related comorbidities may have affected the mobility dimension as was incorporated in the analysis, although the source used was considered the best available evidence in this setting no sub-group analysis for age dependent heterogeneity was performed in the PSA.

To estimate utilities, UK tariffs were used to calculate QALYS since no local tariffs have been estimated in this context. In addition to limitations from extrapolating tariffs of the EQ-5D questionnaire, this approach has been found to be insufficient to reflect social preferences for treating severe illness before less severe illness (Nord, 1996), and also to control for the 'disability paradox' where patients, as a result of adaptation, typically report greater quality of life scores than healthy individuals in similar circumstances (Ubel et al, 2005).

Comparison of methodology and results with existing CUA

Model results were within the wide range of published studies that have estimated incremental costs per QALYs gained. For instance, Miners in 2002 estimated an ICER of £46,500; in 2008 Risebrough estimated an ICER of CAN$542,938 for an escalating dose regime versus OD; in 2009 in the UK Miners updated his previous publication and re-calculated an ICER near £10,000 lower than his previous estimates.

In 2011 Colombo published an ICER of €40,236 in Italy and considered PP as a cost-effective intervention and Farrugia in 2013 stated that prophylaxis was dominant over OD treatment in the UK; his model resulted in an ICER of USD$68,000 within the range of treatments reimbursed in the USA, and of SEK1.1 million in Sweden, which was also within the range of reimbursed treatments in that country.

It is interesting to note how ICER results in this study are much higher than those reported by other authors that have also modelled treatment with rFVIII throughout life and from a similar perspective (COL$174,159,553 or USD$91,494 per QALY gained) versus Miners in 2009 (£38,000 or [COL$144,586,669 or USD$60,970 [50]]), Colombo et al in 2011 (€40,236 [COL$111,676,372 or USD$62,970]), and Farrugia et al, 2013 (USD$68,000 or COL$129,931,000), all these also per QALY gained. This may reflect the substantial influence of the unit cost of clotting factors in unregulated prices settings like Colombia.

As in other publications, the results of the base case model were sensitive to input parameters. The model dosage schedules for PP considered the Mälmo protocol´s recommendations of 25 IU/per Kg for 46 weeks at minimum. This schedule was lower than that used by Colombo (2011) who used 30 IU/Kg every other day, and similar to Farrugia´s (2013) who also used 25 IU/Kg every other day; but it clearly departed from the Miners (2009) approach who used an *in vivo* clotting factor threshold of 1 IU/dl as the clinical target to achieve.

The model also included a lower dose regime than that presented by Manco-Johnson, in the case of bleeding OD 200 IU/Kg were to be administered in the base case model instead of 320 IU/Kg as per the enhanced approach. The different approaches adopted by each author to assess clinical effectiveness of PP may explain the difference in results. The scarceness of published data and variability of methods makes validation of consistency of results from this study more difficult.

The number of bleeding episodes per-year in the base case model with PP was similar to that used by Colombo (2.5- 5.4) and identical to Farrugia (3), but much lower for OD than that reported by these same authors (33.7-36.9 vs. 36 respectively). Other input parameters also differed from previously published studies. For instance, discounting rates of the model were within the range of published studies from 3.5-6% for costs (Risebrough et al, 2008 and Miners et al 2009 vs. Colombo et al, 2011) and from 1.5- 6% for QALYs (Miners et al, 2002 and Farrugia et al, 2013 vs. Colombo et al, 2011). Nonetheless the base case model used the lowest rates reported in the literature. This wide range of input parameters may well also explain the variability of published data.

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[50] Currency Exchange rate at http://www.oanda.com/ as per July 15th 2009 and corrected for inflation to COL$ at present value (Nov 2013). Source of inflation rates 2009-2013 http://www.dane.gov.co/index.php/indices-de-precios-y-costos-indice-de-precios-al-consumidor-ipc

Many of the major limitations of this work lay in the assumptions made for modelling, like all previously published studies on haemophilia have done. For instance, in 2009 Miners assumed that life expectancy for individuals with severe hemophilia was equivalent to that of the general regional male population, whilst this population is expected to live at least 15 years less (Darby, 2007); the present study was no exception and also assumed that life expectancy for patients with SHA in Colombia was similar to those of HICs.

Miners also assumed that HR-QoL of those on PP was equivalent to people with mild/moderate haemophilia, this coincides with Farrugia (2013), although no clinical metric publication comparison of different health states has backed such assumption. Departing from this, this study assumed a milder clinical profile for those who have not developed arthropathy irrespective of treatment allocated. In the publication by Miners (2009) values used to estimate likely outcomes OD were derived from a cross-sectional study of HCV infected haemophiliacs, on its part the HR-QoL estimations of this study where gathered from a small sample of patients using a non-validated (in Colombia) Spanish version of the EQ-5D questionnaire.

In 2011 Colombo developed a model where patients started prophylaxis at birth which does not seem clinically realistic according to bleeding patterns and the natural course of disease. This author obtained the utility of the health state "requires major surgery" from Laupacis (1993) who assumed that all individuals in that state suffered from a painful condition similar to that of individuals with post-surgery osteoarthritis, which is not accurate from a clinical standpoint. This same approach was initially considered but later precluded after further consideration by the panel of local experts.

Lippert et al in 2005 assigned differential utility values for OD and prophylaxis. Also Miners (2009) and Risebrough (2008) used 0.5-0.905 and 0.71-0.95 for OD and PP respectively. Initially the model attempted to estimate differential utility values for all health states of interest but after further consideration about the limited size of the sample and evidence of heterogeneity among sub-groups, an average utility estimate was used for those without joint damage (0.937) and for those with it (0.639) irrespective of treatment allocated. This latter assumption however is more conservative and may have led to different results from using differential utility values for each health state in the model. This estimation of utilities probably represented the major limitation of this part of the study since the health states preferences to estimate QALYS were gathered from a local cohort of only 31 patients.

Issues for conducting HTA by making use of economic models in the case of SHA in Colombia

Haemophilia itself, as a topic of interest, represented a challenge. It was a challenge to deal with the limited number of RCTs comparing PP versus OD for SHA. The rareness of this disease, the potential ethical limitations for conducting new interventional research and the fact that most of the published evidence on the average effect of PP has been produced in HICs, impose additional methodological constraints for researchers conducting economic evaluation not only in Colombia, but also elsewhere in LMICs.

Economic studies comparing PP versus OD treatment were also very limited. Only six CUAs have been published and some of these took different perspectives to that of the health system, as adopted in the case study or modelled short time horizons. Three of the publications adopted a similar standpoint that of this thesis and just two of them specifically modelled the costs and effects of the problem of interest and adopted the same perspective (Miners 2009, Colombo 2011).

The Drummond et al (2009) framework helped the researcher to identify the main issues that prevented the transferability or adaptation of HTA results from other jurisdictions ("general and specific knock out criteria"), but also served to identify methodological factors that may make HTA work difficult in this context.

When referring to the issues for conducting HTA depicted in this case of study in Colombia, it is worth mentioning that although there is an incipient health information system, the methodological challenge of modelling presented the researcher with information constraints about costs and quality of life to fill in the gaps within the base case. Data on costs were fragmented and came from a broad array of sources ranging from tariffs that have regional variations, market reference prices subject to hidden extra loads resulting from intermediation, and variability in the units of consumption resulting from heterogeneous clinical approaches in a context which lacks of CPGs for this condition, especially in the case of treating OD bleeding episodes.

In the case of health states-related quality of life information, utilities were estimated using a small sample of local patients' data, and the researcher was forced to make some strong assumptions in order to simplify the intricate and long-term natural history of disease. The severe shortness of local data about disease-specific or general health preferences (specifically addressing haemophilia A joint damage) was probably the biggest methodological concern for modelling. These contextual data constraints may represent major hurdles to producing quality HTA in this country. It is worth noticing that besides costs and utility data, virtually none of the other parameters were gathered from Latin American sources.

There are some other methodological factors that may make HTA work difficult in Colombia, especially dealing with uncertainty. As noted before there is no "reference case in place", hence the perspective to be adopted by the local HTA authority is not yet clear, no outcome measure to combine quality and quantity of life like (QALYs or DALYs) has officially been adopted and no local discounting rates based on empirical estimations are in use at the moment. The lack of methodological standards in Colombia prompted the researcher to look for standards used in other jurisdictions like the UK. To reach a final decision it was necessary to set up a hypothetical WTP or threshold by looking at international standards such as those of WHO, although with caveats.

According to ICER results, PP would not be cost-effective in Colombia, although the publication of a high cost per QALY is just one input parameter into decision-making, and any drastic change from the clinical standpoint in health policy towards preventing patients from gold standard care could only be envisioned by decreasing the quality of health care. It is worth mentioning that besides the benefit of haemophilic arthropathy prevention from prophylaxis, a marked reduction of intracranial and life-threatening haemorrhages, lower muscular-skeletal pain, lower rates of inpatient admissions and average of stay, improved school and work attendance and improved academic achievement have been reported in the literature (Berntorp et al, 2003 and Carcao et al, 2007), nonetheless this variables were not considered in the model.

Of worth noting that although a willingness to pay (WTP) threshold of up to three times the Colombian GDP per capita was set as the decision rule, and although WHO recommendations use this threshold as WTP for DALYs averted, it was considered that it could serve as a point of reference to inform decision-makers in Colombia.   In Latin America other countries such as Brazil, Mexico and Chile are currently using similar approaches as decision-making rules. In fact IETS is currently working on producing its first "reference case manual" supported by international experts and since there are considerable limitations to empirically estimate an opportunity cost threshold there is a high chance that this "rule of thumb" threshold is the one to be used in the near future in this context. Of worth noting that PP was always way off this range of 1-3 times the Colombian GDP per capita.

There is a lack of consensus about the exact time to initiate PP or the need to continue it into adult years (Berntorp et al, 2003). Up to 10% of SHA patients do not bleed as frequently as expected and two thirds of them suspend PP when they reach adulthood for different reasons. In Colombia, as in other countries, patient compliance with the infusion regimens is not universal (Carcao et al, 2010). Hence differential initiation schemes, mixed patient preferences and reduced compliance should be incorporated into more realistic decision modelling in future research.

According to Farrugia (2013) the current era of safe treatment creates the option for LMICs to exchange exogenous supply of recombinant factors for less costly plasma derived options. Therefore, the findings from this report are just the starting point to inform decision-making in a more systematic and transparent manner in this context. However, the scarceness of published data and variability of published approaches makes validation of consistency of results from this study much more difficult.

There is still the probability that even after robust sensitivity analyses had been conducted, the ICER estimates in the case of SHA in Colombia would not be completely credible. Alternative approaches able to incorporate other and wider relevant criteria into decision-making may be of use in this context. This may also be the case of other rare diseases that compete for public resources, but face similar methodological limitations than SHA derived from limited data. This may also be an opportunity in this context to develop policy frameworks able to produce and incorporate HTA information, bearing in mind the difficulties and challenges imposed by infrequent and costly conditions.

Colombia is currently strengthening its institutional capacity for HTA. The recent establishment of IETS is an opportunity to standardise methods and methodologies, the ability to strengthen local capacity and standards may ease the issues for conducting rigorous HTA in the near future. IETS is currently working on establishing a "reference case" and methods manuals which are expected to be publicly released in 2014. There is also a project sponsored by this institution to elicit societal preferences using the EQ-5D questionnaireThe "general and specific knock-out criteria" (Drummond et al, 2009) described before, may prevent researchers from adjusting international results to Colombia, but create a propitious environment for *de novo* development of HTA processes, methods standards and evaluations in this context.

SUMMARY

This study showed that the incremental cost effectiveness ratio (ICER) of PP compared to OD treatment in Colombia for severe haemophilia A using FVIII was COL$105,081,022 (USD$55,204) per QALY gained, and thus not considered cost-effective according to the threshold of up to three times the current Colombian GDP per-capita (USD$25.335 or COL$48.458.861). When PP was provided throughout life using rFVIII, which is much costlier than FVIII, this ICER reached COL$174,159,553 (USD$91,494) per QALY gained. Moreover, this overall conclusion did not change after conducting extensive sensitivity analysis.

This part of the research adds to the wider understanding of economic issues regarding PP since it attempts to move beyond the usual clinical parameter - joint bleeds - to a long-term frequent consequence-joint damage HR-QoL. Limitations aside, it has attempted to adhere to established good practice at all times and to report its methods and limitations in a clear and transparent manner. Nevertheless, further studies are needed to confirm the assumptions and findings of this model.

Although, early initiation of PP in children has proven beneficial in preventing joint damage, there is a lack of consensus about the need to continue it into adulthood (Berntorp et al, 2003). The publication of a high cost per QALY is just one input parameter into decision-making, and changes in health policy towards preventing patients from accessing gold standard care from a clinical standpoint could only be envisioned by decreasing the quality of health care.

Some of the main methodological factors that may hinder HTA work in Colombia arising from this CUA relate to the availability of data and structural uncertainty. The recent establishment of IETS provides an opportunity to standardise methods and methodologies, and conduct HR-QoL research that may reduce these uncertainties.

CHAPTER 3- Testing the MCDA-EVIDEM and the use of HTA for resource-allocation decision-making in Colombia

INTRODUCTION:

Decision-making in health care is a process that moves from evidence generation to deliberation and communication of the decision made (Goetghebeur et al, 2008). HTA is only a part of this process whereby the best available evidence is assessed with the aim of informing decision-makers about the most efficient use of resources under conditions of uncertainty. Besides the assessment, reimbursement decision-making also involves appraising the available evidence, while bearing in mind societal values and ethical considerations (Miot et al, 2012).

While multiple studies and publications have examined the role of HTA through the collection of data (Heyse et al, 2001, Briggs, 2001, Briggs et al, 2002, Hoch et al, 2002), there is still limited knowledge of the perceived needs and expectations of decision-makers regarding its use as a source of evidence, as well as the challenge of incorporating other broader criteria in an explicit manner. For example, Drummond in 2009 suggested a "divorce" of the evidence produced and decision-making process, since many economic evaluations published in the literature have been performed with no specific decision-maker in mind.

In 2000, Zwart-van Rijkom et al investigated the differences in attitudes, knowledge and actual use of economic evaluations in different groups of decision-makers. They compared results from the Netherlands with the overall regional results of the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET). The authors found that most decision-makers do not want to base their decisions strictly on cost-effectiveness rankings; this was similar to the rest of Europe. According to Miot et al, 2012, systematic and transparent approaches to priority-setting are needed to produce decisions that are sound and acceptable to stakeholders.

Country-specific HTA health organizations and processes for priority setting have emerged and principles such as transparency, robust and appropriate methods for combining costs and benefits, explicit characterization of uncertainty and active engagement with stakeholders have been associated with the robust operation of HTA programmes and institutions (Drummond et al, 2008 and Chalkidou et al, 2009). Nonetheless, according to Pichon-Riviere et al (2010) in Latin America, including Colombia, "the current level of application [of these principles] is considered uniformly poor".

All health systems face the challenge of managing finite resources to address unlimited demand for services (Glassman et al, 2012). Moreover, it is worth noting that even after robust HTA has been conducted, transparent and systematic decision-making is not guaranteed. Rational decision-making requires an efficient and explicit process to ensure transparency and consistency of factors considered (Goetghebeur et al, 2012).

Countries such as England have institutionalised the use of HTA to turn evidence into policy and practice. Under the NICE system for example, clinical recommendations are partly legitimised by the fact that appraisals are conducted by independent committees with close stakeholder engagement. Indeed, NICE's ability to establish a transparent review process to determine the clinical and cost-effectiveness of health care interventions for the NHS[51] continues to attract interest across the world. It is also the case that NICE Technology Appraisal recommendations carry significant weight because the NHS is legally compelled to implement them.

Even in countries where formal HTA activities are ongoing, and in most LMICs, rationing still occurs as an ad hoc, haphazard series of non-transparent choices that reflect the competing interests of governments, donors and other stakeholders (Glassman et al, 2012) – suggesting that the results of research are not being used appropriately. In the case of Colombia, the Regulatory Commission for Health (CRES) was established in 2007 as a decision-making body, nonetheless HTA had played a limited role in this context in terms of providing information to set priorities, allocate resources or formulate evidence-based policies for health and health care. Five years later, in September 2012 IETS was established aimed at informing CRES about the clinical and cost-effectiveness of interventions, but a few months later CRES was disbanded because of a lack of 'legitimacy' and the MoHSP regained reimbursement decision-making responsibilities. This institutional instability has created the opportunity for the development of a more transparent and systematic priority setting process in this context.

There are a number of different methods for attempting to convert HTA reports into recommendations. For instance Culyer and Bombard (2012) proposed a framework targeted to advisory bodies aimed at improving their assessment process, from how they receive their terms of reference; scope the agenda prior to topic selection; prepare background briefing for decision-makers; and help to structure the discussion and composition of stakeholders throughout the process. However, although useful, this framework does not really address the issue of pragmatically converting HTA into evidence based decisions.

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[51] NHS National Health System England and Wales

Another possible approach is to use multi criteria decision analysis (MCDA), which has been widely used in supporting decisions in transport, agriculture, marketing and environmental engineering, and more recently it has emerged as a tool to support decision-making in health care (Miot et al, 2012). Multi-criteria methods are designed to help people make 'better' choices when facing complex decisions involving multiple dimensions (Goetghebeur et al, 2008). In theory, MCDA allows a structured and objective consideration of factors that are both measurable and value-based in an open and transparent manner (Baltussen et al, 2006). It has been said that "MCDA's are especially helpful when there is a need to combine 'hard data' with subjective preferences or to make trade-offs that involve multiple decision-makers" (Dolan, 2010).

In MCDA, the decision problem (e.g. the choice of intervention) is analysed to identify all the factors (i.e. criteria) that may affect its use, and thus develop ex-ante for any evaluation, a full set of decision criteria. A major part of the process is to ask decision-makers to make their values and objectives explicit by assigning weights to each stated criterion. They then score the performance of each intervention of interest with respect to each criterion. This step is designed to prompt explicit consideration of the advantages and disadvantages of each option and to foster discussion within the relevant decision-making group (Goetghebeur, 2012). This forces decision-makers to think hard about what they value, why they value it, and how they value it in a specific context (Goetghebeur, 2012). By combining weights and scores an aggregated measure of each intervention of interest can be produced. Completeness, non-redundancy, mutual independence and operationality of criteria are aspects to take into account to fulfil the MCDA methodological approach.

The EVIDEM framework

In 2008 Goetghebeur et al conducted extensive analyses of the literature and documented decision-making processes worldwide. After this preparatory work, the authors developed a MCDA framework known as Evidence and Value: Impact on Decision-Making (EVIDEM). The framework was intended to help judge the value of interventions from two perspectives: the value system of the evaluator (decision-maker) with regard to the importance of each component (weights) and the actual performance of an intervention according to pre-selected decision-making criteria (scores).

EVIDEM includes 15 core quantifiable components that are currently considered important in decision-making (Tony et al, 2011), these criteria are grouped into six clusters (disease impact, context of intervention, intervention outcomes, type of benefit, economics and quality of evidence). See Appendix 6 for details.

The original EVIDEM criteria included: disease severity, size of population affected by a disease, clinical guidelines for intervention, comparative intervention limitations, improvement of efficacy/ effectiveness, improvement of safety and tolerability, improvement of patient-reported outcomes, public health interest, type of medical service, budget impact on health plan, cost-effectiveness of intervention, impact on other spending, adherence to requirements of decision-making body, completeness and consistency of reporting evidence, and relevance and validity of evidence.

The framework also includes detailed protocols for the collection, analysis, assessment, synthesis and presentation of evidence for each decision criterion (HTA module). It also includes a template to synthesise the HTA evidence needed to assess each criterion which is known as the 'by-criterion HTA report'. Results of the EVIDEM MCDA module can be used to rank health care interventions for reimbursement decisions/prioritisation. Each appraised intervention receives an aggregated MCDA value ranging between 0 and 1 (scores of 0 and 1 indicating lowest and highest priority respectively) which in turn allows for cross comparison of health care interventions.

Modified versions of the EVIDEM framework have allowed for the incorporation of additional criteria considered relevant for the context of interest, and have been tested for clinical and resource-allocation decision-making in developed and developing countries including Canada, the US, Nepal and, more recently, South Africa (Goetghebeur et al, 2010 and 2012, Tony et al, 2011 and Miot et al, 2012).

The overall aim of this chapter was to assess the feasibility and usefulness of using and incorporating HTA to inform resource-allocation decision-making in Colombia by using EVIDEM, since it has not previously been tested in this context. A second objective was as to whether the use of primary prophylaxis should be prioritised over three other chosen health care technologies.

METHODS

The general methodological approach taken in this chapter is similar to the steps followed by Miot et al (2012) when they field tested EVIDEM in South Africa, and by Goetghebeur et al (2012) who also tested EVIDEM for formulary decision-making in Canada. Both studies followed a similar pathway that included a preparatory stage in which the investigators conducted literature searches and produced HTA reports for each one of the interventions of interest, followed by a panel session with decision-makers that included four steps: 1- contextualisation of the broader criteria to be used for decision-making, 2- establishing a panel perspective (weighting of the criteria), 3- appraising the value of the intervention(s) of interest (scoring each criteria) and, 4- discussion of the results. For a graphic representation of this scheme of work when piloting EVIDEM see Figure 15.

Miot el al´s work consisted of field-testing EVIDEM using the example of liquid-based cytology (LBC) for cervical cancer in South Africa, and included a panel of 12 local experts. The authors first invited the panel to contextualise the decision criteria they considered as relevant, hence the four steps described before were undertaken in a panel session. On the other hand, Goetghebeur et al piloted EVIDEM for formulary decision-making using the 15 core criteria with a pan-Canadian panel of 13 health care stakeholders who were asked to appraise 10 medicines; in this case no contextualisation of the criteria was performed.

Figure 15. Scheme of work for piloting EVIDEM

**Preparatory stage
By investigators/
researchers**

Literature review of intervention(s) of interest
❖ Published sources, public domain and other information

HTA report for each intervention of interest
❖ Synthesised data organised into MCDA matrix

**Panel
With decision-makers
(relevant health care
Stakeholders)**

Contextualisation of decision-making criteria
❖ Adopt or adapt EVIDEM core criteria

Panel perspective
❖ Weighting of MCDA decision-making criteria

Appraisal of intervention(s) of interest
❖ Scoring intervention(s) with respect to MCDA criteria

Discussion
❖ Feedback on process, policy implications

Source: adapted from Goetghebeur et al (2012)

The initial research plan for this thesis chapter was to conduct the initial preparatory stage and follow the four steps reported by Miot et al at the panel stage, test the MCDA value of four interventions of interest (including the economic evaluation of primary prophylaxis for haemophilia conducted in the previous chapter) in order to inform/help the Colombian MoHSP in establishing a more systematic and transparent process for updating the publically financed benefits package content (POS). However, during October and November 2012 the preliminary objectives had to change when the former Regulatory Commission for Health (CRES) of Colombia led an independent initiative aimed at selecting broader criteria for reimbursement decision-making to update the POS content, in order to comply with the constitutional court´s mandate of transparently updating and equalizing its content for both the subsidiary and contributory regimes as soon as possible.

The preliminary work developed by CRES consisted of three workshops with 11 senior decision-makers (academics, researchers and civil servants) with broad experience of working in the context of the Colombian health system, and high visibility among stakeholders. The main researcher was invited to participate in the panel as part of the discussion during all three workshops. As in step 1 of Miot´s work, participants were asked to nominate a list of additional contextual aspects they considered relevant for resource-allocation decision-making in Colombia. After three voting rounds in two nominal group sessions a final list with 15 criteria was produced, 13 of these criteria belonged to the EVIDEM core model criteria (one criterion less than Miot´s publication), and two added contextual criteria. See Table 6 for the final list of criteria and weights selected for Colombia, those highlighted are the two added contextual criteria to the original EVIDEM framework.

Table 6. Final list of criteria and weights for Colombian-modified version of the EVIDEM:

CRITERION	DEFINITION	WEIGHT
Disease severity	Severity of the health condition of patients treated with the proposed intervention (or severity of the health condition that is to be prevented) with respect to mortality, disability, impact on quality of life, clinical course (i.e., acuteness, clinical stages).	9.3%
Size of population affected by disease	Number of people affected by the condition (treated or prevented by the proposed intervention) among a specified population at a specified time; can be expressed as annual number of new cases (annual incidence) and/or proportion of the population affected at a certain point of time (prevalence)	8.9%
Improvement of efficacy/effectiveness	Capacity of the proposed intervention to produce a desired (beneficial) change in signs, symptoms or course of the targeted condition above and beyond beneficial changes produced by alternative interventions. Includes efficacy and effectiveness data, as available.	8.7%
Current clinical guidelines applicable in Colombia	Concurrence of the proposed intervention (or similar alternatives) with the current consensus of experts on what constitutes state-of-the-art practices in the management of the targeted health condition; guidelines are usually developed via an explicit process and are intended to improve clinical practice.	7.7%
Type of medical service (clinical benefit)	Nature of the clinical benefit provided by the proposed intervention at the patient-level (e.g., symptom relief, prolonging life, cure).	7.3%
Budget impact on health plan (POS)	Net impact of covering the intervention on the budget of the target health plan (excluding other spending).	6.9%
Improvement of safety and tolerability	Capacity of the proposed intervention to produce a reduction in intervention-related harmful or undesired health effects compared to alternative interventions.	6.6%
Public health interest	Risk reduction provided by the proposed intervention at the population-level (e.g., prevention, reduction in disease transmission, reduction in the prevalence of risk factors)	6.5%
Improvement of patient reported outcomes	Capacity of the proposed intervention to produce benefitial changes in patient-reported aoutcomes (e.g. QoL, improvements in convenience to patients).	6.3%,
Current intervention limitations	Shortcomings of comparative interventions in their ability to prevent, cure, or improve the condition targeted; also includes shortcomings with respect to safety, patient-reported utcomes and convenience.	6.2%
Attention to vulnerable groups of population	**Capacity of the proposed intervention to benefitial impact to vulnerable groups of populations as defined by law in Colombia (e.g. displaced, elderly, disabled, native american, mentally ill, etc).**	5.7%
Cost-effectiveness of intervention	Ratio of the incremental cost of the proposed intervention to its incremental benefit compared to alternatives. Benefit can be expressed as number of events avoided, life-years gained,quality-adjusted life-years gained, additional pain-free days etc	5.5%
Completeness and consistency of reporting evidence	Extent to which reporting of evidence on the proposed intervention is complete (i.e., meeting scientific standards on reporting) and consistent with the sources cited	5.1%
Relevance and validity of evidence	Extent to which evidence on the proposed intervention is relevant to the decision-making body (in terms of population, disease stage, comparator interventions, outcomes etc.) and valid with respect to scientific standards and conclusions (agreement of results between studies). This includes consideration of uncertainty	5.0%
Attention to differential needs for health/health care	**Capacity of the proposed intervention to benefitial impact to people in need of differential care (e.g. orphan disease, paliative care, end of life, etc).**	4.3%

The final 15 criteria considered for Colombia were: completeness and consistency of reporting evidence; relevance and validity of evidence; disease severity; size of population affected by disease; current clinical guidelines; current intervention limitations; improvement of efficacy/effectiveness; improvement of safety and tolerability; improvement of patient-reported outcomes; public health interest; type of medical service; budget impact on health plan; cost-effectiveness of intervention, attention to vulnerable groups of population; and attention to differential needs for health/health care. This first part of CRES work closely resembled Miot´s step 1 of panel stage (contextualisation of criteria). For a detailed description of CRES work and criteria definitions see Appendix 7.

Once the panel had agreed on the final criteria and their definitions, participants were asked to weight each criterion irrespective of any health care intervention of interest (step 2: panel perspective). CRES delivered further consensus meetings with different stakeholders around the country to disseminate the selected list of criteria and ask further participants to weight them. A total of 201 citizens voted on their level of agreement and preferences regarding each of the 15 criteria (CRES, 2012). The list of voting participants included the academics on the same panel, patients' associations, citizen´s councils and representatives from the medical societies. Despite all the above, in December 2012 CRES was dissolved by Ministerial/Presidential Decree 2560 before appraising the value of any intervention (step 3) or discussing the MCDA results with decision-makers (step 4). This thesis chapter completes these final two steps.

To test the overall feasibility and usefulness of EVIDEM, the rest of this chapter takes the following approach. First, a preparatory stage consisting of a synthesis of existing HTA data into MCDA matrices of a) PP with FVIII for SHA throughout life (incorporating the CUA presented in chapter b) zinc supply for diarrhoea prevention, c) anastrozole for breast cancer and d) ticagrelor for acute coronary syndrome.

Since the pilot to test EVIDEM was also intended to inform the MoHSP on how to design a process to update POS in Colombia, two different approaches to incorporate HTA results into decision-making were considered in this 'synthesis stage'. One was the EVIDEM 'by-criterion' framework with the 15 contextualized and weighted criteria for Colombia as it stands and the other a much simpler narrative HTA synthesis of evidence containing the same information as per the by-criterion report, but not summarized into components, and supplemented by a comprehensive budget impact analysis (BIA).

The latter approach took into consideration the MoHSP´s request to incorporate BIA alongside HTA data in a narrative format since this was the previous approach used in 2011 to update POS content by former CRES. Previous attempts to estimate budget impact of technologies into POS have calculated the average cost per-year per-technology per-person, instead of the overall aggregated cost of technologies for the overall population exposed to such technology. The aim of incorporating a comprehensive BIA was to properly test it as a source of information for coverage decision-making. Using this second format means that only an aggregate score would be assigned per- per-technology, rather than summed by criterion.

The starting point for the work presented in this thesis chapter follows on from steps 1 and 2 that had already been developed by CRES prior to its dissolution. Specifically, this required the scoring of each HTA summary by relevant decision makers (step 3) and a discussion regarding the policy implications of the along with feedback on the usefulness of the EVIDEM framework as a whole (step 4). Note that although the CRES work partially departed from the original voting system used by Miot and Goetghebeur in 2012 to select and weight criteria, it was considered that it sufficiently emulated steps 1 and 2 of Miot et al´s work, therefore could serve as starting basis for the research presented in this chapter.

A focus group approach was considered to be the most suitable approach to fulfil the aims of this chapter (Green and Thorogood, 2009). Focus groups are useful to test, evaluate or conduct programme reviews, especially when participants' reasoning behind their views is of interest, they can also obtain input from individuals and interest groups, obtain detailed reaction and input from stakeholders to preliminary proposals or options, collect information on the needs of stakeholders surrounding a particular issue (as in the case of resource-allocation decision-making), determine what additional information or modification may be needed to develop consultation or issues for further discussion (Elliott et al, 2005).

Focus group planning

One focus group was organised as a mock reimbursement decision committee with individuals with potential decision-making responsibilities or academic interest in this field. Three people were assigned roles during the meeting: the moderator/facilitator (the main researcher) would lead a semi-structured discussion to draw out and summarise the views of all participants, a second person would record the session and take informed consent and conflict of interest declarations, and a third person would time the scoring criteria and conduct estimates of the MCDA value of each intervention. The two supporting roles were assigned to technical staff from IETS.

The focus group was planned to last for two hours and follow a pre-determined set of topics including the aims of the meeting, background about deliberation for decision-making, an introduction to the four technologies to be appraised, methods overview, and voting. The feasibility of using and incorporating HTA to inform resource-allocation decision-making and their perception of EVIDEM was planned to be explored during the meeting through a set of open-ended questions to allow participants to guide the discussion, and to diverge if necessary in order to address ideas and concepts not anticipated by the moderator (Britten, 1995).

<u>Selection of the four competing technologies</u>

The list of technologies to be valued during the focus group included PP throughout life for SHA, as well as three other non-haemophilia health technologies; zinc supply for diarrhoea prevention, anastrozole as first line therapy for hormone-receptor-positive postmenopausal women with metastatic breast cancer, and ticagrelor + acetylsalicylic acid (ASA) for patients with acute coronary syndrome (ACS) without ST elevation and moderate to high cardiovascular risk. The three 'competing' non-haemophilia health care technologies were chosen because they created an opportunity to contrast the features of an intervention aimed at treating an orphan disease with others intended for wider populations.

However, technology selection was also partly based on convenience because over the past two years local HTA summaries following good HTA practice for these interventions had been published. In addition, all three non-haemophilia-related technologies were considered as potentially cost-effective whilst prophylaxis was not. Nonetheless, at the time of writing this thesis, no reimbursement decision had been made as to whether they would be listed in the POS. The HTA report of PP for SHA was an extension of the CUA presented in Chapter 2, a brief summary of evidence of the three non-haemophilia technologies is provided below (for the detailed by-criterion HTA report in Spanish and sources of data of all four interventions see Appendix 8):

     a. Zinc supply: Acute diarrheal infection (ADI) occurs at any age, but toddlers and children aged less than 5 are at higher risk of complications such as sepsis, dehydration and death. In 2006, 336 children died in Colombia due to ADI and 374 due to malnourishment. Recent studies suggest that zinc supply may reduce the prevalence of ADI and pneumonia responsible of many deaths per-year globally, improve prognostics and reduce in-patient stay. ICER of prophylactic zinc supply in Colombia was COL\$2,022,322 (USD\$1,011.16) per ADI averted for malnourished children less than 5 years old. It was considered as cost-effective at a WTP threshold of up to three times the Colombian GDP per-capita.

b. Anastrozole as first line therapy for hormone-receptor-positive postmenopausal women with metastatic breast cancer (BC): BC is the most frequent type of cancer in women, there are around 1.38 million new cases per-year in the world in 2008; BC is the most common cause of cancer deaths in females (in LMICs 269,000 deaths per-year). The natural course of disease and severity varies according to type and location. In Colombia from 2002-2006, annual incidence rate was estimated in 32.6 per 100,000 women. Anastrozole has proven superior to tamoxifen on tumour response to treatment, mainly in terms of time free of disease progression. The ICER of anastrozole was 6,173,144 (USD$3,087) per DALY averted, hence considered as cost-effective at a WTP threshold of up to three times the Colombian GDP per-capita.

c. Ticagrelor for patients with Acute Coronary Syndrome (ACS) without ST elevation and moderate to high risk of cardiovascular disease (CVD): CVD is the most common cause of death in Latin America. In Colombia CVD is the main cause of all deaths for people aged more than 45 years. 82,293 of ACS would be expected per-year in Colombia. Ticagrelor is an antiplatelet drug that has proven a major and faster effect when compared with common practice (clopidogrel). Ticagrelor reduced deaths from all cardiovascular causes when compared to clopidogrel. The ICER of ticagrelor was $28,411,503 (USD$14,205) per QALY gained, hence considered as cost-effective at a WTP threshold of up to three times the Colombian GDP per-capita.

Assembling the HTA evidence for the focus group

The EVIDEM framework collaboration group has developed a standard protocol for the search and analysis of data to be synthesised and used for appraising the MCDA value of the technologies of interest. However, this was not used as recent local HTA reports following what is deemed good international practice were available. The clinical practice guidelines by Perry et al in 2012 (BC), Florez et al (ADI) and Senior et al (CVD) in 2013 were used to produce the HTA reports. In the case of PP, the HTA was based on the CUA described in chapter 2 and complemented from the searches by Castro et al (2012), public domain information of the CLH and the MoHSP, and refined with information from local experts when needed.

Two different formats were used and tested to present HTA results to participants. The first format used the EVIDEM by-criterion modified MCDA matrix to assemble the HTA information of the four technologies in Spanish. All reports contained the relevant information organised as per each of the 15 weighted criteria by CRES in 2012.

However, since the pilot was also aimed at informing the MoHSP on how to design a process to update the POS, a second format to be tested included a narrative HTA summary containing the same information, for the same technologies and from the same published sources, nonetheless this time it was not assembled into components as in the by-criterion EVIDEM template. HTA information for this second approach was supplemented with a comprehensive budget impact analyses (BIA) taking into consideration the MoHSP´s request of incorporating the previously used formats in Colombia when POS content was lastly updated by CRES in 2011.

Of worth noting that although EVIDEM includes 'budget impact on health plan' as a relevant criterion, the BIA information traditionally used in Colombia for coverage decision-making was not comprehensive and only estimated individual average cost of technologies per-year. The comprehensive budget impact analyses of the four competing technologies were developed by technical staff from IETS. These were prepared presenting the result of subtracting the average annual cost of a new scenario (new intervention) from the annual cost of the current scenario (current practice). Each scenario accounted for the quantities and estimated cost per-year of the interventions if they were incorporated into POS package for the first year only.

Identifying the decision-makers

The aim of the focus group was to gather a group of individuals able to represent different stakeholders within the Colombian health system with decision-making responsibilities; hence a convenience purposive sample was used in this part of the research. Sampling was judgemental and involved the conscious selection of participants to be included in the study (Crookes and Davis, 1998). The focus group was designed in essence to mimic a resource-allocation decision-making committee.

Relevant eligibility characteristics were established before sampling started, a total of twelve organisations were identified as containing potential sources of participants (government, insurers, providers, patients groups, academics, health care professionals, people´s advocates and lay members). Senior policymakers and 'visible' individuals were to be chosen to assure legitimacy and "buy in" of the pilot. In the case of the lay member it was considered that any available citizen not familiar with health or health care would suit the purpose of the study. Since traditionally resource-allocation decision-making occurs as a centralised process in Colombia, all eligible participants were expected to be located in Bogotá.

<u>The scoring system</u>

To appraise the health care interventions of interest using (method 1), respondents were presented with a synthesised report of the evidence needed for each component of the MCDA (EVIDEM by-criterion HTA summary). They were asked to use the EVIDEM matrix containing the 15 criteria contextualised by CRES, and score each individually on a 4-point scale (0-3), where 3 represents the highest level of fulfilment of each decision criterion and 0 the lowest (as per Miot and Goetghebeur´s work). The calculation of the MCDA value estimates as per the EVIDEM approach was done through a linear model. A linear model is a statistical model in which the value of a parameter for a given value of a factor is assumed to be equal to $a + bx$, where a is a constant, and b is the coefficient on variable x. In this case b is the weight of each criterion and x the score by-criterion, and a is the aggregated weighted score of any previous criterion.

The weights were normalised by distributing them across the 15 criteria to sum up to 1 for each participant, scores were also standardised by dividing them by the maximum possible score of 3 (all as per the EVIDEM approach). Hence the MCDA estimated values would lay between 0 and 1 as a sum of combined weights and scores for all decision criteria. Where 1 is the highest value of an intervention (perceived as an 'ideal' intervention according to criteria) and 0 the lowest. Once weights and scores were obtained, they were tabulated using Excel software and descriptive statistics were used to calculate the mean values. Results were presented to participants only after testing the alternative approach requested by the MoHSP to assist decision-making at the end of the second part of the session.

The second approach (method 2) to appraise the value of interventions consisted of presenting participants with four mini HTA narrative reports for the technologies of interest. This time instead of using a by-criterion format, the same information was presented to participants but not separated into EVIDEM components. Detailed budget impact analyses (BIA) considered the potential cost implications for POS after the first year of incorporation of technologies. To appraise the value of the competing health care interventions with this method, respondents were asked this time to individually rank each intervention on a scale from 1 to 4 based on the merits of the narrative description and BIA, where 1 represented the highest priority intervention and 4 the lowest.

When using the ranking scheme, the number of points given to each technology depended on the total number of technologies being considered; since there were four technologies, each time a technology was ranked as first it obtained 4 points and the one that was ranked as fourth was assigned 1 point, and so on. This approach is known as the Borda count [52] and was the traditionally used approach for ranking technologies by CRES up to its abolishment.

The aggregated value of interventions was obtained by adding the individual ranking scores of each participant, this according to the original authors seems to be more sensitive than estimating ordinal average scores. According to this system, ranking first would mean the technology with the highest value and thus higher priority of reimbursement; the opposite would be true for ranking fourth. Using this second format an aggregated score per-person per-technology, rather than by-criterion was assigned. In order to identify any substantial differences in level of difficulty when scoring using the two methods, average times of assessment per-technology and per-participant were measured.

Promoting discussion

On August 30th, 2013 a two-hour focus group was held in the conference room of IETS to evaluate the usefulness of the EVIDEM framework. All participants were asked to consent to participate and to be recorded throughout the meeting, also to declare any conflicts of interest. As consent was given by all, the meeting was recorded for transcription.

The moderator welcomed the group and provided general background to participants, as well as the outlines and ground rules. The fact that no names were to be used in the final report was emphasised and open participation of all attendees was encouraged. The moderator advised participants on the intended use of the focus group results and what form the data would take. He also explained the scoring mechanism for each approach to be used.

The last part of the focus group was aimed at discussing the results and their policy implications. To promote discussion, participants were presented with a hypothetical scenario where only those two technologies with the highest scores were to be reimbursed by the health system regardless of the format used to present HTA information.

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[52] In Borda count the voter ranks the list of candidates in order of preference. Named after the French mathematician and political scientist Jean-Charles de Borda, who devised the system in 1770, It is also known as the ranked voting system,

The following questions were posed to participants in order to gather their inputs, concerns and expectations about EVIDEM, for example: was there enough information to make resource allocation decisions in Colombia?, should the use of PP be prioritised over the three other non-haemophilia health care technologies?; participants were also asked about which of the methods of presenting HTA information they preferred and what changes or improvements could be added to the processes and methods presented in the pilot for future implementation. At the conclusion of the meeting, the main points of view of participants were summarised, validated for accuracy and group members were thanked for their participation.

Analysis of data

The focus group was recorded and once finished transcribed *verbatim* by an independent transcriber. After transcription, the document was uploaded to ATLAS- ti7 to assist content analysis. In order to interpret emerging data rather than simply describing it, no preliminary hypothesis was considered. Labels such as sufficiency of information, methods concerns, methods comparison, validity of information, incorporation of HTA into decision-making, and the specific value of each intervention were predefined as the relevant categories that may serve to inform the aims of this chapter. Uncertainty about valuation, level of difficulty, specific criterion issues, opportunities for improvement, preferred method, as well as change in final decision to be made and perceived benefits of using HTA were added to the initial list of labels for data analysis. A detailed description of participants´ profiles, MCDA value of interventions and emergent themes during the focus group are given in the results section of this chapter.

RESULTS:

Seven people out of twelve accepted and attended the invitation to participate in the focus group (the remaining five had accepted the invitation but were unable to attend). Participants represented a broad range of stakeholders within the Colombian health system, from members of the MoHSP, academics, insurers, patients and professional associations to lay members of society.

All participants were skilled workers with a graduate and at least one postgraduate degree. All of them declared vested interests, and two had potential conflicts of interest with the technologies to be appraised. Six participants were currently working in the health sector and one was retired. Figure 16 shows a detailed profile of participants. No representatives from hospitals or people´s advocates participated in the meeting, although they were formally invited to attend. Six out of seven participants were health professionals, and four were physicians; four were women.

Figure 16. Profile of participants (Focus group)

	PARTICIPANT 1	PARTICIPANT 2	PARTICIPANT 3	PARTICIPANT 4	PARTICIPANT 5	PARTICIPANT 6	PARTICIPANT 7
Gender	Male	Male	Female	Female	Female	Male	Female
Profession	Medical Doctor	Medical Doctor	Medical Doctor	Nutritionist	Lawyer	Medical Doctor	Nurse
Affiliation	Colombian Association of Scientific Societies	National Academy of Medicine	Ministry of Health & Social Protection	Association of insurers from the subsidiary scheme	Lay member	Public University	Association of high cost diseases at a public insurer
Postgraduate studies	Specialist in intern medicine, cardiology and electrophysiology, MSc in clinical epidemiology	Specialist in ear, nose & throat. Former director of a public hospital	Specialist in economics and health management	Specialist in social security and health	Specialist in administration law & in public contractual affairs	Specialist in anaesthesiology MSc in clinical epidemiology & MSc in University management	MSc in education, research & lecturing
Current experience	Works at a private healthcare institution	Retired professor	Works at the directory of technologies and medicines	Works as coordinator of insurance	Works at the contractual office of a NGO	Works at a directory position	Works as lecturer

All participants valued the interventions using the two alternative methods presented. According to observations after scoring the four technologies of interest using the EVIDEM by-criterion was more time consuming than ranking technologies. The former took an average of 11.15 minutes (ranging from 7-18 minutes) per-health care technology-per-participant and the latter 9.14 minutes (ranging from 7-15 minutes).

<u>The value of interventions</u>

After calculating the relevant EVIDEM scores (method 1), PP for SHA was third out of four with an average weighted score of 0.794 when compared with zinc (0.904), anastrozole (0.822) and ticagrelor (0.708). MCDA estimates of perceived value of PP varied widely from 0.595 to 0.977, but also for all other technologies, zinc (0.782-0.986), anastrozole (0.698-0.934) and ticagrelol (0.449-0.945) reflecting the diverse perspective of participants. Table 7 shows the detailed results of the EVIDEM comparative value of all four interventions, each row represents the average weighted score by-criterion by-technology and the last row the average weighted MCDA score by-technology.

PP performed particularly 'well' when the criteria disease severity, improvement of efficacy/effectiveness, improvement of safety and tolerability, current intervention limitations and attention to vulnerable groups of population were scored. Scoring of participants was consistent and almost all scored PP with a score of 3 in these dimensions. The existence of clinical guidelines, public health interest and cost-effectiveness of intervention were the least scored criteria for PP.

Table 7. Results of the EVIDEM comparative value of interventions by-criterion (method 1)

CRITERION	WEIGHT	STANDARDISED SCORES PER-TECHNOLOGY			
		Zinc	Anastrozole	PP FVIII	Ticagrelol
Disease severity	9.3%	0.093	0.080	0.093	0.075
Size of population affected by disease	8.9%	0.089	0.076	0.076	0.085
Improvement of efficacy/effectiveness	8.7%	0.083	0.079	0.083	0.070
Current clinical guidelines applicable in Colombia	7.7%	0.062	0.066	0.022	0.066
Type of medical service (clinical benefit)	7.3%	0.059	0.063	0.059	0.063
Budget impact on health plan (POS)	6.9%	0.066	0.046	0.049	0.049
Improvement of safety and tolerability	6.6%	0.063	0.066	0.063	0.028
Public health interest	6.5%	0.065	0.046	0.040	0.053
Improvement of patient reported outcomes	6.3%	0.063	0.036	0.051	0.024
Current intervention limitations	6.2%	0.038	0.053	0.059	0.038
Attention to vulnerable groups of population	5.7%	0.057	0.041	0.057	0.030
Cost-effectiveness of intervention	5.5%	0.047	0.050	0.031	0.042
Completeness and consistency of reporting evidence	5.1%	0.039	0.036	0.032	0.027
Relevance and validity of evidence	5.0%	0.040	0.045	0.045	0.033
Attention to differential needs for health/health care	4.3%	0.039	0.039	0.033	0.025
MCDA Value per-technology	100%	0.904	0.822	0.794	0.708

Table 8 presents detailed results of the EVIDEM-MCDA value estimations of PP showing where the variation across participants lies. Each column reflects the minimum and maximum scores by-criterion, and each row the MCDA average weighted value of PP by-criterion. The scores of existence of clinical guidelines ranged from 0 to 3, with five out of seven participants scoring this criterion with 0. The cost-effectiveness of PP was also scored in a range from 0 to 3, and of worth noticing that although it was not considered as being cost-effective two participants scored this criterion with 3 and three with 2.

Table 8. Results of the EVIDEM-MCDA value of primary prophylaxis

CRITERION	WEIGHT	SCORES PER-PARTICIPANT					
		Min		Max		Average	
Disease severity	9.3%	3	0.093	3	0.093	0.093	
Size of population affected by disease	8.9%	1	0.030	3	0.089	0.076	
Improvement of efficacy/effectiveness	8.7%	2	0.058	3	0.087	0.083	
Current clinical guidelines applicable in Colombia	7.7%	0	0.000	3	0.077	0.022	
Type of medical service (clinical benefit)	7.3%	1	0.024	3	0.073	0.059	
Budget impact on health plan (POS)	6.9%	0	0.000	3	0.069	0.049	
Improvement of safety and tolerability	6.6%	2	0.044	3	0.066	0.063	
Public health interest	6.5%	0	0.000	3	0.065	0.040	
Improvement of patient reported outcomes	6.3%	0	0.000	3	0.063	0.051	
Current intervention limitations	6.2%	2	0.041	3	0.062	0.059	
Attention to vulnerable groups of population	5.7%	3	0.057	3	0.057	0.057	
Cost-effectiveness of intervention	5.5%	0	0.000	3	0.055	0.031	
Completeness and consistency of reporting evidence	5.1%	1	0.017	3	0.051	0.032	
Relevance and validity of evidence	5.0%	1	0.017	3	0.050	0.045	
Attention to differential needs for health/health care	4.3%	0	0.000	3	0.043	0.033	
MCDA Value per-participant and overall	100%	1	0.381	3	1.000	0.794	

This wide variability of result among respondents was also a common finding for all the other criteria. For instance when valuing the criterion size of population affected only one individual considered SHA as an infrequent condition whilst the other six considered the number of patients affected by this disease as substantial. Using method 1 (the EVIDEM approach) and assuming a scenario where only the two interventions with the highest scores would be incorporated in to POS, PP would not be reimbursed in Colombia.

Using the second format (method 2) an aggregated score was assigned per-person per-technology, rather than by criterion, using this ranking system does not allow to assess how each technology performed by-criterion or to compare by-criterion results across interventions. When the ranking system was used, PP for SHA was ranked last after ticagrelor, zinc and anastrozole. In this ranking system being first represents the preferred option and fourth the least preferred one. Ticagrelor was ranked first with an overall score of 24, zinc placed second with an aggregated score of 19, anastrozole ranked third scoring 17 and PP placed last with a score of 10. Thus after using method 2 and under the assumption that only the top two ranking interventions would be incorporated in POS, PP would not be reimbursed in Colombia. See Table 9 for detailed results of the ranking value of all interventions.

Table 9. Results of the ranking value of interventions (method 2)

CRITERION	INDIVIDUAL RANKING REPORT							Total score	Final rank
	P1	P2	P3	P4	P5	P6	P7		
Ticagrelor	3	2	1	1	2	1	1	24	1st
Zinc	1	3	3	4	1	2	2	19	2nd
Anastrozole	2	1	2	2	4	3	4	17	3rd
Primary prophylaxis FVIII	4	4	4	3	3	4	3	10	4th

It should be noted that PP was always placed at the bottom positions using either method, it placed third out of four with method 1 and last with method 2. It is also noteworthy that ticagrelor, which was at the bottom of the list when using EVIDEM, climbed to the top after using the ranking system.

Participants' input, concerns and expectations

In order to assess the feasibility of using and incorporating HTA into resource-allocation decision-making, as well as to explore participants´ perception of EVIDEM as a tool to assist decision-making, a set of open-ended questions was presented to guide the discussion as much as possible. The findings that emerged from these research questions are presented in this section.

To the question, 'was there enough information to make resource-allocation decisions?' participants´ perceptions diverged. Some considered the information insufficient, because of gaps or heterogeneous quality of reporting; others thought it was sufficient:

"Well no, some cells […] missed information […]" P6

"[…] many descriptions […] well yes, they provided very complete information, but some others let´s say not that much […] it should be as homogeneous and complete as possible". P4

Some specific criteria emerged as creating more difficulties for interpretation and valuation than others. For instance, according to participants, the existence of CPGs was not considered as sufficient reason to value one intervention higher than other, the financial impact of interventions should be better explained beforehand in order to avoid any potential confusion; clarification as to whether higher weight should be assigned to a costlier or a less costly intervention would be appreciated, also vulnerability as a decision-making criterion should be better defined.

"[…] the existence of a guideline should not be a criterion to determine value […]" P3

"[…] economic impact needs to be clear if three means that it should be favoured and a score of one should not, […] what should the direction of valuing this criterion be […]" P1

"[…] vulnerability of population, is not that clear" P2

According to participant valuation of technologies, the response to the question: 'should the use of PP be prioritised over three other non-haemophilia health care technologies? It appears to be no, since it placed at the bottom of priorities with both methods used. Nonetheless, it seems that the final valuation of technologies was associated with the methods and criteria used to assist decision-making not only in the case of PP, but also for all other technologies; for instance ticagrelor moved from the bottom to the top of the list.

"At first zinc seemed to me as an economic alternative during the first exercise [EVIDEM template], […] they were kids, whatever; but when I go and look in detail at the budgetary impact [method two] and realize that I have to pay that much money for that benefit, my final decision ought to change". P3

"[…] the health technology for Acute Coronary Syndrome [ticagrelor], did not find a real benefit versus current practice [clopidogrel], but when I go and look at the budget impact analysis of method two and find out that new technology is cost-saving […] realized that is worth doing […]" P3

Participants also considered that decision-making in Colombia should go beyond the use of incremental cost effectiveness ratios (ICERs).

"And then one realizes that it [coverage decision-making] goes beyond ICERs, and takes into account equity […]" P2

"[…] cost effectiveness (RATIO) is superior to our ability to pay, but might not be the only element to make a decision, well yes it might not be cost-effective […] but if I only have ten patients countrywide […] it may not be that much […]" P6

There was extensive discussion among participants to reach an agreement on their preferences about methods. Participants found the EVIDEM by-criterion HTA summary useful and comprehensive to inform their preferences, but also considered a detailed budget impact analysis a useful tool to assist coverage decisions. Of worth noting that the budget impact of interventions has been traditionally been estimated in Colombia individually instead of globally as it was presented in this pilot. One method without the other was perceived as incomplete and prone to decision-making bias. Participants came to a final agreement that a mixed methods approach including a by-criterion HTA report, supplemented by a detailed budget impact analysis, would be ideal.

"[…] if I am interested in looking at an HTA summary, either method is useful, but if it is about coverage decision-making […] it is mandatory for decision-makers to bear in mind and take into account the budget implications, so in my view method number one [EVIDEM] should be supplemented with detailed budget impact information" P4

"Uhm, I just would like to say that in my experience the budget analysis was very important for me to be able to rank from one to four" P3

"[…] method one [EVIDEM] […] makes one think about each criterion whenever valuing them, whilst in method two [narrative + BIA] although information is visible there, probably one might not comprehensively value each criterion at a time […] obviously valuation would be biased towards budget impact, but if you assess each item separately incorporating the budget analysis according to its weight, possibly it might be better" P6

"We could try a mixed methodology which includes method one [EVIDEM] *and the detailed budget impact of method two, […] it would be a genius idea" P3*

In answer to the question, 'What changes or improvements could be added to the processes and methods presented in the pilot for future implementation?' participants answered that more explanation should be provided before voting on each technology and criterion, especially regarding grading criteria. Also that information should be as complete, homogeneous and coherent as possible, in order to reduce quality and parametric uncertainty among decision-makers.

"[…] I think at the very beginning some more explanation should be provided, […] regarding the methodology […]" P7

"Whoever is voting should feel comfortable and with no doubts, right? […] Not everyone is familiarised, it requires a level of training of those in charge of decision-making […]" P4

Some concerns and considerations emerged among participants about the methods used to conduct the HTAs; for instance the use of QALYs when conducting CUA, or the reliance on the ICER alone to inform decision-making, and also regarding the validity of data used to estimate both aggregated measures.

"Yes, because here we do not operate with QALYs, no methodology for QALYs has been developed here." P6

"[…] what should really be important is the bibliography supporting the assessment, […] if assessment is solid then decision-making is much easier."P2

Some methodological considerations also emerged about the use of EVIDEM; in particular, cost implications represented a challenge for participants who had doubts when independently valuing this criterion.

"[…] methods, uhm all the time I doubted, if scoring should regard the consistency of information or about my subjective perception of it […]" P7

"[…] I doubted […] uhm because sometimes I had no idea if I was valuing the importance of a criterion or the information about such criterion" P4

"[…] regarding cost, […] of importance to clarify what a score of three means, if such a therapy benefits the system or represents a burden […]" P1

Concerns aside, participants considered HTA and EVIDEM as useful tools to assist decision-making. HTA is perceived as an approach able to incorporate efficacy, effectiveness and cost-utility information.

"Because when you refer to cost-effectiveness it implies efficacy has been assessed, effectiveness has been assessed, utility has been assessed, hence if Health Technology Assessment is understood […] hence eventually no scientist should think that such a big decision has been made only based on economic grounds […]" P1

EVIDEM served as a means to incorporate HTA into decision-making, but also to prioritise different health interventions for decision-making. According to participants' responses regardless of the number of technologies to be appraised systematic priority-setting should take place in Colombia.

"[…] different priorities, but the interesting part about this is that they can be reconciled […], I think it [EVIDEM] is a good methodology, for creating a ranking and deliberating, but it is important to have experts participation" P2

"It does not matter if they are one or one hundred [health technologies] we need a filter for final comparison" P1

DISCUSSION:

The aim of this chapter was to assess the feasibility of incorporating HTA to inform resource-allocation decision-making in Colombia. In answer to the research question: **can EVIDEM be used in Colombia to assist resource-allocation decision-making?** Although they identified limitations, participants found EVIDEM was a means of incorporating HTA into decision-making, and also of prioritising different health interventions for resource-allocation.

Participant perceptions differed as to the adequacy of information presented in the EVIDEM summary. Some specific criteria represented more challenges for interpretation and valuation by participants than others. Some concerns and considerations emerged from participants of the methods used to conduct HTA in Colombia, but also on how to incorporate its results into decision-making; for instance of validity of data used for modelling, the use of QALYs when conducting CUA, or reliance on ICERs alone to inform decision-making.

Extensive discussion took place on methodological preferences; participants found the EVIDEM by-criterion HTA summary useful and comprehensive to inform their preferences, but thought a detailed budget impact analysis would be an important piece of information for coverage decision-making. The final consensus of participants was that a mixed methods approach including a by-criterion HTA report and a detailed budget impact analysis would be ideal for Colombia. It appears from these findings that EVIDEM can be used in Colombia for assisting more systematic and transparent processes for coverage decisions.

After testing EVIDEM, and in a hypothetical scenario that only two out of the four technologies were to be reimbursed, PP for SHA was ranked third of the list compared with three competing non-haemophilia health care priorities. The answer to the question, '**Should the use of primary prophylaxis be prioritised over three other non- haemophilia health care technologies?'** is that regardless of the method used in the pilot, the final coverage decision about PP for severe haemophilia A care would not potentially change; it should not be prioritised given the options presented.

The final valuation of technologies nonetheless was sensitive to the methods and criteria used to assist decision-making not only in the case of PP, but also for all other technologies tested in this pilot. For instance, ticagrelor from being last when using the EVIDEM approach moved to the top of the ranking after method 2 was applied. Perhaps the fact of being the only technology considered as cost-saving may have impacted participants' preferences after using this approach, as one participant referred to BIA information: "*obviously valuation would be biased towards budget impact*", however the weighting system itself and the fact that the pilot was run with only 7 participants may have also impacted final results.

It is noteworthy that the comprehensive BIA was the only additional piece of information presented to participants when testing this latter approach. The other three competing technologies were displaced one position by ticagrelor in the ranking format, but since the aggregated score of this system did not make explicit consideration of preferences by-component it made it difficult to depict other variables that may have impacted prioritisation when using this format.

Strengths and limitations

This part of the study sought to preserve key principles of qualitative research. Data were collected through a focus group with relevant stakeholders resembling a decision-making body (Elliot et al, 2005). It was able to capture the nature and intensity of stakeholders´ concerns and values, and also to obtain a snapshot of their opinions and reactions about the methods presented, also to collect details of their needs relating to information.

The focus group comprised seven participants with decision-making roles or interest in this field, however a total of twelve individuals were initially invited to attend. The limited number of participants who finally attended the focus group may well represent a limitation of the study, although this number was similar to the number and composition of panel members of the previous EVIDEM pilots published by Miot and Goetghebeur (2012). The profile of participants was very broad, as was their familiarity with HTA and decision-making methods, this heterogeneity of knowledge may have had an impact on their ability to participate.

The research processes aimed to minimise the values and assumptions of the moderator that could bias findings. Although the main researcher is now the CEO of IETS, the "distance" between him and participants was not as close or personal as to jeopardise independence; for instance he broadly knew three of the participants. A non-judgemental attitude, no help in valuing each technology and no guidance as to participants' responses to research questions served this purpose.

Nonetheless, as noted by Green and Thorogood, 2009, whenever conducting qualitative enquiry "it is impossible to have a field for study that is untainted by values and impossible for the researcher to stand outside those values and subjectivities". Therefore the venue (IETS) and moderator (CEO of IETS) may have had an impact on the ability of participants to be open and spontaneous. Since participants were aware that the focus group would also serve as a pilot to inform the Colombian MoHSP on how to establish a more transparent process to update POS, this may have impacted their responses and overall expectations.

One limitation of this part of the research relates to language differences between the original EVIDEM tools used (matrix and by-criterion), published in English and the non-validated Spanish versions presented to participants. According to participants, more explanation should be provided before voting on technologies and criteria, especially grading criteria and directionality of scoring, this was similar to the finding reported by Goetghebeur in Canada in 2012, regarding questions of participants as to which perspective should they adopt for weighting and scoring, and whether the same set of weights and scores shall be used for all types of interventions. Some doubts emerged when independently valuing each criterion, especially cost, which represented a challenge for participants.

In this part of research, no strategy was considered to consistently synthesise HTA evidence or avoid double counting (consideration of the same evidence in multiple criteria). This limitation of the current research is being addressed by the original framework developers, who have incorporated a list (Hailey, 2003) that aims to improve transparency and consistency of HTA reports. Nonetheless this HTA module was still under development at the time of testing EVIDEM in Colombia (Goetghebeur et al 2012). Provision of complete information, together with homogeneity and coherence of reports to reduce uncertainty among decision-makers were considered as opportunities of improvement to be added to the processes and methods presented in this pilot.

It is worth noting that although recent economic evaluations were available for each of these four technologies, in the case of zinc researchers had published results of a CEA reporting outcomes in "natural units" i.e. acute episodes of diarrhoea averted. In the cases of PP, ticagrelor and anastrozole the authors had conducted CUAs, but for anastrozole the ICER was expressed in terms of DALYs averted and only in the former two cases QALYs gained were used in the ICER denominators. Although it is quite clear that cross comparison of interventions is only possible if researchers have estimated health outcomes in the same units, it was considered that in a context with no methodological standards in place to conduct an economic evaluation, a broad variety of results should be expected. Since EVIDEM considers cost-effectiveness of interventions as one separate criterion for each intervention and does not cross compare, these technologies and ICER results were considered as suitable for the purpose of this chapter.

Most of the limitations of this part of the research were associated with the methods used to test EVIDEM, not only during the focus group, but also before. Of special consideration is the work developed by CRES, which did not fully comply with the methodological requirements of non-redundancy and mutual interdependence of criteria, since the two added contextual criteria were both associated with vertical equity (treating different people differently).

CRES work also departed from the qualitative approach to contextualise criteria and the 0-5 scale presented by the original EVIDEM authors for weighting; the Delphi approach used to select the contextual criteria and the Borda count used for weighting may have had an impact on selected criteria, final weights and MCDA value of interventions by making respondents to shy away from extremes as it happens with other rating scales (Robinson et al 2001).

There were also limitations in the focus groups related to tools and processes. For instance, the EVIDEM by criterion template presented was a modified version of the original and did not include a directionality guide to assist participants with valuation. Due to time constraints, the explanation of grading criteria was not exhaustive, and since only one of the participants was familiar with EVIDEM and the preliminary work of CRES (in Miot´s work the same participants weighted and valued the intervention of interest), a more detailed explanation or a preparatory workshop would have helped valuation, and perhaps produced different results.

One major limitation of this study is the fact that participants had already read the relevant HTA information when they were presented with method 2 (narrative HTA + BIA), thus presenting a second approach after having read a previous report, may not really make it a 'fair' comparison. Hence average times of assessment with each format and the final impact of the comprehensive BIA on the final ranking with method 2 should be interpreted cautiously. Nonetheless since method 2 does not make explicit account of factors, this latter statement carries substantial uncertainty.

The focus group was recorded and transcribed by an independent transcriber to facilitate analysis. Unfortunately the meeting venue was large and the recording machine was not sufficiently sensitive to capture all the comments, this made transcription more complicated. No full description of bibliographic references was presented to participants during the meeting creating further uncertainty about validity and consistency of data.

MCDA methodological concerns reported by the original authors are also applicable to this research, these are related to methodological requirements of completeness, non-redundancy, mutual independence and operationality. For instance the criterion cost-effectiveness is problematic since it includes other considered criteria such as improvement in efficacy/effectiveness, improvement in safety and tolerability, patient-reported outcomes, impact on other spending, and budget impact on health plan.

Goetghebeur et al (2012) have even proposed the removal of cost-effectiveness from this framework or to make it optional, nonetheless this latter statement probably needs further consideration since the results of a robust ICER after economic modelling may be preferable than presenting disaggregated information about the incremental costs and benefits of interventions without explicit consideration of uncertainty of parameters and results.

Besides the described benefits of MCDA approaches (such as EVIDEM): adaptable to specific contexts, provide the means to reveal the perspectives of decision-makers and facilitate discussion and consensus seeking on recommendations and decisions, there is an issue of consistency of the estimated MCDA value of interventions. Coinciding with Goetghebeur (2012) rankings should never be used as formulaic rules, but as a basis to promote deliberation and explicit consideration of relevant aspects into decision-making. As stated by this same author, MCDA value estimates are committee and context specific and should be interpreted cautiously for coverage decision-making. Although consistent application of a MCDA model by a stable decision-making committee could produce a more robust ranking of interventions.

Under a different context (a softer constraint or other competing technologies) PP could have had a different chance of being prioritised. In this case methods used to incorporate HTA also seemed to have an impact on the final preference of participants. Although EVIDEM weights and scores using simple linear scales may have drawbacks (low discriminatory power or non-linear performance), the whole idea of the framework is to make it simple, intuitive and easy to use (Goetghebeur, 2012).

Methodological concerns aside, participants appeared to consider HTA and EVIDEM as useful tools to assist health care decision-making in Colombia. They were perceived as capable of incorporating efficacy, effectiveness and cost-effectiveness. EVIDEM is a way of prioritising different health interventions for decision-making. According to participants' responses, regardless of the number of technologies, systematic priority-setting should take place in Colombia.

It seems after testing EVIDEM as it stands and an alternative approach using a narrative HTA summary plus a comprehensive BIA, that EVIDEM is superior since it makes explicit consideration of relevant aspects into decision-making. Using a ranking system may limit deliberation since it does not force decision-makers to think hard about what they value, why they value it, and in what context they value it. Nonetheless, when deciding on resource-allocation BIA placed an important role and seemed illustrative to participants. According to participants remarks a MCDA with a comprehensive BIA could be 'ideal' in Colombia (either as a single criteria as in the EVIDEM or as a separate piece of information).

These findings coincide with those of Tanios et al (2013) on decision-makers' perceptions of the relevance of a core set of criteria and on the need to consider a wider range of criteria to assist decision-making, and also Guindo et al (2012) on the perceived importance of considering both normative and feasibility criteria for fair allocation of resources and optimised decision-making. According to these authors sound multi-criteria approaches may be useful to enlighten health care decision-makers and priority setters.

The merit of this part of the research is the relevance of its findings. The use of HTA as a tool to assist decision-making in Colombia is feasible. Structured and objective consideration of the factors that are both measurable and value-based in an open and transparent manner may be feasible through the use of MCDA approaches. This chapter attempts to add to the knowledge about the decision-making process, expand the scope of EVIDEM regarding context and health care intervention, and pilot its use to serve the interest of the MoHSP of Colombia in setting up a more robust process for resource-allocation decision-making. As stated by Goetghebeur et al in 2012, further testing and validation are needed to advance MCDA approaches into health care decision-making.

SUMMARY

In August 2013 a two hour focus group comprising seven participants, was held to assess the feasibility of HTA to be used to support decision-making. The MCDA EVIDEM framework was tested and preferred by participants than an alternative format including a narrative HTA report and comprehensive BIA in the case of four competing health care interventions of interest (including PP for severe haemophilia A).

Participants considered HTA and EVIDEM useful tools to assist decision-making that could be used in Colombia. HTA is perceived capable of incorporating efficacy, effectiveness and cost-utility that will be focused on assessing marginal benefits of health care interventions. EVIDEM can value and prioritise different health interventions for decision-making. Participants believed that systematic priority setting should take place in Colombia, regardless of the number of competing technologies.

After testing EVIDEM and according to its MCDA value, and also after using an alternative preference ranking upon the MoHSP request, PP for severe haemophilia A in Colombia was not prioritised over the other competing technologies. Nonetheless the final valuation of technologies was sensitive to the methods and criteria used to assist decision-making, not only in the case of PP, but also for other tested technologies.

This part of the research attempted to add to the knowledge about the decision-making process, expand the scope of EVIDEM regarding context and health care intervention, and pilot its use to serve the interest of the MoHSP of Colombia on setting up a more systematic and transparent process of resource allocation decision- making.

IV.   CONVERGENT, DIVERGENT AND CONTRADICTORY FINDINGS

As stated by Mays and Pope (2000) there are not mechanical solutions to limit the likelihood that there will be errors in qualitative research. Various ways have been informed for improving the validity of results (i.e. triangulation, respondent validation, clear exposition of methods and analysis, reflexivity, attention to negative cases, and fair dealing amongst others). Triangulation compares the results of two or more methods of data collection or sources of data as a way of ensuring comprehensiveness and encouraging more reflective analysis. Findings from each chapter were triangulated to improve the validity of research. Results from interviews from chapter one, practical observation after conducting economic evaluation from chapter two, and findings of the focus group from chapter three helped to identify convergent, divergent and contradictory findings regarding the feasibility of producing and using HTA in Colombia.

Triangulation was made by listing all salient findings from each empirical chapter separately, then cross-comparison of findings served to classify as coincident those aspects that were similar in at least two of the three empirical chapters. Divergence occurred when a finding from any chapter was not coincident with any other chapter, and contradiction was assumed if either within a chapter or amongst them findings took opposite directions. After considering these aspects, a template was developed to look for patterns of convergence in order to strengthen interpretation of findings, and as a way of ensuring comprehensiveness and more reflective analysis. A traffic light system helped to represent highly convergent findings as green, moderate convergent findings as yellow and divergent findings as red (see figure 17 for a graphic representation of convergent and divergent findings).

In chapter one ten drivers emerged with the potential ability to influence HTA development and use: availability and quality of data, implementation strategy, cultural aspects, local capacity, financial support, policy/ political support, globalisation, stakeholders´ pressure, health system context and usefulness perception.

In chapter two, after conducting economic evaluation for PP those methodological aspects that may make HTA difficult in this context were identified: data constraints about the clinical and cost-effectiveness of PP, a fragmented information system, uncertainty about costs and frequency of services consumed to populate the model, lack of methodical standards (no reference case), the need to transfer international standards, and the recent establishment of a local HTA-IETS were described as aspects to consider.

Figure 17. Convergent and divergent findings regarding the feasibility of HTA being produced and used in Colombia

	Data constraints	Fragmented information system	Lack of methodical standards "reference case"	Available international standards	Local HTA-IETS	
Chapter 2: Conducting HTA for severe haemophilia A in Colombia						**Chapter 3: Testing the MCDA-EVIDEM, and the use of HTA to inform resource allocation decision-making in Colombia**
Availability & Quality of data	*** Costs, quantities and utilities		*** Concerns on data about QALYS, ICER		*** Local surveys using EQ-5D or other generic measures	Sufficiency of information for decision-making
Implementation strategy		** Incipient information system being strengthened	** Uncertainty about perspective, discounting rates, combining measure for quantity and QoL, threshold		*** Local HTA standards and methods to be developed by IETS	Methods used to incorporate HTA into decision-making
Cultural aspects						
Local capacity	** Low production of local data	** Incipient information system underdeveloped	*** Concerns on data about QALYS, ICER		*** Local institutional capacity to be strengthened	Criteria used for decision-making
Financial support						
Policy/ Politics support			** Need of local methods guidance for HTA			
Globalisation				** NICE guidance on discounting rates, use of QALYs. WHO guidance on CE thresholds	*** EVIDEM criteria incorporated into decision-making	
Stakeholder pressure		** Data about costs and quantities from 2ry sources subjected to vested interests				Concerns about reimbursement decision-making
Health system context					*** EVIDEM criteria able to incorporate values and hard criteria into decision-making	
Usefulness perception					*** Need to build up capacity within decision-makers	Explanation or capacity building for decision makers

(Left vertical header: Chapter 1: Exploring the issues of previous experiences of conducting HTA, and academic's perception of its role and future use in Colombia)

Finally, in chapter three it emerged that the main expectations for the use of HTA relate to adequacy of information for decision-making, methods used to incorporate HTA into decision-making, criteria used for decision-making, concerns about reimbursement decision-making, and the need for explanation or capacity building for decision-makers. MCDA and particularly EVIDEM emerged as a tool capable of combining efficacy, effectiveness and cost-utility information useful to value and prioritise different health interventions.

Concerns about the availability and quality of data converged with data constraints of the clinical effectiveness, cost-effectiveness, costs, quality of life amongst others; all these emerged as potential hindrances to better informed decision-making in Colombia. Academics, the main researcher and decision-makers considered information about costs (prices and quantities) and health state preferences the most important of the needs to conduct robust HTA reports and use them in decision making.

The lack of methodological standards and the absence of a "reference case" converged from all methods as a source of structural uncertainty for HTA to be incorporated and used to inform decision-making. The perspective to be adopted, discounting rates for costs and effects, the use of combined measures for quantity and quality of life gained (or lost) and the use of a cost-effectiveness threshold were listed in two of the chapters as sources of concern to be considered in Colombia. All these as well as the need to strengthen the current incipient information system should be borne in mind in a well-planned implementation strategy

It also emerged from all the component studies that there are local capacity constraints that may limit the production and quality of HTAs; capacity building and institutional strengthening of those devoted to HTA like IETS was seen as an opportunity to build capacity not only for HTA work, but also for incorporating its results into broader criteria for decision-making. There was also convergence on the need to develop local capacity among those who will produce HTA, but also among those who will use it for resource-allocation decision-making.

Globalisation emerged as a convergent finding that brought the global trend to institutionalise HTA to Colombia, and EVIDEM as a disposable tool able to incorporate social values and hard criteria into decision-making. Under the current health system´s context, both HTA and EVIDEM are perceived as opportunities to restore trust; these are being considered for the establishment of a more transparent and systematic resource allocation decision-making process.

Another convergent finding was the need for policy formulation about HTA methods guidance in order to avoid transferring methods and standards from other jurisdictions (such as NICE or WHO), as well as promoting local research and a robust information system, thus avoiding the need to rely on data that may not be generalizable to a local population or subject to vested interests (such costs or prices).

As stated by Pluye et al, 2009, mixing qualitative and quantitative methods may reveal some form of divergence and as proposed by these authors, taking divergence into consideration is a key issue for triangulation. Four strategies have been used to take account of divergence of results: reconciliation, initiation, bracketing and exclusion. Conflicting findings between qualitative and quantitative approaches often lead researchers to dismiss or ignore qualitative findings (Patton, 2002).

In this case divergence was considered when findings from one chapter did not coincide with findings from other chapters, reconciliation of findings was used to deal with divergence (results interpretation in a sense-making plausible manner) (Trend, 1978). For instance, cultural aspects and financial support, although considered as potential "drivers" with the ability to help or hinder HTA production and use in Colombia in chapter one, did not coincide with the findings of other chapters.

"Cultural aspects" referred to the social conceptions determined by local custom, meaning, and beliefs in Colombia with the potential to influence the development or use of HTA. These were considered in chapter one as a "driver", and although were not directly explored when conducting economic evaluation for SHA or piloting EVIDEM, it became apparent that such a lack of tradition of HTA methods, priority-setting and planning had methodological implications for the development of HTA in a context without a "reference case" or a transparent decision-making process in place. Even the current financial and "trust" crisis within the health sector may be a result of these so-called cultural aspects.

Similarly the "driver" financial support was explored and emerged from the participant interviews described in chapter one, but was not addressed or re-explored when conducting economic evaluation or when testing haemophilia HTA results for decision-making. Nonetheless, financial support was associated with resources devoted to HTA research, meaning the need of funding to strengthen groups and institutions, but also to strengthen information systems as sources of reliable data for economic modelling.

The strategies of exclusion (not taking into consideration conflicting data), bracketing (used when qualitative and quantitative data are irreconcilable) and initiation (which requires asking new research questions and collecting and analysing new data from a different perspective) were not used to deal with divergence. Divergence was considered relative, and other indirect findings supported the view that cultural aspects and financial support had the ability to influence the feasibility of conducting and using HTA in Colombia.

No findings were considered as consistently contradictory, although aspects like globalisation emerged as having a broad range of influence on HTA use and development in Colombia. On the one hand, globalisation has enabled Colombian staff and students to study HTA methods overseas in world-class universities, brought renowned HTA representatives and granted access to HTA guidance from consolidated institutions (such as NICE or WHO). In chapter one, academics perceived globalisation as creating "peer pressure" to produce HTA but also representing an opportunity to create networks of cooperation.

On the other hand, globalisation creates technological pressure with new and costly technologies that may create further financial strain within the health system, and a risk of "brain drain" of skilled HTA experts. In chapter three participants' concerns emerged about the potential ability of globalisation to promote the use of methods or the use of controversial decision-making criteria without the accuracy of locally-produced data (e.g. QALYs, ICERs, cost-effectiveness thresholds).

There were some contradictory findings about the adequacy of information for resource-allocation decision-making; some participants considered it adequate and others did not. Views of participants on the use of the ICER were also contradictory. Some considered HTA and economic modelling as comprehensive tools able to incorporate efficacy, effectiveness and cost implications into a single measure to assist decision-making whilst others thought decision-making criteria should go beyond ICERs.

<u>Reflexivity, positionality and power relations in the process of data collection and interpretation</u>

As mentioned before, throughout the process of conducting research on HTA and priority setting in Colombia the researcher adopted multiple identities, this may have shaped the process of data collection and interpretation. For instance, during the OPA at NICE international the researcher preliminary explored how HTA has been used to assist resource allocation decisions in different contexts; he also interviewed as part of the consultancy project relevant stakeholders in Colombia, this may have shaped his vision on the feasibility of HTA in this country, but also provided him with preliminary insights that were useful to design the questionnaire to be used during the interviews.

By the time of data collection for Chapter 1, the main researcher was a consultant at the MoHSP, perhaps the power relations between him and interviewees were expected to change as he was working for the Minister, nonetheless adopting a flexible approach during the interviews and selecting neutral venues agreed with participants may have reduced this risk of bias, also since he was presented to participants just as "a researcher". The development of the economic evaluation for SHA and the pilot to test EVIDEM (Chapters 2 and 3) were conducted after the main researcher had already been appointed as CEO of IETS, the latter rather than the former may had been subjected to the influence of the power position of the researcher who acted as moderator during the focus group, also the venue (IETS) for gathering insights when testing the MCDA approach may have had an impact on the ability of participants to be open and spontaneous. The fact that participants were informed that the pilot would also serve to inform the MoSHP interest on developing a more transparent decision-making process may have also shaped their expectations and answers.

V.   OVERALL DISCUSION AND CONCLUSIONS

The challenge of allocating finite health care resources is a problem common to all health systems. Decision-making in health care requires the consideration of scientific, medical, economic, social and ethical aspects and calls for objective-scientific and value judgment (Goetghebeur et al, 2012). HTA is a part of the process where the consequences of the application of health technologies are examined with the aim of better informing decision-makers. In recent decades different countries have established specialised HTA organisations; in September 2012 Colombia established IETS.

In most LMICs decision-making for health care occurs as an ad hoc and non-transparent process. The level of application of HTA procedural principles, such as transparency, robust and appropriate methods for combining costs and benefits, as well as the explicit characterization of uncertainty and active engagement with stakeholders, are often limited in these contexts. This was the case in Colombia where until the establishment of IETS HTA had played a limited role.

Since the 1993 health sector reform in Colombia, the health system has reached almost universal coverage (96%); nonetheless, the country still struggles to set priorities and allocate resources for health care in an efficient manner. By late 2009 a COL$2 Billion (USD$ 1.045 billion) deficit in the total health budget was announced by the government. At the peak of the crisis, the constitutional court mandated the government to equalise the publicly financed benefits package (POS) for the entire population, and update its content as soon as possible. All these represent an additional financial burden to the system. This financial crisis within the health sector has led to new legislation and a new health sector reform that is on its way in the Congress.

The interest of the Colombian government in relying on scientific evidence to better inform health policies began in the mid-2000s, but it has only been in the last three years that policymakers have paid attention to the methods and processes for assessing and appraising the evidence used in other countries. However, some of these processes, methods and methodologies may not be applicable to a setting like Colombia. For instance there are substantial differences in the architectural arrangements and roles played by institutions in countries, as well as differences in the involvement of stakeholders in decision-making.

As an example, NICE in England and Wales has operated since 1999 as an institution responsible for appraising evidence and formulating recommendations, supported by independent appraisal committees. In Colombia, however, IETS has been established just recently, and is expected to assess the evidence, but the MoHSP remains the organisation responsible for appraising it and making coverage decisions. It is worth noting that the UK has a relatively long tradition of performing and using the results from economic evaluations, applying WTP thresholds and including stakeholders throughout assessment processes. In Colombia, on the other hand, stakeholder engagement or the consideration of societal values are not current practice and the institutional arrangements for reimbursement decision-making and communicating of decisions to the general public are yet to be implemented.

The current government in Colombia has taken incremental steps to control costs and strengthen its institutional capacity. Besides creating IETS, it disbanded CRES in December 2012 and re-assumed its role of resource-allocation decision-maker. Since in Colombia there is no systematic process in place to set priorities or transparently and actively engage with stakeholders, nor is there a "reference case" to standardise methods or methodologies to produce HTA, the case of PP for SHA perhaps serves as an example of how the progressive adoption of newly developed health care technologies can dramatically change the natural course of a disease while challenging the financial sustainability of health systems.

In Colombia there may be potential for the use of alternative processes, methods and methodological approaches to incorporate HTA into decision-making moving beyond appraisal committees and the use of ICERs, such as MCDA to assess the value of new interventions. Given this context, the aim of this thesis was to assess the feasibility of conducting and using HTA to inform decision-making in Colombia. The main questions of interest were:

- What are the main aspects that may help or hinder HTA development and use in Colombia?

- What is the incremental cost-effectiveness of primary prophylaxis compared to on-demand treatment in Colombia?

- Can EVIDEM be used in Colombia to assist resource-allocation decision-making, and should the use of primary prophylaxis be prioritised over three other non-haemophilia health care technologies?

These questions were addressed using a mixed methods approach in three different empirical chapters.

The issues around previous HTA work in Colombia were studied through a qualitative approach presented in the first empirical chapter. The aim of this first empirical chapter was to explore previous experiences of conducting HTA and perceptions of its role and future use in Colombia. A qualitative methodology that included purposive homogeneous sampling, semi-structured interviews, rigorous transcription, and thematic content analysis was used.

Historically HTA has been developed in Colombia by research groups mostly motivated by academic interest, and interviews confirmed it was advanced in Colombia in the early 1990s by academics who returned from overseas studies and started using methods related to those used by EBM and HTA. From 2010-2011 onwards this research interest converged with political support to use HTA as a tool to inform decision-making.

Chapter 1 identified ten potential "drivers" that may help or hinder HTA activities in Colombia. However, findings from this project are the result of an in-depth exploration of the topic of interest in a particular setting and thus these "drivers" may not be generalizable to other countries. Nevertheless, the conceptual transferability of the term "drivers" although with caveats, may be of interest for similar settings trying to incorporate HTA processes and institutions into decision-making.

The case of primary prophylaxis (PP) versus on-demand (OD) treatment with FVIII for severe haemophilia A (SHA) was chosen as a case study because in recent decades PP has proven to be superior to OD treatment in preventing bleeding, but much more costly to provide. Despite much media attention to SHA in Colombia, no HTA work for this health condition has been developed so far. A CUA was developed to assess the feasibility of conducting economic evaluation in this setting and the incremental cost per QALY gained of PP using FVIII versus OD throughout life for severe cases following what is deemed good practice. A Markov model was designed from the local health system perspective and populated making use of the best available evidence, and completed and refined with local sources when necessary.

The results from the CUA presented in chapter 2, strongly suggest PP is not cost-effective if a willingness to pay for an additional QALY threshold of up to three times the current Colombian GDP per-capita is used, and that there is relatively little uncertainty around this conclusion despite the overall paucity of underpinning clinical evidence. This finding is broadly in line with the results of existing literature. This work additionally served to identify some methodological factors that may hamper HTA activities in Colombia such as the availability of local data and structural uncertainties. Although IETS is working on establishing a "reference case" and methods manuals for Colombia, there are currently no methodological standards in place to minimise uncertainty in HTA results.

To assess the feasibility of using HTA as a tool to assist decision-making in Colombia and answer the third set of questions, a focus group resembling a decision-making panel was held. This served to assess local decision-makers' views of the potential use of HTA to inform resource-allocation decision-making for health, and to test EVIDEM in the case of PP for SHA, comparing it with zinc supply for diarrhoea prevention, anastrozole for breast cancer and ticagrelor for acute coronary syndrome.

The results presented in chapter 3 suggest that EVIDEM could be used in Colombia to incorporate HTA and assist resource-allocation decision-making. Participants considered HTA and EVIDEM useful to assist decision-making. HTA is perceived as capable of incorporating efficacy, effectiveness and cost-utility information. EVIDEM may serve to value, cross compare and prioritise different health interventions for decision-making. According to the MCDA-EVIDEM valuation of PP for SHA, it would not be prioritised, nonetheless it should also be noted that the final valuation of technologies was sensitive to the methods and criteria used to make these judgements. Besides the methodological limitations of the tools and linear scoring system used by EVIDEM, it appears that the MCDA value of interventions are also committee and context specific, hence results for coverage decision-making should be interpreted cautiously. Participants also believed that regardless of the number of technologies, transparent and systematic priority-setting should take place in Colombia.

EVIDEM may offer a way to incorporate cost implications and societal values to rank health care interventions and develop "league tables", departing from the "hard" methodological constraints imposed by unmeasured opportunity costs. This represents an opportunity for prioritising interventions departing from ICERs in severely data and resource constrained settings, such as Colombia. This framework is a pragmatic step adaptable to specific contexts with the ability to reveal the different perspectives of decision-makers, facilitating discussion and consensus seeking on both recommendations and decisions (Goetghebeur et al, 2010). Nonetheless, it still requires further testing and development in order to advance the integration of MCDA and HTA for more effective and transparent evidence-informed policies and practice.

After triangulating results from all chapters, most findings converged. For instance the adequacy of information, lack of methodological standards, the need to develop capacity, the impact of globalisation, and the need for policy formulation on HTA. Divergence occurred and was dealt using reconciliation of findings, such as cultural aspects and financial support. No findings were considered as consistently contradictory. Nonetheless, aspects such as globalisation emerged as having a broad range of influences on HTA use and development in Colombia. There were also contradictory findings in reference to the preferred method for incorporating HTA into coverage decision-making. However, there was a final convergence that a mixed approach of MCDA-EVIDEM criteria supplemented by a comprehensive budget impact analysis could be the preferred process looking forward.

This thesis (limitations notwithstanding) has described factors that may enable or hinder the use of HTA in Colombia which are particularly relevant for the current implementation stage of HTA that is being led by IETS. It has also added to the existing evidence base about the cost-effectiveness of primary prophylaxis for severe haemophilia A, especially in LMICs where no CUA has been published for this health condition so far. This thesis also contains information of MCDA (EVIDEM) as a tool for decision-making that may serve as a starting point to assist the Colombian MoHSP on its interest of setting up a more robust and transparent priority-setting process.

There are three models for HTA promotion and initiation (Rajan et al, 2011), top-down whenever HTA is initiated from political interest, bottom-up whenever HTA is initiated and promoted from academic or research interest, and converging that combines both the political and academic/research interests. In Colombia, although academic interest in HTA started in the 1990s as a bottom-up initiative, it is only in recent years that HTA has attracted the attention of policymakers and been top-down formulated as a policy solution. Both bottom-up and top-down interests converged with the enactment of Law 1438 of 2011 that enabled the establishment of IETS, thus HTA formal initiation could be considered as converging in this country.

According to focus group participants decision-making criteria should go beyond ICERs in Colombia, coinciding with the views of Zwart-van Rijkom et al (2000), also in agreement with Oliver et al (2001) participants in both the semi-structured interviews described in chapter 1 and the focus group described in chapter 3 considered that cultural aspects and a need for skills development amongst consumers of HTA were to be borne in mind for its successful implementation in this context.

Performing rigorous HTA in LMICs may be challenging in the short-term, but may also help local researchers identify the methodological aspects that need to be considered or strengthened to follow what is deemed "good practice". In these contexts where scarcity of all types of data is common, transferability of HTA results from other jurisdictions may be seen as an option, but factors that may preclude transferability ("specific knockout criteria") and aspects of analysis that need to be addressed before transferring estimates should be borne in mind whenever conducting HTA in these jurisdictions. All these aspects may prevent researchers from adjusting international results to Colombia, but create a propitious environment for the development of HTA processes, methods standards and evaluations in such context. Conducting HTA for SHA as a case study could have therefore provided the framing to address some of these methodological concerns.

There is still limited knowledge of the needs and preferences of decision-makers regarding broader criteria for decision-making and this work has attempted to explore them. As stated by Kanavos and Angelis (2013), "a new approach is needed for assessing the value of new medical technologies that takes into account a more comprehensive set of parameters than just the incremental cost-per-unit of additional therapeutic benefit". MCDA may be able to link through weighting and scoring the multiple considerations affecting decisions by making them explicit and creating a clear link between HTA and health care decision-making, hence the use of alternative methodological approaches like MCDA as described by Baltussen et al (2007) and Miot (2012) could be an important step towards rational priority-setting in developing countries.

The aim of this thesis was to assess the feasibility of conducting and using HTA to inform decision making in Colombia where there is limited capacity, data and resources to conduct it, as well as a very recent a tradition and interest in using it as a tool to support decision-making. It seems from the findings of this project that HTA development and use is feasible. HTA has incrementally gained space in policy making in this country.

Resource-allocation decisions about haemophilia care and many other health conditions in Colombia so far have been made without enough evidence-based information. Institutional efforts aside, the Colombian system´s allocation of health care resources is still far from efficient and equitable. It also lacks transparency and "buy in". The use of HTA has increased in recent years and although, the country faces some contextual constraints, there are many opportunities to further assess the aspects that may help or hinder its use and institutionalisation.

This thesis has attempted to add to existing knowledge about the decision-making process by making explicit the processes and factors considered for health care decision-making. It expanded the scope of EVIDEM regarding context and health care intervention, and pilot its use for the MoHSP of Colombia. Although EVIDEM allows for incorporation of additional contextual criteria considered relevant, concerns arise on the possibility of double counting when assessing criteria such as cost-effectiveness or the two contextually added criteria for Colombia; hence further research should focus on testing the validity and consistency of the reported MCDA-EVIDEM values of interventions.

Lessons learnt, steps forward and further research on HTA and priority setting in Colombia

Throughout the process of conducting research on priority setting in Colombia the researcher has adopted multiple identities. During the preparatory stage of this thesis and being a consultant at NICE international (as part of the OPA) the main lessons learnt were, that there is a global trend to use or institutionalise HTA in many countries and that decision making is an intricate and incremental process whereby the use of evidence is just a part of it.

At the first stages of research (being a consultant at the MoHSP of Colombia), especially when conducting semi-structured interviews and developing *de novo* economic evaluation, it became apparent that that there are relevant aspects and a contested scenario that need to be considered for the successful introduction of HTA in a context like Colombia. After conducting a focus group to assess the feasibility to implement HTA into decision-making it emerged that decision-making criteria should go beyond ICERs and HTA in order to capture other relevant aspects that these methods are incapable of, this in order to reach sustainable, but also fair resource allocation. Finally after being appointed CEO of IETS the importance of bridging the gap between research and policy and practice was of unsurmountable value since all findings from this thesis have nurtured and shaped the development of IETS in Colombia.

In order to establish a more systematic and transparent priority setting process in Colombia establishing IETS could be considered as step number one, but institutions such as the regulatory agency (INVIMA) and the MoHSP itself need to be strengthened as well. Aspects such as comparative efficacy and safety for market authorization or managed entry agreements could be incorporated in this country. The restitution of a decision-making body with the ability to appraise the HTA evidence produced by IETS and transparently engage with stakeholders and reflect their values and preferences would be another step forward on the attempt to establish a more transparent and systematic process. Under such an ideal institutional arrangement INVIMA, IETS and the MoHSP shall consider different frameworks for producing and incorporating HTA results for coverage decision-making for frequent and infrequent disorders.

Future research agendas for HTA and priority setting in this setting shall focus on strengthening the methods and methodologies for HTA (i.e. societal elicitation of health state preferences or empirical estimation of thresholds), but also on the incorporation of wider aspects and broader criteria into decision making in order to reach sustainable universal health coverage, especially under the current context of the new enacted statutory law which upgraded health as a fundamental constitutional right to all citizens.

It is hoped that the results of this doctoral research project could be of significant value to the field of public health and policy since non-explicit priority-setting processes, poor information, lack of policy on HTA, barriers to implementation, political agendas and limited resources are common findings in developing countries (Youngkong et al, 2009), the final results from this research may be applicable to a wider context than Colombia, SHA and the competing technologies chosen for the pilot.

VI.APPENDICES

APPENDIX 1. SEARCH HISTORY AND TERMS

APPENDIX 1.1 SEARCH HISTORY SYSTEMATIC SEARCH OF CLINICAL EFFECTIVENESS (Primary prophylaxis vs. on- demand) SEVERE HEMOPHILIA A-May 8th 2013

1. hemophilia A.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
2. haemophilia A.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
3. (coagulation adj3 disorder*).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
4. (clot* adj3 deficiency).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
5. (clot* adj3 disorder*).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
6. 1 or 2 or 3 or 4 or 5
7. prophylaxis.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
8. (primary adj3 prophyl*).mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
9. on demand.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
10. on- demand.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
11. arthropath*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
12. arthrosis.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
13. joint damage*.mp. [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, tx, sh, ct, tn, dm, mf, dv, kw]
14. 7 or 8
15. 9 or 10
16. 11 or 12 or 13
17. 6 and 14 and 15 and 16
18. remove duplicates from 17

APPENDIX 1.2 SEARCH HISTORY SYSTEMATIC SEARCH OF ECONOMIC STUDIES OF SEVERE HEMOPHILIA A (Primary prophylaxis vs. on- demand)- May 15th 2013

1. hemophilia.m_titl.
2. haemophilia.m_titl.
3. 1 or 2
4. cost.m_titl.
5. economic- analysis.m_titl.
6. economic- evaluation.m_titl.
7. economic- study.m_titl.
8. cost-effectiveness.m_titl.
9. cost-utility.m_titl.
10. cost- benefit.m_titl.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. remove duplicates from 12

APPENDIX 2. PROCESS AND SUMMARY OF FINDINGS OF SYSTEMATIC SEARCHES OF CLINICAL EFFECTIVENESS AND ECONOMIC STUDIES OF SEVERE HEMOPHILIA A

The summary of evidence retrieved on the clinical effectiveness of treatments for SHA showed that although there is a growing stock of knowledge about the benefits of prophylaxis, most of it is derived from observational studies. From the 56 eligible publications, only two were systematic reviews - one of which was narrative (Castro, 2012) and the other a partial meta-analysis (Lorio, 2011); three RCTs were retrieved. All retrieved studies were considered as important sources of information of the natural course of disease and estimates that may of use to inform the decision problem of interest.

The systematic review by Lorio et al (2011) compared previous results of six RCTs studies of prophylaxis in people with haemophilia A and B (including 142 participants). Pooled results from two of these studies (Manco-Johnson et al, 2007 and Gringeri et al, 2011) showed a RR of 0.30 (95% CI; 0.12 to 0.76; p=0.012) for all bleeds and 0.22 (95% CI; 0.08 to 0.63; p=0.005) for joint bleeds favouring prophylaxis (three-times-a-week) with OD in children with haemophilia. Nonetheless, results for the number of patients with preserved joints after three to seven years of follow-up were not pooled due to significant heterogeneity of dosing regimens.

Three of the remaining four studies evaluated haemophilia A alone (Aronstam et al, 1996 and 1977) or compared different prophylaxis regimens (Carlsson et al, 1997). However, they did not present results of patients exposed to PP at early ages and stages of the disease hence were not considered as relevant to the decision problem of interest. A fourth study by Morfini et al (1976) evaluated hemophilia B, which was not the primary aim of this research.

Of interest for the case of study was a study by Manco-Johnson et al (2007) that randomly assigned young boys with SHA to regular infusions of rFVIII (PP) at doses of 25 IU/Kg every other day or to an enhanced OD schedule (40 IU/Kg) at the time of a joint haemorrhage. The primary outcome of the study was the incidence of bone or cartilage damage as detected in index joints (ankles, knees, and elbows) by radiography or magnetic resonance imaging (MRI). Boys under 30 months of age were randomly assigned to PP (n=32) or to enhanced episodic therapy (n=33). When the boys reached 6 years of age, 93% of those in PP and 55% of those in OD were considered to have a normal index-joint structure on MRI (p=0.006).

Many observational studies retrieved were considered as additional sources of information regarding the decision problem of interest. In 2007, Darby et al reported the mortality rates, life expectancy, and causes of death in people with haemophilia A or B in the UK who were not infected with HIV over a 22 year period of observation (from the late 1970s to late 1990s).

Mingot et al in 2009 reported that after following for 31 months, 22 haemophilia A patients treated with FVIII who switched to another plasma derived FVIII or rFVIII both FVIII and rFVIII are safe and effective products, with similar recovery and adverse events rates. Another cohort study published by Kurnik et al (2010) showed that the highest risk of developing inhibitors is during the first 20 exposure days, and that minimizing exposure to exogenous FVIII by using low dose prophylactic schemes during the early ages of life may reduce the risk of inhibitor formation.

Saulyte et al (2010) showed the utility of using the Haemophilia Joint Health Score (HJHS) for assessing early joint damage in a cohort of SHA and B patients in Lithuania. It was also assumed that FVIII and rFVII are interchangeable, in 2013 Gouw et al reported that after evaluating 574 patients treated with recombinant and plasma-derived clotting products both conferred similar risks of inhibitor development. In such cases the chances to develop inhibitors were expected to be similar in both regimes and thus this complication was not considered in the base case model.

It is worth noting that most retrieved publications were cross-sectional studies, historic or narrative reviews, and just a few of them economic studies. A remarkable finding from this search was the limited number of RCTs for SHA, perhaps owing to the fact that it is a rare lifelong disease and ethical limitations of randomization after observational designs in the late 1970s suggested that prophylaxis was clinically effective.

Institutions like the WFH, the US National Foundation of Haemophilia and WHO recommend continuing prophylaxis in adulthood, because adults remain at risk of developing joint or other kinds of bleeding, and no publication was found that supported the interruption of prophylaxis in adulthood. Of all interventional studies only the one by Manco-Johnson et al was considered relevant to the decision problem of interest since it exactly compared the two approaches of interest and presented results of joint outcomes associated to chronic bleeding.

On the other hand, the summary of the evidence of economic evaluations retrieved showed that since 1996 only 12 economic studies have been published assessing PP versus OD treatment for haemophilia A (one more than the number reported by Miners in 2013); five of these (Smith 1996, Szucs 1996, Bohn 1998, Miners 1998 and Daliri 2009) were cost-effectiveness analyses (CEA), one a cost-benefit analysis (Steen-Carlsson 2004), and six were CUA (Miners 2002 and 2009, Lippert 2005, Risebrough 2008, Colombo 2011, and Farrugia 2013) all showing a broad variety of results and structural approaches.

All reported studies accounted for information from HICs, except that by Daliri et al (2009), which reported information from a CEA in Iran. Only five of these CUA specifically compared PP with OD treatment (Miners et al, 2002 and 2009, Risebrough et al, 2008, Colombo et al, 2011 and Farrugia et al, 2013). Of these, only four (Miners 2009, Daliri 2009, Colombo 2011 and Farrugia 2013) adopted a health system perspective, and only three of these had modelled the costs and effects of treatment throughout life using QALYs (Miners 2009, Colombo, 2011 and Farrugia 2013). Of these, only Miners and Colombo had modelled the disutility associated with joint outcomes.

Coinciding with Miners findings (2013), a number of these publications have estimated high incremental cost-effectiveness ratios (ICERs) for PP. For instance, a study in Canada by Risebrough et al (2008) reported ICERs per QALY gained of CAN$500,000 for an escalated prophylactic scheme and CAN$1 million for a fixed PP scheme when compared to OD provision of clotting factor. UK estimates revealed £46,500 per QALY gained in 2002 (Miners et al) and after refining some methodological aspects more recently (Miners 2009) this figure was rounded to £38,000 per QALY gained which, although still above the threshold used for reimbursement decision-making by the UK NHS, is somewhat closer.

The Italian study by Colombo et al (2011) considered prophylaxis to be cost-effective and showed ICERs per QALY gained of €40,229 to €40,236 for individuals with haemophilia A who receive primary and secondary prophylaxis respectively, versus OD. Of worth noting that no explicit CE threshold was formally in operation as a decision rule in this context, nonetheless the Italian Health Economics Association had recommended a threshold between €25,000 and €40,000 which would mean that PP is still above such threshold. A cost benefit analysis by Steen-Carlsson et al (2004) in Sweden concluded that prophylaxis was cost-effective. However, total costs of treating patients were divided by the national general population and monetary benefits subtracted were based on the mean WTP per patient, which do not really represent the monetary benefit for this population.

In 2013, Farrugia et al reported PP to be dominant (lower cost and higher QALYs) from a UK perspective, and cost-effective in the USA with an ICER of USD $68,000 per QALY gained and in Sweden with SEK 1.1 million per QALY gained; both figures within the range of treatments reimbursed in these countries. The authors conducted a CUA modelling PP versus OD throughout life using a health care perspective, but using inhibitor development instead of arthropathy as the relevant outcome associated with QALYs. All published results were sensitive to the unit cost of clotting FVIII, frequency of bleeding and discounting rates (See appendix 2.4 for a narrative synthesis of published economic studies).

APPENDIX 2.1 - PRISMA FLOW DIAGRAM OF SYSTEMATIC SEARCH OF CLINICAL EFFECTIVENESS OF PRIMARY PROPHYLAXIS VS. ON- DEMAND HEMOPHILIA A- May 8th 2013
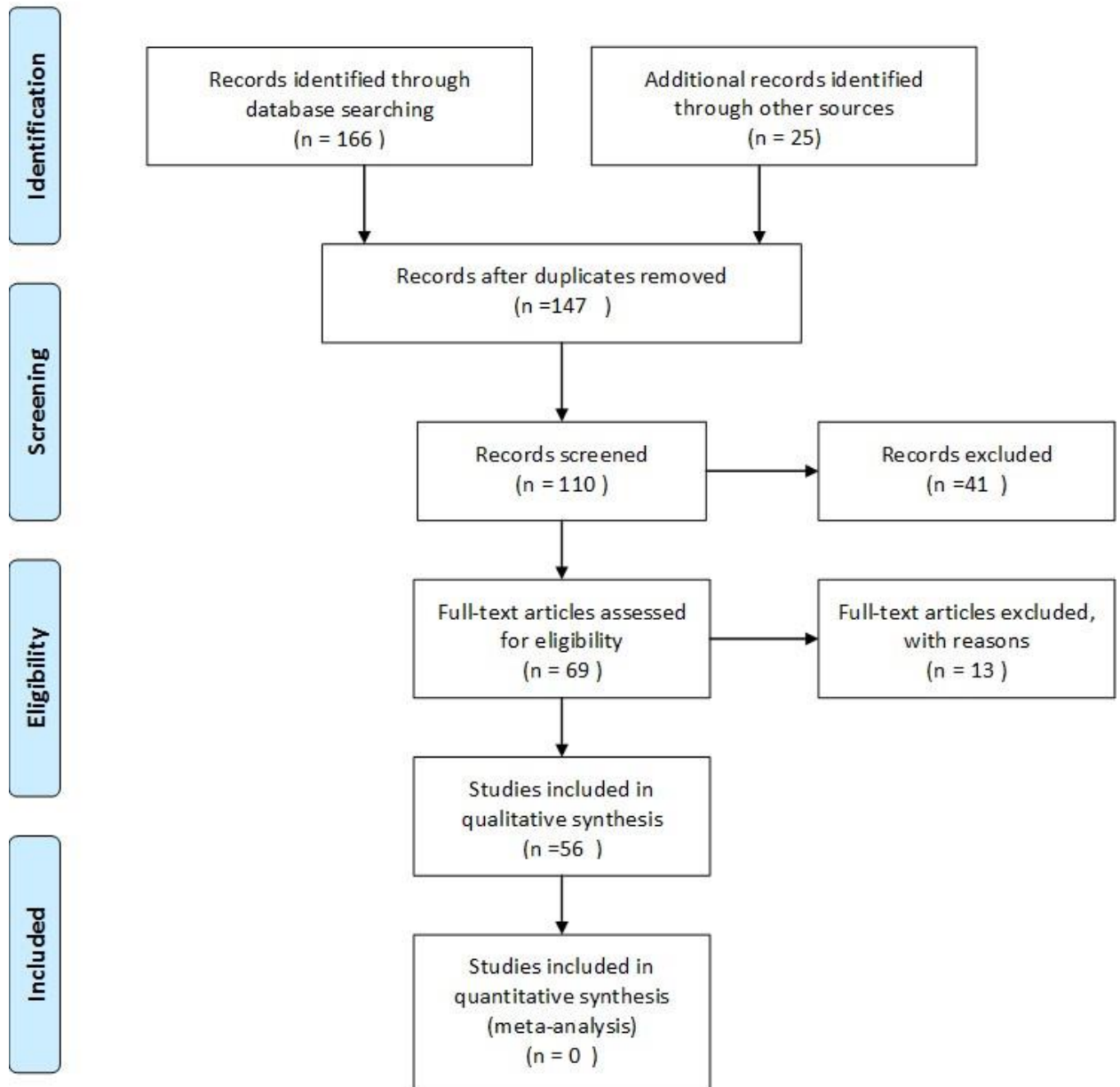
APPENDIX 2.2 - PRISMA FLOW DIAGRAM OF SYSTEMATIC SEARCH OF ECONOMIC STUDIES OF SEVERE HEMOPHILIA A (Primary prophylaxis vs. on- demand)- May 15th 2013

Identification

Records identified through database searching
(n = 178)

Additional records identified through other sources
(n = 0)

Records after duplicates removed
(n =113   )

Screening

Records screened
(n = 23)

Records excluded
(n =6)

Eligibility

Full-text articles assessed for eligibility
(n = 17)

Full-text articles excluded, with reasons
(n = 4)

Included

Studies included in qualitative synthesis
(n =13)

Studies included in quantitative synthesis (meta-analysis)
(n = 0)
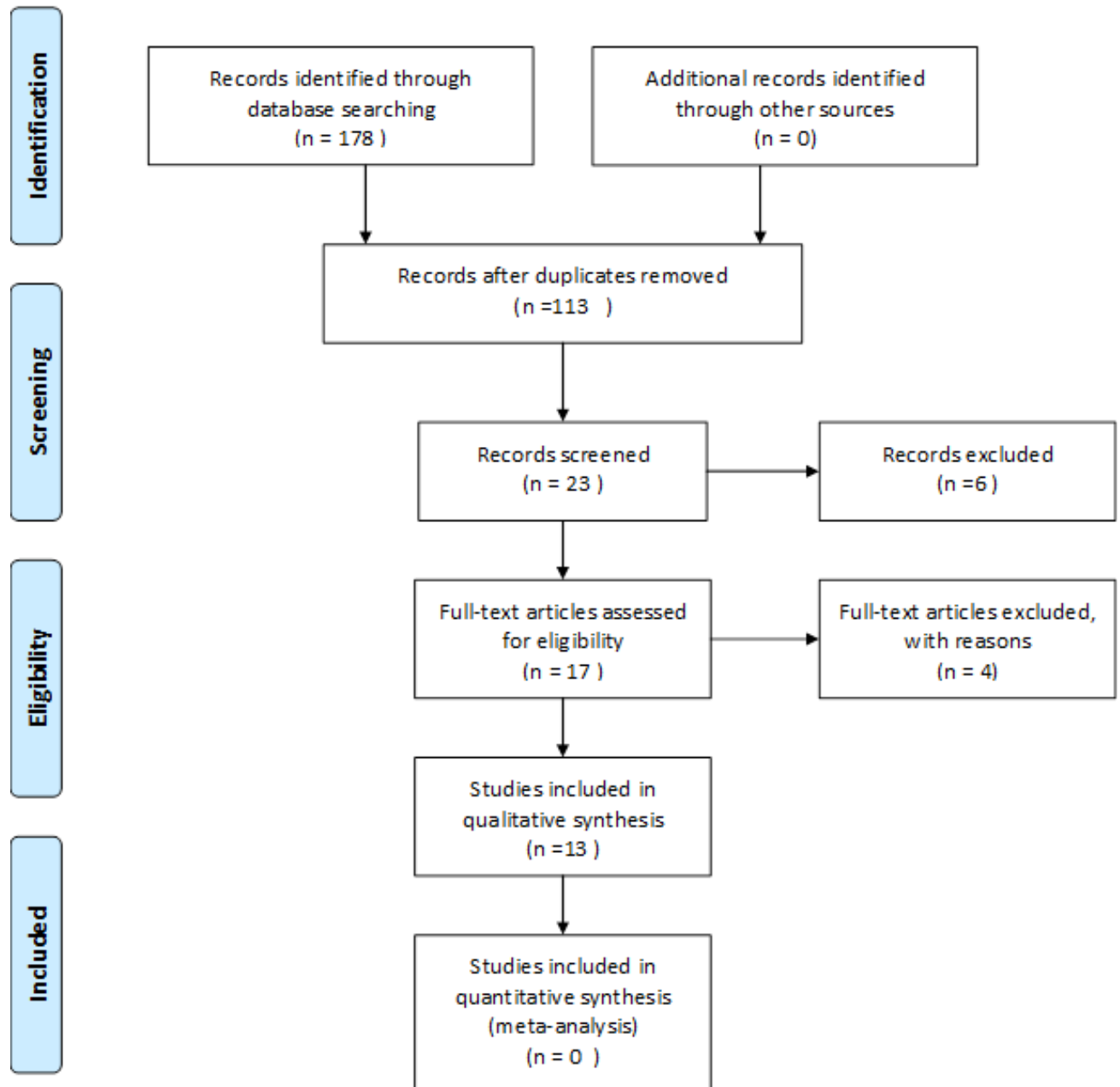
APPENDIX 2.3 NARRATIVE SYNTHESIS OF PUBLISHED STUDIES AND QUALITATIVE ASSESSMENT MATRIX

Year of Publication	Title	Author	Summary	Type of publication	Score
2008 Haemophilia. 2008. Sep; 14(5):923-30. EPub 2008 Jul 14.	The Use of Prophylaxis in 2663 Children and Adults with Haemophilia: Results of the 2006 Canadian National Haemophilia Prophylaxis Survey.	Biss TT, Chan AK, Blanchette VS, Iwenofu LN, Mclimont M, Carcao MD. Association of Haemophilia Clinic Directors of Canada (AHCDC); Canadian Association of Nurses In Haemophilia Care (CANHC).	Data on 2663 individuals (2161 haemophilia A; 502 haemophilia B), were returned by 22 /25 Canadian haemophilia treatment centres. Represented 98% of Canadian haemophilia population. Among individuals with severe HA, the frequency of prophylaxis use was 84% in children (</=18 years) and 55% in adults (>18 years). Prophylaxis is no longer confined to children with severe haemophilia A. Prophylaxis is being started earlier in boys with severe haemophilia A.	Observational Cross sectional	+
2002 Haemophilia. 8 (6) (pp 745-752)	Prophylactic versus on-demand treatment strategies for severe haemophilia: A comparison of costs and long-term outcome.	Fischer K., Van Der Bom J.G., Molho P., Negrier C., Mauser-Bunschoten P., Roosendaal G., De Kleijn P., Grobbee D.E., Van den Berg H.M.	49 Dutch patients with PP compared with 106 French patients OD. Median bleeds py PP 2,8 OD 11,5. Less arthropathy PP.	Observational Cohort	+
2002 Haemophilia. 8 (SUPPL. 2) (pp 38-42),	Results of an orthopaedic survey in young patients with severe haemophilia in Spain	Gorina E., Alberca I., Aznar J.A., Garcia Talavera J., Gutierrez R., Lucia F., Magallon M., Moreno M., Paloma I., Querol F., Quintana M., Rodriguez-Pinto C., Sedano C., Tusell J.M., Uranga M.	70 Spanish patients from 11 hospitals receiving OD or secondary prophylaxis. Mean age 21,6 y.o. Articular complaints in 84,3% to 85,7% of patients	Observational Cross sectional	+
2007 Haemophilia. 13(4):345-50	RCTs and observational studies to determine the effect of prophylaxis in severe haemophilia.	Fischer K. Grobbee DE. Van den Berg HM.	Several valid observational studies comparing prophylaxis and OD have reported both a short term reduction of 75%- 90% in bleeding frequency, and significant improvement in arthropathy, QoL and socio-economical parameters after more than 20 years of prophylaxis	Review article	0
2005 Haemophilia. 11(5):438-43	Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed.	Van Dijk K, Fischer K, Van der Bom JG, Grobbee DE, Van den Berg HM	171 severe HA patients. Age at first joint bleed 0,2 to 5,8 years. The onset of bleeding is inversely related with treatment requirement and arthropathy	Observational Cohort	++
2003 Haemophilia 9(4):376-81	Prophylaxis for severe haemophilia: clinical and economical issues.	Fischer K. Van Den Berg M.	3 cohorts of patients with severe HA were compared. 106 French OD, 49 Dutch intermediate dose PP and 24 Swedish high dose PP. PP reduced bleeds and arthropathy. For high dose PP the frequency of bleeds /year were 0,5. The cost of PP is twofold higher than OD.	Observational Cohort	+
2009 International Journal of Technology Assessment in Health Care, 25(4): p. 584-587.	Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran	Daliri AA, Haghparast H, and Mamikhani J.	A retrospective chart review of twenty-five type A haemophiliacs who were treated in three haemophilia treatment centres was conducted. Data were extracted during a period of approximately 6 months. The patients receiving prophylactic treatment had fewer bleeding events each month (mean, 0.26 versus 2.74) but used more concentrate (225.31 versus 87.20 units/kg per month). Average monthly cost per patient in the prophylaxis group was approximately 1.9 times higher than in the on-demand group. Compared with on-demand infusion, prophylaxis costs 3,201,656 Rials (euro213.45) per bleeding event prevented.	Observational Cross sectional Cost study	0

Year of Publication	Title	Author	Summary	Type of publication	Score
2012 Haemophilia 18(2):152-157	Health technology assessment and haemophilia.	Farrugia A, O'Mahony B, Cassar J.	In this review comments principles utilized in a recent systematic review of the use of haemophilia products carried out in Sweden as part of an HTA. Authors suggest that ranking haemophilia related interventions with the standard interventions of therapeutics and public health in CUA comparisons is inappropriate and suggest that haemophilia therapies should be assessed differently from mainstream interventions.	Review article	0
2013 Haemophilia. 18 (5) (pp 828-829).	Treatment for life for severe haemophilia A– A cost-utility model for prophylaxis vs. on-demand treatment.	Farrugia A., Cassar J., Kimber M.C., Bansal M., Balboni S.	A Markov model was applied to a single provider national health system exemplified by the United Kingdom's National Health Service and a third party provider in the United States. The incremental cost- effective ness ratio (ICER) was estimated and compared to threshold values used by payer agencies to guide reimbursement decisions. A cost per quality-adjusted life year (QALY) was also estimated for Sweden. Prophylaxis was dominant over OD treatment in the UK. The model resulted in an ICER – $68 000 –within the range of treatments reimbursed in the USA. In Sweden, a cost/QALY of SEK 1.1 million was also within the range of reimbursed treatments in that country. Dosage- and treatment-induced inhibitor incidence were the most important variables in the model. Subject to continuing clinical evidence of the effectiveness of pharmacokinetic dosage and the role of prophylaxis in decreasing inhibitor incidence, treatment for life with prophylaxis is a cost-effective therapy, using current criteria for the reimbursement of health care technologies in a number of countries.	Economic Evaluation CUA	++
2001 Haemophilia. 7(5):446-52	Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy.	Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G. Prejs R, Grobbee DE, Van den Berg HM.	Cohort of 214 patients with severe HA. Median follow up 17 years. Over 3 decades clotting factor consumption per Kg increased 260%. CF consumption stabilized in adulthood for those who received intensive treatment	Observational Cohort	++
2000 Haemophilia. (3):170-6.	The orthopaedic status of severe haemophiliacs in Spain	Aznar JA, Magallon M, Querol F, Gorina E, and Tusell JM.	Cross- sectional study aimed at assessing orthopaedic complications of young severe haemophiliacs (A and B). Eleven Spanish hospitals participated. 70 patients on- demand 348 bleeding episodes per patient year (mean 16,1)	Observational Cross sectional	+
2012 Indian Journal of Hematology and Blood Transfusion. November 2012.	The History and Evolution of the Clinical Effectiveness of Haemophilia Type A Treatment: A Systematic Review.	Castro HE, Briceño MF, Casas C and Rueda JD.	A systematic search of the literature aimed at assessing the evidence of different treatment options for haemophilia type A over the past four decades. The introduction of prophylactic schemes during the 1970s have proved to be more effective that the classic on-demand replacement of clotting factors, Main concerns for haemophilia healthcare are shifting from clinical aspects to the economic considerations of long-term replacement therapy.	Systematic review	+

Year of Publication	Title	Author	Summary	Type of publication	Score
2012 Haemophilia. 18 (5) (pp 738-742)	Is on-demand treatment effective in patients with severe haemophilia?	Aznar J.A., Marco A., Jimenez-Yuste V., Fernandez-Fontecha E., Perez R., Soto I., Parra R., Moreno M., Mingot M.E., Moret A.	167 patients from 37 centres (92% HA). OD and short term prophylaxis. 13% of biologically severe patients had no bleeding phenotype. OD therapy not effective in preventing arthropathy.	Observational Cross sectional	+
2012 Haemophilia. 18 (pp 143), 2012	Association of prophylaxis regimen with FVIII and treatment outcomes in Latin America patients with severe hemophilia A.	Perez Bianco P., Berges A., Soto V., Linares A., Krishnan S., Xiong Y., Aguilar L., Gomez J., Arvizu J., Brabata C	444 patients from Argentina, Chile, Colombia and Mexico. 53,4% patients OD. PP 68,7 % reduction in total number of bleeds, and 82,6% reduction in joint bleeds per year (p< 0.00001). Odds of having limited ROM 4.42 for OD vs. PP	Observational Cross sectional	+
2012 Haemophilia. 18 (pp 124-125).	Diagnostic, cross-sectional evaluation of joint status using magnetic resonance imaging in patients with severe hemophilia a: Biomarker analysis.	Oldenburg J., Zimmermann R., Katsarou O., Theodossiades G., Zanon E., Niemann B., Kellermann E., Lundin B.	Multiple schemes of prophylaxis and on-demand. MRI performed on 4 index joints (2 ankles and 2 knees). MRI vs physical examination (Gilbert score). MRI is highly sensitive to detect joint damage. Prophylaxis beneficial vs. OD.	Observational Cross sectional	+
2012 Haemophilia.). 18 (pp 25)	Regional differences in baseline patient-reported outcomes in a randomized, controlled, prospective trial of secondary prophylaxis VS on-demand treatment in patients with severe hemophilia A.	Kempton C., Valluri S., Reding M., Lissitchkov T., Goranov S., Gercheva L., Rusen L., Ghinea M., Uscatescu V., Rescia V., Hong W., Manco-Johnson M.	3 year RCT Argentina, Bulgaria, Romania and US. PRO EQ-5D, VAS, Hemo- QoL- A. 84 patients. US scores 0,84, non- US 0,78 EQ-5D (p< 0.04)and 0,81, non- US 0.68 VAS (p<0.001)	Interventional RCT	+
Biodrugs; 18 (4): 225-234	Present and Future.		Cryoprecipitate still the mainstay of therapy in many developing countries. Many patients were infected with hepatitis and/or HIV through the use of coagulation factor concentrates before the introduction of physical methods of viral inactivation in the mid-1980s. Coagulation factor concentrates are expensive, and cost-benefit and quality-of-life studies will assume an increasing importance in guiding the selection of products. Looking to the future, genetic engineering offers the potential to create coagulation factors with enhanced properties, such as reduced immunogenicity and prolonged half-life.	Review Article	0
2012 Haemophilia. 18 (3) (pp 369-374)	Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis.	Olivieri M., Kurnik K., Pfluger T., Bidlingmaier C.	Single- centre retrospective cohort study, MRI performed in symptomatic and asymptomatic ankles in haemophiliac A and B patients in prophylaxis. Since 2000, 38 MRIs performed in 26 patients. 5 of 26 patients worsened MRI findings without joint bleed. Early morphological changes in asymptomatic ankles detected with MRI in patients with prophylaxis.	Observational Cohort	+
2013 N Engl J Med. 368(3):231-9	PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A	Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, van Geet C, Kenet G, Mäkipernaa A, Molinari AC, Muntean W, Kobelt R,Rivard G, Santagostino E, Thomas A, van den Berg HM; .	Evaluated 574 patients with severe haemophilia A born between 2000 and 2010 and collected data on all clotting-factor administration for up to 75 exposure days. Inhibitory antibodies developed in 177 of the 574 children (cumulative incidence, 32.4%); 116 patients had a high-titre inhibitory antibody, defined as a peak titre of at least 5 Bethesda units per millilitre (cumulative incidence, 22.4%). Plasma-derived products conferred a risk of inhibitor development that was similar to the risk with recombinant products (adjusted hazard ratio as compared with recombinant products, 0.96; 95% confidence interval [CI], 0.62 to 1.49). Recombinant and plasma-derived factor VIII products conferred similar risks of inhibitor development.	Observational Cohort	+

Year of Publication	Title	Author	Summary	Type of publication	Score
2011 Cochrane database of systematic reviews (Online). 9 (pp CD003429)	Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B	Lorio A., Marchesini E., Marcucci M., Stobart K., Chan A.K.	SLR of six studies (142 participants). PP compared with OD. RR of 0,3 (95% CI; 0,12-0,76) for all bleedings and 0,22 (95% CI; 0,08-0,63) for joint bleeds favouring prophylaxis. Non-significant increases in both inhibitors and infectious complications OD vs. PP, except for PP when using long term venous access.	Systematic review	++
2011 Haemophilia. 17 (SUPPL. 2) (pp 1-23)	Joint protection in haemophilia.	Rodriguez-Merchan E.C., Jimenez-Yuste V., Aznar J.A., Hedner U., Knobe K., Lee C.A., Ljung R., Querol F., Santagostino E., Valentino L.A., Caffarini A.	Joint aspiration plays a roles in acute and profuse haemarthroses. Ultra-sonography is appropriate diagnostic technique to assess evolution of bleeding.	Review article	0
2011 ClinicoEconomics and Outcomes Research. 3 (1) (pp 55-61)	Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A.	Colombo G.L., di Matteo S., Elisa Mancuso M., Santagostino E.	CUA of hybrid prophylaxis, OD, PP and secondary prophylaxis. Showed that PP is cost-effective with and ICER €40.229 per QALY gained compared to OD, results sensitive to unit cost of FVIII, bleeding frequency, discounting rates.	Economic evaluation	+
2011 Arthritis & care.Vol 63 No 2. Pp 223- 30	Validation of the new pediatric joint scoring system from the international haemophilia prophylaxis study group: validity of the heamophilia joint health score.	Feldman B, Funk S, Bergstrom BM, Zourikian N, Hilliard P, Van der Net J, Engelbert R, Petrini P, Van der berg H, Manco M, Rivard G, Abad A	HJHS was developed to be more sensitive for detecting arthropathy than WFH. Validity compared in 226 boys with mild, moderate and severe haemophilia in 5 centres. HJHS is 97% more efficient than WFH at differentiating mild from moderate haemophilia, and 74% from differentiated those OD vs. prophylaxis. Both HJHS and WFH showed strong construct validity. HJHS more sensitive for mild arthropathy	Diagnostics	++
2011 Journal of Thrombosis and Haemostasis. 9 (pp 694	Mild vs. severe haemophilia A: The dilemma of an underestimated disease	Bidlingmaier C., Knorr S., Olivieri M., Kurnik K.	42 mild and moderate patients with haemophilia compared to 46 birth matched severe patients. Reasons for diagnosis bleeding vs. family history	Observational Cross sectional	+
2011 Journal of Thrombosis and Haemostasis. 9 (pp 373)	Subgroup analyses of annualized number of bleeds with three-times-per-week prophylaxis with rFVIII-FS.	Lalezari S., Coppola A., Lin J., Enriquez M.M.	LIPLONG study, RCT, randomized, double blind, non-inferiority of 52 wks. Compared prophylaxis 1 x wk vs. 3 times x wk previously treated patients. Number of bleeds per year prophylaxis 1,4 (CI 0- 20,9) p= 0,6152. Number bleeds and presence of target joints determined rate of response to prophylaxis.	Interventional RCT	++
2011 Haemophilia. 17 (2) (pp 360).	The Russian children study: A prospective study to evaluate the effect of rFVIII-fs in different prophylactic regimens on frequency of bleeding events and development of arthropathy in a previously treated and minimally treated haemophilia A paediatric population.	Vdovin V.V., Andreeva T.A., Chernova T.A., Perina F.G., Maasenriquez M., Rauchensteiner S. Haemophilia.	Non randomized open- label study evaluated 3 different prophylactic regimes: 70 IU 1x w/ 30+ 40 IU x w/ 25 IU 3x w. Joint bleeds, all bleeds, joint status in 32 paediatric patients. Median number of bleeds per year ranged 1,5- 3. #x w prophylaxis safely and effectively decreases overall bleedings and prevents subsequent joint damage.	Interventional non-randomized	+

Year of Publication	Title	Author	Summary	Type of publication	Score
2010 Journal of Rheumatology and Medical Rehabilitation. 21 (2) (pp 29-36)	Outcome of joint functions in hemophilic patients: A twelve year retrospective study.	Capaci K., Balkan C., Yilmaz D., Yilmaz A.Y., Kirazli Y., Durmaz B., Kavakli K.	31 patients after 12 year follow up. Gilbert score was used to assess joint status. Grouped by severity of disease. Joint assessment results in patients with severe haemophilia that received prophylaxis were almost as good as those of mild cases. (p< 0,05)	Observational Cohort	+
2010 Haemophilia; 16: 256–62	New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development.	Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G..	The highest risk of developing inhibitors is during the first 20 exposure days (EDs). Developed a prophylaxis regimen for the first 20-50 EDs specifically designed to induce tolerance to the administered FVIII and to minimize inhibitor development by avoiding immunological danger signals. Twenty-six consecutive previously untreated patients (PUPs) with severe haemophilia A were treated with the new prophylaxis regimen and the incidence of inhibitor development in this group was compared with that in a historical control group of 30 consecutive PUPs treated with a standard joint protection prophylaxis regimen (40-50 IU kg(-1), three times a week). There were no significant differences between the study and control groups. Our results indicate that minimizing danger signals during the first 20 EDs with FVIII may reduce the risk of inhibitor formation. These results should be confirmed in a larger prospective clinical study.	Observational Cohort	+
2010 Haemophilia. 16 (3) (pp 479-486), 2010	Utility of the Haemophilia Joint Health Score in study of episodically treated boys with severe haemophilia A and B in Lithuania.	Saulyte Trakymiene S., Ingerslev J., Rageliene L.	Lithuanian patients 4- 17 years with SH A and B, no inhibitors and OD. Grouped by age HJHS, most affected joints ankles. HJHS useful in evaluating musculoskeletal outcome in patients OD	Observational Cohort	+
2010 Value in Health. 13 (3 SUPPL. 3) (pp A216).	US cost effectiveness analysis of primary prophylaxis versus on-demand treatment in hemophilia: Design and rationale of a comprehensive model.	Boer R., Lalla A., Mathew P., Preblick R., Pocoski J.	Lifetime Markov model compared PP vs. OD, took into account the probability of inhibitor development, use of central catheter, and total bleeding risk. Prophylaxis assumed to be from birth to 16 years of age. ICER results not available	Economic evaluation Gray literature	0
2009 Hamostaseologie. 29 Suppl 1 (pp S77-79),	Cross sectional study to investigate the influence of treatment regimens on the development of haemophilic arthropathy	Hilberg T., Czepa D	Only a small amount and a short exposure to blood in vitro are able to induce impairment of joint cartilage. Bone and cartilage damage are induce by macrophages and monocytes, cytokines and inflammatory processes, at worst H arthropathy occurs reducing QoL. No consensus on treatment of adult population	Observational Cross sectional	+
2009 Haemophilia 15.6: 1219-27	Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens.	Berntorp, E.	Early evidence from Sweden suggested that prophylaxis improved patient outcomes, this has been proven by recent RCTs. This applies for HA and HB. Barriers to prophylaxis: cost, venous access difficulties, time required for infusions	Review article	0
2005 Coagulation and Fibrinolysis, 16(7): p. 477-485	Cost effectiveness of haemophilia treatment: A cross-national assessment.	Lippert, B., Berger, K., Berntorp, E., Giangrande, P., Van Den Berg, M., Schramm, W. and Siebert, U. Blood	The aim was to assess the ICER of on-demand versus prophylactic haemophilia therapy in Germany, Sweden, the United Kingdom and The Netherlands from the third-party payers' perspective. Using a decision tree model, based on decision analysis, the use of prophylactic treatment was overall more effective than on-demand therapy in young haemophiliacs, but at extremely high cost.	Economic Evaluation	+

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2007 Br J Haematology; 138: 580–6.	The Risk Associated With Indwelling Catheters In Children With Haemophilia. .	Ljung R.	Infections most frequent complication of use of CVL in haemophiliac patients. 0,2- 0,3 infections per 1000 catheter days, some other studies 1- 2/ 1000 CD. Despite risks are useful.	Review article	0
2002 PharmacoEconomics; 20 (11) (pp 759-774).	Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia.	Miners A, Sabin C, Tolley K, Lee C.	CUA analysis with primary data and modelling. Societal perspective, lifetime horizon. Primary prophylaxis ICER £46.500 per QALY gained	Economic Evaluation CUA	+
2009 Journal of Thrombosis and Haemostasis. 7 (S2) (pp 1124)	Impact of FVIII product change in severe haemophilia A patients previously treated with plasma-derived FVIII.	Mingot M.E., Heiniger A.I., Garcia M., Fernandez J.A.	22 HA patients treated with pdFVIII switched to another pdFVIII or rFVIII. Median follow up of 31 +/- 9 months. Both pdFVIII and rFVIII are safe and effective products, similar recoveries and no adverse events.	Observational Cohort	+
2013 Haemophilia. 19(2):174-180,	Economic evaluations of prophylaxis with clotting factor for people with severe haemophilia: why do the results vary so much?	Miners A H.	Review of literature, 11 economic evaluations identified. ICERs reported ranging from prophylaxis being cost saving to over € 1 million per QALY gained. Differences in structural design as well as parametric variability explain reasons. Concerns about appropriate methodology.	Review article	0
2008 Blood Transfusion. 6 (SUPPL. 2) (pp s4-s11),	Primary prophylaxis in children with haemophilia.	Coppola A., Di Capua M., De Simone C.	This review summarizes available data from which current clinical practice of primary (and early secondary) prophylaxis in children with severe haemophilia was drawn. Observational studies clearly established the superiority of prophylaxis over on-demand treatment in reducing the risk of arthropathy, also showing that starting prophylaxis earlier in life and after very few joint bleeds was associated with better joint outcomes, and led to the current definitions of primary (started before the age of 2 yrs and after no more than one joint bleed) and secondary prophylaxis. More recently, evidences from randomized trials, which were previously lacking in this setting, were also provided.	Review article	0
2008 Haemophilia. 14 (4) (pp 743-752), 2008	Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A.	Risebrough N., Oh P., Blanchette V., Curtin J., Hitzler J., Feldman B.M.	From a societal perspective, this study compared the incremental cost per joint-haemorrhage that is avoided and quality-adjusted-life-year (QALY) gained of SP and EscDose to on-demand (Demand) therapy in severe haemophilia A boys treated to age 6 using a decision analytic model. Costs included factor VIII (FVIII), professional visits and tests, central venous placement/complications, hospitalization, home programmes and parents' lost work-days. Resource utilization was estimated by surveying 17 Canadian clinics. The natural history of bleeding and other probabilities were determined from a longitudinal chart review (n = 24) and published literature. EscDose costs an additional $3192 per joint-haemorrhage that was avoided compared with Demand whereas SP costs an additional $9046 per joint-haemorrhage that was avoided compared with EscDose. Clinic costs and lost wages were reduced by 60-80% for EscDose and SP compared with Demand. EscDose attained more QALYs than SP and Demand on account of less bleeding than Demand and lower need for ports than SP. The incremental cost per QALY for EscDose vs. Demand was $542938. EscDose was less expensive with similar QALYs compared to SP. Sensitivity analysis showed the model was sensitive to the cost of FVIII and the SP and target joint utilities. In conclusion, prophylaxis will substantially improve clinical outcomes and quality of life compared to Demand treatment, but with substantial cost	Economic evaluation CUA	++

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1992 Journal of Internal Medicine, 232(1): p. 25-32.	Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B.	Nilsson M, Berntorp E, Lofqvist T, and Pettersson H.	Population consisted of 60 severe haemophiliacs (52 A, 8 B), aged 3–32 years. Treatment is started when the boys are 1–2 years of age, the regimens used being 24–40 IU F VIII kg^{-1} three times weekly in haemophilia-A cases (i.e. > 2000 IU kg^{-1} annually) and 25–40 IU F IX kg^{-1} twice weekly in haemophilia-B cases. The orthopaedic and radiological joint scores (maximum scores of 90 and 78, respectively) are evaluated as recommended by the World Federation of Haemophilia. Of those subjects aged 3–17 years, 29 out of 35 individuals had joint scores of zero. The oldest group had only minor joint defects. The VIII:C and IX:C concentrations had usually not fallen below 1% of normal. All 60 patients are able to lead normal lives. In conclusion, it appears to be possible to prevent haemophilic arthropathy by giving effective continuous prophylaxis from an early age, and preventing the VIII:C or IX:C concentration from falling below 1% of normal.	Observational Cohort	++
2008 Haemophilia. 14 (SUPPL. 3) (pp 196-201)	Prophylaxis for severe haemophilia: Clinical challenges in the absence as well as in the presence of inhibitors.	Fischer K., Valentino L., Ljung R., Blanchette V.	Extensive data from observational studies and a recent randomized controlled trial (have established that early prophylactic treatment prevents bleeds and arthropathy in boys with severe haemophilia. The initiation of prophylaxis in young children remains challenging. To prevent arthropathy, prophylaxis should be started early, before the onset of joint damage. Alternative strategies of starting include starting before the age of 2 years, or starting before the third joint bleed. Dose and frequency vary between the original Swedish regime of 20-40 IU kg(-1) three times per week and lower dosed and step up regimes starting with 50 IU kg(-1) once weekly and rapidly increasing dose and frequency in case of bleeds. The third decade of life often represents a change in lifestyle. Patients may get a job and periods of physical activity may be more confined. About two thirds of patients experiment with discontinuing prophylaxis in their early twenties, and 20-30% with mild bleeding patterns switch to on-demand treatment for prolonged periods or	Review article	0
2011 Haemophilia, 1-2	A survey of the outcome of prophylaxis, on-demand or combined treatment in 20-35 year old men with severe haemophilia in four European countries.	Noone D, Mahony O and Prihodova L.	This study was carried out to examine the long-term effects of prophylaxis and the continuing benefit of the therapy in adulthood. National Haemophilia patient organizations in Ireland, UK, France and Sweden were asked to participate by randomly selecting 20 severe haemophilia patients between 20 and 35 years from their database. Overall, on-demand treatment results in a lower utility value in relation to quality-of-life for people with severe haemophilia. Prophylaxis started at an early age and continued into adulthood results in less bleeding, less damage to joints and less time missed at work. Prophylaxis increases mobility and the ability to do everyday activities and improves the health-related quality of life of people with severe haemophilia.	Observational Cross sectional	+

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1996. Journal of Pediatrics, 129(3): p. 424-431	Episodic versus prophylactic infusions for hemophilia A: a cost-effectiveness analysis.	Smith, P.S., Teutsch, S.M., Shaffer, P.A., Rolka, H. and Evatt, B.	A random sample of patients from 11 haemophilia treatment centres receiving episodic care and prophylactic care were included in the study. The final sample size comprised 117 boys. Of these, 90 were treated episodically (control) and 27 prophylactically (intervention). No power calculations were undertaken to determine an appropriate sample size. A model was used to estimate both costs and benefits. The model comprised three hypothetical cohorts of patients (aged 3 to 50 years) who were receiving either episodic or one of two types of prophylactic treatment. In the first model of prophylaxis, treatment begins at the age of three (when regular bleeding usually begins) and continues until the age of 50. In the second model, prophylaxis is administered from the age of three to 20 years only (when the frequency of regular bleeding begins to decline). The total direct medical costs to treat prophylactically were increased approximately threefold, from $23,435 to $75,574 (p<0.005).	Economic evaluation CEA	0
2004. Haemophilia, 10(5): p. 527-541	Willingness to pay for on-demand and prophylactic treatment for severe haemophilia in Sweden.	Steen Carlsson, K, Höjgård, S, Lethagen, S, Lindgren, A, Berntorp, E, Lindgren, B.	CBA compered prophylaxis with on-demand used primary data time horizon 1 year. Greater expected net benefit with prophylaxis than with on-demand	Economic evaluation CBA	+
2005 Polskie archiwum medycyny wewntrznej. 113 (6) (pp 562-569)	The orthopaedic status of a selected severe haemophilia group.	Windyga J., Stefanska E., Lopaciuk S., Juszynski A., Wozniak D., Strzelecki O.	Study aimed at describing the orthopaedic status of patients with severe haemophilia, regarding the type of replacement therapy received by patients prior to the study. 92 haemophiliacs with median age 26 were included. Six joints--knees, elbows and ankles were evaluated clinically using the Gilbert scale. Knees were the most affected joints. 84 patients (91.3%) reported pain. 37 % of patients used orthopaedic equipment occasionally or constantly. 25 % of patients had a history of orthopaedic surgery. 38% were unemployed and received some form of social subvention. On demand treatment was applied. None of the patients received primary prophylaxis. The mean consumption of clotting factor concentrates was 68,054 IU per patient during the 12 months period prior to the current study. The results of this study indicate that vast majority of severe haemophilia patients in Poland above 20 are affected by haemophilic arthropathy.	Observational Cross sectional	+
2003 Haemophilia. 9 (SUPPL. 1) (pp 27-31)	Comparing outcomes of different treatment regimens for severe haemophilia.	Van Den Berg H.M., Fischer K., Van Der Bom J.G.	Published retrospective reports from France, the Netherlands and Sweden were analysed for data relating to the long-term outcomes (primarily the development of arthropathy) of three regimens for the management of severe haemophilia: on-demand treatment, intermediate-dose prophylaxis and high-dose prophylaxis. These data indicate that both prophylaxis regimens resulted in significantly improved long-term outcomes, as assessed by pain, clinical and radiological assessment scores. At the same time, the most recently reported annual factor consumption levels of these young adult patients are comparable in the on-demand and intermediate-dose prophylaxis cohorts, suggesting that the improvement in long-term clinical outcomes and reduced risk of arthropathy may lead to reduced factor consumption in adult patients who received early prophylactic therapy.	Observational Cross sectional	0

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2002 Current Opinion in Pediatrics. 14 (1) (pp 46-49)	Current treatment of hemophilic arthropathy.	Hilgartner M.W.	Regular infusions of recombinant factor or treated plasma derived factor given prophylactically to prevent spontaneous bleeding are recommended for all children to maintain a plasma factor level of >1%. Recombinant factor product or treated plasma derived product should be used. Prophylaxis should begin when bleeding occurs repeatedly and is superior to on-demand therapy. Hypertrophied synovium should be removed surgically or with a sclerosing agent, either radioactive or chemical material, to impede further cartilaginous and bony deterioration. Arthroplasty of the knee and hip have been successful in reducing pain and loss of motion when other efforts to control synovial hypertrophy fail	Review article	0
2009 Haemophilia 15.4: 881-87	Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A.	Miners, A.	A 2002 evaluation of primary prophylaxis suggested an ICER of approximately £50,000 per additional (QALY). The primary aims of this study were to update a previously published cost-effectiveness analysis of primary prophylaxis vs. treating on-demand in terms of methods and to estimate the value of undertaking further primary research. The base case incremental cost-effectiveness ratio was shown to be approximately 37,000 pounds, 10,000 pounds lower than the value published in 2002. The main reason for this difference was the use of different structural assumptions and methods to fit the various model parameters. At a WTP per additional QALY threshold of 30,000 pounds, the probability prophylaxis is cost-effective was 13%. However, this increased to over 90% when alternative structural assumptions were employed, such as the rate at which future QALYs are discounted. There is considerable value in conducting further primary research related to economic aspects of primary prophylaxis.	Economic evaluation CUA	++
2007 Haemophilia 13 Supplement 2: 16-22.	Identifying and overcoming barriers to prophylaxis in the management of haemophilia.	Petrini, P.	Current treatment for patients with severe haemophilia involves clotting factor replacement given on demand or through long-term prophylaxis. Although prophylaxis has many advantages, its practice varies widely even among developed countries because of several barriers. Such barriers include CFC costs and availability; patient perceptions, lifestyles and bleeding patterns; difficulties and complications arising from the use of intravenous access devices (IVADs); the development of inhibitors; and the lack of randomized clinical trials. These barriers can be overcome by tailoring treatment regimens according to individual patient bleeding patterns and CFC pharmacokinetic profiles, using IVADs selectively and judiciously, helping patients maintain normal weight and physical exercise and providing the families of patients with continuous support from healthcare providers.	Review article	+
2007 Haemophilia 13.3: 227-32	Prophylaxis in the haemophilia population-optimizing therapy.	Carcao, M. D., L. M. Aledort, The Round Table Group.	A one day meeting report held by Dr Aledort in 2005. The meeting brought together unsolved issues about prophylaxis and affordability. Meeting attendees tackled these issues, as well as the socio- economic challenges of implementing prophylaxis	Review article	0

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2002 Haemophilia 8.1: 44-50.	Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients.	Royal, S., Schramm, W, Bertntorp, E, Giagrande, A, Gringeri, Gringeri, A, Ludlam, C, Kronker, B, Szucs, T.	The European Study on the Clinical Outcomes and Resource Utilization associated with Haemophilia Care was designed to compare various health outcomes associated with on-demand and prophylactic factor substitution. A total of 1033 haemophilia patients from 16 European haemophilia treatment centres were enrolled in this study. The SF-36, a multidimensional quality-of-life instrument, was administered to all participants. All haemophilia subjects enrolled in the study scored significantly lower than the population normative means in the three physical dimensions and in the general health dimension. Univariate indicated that patients treated prophylactically reported significantly less bodily pain, better general health, and scored significantly higher in the physical functioning, mental health, and social functioning dimensions. While these results suggest that health-related quality-of-life may be better for haemophilia patients treated prophylactically, future prospective studies that gather periodic quality-of-life data over time should be conducted.	Observational Cross sectional	+
2006 J Thromb Haemost; 4: 1228–36.	Tailored Prophylaxis In Severe Haemophilia A: Interim Results From The First 5 Years Of The Canadian Haemophilia Primary Prophylaxis Study.	Feldman BM, Pai M, Rivard GE Et Al.	Prophylactic treatment for severe haemophilia A is likely to be more effective than treatment when bleeding occurs, however, prophylaxis is costly. Study of inception cohort of 25 boys using a tailored prophylaxis approach to see if clotting factor use could be reduced with acceptable outcomes. 10 Canadian centres enrolled subjects, children were followed every 3 months. Initially treated with once-weekly clotting factor; the frequency was escalated in a stepwise fashion if unacceptable bleeding occurred. Bleeding frequency, target joint development, physiotherapy and radiographic outcomes, as well as resource utilization, determined prospectively. The median follow-up time was 4.1 years (total 96.9 person-years). The median time to escalate to twice-weekly therapy was 3.42 years (lower 95% confidence limit 2.05 years). Nine subjects developed target joints at a rate of 0.09 per person-year. There was an average of 1.2 joint bleeds per person-year. The cohort consumed on average 3656 IU $kg^{-1}year^{-1}$ of factor (F) VIII. Ten subjects required central venous catheters	Observational Cohort	++
2010 Haemophilia Mar;16 Suppl 2:4-9.:4-9.	Devising a best practice approach to prophylaxis in boys with severe haemophilia: evaluation of current treatment strategies.	Carcao M, Chambost H, Ljung R.	Data from prospective studies clearly demonstrate the efficacy of prophylactic treatment of haemophilia in reducing joint- or life-threatening bleeding and the associated consequences for quality of life. Debate remains, however, regarding the optimal implementation of prophylaxis. The aim in this review was to identify a best practice approach to factor replacement prophylaxis in boys with haemophilia. Evaluated prophylactic treatment regimens currently used in Swedish, Canadian and French centres and highlight key issues, including the optimal age for starting prophylaxis, the optimal treatment dosage/schedule and patient compliance.	Review article	0

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2003 Haemophilia. 9 (Suppl. 1) (pp 1-4)	Consensus perspectives on prophylactic therapy for haemophilia: summary statement.	Berntorp E, Astermark J., Bjorkman S., Blanchette VS, Fischer K, Giangrande PLF, Gringeri A, Ljung R., Manco-Johnson MJ, Morfini M, Kilcoyne RF, Petrini P, Rodriguez- Merchan EC, Schramm W, Shapiro A, Van De Berg HM and Hart C.	Participants in an international conference on prophylactic therapy for severe haemophilia developed a consensus summary of the findings and conclusions of the conference. In the consensus, participants agreed upon revised definitions for primary and secondary prophylaxis and also made recommendations concerning the need for an international system of pharmacovigilance. Considerations on starting prophylaxis, monitoring outcomes, and individualizing treatment regimens were discussed. Several research questions were identified as needing further investigation, including when to start and when to stop prophylaxis, optimal dosing and dose interval, and methods for assessment of long-term treatment effects. Such studies should include carefully defined cohorts, validated orthopaedic and quality-of-life assessment instruments, and cost-benefit analyses.	Review article	0
2007 Blood. (110) (pp 815- 825),	Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV.	Darby SC, Kan SW, Spooner RJ, Giangrande PLF, Hill F, Hay C, Lee CA, Ludlam and Williams M.	Since the 1970s, mortality in the haemophilia population has been dominated by HIV and few reports have described mortality in un-infected individuals. This study presents mortality in 6018 people with haemophilia A or B in the United Kingdom during 1977 to 1998 who were not infected with HIV, with follow-up until January 1, 2000. All-cause mortality did not differ significantly between haemophilia A and B. In severe haemophilia, all-cause mortality did not change significantly during 1977 to 1999. During this period, it exceeded mortality in the general population by a factor of 2.69 (95% [CI]: 2.37-3.05), and median life expectancy in severe haemophilia was 63 years. In moderate/mild haemophilia, all-cause mortality did not change significantly during 1985 to 1999, and median life expectancy was 75 years. Compared with mortality in the general population, mortality from bleeding and its consequences, and from liver diseases and Hodgkin disease, was increased, but for ischemic heart disease it was lower, at only 62% (95% CI: 51%-76%) of general population rates, and for 14 other specific causes it did not differ significantly from general population rates. There was no evidence of any death from variant Creutzfeldt-Jakob disease or from conditions that could be confused with it.	Observational Cohort	++

Year of Publication	Title	Author	Summary	Type of publication	Score
2007 New England Journal of Medicine. 357 (vol 6) (pp. 535-544).	Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia.	Manco- Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker M, Kilkoyne R, Ingram D, Manco-Johnson ML , Funk S, Jacobson L, Valentino LA, Hoots K, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P, Matsunga A, MAdeiros D, Nugent D, Thomas G, Thompson A, McRedmond K, Soucie M and Austin H	This study randomly assigned young boys with severe haemophilia A to regular infusions of rFVIII (prophylaxis) or to an enhanced episodic infusion schedule of at least three doses totalling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint haemorrhage. The primary outcome was the incidence of bone or cartilage damage as detected in index joints (ankles, knees, and elbows) by radiography or magnetic resonance imaging (MRI). Sixty-five boys < 30 mo of age were randomly assigned to prophylaxis (32 boys) or enhanced episodic therapy (33 boys). When the boys reached 6 years of age, 93% of those in the prophylaxis group and 55% of those in the episodic-therapy group were considered to have normal index-joint structure on MRI (P = 0.006). The RR of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% confidence interval, 1.5 to 24.4). Mean annual numbers of joint and total haemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group (P<0.001 for both comparisons). High titres of inhibitors of factor VIII developed in 2 boys who received prophylaxis; 3 boys in the episodic-therapy group had a life-threatening haemorrhage. Hospitalizations and infections associated with central-catheter placement did not differ significantly between the two groups. Prophylaxis with rFVIII can prevent joint damage and decrease frequency of joint and other haemorrhages in young boys with severe haemophilia A.	Interventional RCT	++

Author	Country	Treatments	Price Year	Type of evaluation	Perspective	Time Horizon	Utility OD	Utility Proph.	Discount Rates	Cost FVIII per IU	Summary of base case results
Smith 1996	USA	2⁰ proph (?) vs OD	N/S	CEA, primary data and modelling	Societal	Up to 50 years	N/A	N/A	Costs 5% Benefits 0%	$0.53	$1,100-1,380 per bleed averted
Szucs, 1996	Europe	2⁰ proph (?) vs OD	N/S	CEA, primary data	Societal	1 year	N/A	N/A	N/A	N/S	DM 2,536 per averted joint bleed
Bohn, 1998	US, Japan, Europe	1⁰ and 2⁰ proph (?) vs OD	1992 (?)	CMA, primary data	Societal	?	N/A	N/A	N/S	N/S	USD30,800 PPY OD, 79,600 PPY partial prophylaxis; 87,900 full time prophylaxis
Miners, 1998	UK	2⁰ proph vs OD	N/S	CEA, primary data	Health care (clotting factor only)	9 years	N/A	N/A	Costs 6% Benefits 0%	N/S	£547 per bleed averted
Miners, 2002	UK	1⁰ proph vs OD	2002	CUA, primary data and modelling	Societal	Lifetime	0.66	0.87	Costs 6% Benefits 1.5%	£0.325	£46,500 per QALY gained
Steen Carlsson, 2004	Sweden	Proph vs OD	2002	CBA, primary data	Societal (?)	1 year (?)	N/A	N/A	N/A	€0.59	OD and prophylaxis produce +net benefits. Greater expected net benefit with prophylaxis than OD
Lippert, 2005	Europe	2⁰ proph (?) vs OD	N/S	CUA, primary data and modelling	Health care	1 year	0.73	0.77	N/A	€0.7-0.9	Results range from OD being dominant to >€1 million per additional QALY for prophylaxis
Risebrough, 2008	Canada	1⁰ proph (2 different dosing schedules) vs OD*	2008	CUA, primary data and modelling	Societal	5 years	0.905	0.95	Costs 3% QALYs 3%	CAN $1.38	EscDose vs OD demand $543,00 per QALY gained; Prophylaxis vs. EscDose >$1m per QALY gained
Miners, 2009	UK	1⁰ proph vs OD	2009	CUA, primary data and modelling	Health care	Lifetime	0.50	0.71	Costs 3.5% QALYs 3.5%	£0.325	£38,500 per QALY gained
Daliri, 2009	Iran	Prophylaxis for at least 6 months vs OD	2008 Rials	CEA, primary data	Health care (clotting factor only)	6 months	N/A	N/A	N/A	N/S	3,201,656 Rials per bleed avoided (approximately €220)
Boer, 2010	USA	Prophylaxis from birth until 16 years of age vs OD	N/S	CEA, secondary data and modelling	Health care?	Lifetime	N/A	N/A	N/A	N/S	Study aimed at modelling, grey literature. Limitations related to the lack of data for model assumptions.
Colombo, 2011	Italy	OD, hybrid*, 1⁰ proph and 2⁰ proph	N/S	CUA	Health care	Lifetime	0.66	0.87	Costs 6% QALYs 6% ?	€0.68	Per QALY gained compared with OD; 10 proph €40,236; 20 proph €40,229, hybrid €119,134
Farrugia, 2013	USA, Australia, Europe	1⁰ proph vs OD for severe HA and inhibitor formation	2013	CUA, secondary data and modelling	Health care (considered also treatment of inhibitors)	Lifetime	0.67	0.67 Sweden and 0.938 USA and UK	Costs 3,5% QALYs 1,5%	USA $ 1.00; Swe SEK 6.15; UK £ 0.35	PP was dominant over OD treatment in the UK. ICER of USD$68 000 per QALY gained –within the range of treatments reimbursed- in the USA. In Sweden, a Cost/QALY of SEK 1.1 million, also within the range of reimbursed treatments in that country.

Adapted from: Miners A, 2013 *Haemophilia*. 19(2):174-180, 2013.

APPENDIX 3. FULL TABLE OF ESTIMATED COSTS, UNITS, ASSOCIATED PROBABILITIES, FREQUENCY WEIGHTS AND SOURCES OF DATA

	Name	Description	Source	Root Definition
	p_articular_bleeding	Probability of having an articular bleeding	Stachnik, 2010, Wong, 2011; Vdovin, et al, 2011 and Kempton et al, 2012	0.8
	p_extrarticular_bleeding	Probability of extrarticular bleeding	Stachnik, 2010, Wong, 2011; Vdovin, et al, 2011 and Kempton et al, 2012	1-p_articular_bleeding
	p_die_bleeding	Probability to die from bleeding of any type	Darby et al, 2007	0,00525
V	p_develop_arthropahty_prophylaxis	Probability to develop arthropathy with primary prophylaxis	Manco-Johnson et al, 2007	0,0188
A	p_develop_arthropathy_on_demand	Probability to develop arthropathy on demand	Manco-Johnson et al, 2007	0,145
R	p_central_catheter_PP	Probability of needing a central catheter for on demand	Manco-Johnson et al, 2007	0.5659
I	p_central_catheter_OD	Probability of needing a central catheter for prophylaxis	Manco-Johnson et al, 2007	0.3420
A	p_infection_from_central_venous_access	Probability of infection from central venous access	Manco-Johnson et al, 2007	0,0615
B	p_major_orthopaedic_surgery_OD	Plobability of major orthopaedic surgery per year on-demand	Smith et al, 1996	0,0307
L	U_alive_no_arthropathy_PP	Utility of alive without arthropathy under primary prophylaxys	Secondary local source 31 patients	0.937
E	U_alive_with_arthropathy_PP	Utility of alive with arthropathy under primary prophylaxis	Secondary local source 31 patients	0.739
S	U_alive_no_arthropathy_on_demand	Utility of alive without arthropathy on demand	Secondary local source 31 patients	0.937
	U_alive_with_arthropathy_on_demand	Utility of alive with arthropathy on demand	Secondary local source 31 patients	0.739
	Dosage_PP_per_Kg_year	Dosage per Kg per year PP	Manco-Johnson et al, 2007	3450
C	Dosage_perKg_OD_joint_bleed	Dosage per Kg per joint bleeding episode OD	Manco-Johnson et al, 2007 modified	200
O	Dosage_perKg_PP_any_bleed	Dosage per Kg infuse on PP when joint bleed	Manco-Johnson et al, 2007	40
S	Dosage_perKg_OD_any_other_bleed	Dosage per Kg OD any other bleeding	Smith et al, 1996 & Mannucci et al, 2009	100
T	Number_bleeding_episodes_py_OD	Number of all bleeds On-demand	Manco-Johnson et al, 2007	17
S	Number_bleeding_episodes_py_PP	Number of all bleeding episodes per year Primary prophylaxi	Manco-Johnson et al, 2007	3
	Discount_costs	Discounting rates costs	NICE Guidance 2011 & Farruigia et al, 2013	0.035
	Discount_effects	Discounting rate effects	NICE Guidance 2011 & Farruigia et al, 2013	0.015
	_Stage	Number of cycles-Life expectancy of severe haemophilics 60	Darby et al, 2007, Larsson 1985	70
	WeightP50_stage	Table of weights boys 50 percentile	Center for Disease Control- CDC, 2000	Age specific

	Name	Source	Unit Cost COL$2013	Total Units	Frequency py	Total Costs py COL$2013
	c_rFVIII	Local market reference, payers perspective	$ 1.450,00	3450 IU/Kg 46 wks	1	$ 5.002.500,00
	c_FVIII	Local market reference, payers perspective	$ 900,00	3450 IU/Kg 46 wks	1	$ 3.105.000,00
	c_General_practitioner's_visit_PP	Local experts; Tariff manual ISS 2001 +30%	$ 20.000,00	12	1	$ 240.000,00
	c_General_practitioner's_visit_per_bleeding	Local experts; Tariff manual ISS 2001 +30%	$ 20.000,00	2	1	$ 40.000,00
	c_Haemoatologist_visits_PP	Manco-Johnson et al, 2007, ISS 2001 Purchasing manual + 30%	$ 120.000,00	4	1	$ 480.000,00
	c_Haemoatologist_visits_OD	Aznar et al, 2000; Local experts; Tariff manual ISS 2001 +30%	$ 120.000,00	9	1	$ 1.080.000,00
C	c_Orthopedist_visits_PP	Rodriguez et al, 2011; Capaci et al, 2010, Local experts; Tariff manual ISS 2001 +30%	$ 47.500,00	2	0,5659	$ 95.000,00
O	c_Orthopaedist_visits_OD	Aznar et al, 2000; Local experts; Tariff manual ISS 2001 +30%	$ 47.500,00	2,5	0,342	$ 118.750,00
S	c_Central_venous_catheter_PP_per_year	Coppola et al, 2008; Gringeri et al, 2009; Manco-Johnson et al 2007 adapted; Tariff manual ISS 2001 + 30%	$ 1.502.681,00	1	0,5659	$ 850.367,18
T	c_Central_venous_catheter_OD_per_year	Manco-Johnson et al 2007 adapted; local experts; Tariff manual ISS 2001 + 30%	$ 1.502.681,00	1	0,342	$ 513.916,90
S	c_Central_catheter_infection	Manco-Johnson et al, 2007; Local experts; Tariff manual ISS 2001 + 30%; SISMED 2013	$ 1.448.327,00	1	0,0615	$ 89.072,11
	c_MRI_OD_or_PP	Oldenburg et al, 2012; local experts; Tariff manual ISS 2001 + 30%	$ 257.183,00	1	1	$ 257.183,00
	c_Radiology_OD_or_PP	Aznar et al, 2000; Local experts; Tariff manual ISS 2001 +30%	$ 24.817,00	1	1	$ 24.817,00
	c_Ultrasonography_OD	Rodriguez et al, 2011; Manco-Johnson et al 2007 adapted; Local experts; Tariff manual ISS 2001 +30%	$ 36.550,00	1	0,0111	405,71
	c_Arthrocentesis_OD	Rodriguez et al, 2011; Manco-Johnson et al 2007 adapted; local experts; Tariff manual ISS 2001 +30%	$ 33.020,00	1	0,0111	366.52
	c_Sinovectomy_OD	Hilgartner, 2002; Windiga, et al, 2005; Tariff manual ISS 2001 +30%	$ 983.118,00	1	0,0038	3.735.85
	c_Arthroplasty_OD	Hilgartner, 2002; Aznar et al, 2000; Local experts; Tariff manual ISS 2001 +30%	$ 320.200,00	1	0,0307	9.830,14
	c_Major_Orthopaedic_surgery_and_material	Windyga et al, 2005; Gorina et al, 2002; Aznar et al, 2000; local experts, payers perspective	$ 8.857.172,00	1	0,0307	271.915,18
	c_Walking_aids_OD	Windyga et al, 2005; Key et al, 1998; Local market references	$ 123.325,00	1	0,006	739,95
	c_Medicines_Prednisone	Windyga et al, 2005; Gorina et al, 2002; Local experts; SISMED 2013	$ 43,28	15	0,013	8,44

APPENDIX 4. HAEMOPHILIA JOINT HEALTH SCOREAND HR-QoL- HEALTH STATES COLOMBIAN COHORT SCORES 2012

n	Type of treatment	VAS examiner	VAS patient	EQ- 5D patient	EQ- 5D UK tariff	Mean age	Mean bleeding episodes per year
1	1ry prophylaxis	0.980	0.950	21121	0.727	6	2
2	1ry prophylaxis	0.900	0.800	21111	0.850	4	5
3	1ry prophylaxis	0.760	0.900	21221	0.691	18	1
	Total PP with arthropathy	0.880	0.883		0.756	9.3	2.7
1	1ry prophylaxis	0.740	0.600	12121	0.692	8	2
2	1ry prophylaxis	0.900	1.000	11111	1.000	5	3
3	1ry prophylaxis	1.000	1.000	11111	1.000	6	4
4	1ry prophylaxis	0.960	1.000	11111	1.000	8	1
5	1ry prophylaxis	1.000	1.000	11111	1.000	10	2
6	1ry prophylaxis	0.900	0.900	11111	1.000	15	1
7	1ry prophylaxis	0.900	0.900	11111	1.000	17	1
8	1ry prophylaxis	0.800	0.950	11122	0.725	2	1
9	1ry prophylaxis	1.000	1.000	11111	1.000	5	9
10	1ry prophylaxis	1.000	1.000	11111	1.000	4	1
	Total PP w.o arthropathy	0.920	0.935		0.942	8.0	2.5

n	Type of treatment	VAS examiner	VAS patient	EQ- 5D patient	EQ- 5D UK tariff	Mean age	Mean bleeding episodes per year
1	On-demand	0.300	0.600	22221	0.587	53	1
2	On-demand	0.900	0.800	21111	0.850	13	5
3	On-demand	0.200	0.800	21221	0.691	34	2
4	On-demand	0.900	0.800	21221	0.691	32	3
5	On-demand	0.700	0.660	21222	0.620	38	2
6	On-demand	0.800	0.900	21111	0.850	16	1
7	On-demand	0.760	0.800	21111	0.850	22	2
8	On-demand	0.400	0.800	21111	0.850	20	2
9	On-demand	0.600	0.900	22121	0.623	27	2
10	On-demand	0.500	0.600	21233	-0.077	26	5
11	On-demand	0.500	1.000	21211	0.814	36	0
12	On-demand	0.800	0.600	21221	0.691	11	8
13	On-demand	0.750	0.900	21222	0.620	37	1
14	On-demand	0.666	0.860	21111	0.850	34	6
	Total OD with arhropathy	0.627	0.787		0.679	28.5	2.9
1	On-demand	0.633	0.700	11112	1.000	33	2
2	On-demand	0.900	1.000	11111	1.000	9	0
3	On-demand	0.900	1.000	11211	0.883	12	6
4	On-demand	1.000	1.000	12111	0.815	4	1
	Total OD w.o arthropathy	0.858	0.925		0.925	14.5	2.3

14	Overall total SHA without A	0.902	0.932		0.937	9.9	2.43
17	Overall total SHA with A	0.672	0.804		0.693	25.12	2.82

APPENDIX 5. DETAILED DESCRIPTION OF MEANS, STANDARD ERRORS, PROBABILITIES AND OTHER PARAMETERS USED TO CALCULATE PROBABILITIES DISTRIBUTIONS FOR PSA

Variable name	p	x squared	n	S squared	Alpha (p)	Beta (q)
Probability of arthropathy after bleeding PP	0.0188	0.00035	27	0.00068	0.508	26.492
Probability of arthropathy after bleeding OD	0.1450	0.02103	29	0.00428	4.205	24.795
Probability of articular bleeding	0.80	0.64000	100	0.00160	80.0	20.0
Probability of dying from bleeding	0.00525	0.00003	1070	0.00000	5.618	1064.383
Utility PP or OD without arthropathy*	0.937	0.87797	14	0.01250	4.426	0.298
Utility PP or OD with arthropathy*	0.693	0.48025	17	0.04896	3.011	1.334

Λ parameter for Poisson 1 for PP and 17 for OD

* Standard deviation calculated directly from the data of the local cohort of patients using Excel.

APPENDIX 6. ORIGINAL EVIDEM MATRIX WEIGHTING AND SCORING CRITERIA

Weighting criteria of the MCDA Core Model

Cluster	Scientific criteria	Relative weight Low ⟶ High	Should not be considered
Disease impact			
D1	Disease severity	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
D2	Size of population affected by disease	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Context of intervention			
C1	Clinical guidelines for intervention	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
C2	Comparative intervention limitations (*unmet needs*)	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Intervention outcomes			
I1	Improvement of efficacy/effectiveness	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
I2	Improvement of safety & tolerability	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
I3	Improvement of patient reported outcomes	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Type of Benefit			
T1	Public health interest *(e.g., prevention, risk reduction)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
T2	Type of medical service *(e.g., symptom relief, cure)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Economics			
E1	Budget impact on health plan *(cost of intervention)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
E2	Cost-effectiveness of intervention	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
E3	Impact on other spending (e.*g, hospitalization, disability)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Quality of evidence			
Q1	Adherence to requirements of decision making body	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Q2	Completeness and consistency of reporting evidence (*meeting scientific reporting standards and consistency with sources)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐
Q3	Relevance and validity of evidence (*relevant to decision-makers & meeting scientific standards)*	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐	0 ☐

Source: https://www.evidem.org/tiki/tiki-index.php?page=FRAME-Menu

Note: Impact on other spending (e.*g, hospitalization, disability*) and Adherence to requirements of decision making body were changed in Colombia and contextualised by including Attention to vulnerable groups of population and Attention to differential needs for health/health care

APPENDIX 7. THE PRELIMINARY WORK DEVELOPED BY CRES FOR FIELD TESTING EVIDEM

CRES was established by Law 1122 in 2007 as an arm of the Ministry of Social Protection aimed at making decisions about health care coverage within POS and annually updating the premiums to be reimbursed from the central fund of pooling (FOSYGA) to health insurers. The preliminary work developed by CRES in 2012 consisted of three workshops with 11 senior academics and decision-makers (academics, researchers, and civil servants) with broad experience of working in the context of the Colombian health system, and visibility among stakeholders. The main researcher was invited to participate in the panel as part of the discussion during all three workshops.

Prior to the first meeting CRES experts had attempted to group 59 frequently-used criteria for decision-making and develop a new MCDA matrix; however, the main researcher argued against "re-inventing the wheel", and suggested EVIDEM, with which he was familiar, to panel members as a feasible solution to be tested and implemented in Colombia. Since EVIDEM already existed and had been operationalised and tested elsewhere, it appeared to be a pragmatic solution to move forward. All participants agreed to use EVIDEM as a means to contextualise local criteria, adapting it if necessary and weighting pre-selected criteria throughout these panel sessions.

Participants invited by CRES were presented with a search of international evidence of experiences regarding the use of explicit criteria to inform resource-allocation around the globe (Byskov et al, 2009; Diederich et al, 2011, Gonzalez- Pier et al, 2007 and Guindo et al, 2012). As in step 1 of Miot´s work, participants were asked to nominate a list of additional contextual aspects they considered relevant for resource-allocation decision-making in Colombia. After this, from the six original clusters of EVIDEM, an additional contextual dimension was added to capture any local preferences not included in the original list. The preliminary list consisted of 18 criteria, thus as per Miot´s work, it was necessary to ask panel members whether specific decision criteria should be considered in decision-making in Colombia or not.

In order to decide on the final criteria for Colombia, CRES asked participants, through an electronic survey, to vote for criteria according to their perceived importance in decision-making; all participants voted. The voting system used the Delphi method approach [Linstone et al, 1975 and Astisagarra, 2003]). A quantitative scale from 1 to 9 was used to decide on the final list of selected criteria, where 9 represented the greatest importance in decision-making and 1 the lowest (Sanchez et al, 2009). This voting system departed from the qualitative approach presented by Miot (always/sometimes/never) to the South African panel. Scores were assigned in the context of the local health system without considering any specific health care intervention, as in the original author's work.

After three voting rounds in two nominal group sessions the final list was reduced to 15 criteria, of which 13 belonged to the original decision criteria listed in the EVIDEM framework (one criterion less than Miot´s publication), and two added contextual criteria. Original EVIDEM core criteria excluded by consensus were: convenience and adherence to requirements of the decision-making body (similar to Miot, 2012) and impact on other spending. These were considered irrelevant (i.e. no decision-making body rules were in place at the time of voting) or limited by lack of available data in the country about shadow costs.

The initially added contextual dimension was entitled "equity concerns" by participants, Thus the final 15 criteria considered were: completeness and consistency of reporting evidence; relevance and validity of evidence; disease severity; size of population affected by disease; current clinical guidelines; current intervention limitations; improvement of efficacy/effectiveness; improvement of safety and tolerability; improvement of patient-reported outcomes; public health interest; type of medical service; budget impact on health plan; cost-effectiveness of intervention, attention to vulnerable groups of population; and attention to differential needs for health/health care. This first part of CRES work closely resembled Miot´s step 1 of contextualisation of criteria.

Once the panel had agreed on the final criteria and their definitions, participants were asked to weight each criterion irrespective of any health care intervention of interest (step 2: weighting of criteria). Instead of the 1 to 5 scale of the original work, CRES used a Borda count approach[53] (Saari, 2000) which is a ranking system where the number of points given to candidates for each ranking is determined by the number of candidates standing in the election. CRES delivered further consensus meetings with different stakeholders around the country to disseminate the selected list of criteria and ask participants to weight each of them using the same approach.

During November and December 2012 CRES visited seven major cities (Medellin, Cali, Bucaramanga, Valledupar, Pereira, Barranquilla and Bogotá), and asked a total of 201 citizens to vote on their level of agreement and preferences regarding each of the 15 criteria (CRES, 2012). The list of voting participants included the academics on the same panel as the main researcher, patients' associations, citizen´s councils and representatives from the medical societies. (See below the final list of criteria and weights selected for Colombia, those highlighted coincided with original criteria of the EVIDEM framework).

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[53] In Borda count the voter ranks the list of candidates in order of preference. Named after the French mathematician and political scientist Jean-Charles de Borda, who devised the system in 1770, It is also known as the ranked voting system,

APPENDIX 8. BY-CRITERION EVIDEM MATRIX (SPANISH VERSION) AND SOURCES OF HTA DATA

CRITERIO	DEFINICIÓN	TECNOLOGÍA: suplementación con zinc a fin de disminuir la incidencia de enfermedad diarreica aguda, en niños con bajo peso al nacer, déficit nutricional y del crecimiento
Gravedad de la enfermedad o condición de salud	Severidad de la condición de salud de los pacientes tratados con la intervención propuesta (o la gravedad de la condición de salud que se ha de prevenir) respecto a la mortalidad, discapacidad, impacto en la calidad de vida, curso clínico (es decir agudeza, etapas clínicas).	La Enfermedad diarreica aguda (EDA) puede ocurrir a cualquier edad de la vida, pero son los lactantes y niños menores de cinco años los más predispuestos a desarrollar la enfermedad y a presentar complicaciones como sepsis, deshidratación y muerte. La diarrea puede durar varios días y puede privar al organismo del agua y las sales necesarias para la supervivencia. La mayoría de las personas que fallecen por enfermedades diarreicas en realidad mueren por una grave deshidratación y pérdida de líquidos. Los niños desnutridos o inmunodeprimidos son los que presentan mayor riesgo de enfermedades diarreicas potencialmente mortales. Las enfermedades diarreicas son la segunda causa de muerte en niños menores de cinco años, y ocasionan la muerte de 760,000 niños cada año (1). Durante el año 2006, fallecieron en Colombia 336 niños por enfermedad diarreica y 374 por problemas nutricionales; estas últimas, con mucha frecuencia relacionadas directa o indirectamente con la diarrea. Según la OMS, las muertes por enfermedad diarreica aguda en Colombia, constituyeron el 9% de todas las muertes en menores de 5 años en el año 2010, y según las estadísticas del DANE, para el año 2011 se reporta una tasa de mortalidad por EDA en menores de 5 años de 2.87 por cada 100,000 muertes en menores de 5 años (2).
Número de personas afectadas por la población objeto de la intervención (prevalencia/incidencia)	Número de personas afectadas por la enfermedad (tratada o prevenida con la intervención propuesta) en una población específica y en un momento determinado; puede expresarse como en número anual de nuevos casos (incidencia anual) y /o la proporción de la población afectada en un momento dado en el tiempo (prevalencia).	En países en desarrollo, los niños menores de tres años sufren en promedio, tres episodios de diarrea al año, y cada episodio priva al niño de nutrientes necesarios para su crecimiento (1). En Colombia, casi la mitad de los niños tiene deficiencia de zinc, lo que los predispone a desarrollar episodios diarreicos. Los datos de la Encuesta Nacional de la situación nutricional en Colombia 2010 (3), muestran que el 50% de la población entre 1 y 4 años presentó valores inferiores a 70ug/ml, muy cercano al límite inferior, y 2 de cada 5 niños menores de 5 años presentaron deficiencias de este micronutriente. La prevalencia más alta se encontró en la población indígena con un 56.3%. En general, un 44% de los menores de 5 años tiene déficit de zinc, con un estimado de 1,700,000 niños, de acuerdo con las proyecciones poblacionales del DANE para la población entre 1 y 4 años para el 2013. (4).
Mejora en eficacia/efectividad	Capacidad de la intervención prouesta para producir un efecto deseado (beneficioso) cambio en los signos, los síntomas y el curso de la afección específica por encima y más allá de los cambios beneficiosos producidos por las intervenciones alternativas. Incluye datos sobre la eficacia y la efectividad.	En Colombia, aproximadamente el 44% de los niños tiene deficiencia de zinc, la cual se encuentra directamente relacionada con el déficit nutricional; el zinc juega un papel muy importante en el sistema inmunológico (de defensa), y su deficiencia afecta la función del mismo, lo que predispone al desarrollo de episodios diarreicos. La evidencia sugiere que cerca de la tercera parte de la poblacion mundial vive en ciudades con alto riesgo de deficiencia de zinc. Según la Encuesta Nacional de la situación nutricional en Colombia 2010 (3), estudios sugieren que la suplementacion con zinc puede reducir la prevalencia de enfermedad diarreica y de neumonía, que son las responsables, de un número importante de muertes en el mundo cada año, ademas de mejorar el pronóstico y disminuir días de hospitalización.
Guías de práctica clínica basadas en evidencia, válidas en Colombia	Concurrencia de la intervención propuesta (o alternativas similares) con el consenso actualizado de expertos sobre lo que constituye el estado del arte, las prácticas y manejo de las condición de interés; estas recomendaciones suelen ser desarrolladas a través de un proceso explícito y tienen por objeto mejorar la clínica práctica.	Dentro del marco de la Convocatoria 500 de Colciencias, para la elaboración de guías basadas en evidencia científica, se desarrolló la Guía de Práctica Clínica para la prevención, diagnóstico y tratamiento de la enfermedad diarreica aguda en niños menores de cinco años, las cuales han sido lanzadas recientemente en el país.
Tipo de beneficio clínico	Naturaleza del beneficio clínico proporcionado por la intervención propuesta a nivel del paciente (por ejemplo alivio de síntomas, prolongación de la vida, curación).	En Colombia casi la mitad de los niños tienen deficiencia de zinc, lo que los predispone a desarrollar episodios diarreicos, entre otras alteraciones y enfermedades. La evidencia clínica ha demostrado reducción en la incidencia de diarrea entre un 15% - 20%. Los hallazgos del meta-análisis realizado por el grupo desarrollador de la guía de práctica clínica para la prevención, diagnóstico y tratamiento de la enfermedad diarreica aguda en niños menores de cinco años, reporta una disminución del 12% en la incidencia de la EDA, con suplementación diaria de zinc durante 3 meses (5).
Impacto en el presupuesto en el plan de salud	Impacto económico neto de la cobertura de la intervención sobre el presupuesto del plan de salud (excluyendo otros gastos). Esto representa la diferencia entre los gastos previstos para la intervención propuesta y los posibles ahorros de costos que pueden derivarse de la sustitución de la intervención de otro (s) actualmente cubierto por el plan de salud. Limitada al costo de la intervención (por ejemplo costo de adquisición implementación y mantenimiento).	El costo base para el sulfato de zinc en jarabe (2mg/ml), es de $ 10.117 para la presentación de 80ml, y de $ 12.623 para la presentación de 120ml. Se recomienda para el tratamiento profiláctico la dosis de 5mg/día para menores de 6 meses durante 3 meses, para un costo total promedio de tratamiento de $51.165. En niños mayores de 6 meses, la dosis recomendada es de 10mg/día por 3 meses, para un costo total promedio de tratamiento de $102.330. Fuente: SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012 (6).
Mejora de seguridad y tolerancia	Reducción en efectos sobre la salud relacionados con la intervención que son dañinos o no deseados, en comparación con intervenciones alternativas.	El zinc administrado en niños con déficit nutricional, es una intervención segura, ya que a pesar que el único evento adverso importante a las dosis recomendadas es el vómito, es considerado bien tolerado en la mayoría de las ocasiones (5).
Interés en salud pública	Reducción de riegos producto de la intervención a nivel de la población general (ej: prevención, reducción de transmisión de la enfermedad, reducción de la prevalencia de factores de riesgo).	Dentro de las estrategias del Plan Decenal de Salud Pública 2012-2021 en el componente de Atención integral y diferencial de las niñas, niños y adolescentes en el entorno de los servicios de salud, se encuentra disminuir la mortalidad nacional en la niñez a 15 x1000 nacidos vivos o menos. Así mismo, la disminución de la mortalidad en menores de 5 años hace parte de los objetivos de desarrollo del milenio.
Mejora resultados en salud reportados por paciente	Capacidad de la intervención propuesta de producir cambios benéficos en desenlaces reportados por pacientes (DRP) (por ejemplo calidad de vida) por encima y más allá de los cambios benéficos producidos por las intervenciones alternativas; también incluye mejoras en conveniencia para laos pacientes.	La suplementación con zinc como estrategia preventiva en niños menores de 5 años con bajo peso al nacer, o déficit nutricional y del crecimiento, ha demostrado disminuir la incidencia de enfermedad diarreica aguda en este grupo de pacientes, lo que interviene en desenlaces de severidad relacionados con el episodio diarreico agudo, tales como deshidrtación grave, pronóstico, días de hospitalización y mortalidad. Adicionalmente, se suplen los requerimientos nutricionales dados en las condiciones de bajo peso o desnutrición, lo que lleva a un menor riesgo de presentar episoios diarreicos.
Limitación en desempeño de tecnologías alternativas para la enfermedad o condición	Limitación de desempeño de tecnologías comparativas en su capacidad de prevenir, curar o mejorar la condición de interés; también incluye limitaciones de desempeño en materia de seguridad, desenlaces reportados por los pacientes y la conveniencia.	En este caso la alternativa es no realizar la suplementación con zinc.
Equidad en grupos vulnerables	Grado en que la tecnología evaluada suple necesidades prioritarias de grupos específicos de poblaciónque están definidos por la sociedad como vulnerables.	Los niños menores de cinco años son los más predispuestos a desarrollar enfermedad diarreica aguda y a presentar complicaciones como sepsis, deshidratación y muerte. En Colombia el 43,3% de los niños menores de 5 años tienen deficiencia de zinc, comprometiendo en mayor proporción a la población indígena y afrodescendiente: 56,3% y 45,6%, respectivamente (3,5).
Costo-efectividad de la intervención	Razón incremental de costo comparada con el beneficio incremental de la tecnología comparada con alternativas existentes. El beneficio puede expresarse como número de eventos evitados, años de vida ganados, QALYs/AVACs ganados, días adicionales libres de dolor, etc.	El estudio de costo-efectividad realizado por el grupo desarrollador de la GPC para la prevención, diagnóstico y tratamiento de la enfermedad diarreica aguda en niños menores de 5 años, muestra como resultados, que el uso de zinc para prevención, genera unos elevados costos por episodio de diarrea evitado: $2.022.322 por caso evitado de diarrea aguda y $3.634.523 por caso evitado de diarrea persistente. El estudio concluye que la suplementación con zinc para niños menores de 5años con deficiencias de zinc y alto riesgo de presentar un episodio de EDA puede ser una estrategia costo efectiva para el país, pero no para toda la población menor de 5 años (5).
Completitud y calidad del reporte	Grado en que la notificación de datos sobre la intervención propuesta está completa (ej: cumple con estándares científicos de notificación) y es consistente con las fuente bibliográficas citadas.	El Instituto Nacional de Salud mediante el Sistema de vigilancia y control en salud pública (SIVIGILA) (8), realiza el seguimiento continuo y sistemático de las muertes por enfermedad diarreica aguda (EDA) en menores de 5 años, así como la consolidación de casos de EDA (reporte colectivo) de periodicidad semanal, de acuerdo con procesos establecidos para su notificación, recolección y análisis de los datos.
Relevancia y validez de la evidencia	Grado en que la evidencia sobre la intervención propuesta es relevante para la toma de decisiones (en términos de población, estadio de la enfermedad, descripción de comparadores, desenlaces, etc) y válida respecto a los estándares científicos (ej. diseño del estudio). Esto incluye consideraciones respecto a la incertidumbre (ej. resultados contradictorios entre varios estudios, limitado número de estudios y/o participantes).	Existe evidencia relacionada con la suplementación de zinc tanto observacional como experimental, así como revisiones sistemáticas y meta-análisis de ensayos clínicos, que evalúan la efectividad y seguridad del zinc para la prevención de enfermedad diarreica. Debido a que la evidencia presenta un alto componente de heterogeneidad tanto en las edades estudiadas, como en las estrategias de administración de la intervención (tiempo, periodicidad y presentación de la tecnología) la evidencia se califica según SIGN como de calidad moderada (5).
Necesidad diferencial en salud (cronicidad, paleación)	Grado en que la tecnología evaluada suple necesidades en salud de grupos especificos de población que sin necesariamente ser catalogados como vulnerables requieren servicios diferenciales de salud (ej. cronicidad, paloación, manejo del dolor, etc).	La enfermedad diarréica aguda es una entidad de inicio agudo y resolución que no debe superar los 14 días.

CRITERIO	DEFINICIÓN	TECNOLOGÍA: ticagrelor más ASA, en pacientes con SCA sin ST de riesgo intermedio o alto independiente de la estrategia de tratamiento inicial, incluyendo aquellos que recibieron previamente clopidogrel, el cual debe suspenderse una vez se inicie ticagrelor.
Gravedad de la enfermedad o condición de salud	Severidad de la condición de salud de los pacientes tratados con la intervención propuesta (o la gravedad de la condición de salud que se ha de prevenir) respecto a la mortalidad, discapacidad, impacto en la calidad de vida, curso clínico (es decir agudeza, etapas clínicas).	La enfermedad cardiovascular es la principal causa de muerte en Latinoamérica. Datos de la Organización Mundial de la Salud indican que la región cursa con una epidemia de enfermedad cardiovascular de grandes proporciones, lo que se puede atribuir a cambios demográficos y de hábitos de vida inherentes a la transición epidemiológica. La enfermedad coronaria (EC) es la principal causa de muerte en el mundo occidental, y fue la responsable de 1 de cada 5 muertes en Estados Unidos en el 2004 (1). Según el NHLBI (Instituto Nacional de Sangre, Corazón y Pulmón) y el NCHS (Centro Nacional de Estadísticas en Salud), en el 2004 la tasa global de muertes por EC fue de 150.5 por 100.000 habitantes (2). De acuerdo con las estadísticas publicadas por el Ministerio de la Protección Social en el informe sobre la Situación de salud en Colombia -Indicadores de salud 2007-, la enfermedad isquémica del corazón es la principal causa de muerte, tanto en hombres como en mujeres mayores de 45 años. La tasa de mortalidad atribuible a esta enfermedad fue de 107,3 por 100.000 habitantes en personas de 45 a 64 años, y de 867,1 por 100.000 habitantes para personas de 65 años o más. (3) Según el registro de estadísticas vitales del Departamento Administrativo Nacional de Estadística (DANE), de la mortalidad por enfermedades del sistema circulatorio, la enfermedad isquémica del corazón fue la causa del 49,5% del total de muertes, siendo la principal etiología en personas mayores de 55 años, por encima del cáncer y la agresión (4).
Número de personas afectadas por la población objeto de la intervención (prevalencia/incidencia)	Número de personas afectadas por la enfermedad (tratada o prevenida con la intervención propuesta) en una población específica y en un momento determinado; puede expresarse como en número anual de nuevos casos (incidencia anual) y /o la proporción de la población afectada en un momento dado en el tiempo (prevalencia).	En Estados Unidos, según el registro GRACE (Global Registry of Acute Coronary Events) (5) se reportan 9,000,000 de consultas al año por dolor torácico, de las cuales el 13% (1,072,000) corresponden a síndromes coronarios agudos; 731,000 corresponden a IAM (68%); aproximadamente 38% se clasifican como Síndrome Coronario Agudo con elevación del ST (SCACEST), y 30% a Síndrome Coronario Agudo sin elevación del ST (SCASEST) (6). Según un estudio para la estimación de costos del SCA en Colombia (7), tomando la referencia del Instituto Nacional de Sangre, Corazón y Pulmón de los Estados Unidos (NHLBI), que reporta la incidencia anual de IAM de 565.000 nuevos eventos y 300.000 ataques recurrentes cada año, y aplicando esta misma proyección de incidencia con base en la población proyectada por el DANE (8) para Bogotá y Colombia se esperarían al año 82.293 casos para el país y 13.462 para Bogotá al año.
Mejora en eficacia/efectividad	Capacidad de la intervención prouesta para producir un efecto deseado (beneficioso) cambio en los signos, los síntomas y el curso de la afección específica por encima y más allá de los cambios beneficiosos producidos por las intervenciones alternativas. Incluye datos sobre la eficacia y la efectividad.	La activación plaquetaria y su posterior agregación desempeñan un papel predominante en la formación de trombos (coágulos), y por lo tanto, son objetivos terapéuticos críticos en el manejo del Síndrome Coronario Agudo. El tratamiento antiplaquetario debe instaurarse lo más rápidamente posible después del diagnóstico de Síndrome Coronario Agudo sin elevación del ST (SCASEST), con el objetivo de reducir el riesgo de complicaciones isquémicas agudas y la recurrencia de episodios trombóticos (9). El ticagrelor es un medicamento antiplaquetario el cual ha demostrado ejercer un mayor y más rápido efecto en comparación con la alternativa más comunmente utilizada, el clopidogrel. De acuerdo con los datos del estudio PLATO (Study of Platelet Inhibition and Patient Outcomes), El Ticagrelor redujo las muertes por causa cardiovascular (4.0% vs. 5.1% en el grupo de ticagrelor, p = 0.001), así como el Infarto Agudo de Miocardio (5.8% en el grupo de ticagrelor vs. 6.9% en el grupo de clopidogrel, p = 0.005) (10).
Guías de práctica clínica basadas en evidencia, válidas en Colombia	Concurrencia de la intervención propuesta (o alternativas similares) con el consenso actualizado de expertos sobre lo que constituye el estado del arte, las prácticas y manejo de la condición de interés; estas recomendaciones suelen ser desarrolladas a través de un proceso explícito y tienen por objeto mejorar la clínica práctica.	Dentro del marco de la Convocatoria 500 de Colciencias para la elaboración de guías basadas en evidencia científica, se desarrolló la Guía de Práctica Clínica para pacientes con diagnóstico de Síndrome Coronario Agudo, las cuales han sido lanzadas recientemente en el país.
Tipo de beneficio clínico	Naturaleza del beneficio clínico proporcionado por la intervención propuesta a nivel del paciente (por ejemplo alivio de síntomas, prolongación de la vida, curación).	En pacientes con Síndrome Coronario Agudo sin elevación del ST, el Ticagrelor ha demostrado reducir las tasas de muerte por causa cardiovascular, así como las tasas de Infarto Agudo de Miocardio. De acuerdo con los datos del estudio PLATO (Study of Platelet Inhibition and Patient Outcomes), el riesgo de muerte por causas vasculares se redujo en un 21% en comparación con clopidogrel (HR = 0,79; IC95%, 0,69-0,91; p = 0,001) y el riesgo de presentar IAM en un 16% (HR = 0,84; IC95%, 0,75-0,95; p = 0,005) (9,10,11).
Impacto en el presupuesto en el plan de salud	Impacto económico neto de la cobertura de la intervención sobre el presupuesto del plan de salud (excluyendo otros gastos). Esto representa la diferencia entre los gastos previstos para la intervención propuesta y los posibles ahorros de costos que pueden derivarse de la sustitución de la intervención de otro (s) actualmente cubierto por el plan de salud. Limitada al costo de la intervención (por ejemplo costo de adquisición implementación y mantenimiento).	El costo base del ticagrelor en tabletas de 90mg, es de aproximadamente $86.062 para la presentación de 30 tabletas. Para la dosis recomendada de 90mg c/12horas, se estima un costo anual de tratamiento de $2.065.488. Fuente: SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012 (12).
Mejora de seguridad y tolerancia	Reducción en efectos sobre la salud relacionados con la intervención que son dañinos o no deseados, en comparación con intervenciones alternativas.	La evidencia muestra que no existen diferencias significativas en las tasas de sangrado mayor, o sangrado que amenaza la vida, cuando se compara el ticagrelor con el clopidogrel (10,11).
Interés en salud pública	Reducción de riegos producto de la intervención a nivel de la población general (ej: prevención, reducción de transmisión de la enfermedad, reducción de la prevalencia de factores de riesgo).	En el Plan decenal de Salud Pública 2012-2021, la enfermedad isquémica del corazón hace parte de las patologías a intervenir dentro del grupo de enfermedades crónicas no transmisibles (13). En el Plan Nacional de Salud Pública, la enfermedad aterosclerótica cardiaca y los SCA, como principal manifestación, fue considerada dentro del grupo de enfermedades catastróficas, crónicas no transmisibles.
Mejora resultados en salud reportados por paciente	Capacidad de la intervención propuesta de producir cambios benéficos en desenlaces reportados por pacientes (DRP) (por ejemplo calidad de vida) por encima y más allá de los cambios benéficos producidos por las intervenciones alternativas; también incluye mejoras en conveniencia para los pacientes.	Un estudio que evalúa la calidad de vida relacionada con la salud en pacientes con SCA mediante el cuestionario EQ-5D no muestra diferencias significativas en percepción de calidad de vida relacionada con el tratamiento con clopidogrel o ticagrelor durante un año (14). Sin embargo, estudios recientes reportan que basados en evidencia clínica y de economía de la salud, el tratamiento con ticagrelor durante 12 meses se encuentra asociado con un costo por QUALY (años de vida ajustados por calidad) por debajo de los umbrales aceptados como costo-efectivos (15).
Limitación en desempeño de tecnologías alternativas para la enfermedad o condición	Limitación de desempeño de tecnologías comparativas en su capacidad de prevenir, curar o mejorar la condición de interés; también incluye limitaciones de desempeño en materia de seguridad, desenlaces reportados por los pacientes y la conveniencia.	El uso de clopidogrel, considerado como el agente más comunmente usado dentro del tratamiento antiplaquetario en pacientes con SCA sin elevación del ST, muestra una menor efectividad en términos de disminución del riesgo de muerte por causa cardiovascular, así como disminución del riesgo de Infarto Agudo de Miocardio. No se reportan diferencias significativas en eventos adversos cuando se compara con el ticagrelor.
Equidad en grupos vulnerables	Grado en que la tecnología evaluada suple necesidades prioritarias de grupos específicos de poblaciónque están definidos por la sociedad como vulnerables.	La enfermedad coronaria afecta principalmente a los mayores de 45 años. Es la primera causa de muerte en adultos mayores (mayores de 65 años) (9).
Costo-efectividad de la intervención	Razón incremental de costo comparada con el beneficio incremental de la tecnología comparada con alternativas existentes. El beneficio puede expresarse como número de eventos evitados, años de vida ganados, QALYs/AVACs ganados, días adicionales libres de dolor, etc.	El análisis de costo-utilidad realizado dentro del marco del desarrollo de la Guía de Práctica Clínica del Síndrome Coronario Agudo en Colombia, concluye que el uso de ticagrelor para el tratamiento de pacientes con SCA es una estrategia costo-efectiva para el SGSSS. En el caso base, el costo por año de vida ajustado por calidad (AVAC) ganado con ticagrelor es de $28.411.503. Para un umbral de disposición a pagar equivalente a 3 veces el PIB per cápita en Colombia, la probabilidad de que el ticagrelor sea una estrategia costo-efectiva es cercana al 75% (9).
Completitud y calidad del reporte	Grado en que la notificación de datos sobre la intervención propuesta está completa (ej: cumple con estándares científicos de notificación) y es consistente con las fuente bibliográficas citadas.	Los datos reportados hacen parte de proyectos internacionales tales como el GRACE (Global Registry of Acute Coronary Events) que reune datos de 10.693 pacientes con SCA entre 1999 y 2001 en Europa, América, Australia y Nueva Zelanda, o la Encuesta del corazón Minnesota (tendencias de la enfermedad coronaria aguda mortalidad, morbilidad y cuidado médico de 1985 - 1997). A nivel nacional no existen protocolos de vigilacia para la notificación o registro de eventos coronarios agudos.
Relevancia y validez de la evidencia	Grado en que la evidencia sobre la intervención propuesta es relevante para la toma de decisiones (en términos de población, estadio de la enfermedad, descripción de comparadores, desenlaces, etc) y válida respecto a los estándares científicos (ej. diseño del estudio). Esto incluye consideraciones respecto a la incertidumbre (ej. resultados contradictorios entre varios estudios, limitado número de estudios y/o participantes).	La evidencia científica relacionada con el tratamiento con ticagrelor como antiplaquetario en pacientes con SCA sin elevación del ST, se califica como de moderada calidad, con disponibilidad de ensayos clínicos multicéntricos, aleatorizados. En su mayoría, los datos reportados en la literatura, y en los cuales se basan las recomendaciones actuales de la Guía de Práctica Clínica para pacientes con diagnóstico de Síndrome Coronario Agudo, se basan en estudios de buena calidad metodológica (9).
Necesidad diferencial en salud (cronicidad, paliación)	Grado en que la tecnología evaluada suple necesidades en salud de grupos específicos de población que sin necesariamente ser catalogados como vulnerables requieren servicios diferenciales de salud (ej. cronicidad, paliación, manejo del dolor, etc).	El Ticagrelor hace parte de la estrategia terapéutica antiplaquetaria indicada posterior a un evento coronario agudo; a pesar de no ser un tratamiento crónico, previene las complicaciones derivadas de la enfermdad coronaria y el síndrome coronario agudo.

CRITERIO	DEFINICIÓN	TECNOLOGÍA: Inhibidores de aromatasa (Anastrozol) como tratamiento de primera línea en pacientes posmenopáusicas con cáncer de mama metastásico receptor hormonal positivo.
Gravedad de la enfermedad o condición de salud	Severidad de la condición de salud de los pacientes tratados con la intervención propuesta (o la gravedad de la condición de salud que se ha de prevenir) respecto a la mortalidad, discapacidad, impacto en la calidad de vida, curso clínico (es decir agudeza, etapas clínicas).	El cáncer de mama es el cáncer más frecuente en mujeres, con un estimado de 1.38 millones de nuevos casos diagnosticados en el 2008 (23% de todos los cánceres). Actualmente, es el cáncer de mayor incidencia del sexo femenino, con una mortalidad similar a la del cáncer de cérvix. Aunque las tasas globales de mortalidad son menores, debido a la mayor sobrevida en regiones desarrolladas, el cáncer de mama continúa siendo la causa más frecuente de muerte por cáncer en mujeres, tanto en los países desarrollados (189,000 muertes/año) como en los países en vías de desarrollo (269,000 muertes/año) (1). El cáncer de mama es una enfermedad con una evolución natural compleja por lo que, a pesar de los avances de la oncología moderna, es la primera causa de muerte por neoplasia en la mujer a nivel mundial, con más de un millón de casos nuevos cada año, de los cuales, aproximadamente la mitad ocurren en países desarrollados; sin embargo, es en los países en vías de desarrollo donde ocurren la mayoría de las muertes por esta causa (2).
Número de personas afectadas por la población objeto de la intervención (prevalencia/incidencia)	Número de personas afectadas por la enfermedad (tratada o prevenida con la intervención propuesta) en una población específica y en un momento determinado; puede expresarse como un número anual de nuevos casos (incidencia anual) y/o la proporción de la población afectada en un momento dado en el tiempo (prevalencia).	Las tasas de incidencia a nivel mundial varían entre regiones, siendo mayores en los países desarrollados (mayor a 80 por 100,000 mujeres), y más bajas en la mayoría de países en vías de desarrollo (menor a 40 por 100,000 mujeres). Para el caso de Colombia, durante el periodo de 2002-2006, estudios locales reportan una tasa cruda de incidencia anual de 32.6 por 100.000 mujeres y una tasa cruda corregida de la mortalidad anual de 9.5 por 100.000 muertes en mujeres (3). Según datos reportados por la Agencia Internacional para la Investigación en Cáncer (IARC), la incidencia anual estandarizada por edad para Colombia es de 31.2 por cada 100.000 mujeres, y la mortalidad de 10 por cada 100.000 muertes de mujeres (4). Para el caso de cáncer metastásico, datos colombianos reportan que los estadíos avanzados corresponden al 8.1% del total de casos en el año 2005 , y al 8.6% en el año 2008 (5).
Mejora en eficacia/efectividad	Capacidad de la intervención propuesta para producir un efecto deseado (beneficioso) cambio en los signos, los síntomas y el curso de la afección específica por encima y más allá de los cambios beneficiosos producidos por las intervenciones alternativas . Incluye datos sobre la eficacia y la efectividad.	La mayoría de los casos de cáncer de mama metastásico son sensibles a las hormonas estrogénicas femeninas; estas células malignas sensibles, necesitan de los estrógenos para mantenerse vivas; por lo tanto, la eliminación de cualquier estrógeno circulante constituye una terapia muy efectiva en el tratamiento de este tipo de neoplasias sensibles a hormonas. La terapia hormonal elimina la influencia del estrógeno en las células malignas del seno. Dentro de las alternativas terapéuticas para el cáncer de seno avanzado se encuentran el tamoxifeno y los inhibidores de aromatasa (6). El anastrozol es un inhibidor competitivo de la aromatasa, que ha demostrado reducir la concentración plasmática de estradiol en más del 80%, sin modificar la producción de otras hormonas. El anastrozol ha demostrado eficacia superior al tamoxifeno con efectos positivos estadísticamente significativos en la respuesta tumoral, principalmente en términos de progresión libre de enfermedad; una revisión sistemática publicada en el año 2009, reporta un HR 0.78 (IC 95% 0.71 - 0.86); es decir, que el riesgo relativo de progresión de la enfermedad disminuye en un 22% con el anastrozol, comparado con el tamoxifeno (7).
Guías de práctica clínica basadas en evidencia, válidas en Colombia	Concurrencia de la intervención propuesta (o alternativas similares) con el consenso actualizado de expertos sobre lo que constituye el estado del arte, las prácticas y manejo de las condición de interés; estas recommendaciones suelen ser desarrolladas a través de un proceso explícito y tienen por objeto mejorar la clínica práctica.	Dentro del marco de la Convocatoria 500 de Colciencias para la elaboración de guías basadas en evidencia científica, se desarrolló la Guía de Práctica Clínica para la detección temprana, tratamiento integral, seguimiento y rehabilitación del Cáncer de Mama, las cuales han sido lanzadas recientemente en el país.
Tipo de beneficio clínico	Naturaleza del beneficio clínico proporcionado por la intervención propuesta a nivel del paciente (por ejemplo alivio de síntomas, prolongación de la vida, curación).	En pacientes posmenopáusicas con cáncer de mama metastásico, el anastrozol ha mostrado diferencias significativas en progresión libre de enfermedad, y respuesta clínica (disminución del tamaño del tumor parcial o total, y enfermedad estable por más de 24 semanas), (6,7).
Impacto en el presupuesto en el plan de salud	Impacto económico neto de la cobertura de la intervención sobre el presupuesto del plan de salud (excluyendo otros gastos). Esto representa la diferencia entre los gastos previstos para la intervención propuesta y los posibles ahorros de costos que pueden derivarse de la sustitución de la intervención de otro (s) actualmente cubierto por el plan de salud. Limitada al costo de la intervención (por ejemplo costo de adquisición implementación y mantenimiento).	El costo base para el inhibidor de aromatasa, Anastrozol (tab 1mg), es de aproximadamente $513.056 para la presentación de 28 tabletas. Teniendo en cuenta que la dosis indicada es de 1mg/día, el costo del tratamiento anual será de aproximadamente $6.596.434. Fuente: SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercialización de Medicamentos. Enero a Septiembre de 2012 (8).
Mejora de seguridad y tolerancia	Reducción en efectos sobre la salud relacionados con la intervención que son dañinos o no deseados, en comparación con intervenciones alternativas.	El anastrozol provee un adecuado perfil de seguridad, y presenta de acuerdo con datos de un meta- análisis del 2011 (9), una disminución en la probabilidad de producir eventos tromboembólicos en un 53%, y de sangrado vaginal en un 70%, cuando son comparados con tamoxifeno.
Interés en salud pública	Reducción de riegos producto de la intervención a nivel de la población general (ej: prevención, reducción de transmisión de la enfermedad, reducción de la prevalencia de factores de riesgo).	Se encuentra dentro de las líneas estratégicas, tanto de detección temprana, como de atención, recuperación y superación de los daños causados por el cáncer dentro del Plan Decenal para el Control del Cáncer de Colombia 2012-2021, en donde una de las metas específicas incluye Implementar la Política Farmacéutica Nacional (Documento Conpes 155 de 2012), en relación con la gestión y control de medicamentos oncológicos, cuyo objetivo es garantizar el acceso oportuno y de calidad al diagnóstico y tratamiento de cinco cánceres con mortalidad prematura evitable, en el 100% de los casos, dentro de los que se encuentra el cáncer de mama (10).
Mejora resultados en salud reportados por paciente	Capacidad de la intervención propuesta de producir cambios benéficos en desenlaces reportados por pacientes (DRP) (por ejemplo calidad de vida) por encima y más allá de los cambios benéficos producidos por las intervenciones alternativas; también incluye mejoras en conveniencia para los pacientes.	La evidencia disponible en relación con calidad de vida es limitada; sin embargo, se han encontrado algunas diferencias en algunas escalas de medición de este desenlace a favor de los inhibidores de aromatasa como el anastrozol. Adicionalmente, aunque la evidencia científica no demuestra diferencias significativas en relación con eventos adversos como náuseas, vómito, diarrea, ni dolor articular, si existe un menor riesgo de presentar eventos tromboembólicos y sangrado vaginal con el uso de anastrozol, en comparación con tamoxifeno (7).
Limitación en desempeño de tecnologías alternativas para la enfermedad o condición	Limitación de desempeño de tecnologías comparativas en su capacidad de prevenir, curar o mejorar la condición de interés; también incluye limitaciones de desempeño en materia de seguridad, desenlaces reportados por los pacientes y la conveniencia.	El uso de tamoxifeno, considerado como el agente más comunmente usado dentro del tratamiento hormonal de primera línea en pacientes posmenopáusicas con cáncer de mama metastásico receptor hormonal positivo, muestra una menor efectividad en términos de supervivencia libre de progresión, y mayor probabilidad de producir eventos adversos, cuando se compara con anastrozol. Sin embargo, no se han demostrado diferencias entre estos dos medicamentos en la supervivencia global (7).
Equidad en grupos vulnerables	Grado en que la tecnología evaluada suple necesidades prioritarias de grupos específicos de poblaciónque están definidos por la sociedad como vulnerables.	El anastrozol se encuentra indicado en todas las pacientes posmenopáusicas con cáncer de mama metastásico receptor hormonal positivo.
Costo-efectividad de la intervención	Razón incremental de costo comparada con el beneficio incremental de la tecnología comparada con alternativas existentes. El beneficio puede expresarse como número de eventos evitados, años de vida ganados, QALYs/AVACs ganados, días adicionales libres de dolor, etc.	El estudio de Costo efectividad de inhibidores de aromatasa en cáncer de mama avanzado realizado en el marco de la Guía de Práctica Clínica de Cáncer de mama, concluye que en mujeres con cáncer de mama avanzado receptor hormonal positivo, los inhibidores de la aromatasa comparados con tamoxifeno en primera línea de tratamiento hormonal, serían costo-efectivos para Colombia. Los resultados muestran que en términos de supervivencia global no hay diferencia entre los tratamientos; sin embargo los hay para supervivencia libre de progresión y eventos adversos los cuales son significativos con eventos tromboembólicos. Para esta evaluación las medidas de resultado en salud fueron los años de vida libres de enfermedad (AVLE) y los años de vida perdidos ajustados por discapacidad (AVAD o DALYs en inglés). Los inhibidores de aromatasa fueron más costosos y efectivos que el tamoxifeno, el costo por AVGLE fue de $2.812.147,08 con descuento y de $5.564.228,57 sin descuento. El costo por AVAD evitado fue $6.173.144,15 y de $3.170.898,35 sin y con descuento. De acuerdo al umbral de PIB, los inhibidores serían costo-efectivos para el país en esta indicación (11).
Completitud y calidad del reporte	Grado en que la notificación de datos sobre la intervención propuesta está completa (ej: cumple con estándares científicos de notificación) y es consistente con las fuente bibliográficas citadas.	Existen a nivel nacional los servicios de vigilancia epidemiológica de cáncer, distribuidos por ciudades (registro poblacional de cáncer), y grupos de vigilancia epidemiologica del cáncer, como el del Instituto Nacional de Cancerología. A nivel mundial, el proyecto GLOBOCAN provee información acerca de incidencia, mortalidad, prevalencia y años de vida perdidos ajustados por discapacidad (AVAD o DALYs en inglés) de los tipos de cáncer más frecuentes en 184 países, dentro de los cuales se encuentra Colombia.
Relevancia y validez de la evidencia	Grado en que la evidencia sobre la intervención propuesta es relevante para la toma de decisiones (en términos de población, estadio de la enfermedad, descripción de comparadores, desenlaces, etc) y válida respecto a los estándares científicos (ej. diseño del estudio). Esto incluye consideraciones respecto a la incertidumbre (ej. resultados contradictorios entre varios estudios, limitado número de estudios y/o participantes).	La evidencia científica relacionada con el tratamiento hormonal con inhibidores de aromatasa en pacientes con cáncer de mama metastásico en este grupo de pacientes, y en particular del anastrozol, es de buena calidad, con disponibilidad de revisiones sistemáticas y meta-análisis de ensayos clínicos. En su mayoría, los datos reportados en la literatura, y en los cuales se basan las recomendaciones actuales de la Guía de Práctica Clínica para la detección temprana, tratamiento integral, seguimiento y rehabilitación del Cáncer de Mama, se basan en estudios de buena calidad metodológica.
Necesidad diferencial en salud (cronicidad, paliación)	Grado en que la tecnología evaluada suple necesidades en salud de grupos específicos de población que sin necesariamente ser catalogados como vulnerables requieren servicios diferenciales de salud (ej. cronicidad, paliación, manejo del dolor, etc).	El cáncer de mama metastásico en mujeres posmenopáusicas, confiere un estadío tratable, pero no curable de la enfermedad; las intervenciones en estas pacientes se dirigen a estrategias paliativas, inhibición de progresión de la enfermedad, mayor tiempo de sobrevida, y a una mejor calidad de vida (9).

CRITERIO	DEFINICIÓN	Profilaxis con Factor VIII en pacientes con Hemofilia A severa
Gravedad de la enfermedad o condición de salud	Severidad de la condición de salud de los pacientes tratados con la intervención propuesta (o la gravedad de la condición de salud que se ha de prevenir) respecto a la mortalidad, discapacidad, impacto en la calidad de vida, curso clínico (es decir agudeza, etapas clínicas).	La hemofilia A es una enfermedad genética ligada al cromosoma X, que se expresa por una disminución del Factor VIII de la coagulación, produciendo una tendencia permanente al sangrado (1). La edad de presentación, la localización y la severidad del sangrado dependen del grado de severidad de la enfermedad, la cual se determina por el nivel de actividad del factor VIII; los pacientes con hemofilia A severa presentan menos del 1% de actividad del factor, presentando una tendencia a desarrollar sangrados espontáneos, principalmente del tipo hemartrosis o hemorragias intra-articulares que constituyen entre el 70-80% de todas las hemorragias en hemofílicos (2). Esto origina una patología característica denominada artropatía hemofílica, que desarrolla lesiones articulares progresivas, las cuales conducen a una severa limitación de la función articular, dolor y serias secuelas invalidantes. Por su frecuencia y evolución crónica, la artropatía hemofílica es la complicación de la enfermedad con mayor morbilidad, siendo como objetivo primario del tratamiento, la prevención de su desarrollo (3, 4)
Número de personas afectadas por la población objeto de la intervención (prevalencia/incidencia)	Número de personas afectadas por la enfermedad (tratada o prevenida con la intervención propuesta) en una población específica y en un momento determinado; puede expresarse como en número anual de nuevos casos (incidencia anual) y /o la proporción de la población afectada en un momento dado en el tiempo (prevalencia).	La hemofilia A afecta a uno de cada 5.000-10.000 varones, y representa aproximadamente un 85% de los casos de hemofilia. (2). Según datos de la Federación Mundial de Hemofilia, Encuesta Global de 2010 (WFH Global Survey 2010), 162.781 personas viven con hemofilia en el mundo, de las cuales 125.049 son pacientes con hemofilia tipo A. Para Colombia se reportan 1,915 pacientes con hemofilia, con 1,446 correspondientes a Hemofilia A (5), de los cuales se estiman aproximadamente 800- 1040 casos clasificados como severos, correspondientes al 55% del total de pacientes con Hemofilia A. (2) .
Mejora en eficacia/efectividad	Capacidad de la intervención prouesta para producir un efecto deseado (beneficioso) cambio en los signos, los síntomas y el curso de la afección específica por encima y más allá de los cambios beneficiosos producidos por las intervenciones alternativas . Incluye datos sobre la eficacia y la efectividad.	Los concentrados del Factor VIII derivados del plasma humano, tienen una alta seguridad y similar eficacia que los concentrados recombinantes (1). Una revisión sistemática de 6 ensayos clínicos randomizados, con 142 participantes en total, que comparan el tratamiento profiláctico vs el tratamiento según demanda (factor VIII), demuestra una disminución del riesgo de presentar cualquier tipo de sangrado del 70% (RR de 0.3; 95% IC; 0.12 a 0.76), y del 78% (RR 0.22; 95% IC; 0.08 a 0.63) para sangrado de articulaciones a favor del tratamiento profiláctico, aportando que además una profilaxis iniciada tempranamente previene el desarrollo de inhibidores y ayuda a prevenir las hemorragias con riesgo vital (6).
Guías de práctica clínica basadas en evidencia, válidas en Colombia	Concurrencia de la intervención propuesta (o alternativas similares) con el consenso actualizado de expertos sobre lo que constituye el estado del arte, las prácticas y manejo de las condición de interés; estas recomendaciones suelen ser desarrolladas a través de un proceso explícito y tienen por objeto mejorar la clínica práctica.	No se han desarrollados Guías de práctica clinica basadas en evidencia en Colombia; sin embargo, existen la Guía Clínica de Hemofilia, desarrollada en Chile, por el Ministerio de Salud en el año 2013, así como Guía de tratamiento de la hemofilia - Consenso de Médicos especialistas en Hemofilia de la República Argentina , 2011.
Tipo de beneficio clínico	Naturaleza del beneficio clínico proporcionado por la intervención propuesta a nivel del paciente (por ejemplo alivio de síntomas, prolongación de la vida, curación).	Los pacientes hemofílicos con niveles de Factor VIII por encima del 2% raramente presentan enfermedad articular grave. A partir de esta observación se instaura la terapia profiláctica, la cual previene los episodios de sangrado, y busca mantener niveles de Factor VIII > 1% con una administración intermitente del Factor deficitario (1). Este tipo de tratamiento, considerado como el de elección en los pacientes con hemofilia severa, ha demostrado ser más efectivo en reducir las secuelas articulares y la invalidez secundaria en los pacientes hemofílicos severos, traduciéndose en una mejoría de la calidad de vida (2).
Impacto en el presupuesto en el plan de salud	Impacto económico neto de la cobertura de la intervención sobre el presupuesto del plan de salud (excluyendo otros gastos). Esto representa la diferencia entre los gastos previstos de la intervención propuesta y los posibles ahorros de costos que pueden derivarse de la sustitución de la intervención de otro (s) actualmente cubierto por el plan de salud. Limitada al costo de la intervención (por ejemplo costo de adquisición implementación y mantenimiento).	El costo base para el Factor humano anihemofílico (derivado del plasma) es de aproximadamente $ 265.853 para el frasco por 220UI, de $431.727 para el de 500UI, y de $956,433, para la presentación por 1000UI. Se establece un costo promedio por UI de $900. Para la estrategia profiláctica se estima un requerimiento de 25UI/kg 3 veces a la semana por 46 semanas al año, para un costo promedio anual de tratamiento de $108.675.000 (7) Fuente: SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012
Mejora de seguridad y tolerancia	Reducción en efectos sobre la salud relacionados con la intervención que son dañinos o no deseados, en comparación con intervenciones alternativas.	La estrategia profiláctica, considerada como la de elección en los pacientes con hemofilia severa, ha demostrado ser más efectiva en reducir las secuelas articulares y la invalidez secundaria en los pacientes hemofílicos severos, traduciéndose en una mejoría de la calidad de vida en comparación con la estrategia a demanda (2).
Interés en salud pública	Reducción de riegos producto de la intervención a nivel de la población general (ej: prevención, reducción de transmisión de la enfermedad, reducción de la prevalencia de factores de riesgo).	La hemofilia se considera una enfermedad huérfana. Su prevalencia es de menos de 1 por cada 5000 habitantes y, por consiguiente, está reconocida en la Ley 1392 de 2010 y la Ley 1438 de 2011 (8).
Mejora resultados en salud reportados por paciente	Capacidad de la intervención propuesta de producir cambios benéficos en desenlaces reportados por pacientes (DRP) (por ejemplo calidad de vida) por encima y más allá de los cambios benéficos producidos por las intervenciones alternativas; también incluye mejoras en conveniencia para laos pacientes.	Se define como profilaxis, al tratamiento inyectable endovenoso de concentrado de factor VIII en forma regular y con anticipación, con el fin de prevenir las hemorragias. El fundamento de la profilaxis primaria es impedir el daño articular y de la prevención secundaria, detener o minimizar este daño (1).
Limitación en desempeño de tecnologías alternativas para la enfermedad o condición	Limitación de desempeño de tecnologías comparativas en su capacidad de prevenir, curar o mejorar la condición de interés; también incluye limitaciones de desempeño en materia de seguridad, desenlaces reportados por los pacientes y la conveniencia.	La alternativa y abordaje clásico en el tratamieto de la Hemofilia A consiste en la administración a demanda del factor VIII exógeno; es decir, solamente en los casos en que se presente un episodio de sangrado articular o extra-articular. Este tipo de abordaje, aunque sigue siendo el más prevalente, a demostrado ofrecer resultados clínicos sub-óptimos, ya que el sangrado sigue ocurriendo, asi como el daño articular, traduciéndose en una pero calidad de vida relacionada con la salud. (HR-Qol) (2).
Equidad en grupos vulnerables	Grado en que la tecnología evaluada suple necesidades prioritarias de grupos específicos de poblaciónque están definidos por la sociedad como vulnerables.	El Ministerio de Salud y Protección Social, mediante la Resolución 430 de 2013, define al déficit congénito del Factor VIII (Hemofilia A) en el listado de enfermedades huérfanas; lo anterior en cumplimiento de la Ley 1392 de 2010, por la cual se reconocen las enfermedades huérfanas como de especial interés, para las que se adoptan normas tendientes a garantizar la protección social por parte del Estado colombiano a la población que padece de enfermedades huérfanas y sus cuidadores (8).
Costo-efectividad de la intervención	Razón incremental de costo comparada con el beneficio incremental de la tecnología comparada con alternativas existentes. El beneficio puede expresarse como número de eventos evitados, años de vida ganados, QALYs/AVACs ganados, días adicionales libres de dolor, etc.	Análisis de costo-utilidad que compara la profilaxis primaria con factor VIII de por vida, con el tratamiento a demanda en hemofilia A severa en Colombia, muestra una razón incremental de costo efectividad de COL$110,947,357.8 (USD$ 58,224.8)por QALY ganado, considerándose una estrategia no costo-efectiva, de acuerdo con el umbral teórico de 3 veces el PIB per capita, establecida como la regla de disposición a pagar de $48.458.861 (2).
Completitud y calidad del reporte	Grado en que la notificación de datos sobre la intervención propuesta está completa (ej: cumple con estándares científicos de notificación) y es consistente con las fuente bibliográficas citadas.	En 1998, se inicia la recolección de información acerca de hemofilia por parte de la Federación Mundial de Hemofilia al rededor del mundo. La encuesta mundial recolecta información demográfica básica, datos relacionados con recursos en el cuidado de pacientes, e información de prevalencia de complicaciones infecciosas tales como VIH y Hepatitis C. El documento más reciente es publicado en el año 2010 (5).
Relevancia y validez de la evidencia	Grado en que la evidencia sobre la intervención propuesta es relevante para la toma de decisiones (en términos de población, estadio de la enfermedad, descripción de comparadores, desenlaces, etc) y válida respecto a los estándares científicos (ej. diseño del estudio). Esto incluye consideraciones respecto a la incertidumbre (ej. resultados contradictorios entre varios estudios, limitado número de estudios y/o participantes).	Existe en la literatura mundial evidencia de buena calidad; se encuentran publicadas revisiones sitemáticas que comparan la estrategia profiláctica versus la terapia a demanda, que demuestran que la estrategia profiláctica proporciona un efecto protector en el desarrollo, tanto de sangrados de cualquier tipo, como de sangrado articular. Múltiples estudios de cohorte son consistentes con estos hallazgos, y respaldan la efectividad de la profilaxis primaria para disminuir la incidencia de eventos hemorrágicos y pronóstico de la artropatía (1).
Necesidad diferencial en salud (cronicidad, paleación)	Grado en que la tecnología evaluada suple necesidades en salud de grupos específicos de población que sin necesariamente ser catalogados como vulnerables requieren servicios diferenciales de salud (ej. cronicidad, palición, manejo del dolor, etc).	Tras la adopción de nuevas tecnologías en salud, la Hemofilia A se a convertido en una condición crónica manejable en los últimos años.

REFERENCES OF HTA BY-CRITERION REPORTS

REFERENCIAS- ZINC

1. WHO childhood mortality by cause, Diarrhoeal diseases. http://www.who.int/mediacentre/factsheets/fs330/en/index.html.

2. Tasa de Mortalidad por EDA en menores de 5 años 2011p. Así vamos en Salud 2012. http://www.asivamosensalud.org/inidicadores

3. Instituto Colombiano de Bienestar Familiar. Fonseca Z. Encuesta Nacional de la situación nutricional en Colombia 2010- ENSIN. Agosto 2011

4. Departamento Administrativo Nacional de Estadística (DANE). Proyecciones de población 2005-2020 nacional y departamental. http://www.dane.gov.co

5. Universidad de Antioquia, Ministerio de Salud y Potección Social, Colciencias. Guía de Práctica Clínica para la prevención, diagnóstico y tratamiento de la enfermedad diarreica aguda en niños menores de 5 años. 2013-8

6. SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012

7. Ministerio de Salud y Protección Social. Plan Decenal de Salud Pública 2012-2021. Bogotá, Marzo 2013.

8. Sistema de vigilancia y control en salud pública (SIVIGILA) Protocolo de vigilancia y control de la mortalidad por enfermedad diarreica aguda en menores de 5 años. Instituto Nacional de Salud. 2011

REFERENCIAS- ANASTROZOL

1. International Agency for Research on Cancer (IARC). GLOBOCAN 2008.Breast Cancer Incidence, Mortality and Prevalence Worldwide in 2008 Summary. http://globocan.iarc.fr/factsheet.asp

2. Sociedad Mexicana de Oncología. Tercera revisión del consenso nacional sobre diagnóstico y tratamiento del cáncer mamario. Gamo Vol. 7 Suplemento 6, 2008

3. Pardo C., Cendales R. Incidencia estimada y mortalidad por cáncer en Colombia , 2002-2006. Ministerio de la Protección Social. Instituto Nacional de Cancerología. Bogotá, 2010.

4. International Agency for Research on Cancer (IARC). GLOBOCAN 2008. http//globocan.arc.fr/factsheet.asp

5. Instituto Nacional de Cancerología. Casos nuevos de cáncer de mama, según estadio clínico y régimen de afiliación al ingreso, INC, Colombia, 2008. Registro Institucional de Cáncer. http://www.cancer.gov.co

6. F. Cardoso etal. A review ofthe treatment of endocrine responsive metastatic breast cancer in postmenopausal women. Cancer Treatment Reviews 39 (2013); 457–465

7. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review). The Cochrane Collaboration. 2009

8. SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012.

9. Hong-Bin Xu, Yu-Jin Liu, Ling Li. Aromatase Inhibitor Versus Tamoxifen in Postmenopausal Woman With Advanced Breast Cancer: A Literature-Based Meta-Analysis. Clinical Breast Cancer, Vol. 11, No. 4, 246-51

10. Ministerio de Salud y Protección Social - Instituto Nacional de Cancerología, ESE. Plan Decenal para el Control del Cáncer en Colombia, 2012 – 2021. Bogotá 2012

11. Ministerio de Salud y Potección Social, Colciencias, Instituto Nacional de Cancerología. Guía de Práctica Clínica para la detección temprana, tratamiento integral, seguimiento y rehabilitación del Cáncer de Mama. 2013-19

REFERENCIAS- TICAGRELOR

1. Hernandez E. Epidemiología del síndrome coronario agudo y la insuficiencia cardiaca en Latinoamérica. Rev Esp Cardiol. 2011;64(Supl 2):34-43

2. Cassiani C., Cabrera A. Síndromes coronarios agudos: epidemiología y diagnóstico. Salud Uninorte. Barranquilla (Col.) 2009; 25 (1): 118-134

3. Sociedad Colombiana de Cardiología y Cirugía Cardiovascular. Guías Colombianas de cardiología. Síndrome Coronario Agudo sin elevación del ST. Revista Colombiana de Cardiología, Diciembre 2008. Vol. 15 Suplemento 3

4. Ministerio de Salud y Protección Social. Plan Decenal de Salud Pública 2012-2021. Bogotá, Marzo 2013.

5. Steg P., Goldberg R., Gore J., et al. Baseline Characteristics, Management Practices, and In-Hospital Outcomes of Patients Hospitalized With Acute Coronary Syndromes in the Global Registry of Acute Coronary Events (GRACE). The American Journal of Cardiology Vol. 90 August 15, 2002

6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association.Circulation. 2012 Jan 3;125(1)

7. Castellanos J. Proyección de costos en Colombia de la atención inicial del síndrome coronario agudo. Univ. Méd. Bogotá (Colombia), 2011; 52 (1): 36-43.

8. DANE. Proyecciones de población. Colombia. Proyecciones de población departamentales y municipales por área 2005 - 2020. Disponible en: http://www.dane.gov.co/files/investigaciones/ poblacion/proyepobla06_20/ProyeccionMunicipios2005_2020.xls

9. Universidad de Antioquia, Ministerio de Salud y Potección Social, Colciencias. Guía de Práctica Clínica para el Síndrome coronario Agudo. 2013-17

10. Hamm Ch., Bassand JP., Agewall S., et al. Guía de práctica clínica de la ESC para el manejo del síndrome coronario agudo en pacientes sin elevación persistente del segmento ST. Rev Esp Cardiol. 2012;65(2):173.e1-e55

11. Wallentin L., Becker R., Budaj A., et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;361:1045-57.

12. SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012

13. Ministerio de Salud y Protección Social. Plan Decenal de Salud Pública 2012-2021. Bogotá, Marzo 2013.

14. Levin L., Wallentin L., Bernfort L., et al. Health-Related Quality of Life of Ticagrelor versus Clopidrogrel in patients with Acute Coronary Syndromes-Results from the PLATO Trial. Value in Health 16 (2013) 574-580.

15. Nikolic E., Janson M., Hauch Q., et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months. Results from the PLATO study. European Heart Journal 34(3):220-8, 2013 Jan.

REFERENCIAS- PROFILAXIS PRIMARIA

1. Ministerio de Salud. "Guía Clínica Hemofilia". Santiago: Minsal, 2013

2. Castro H.Assesing feasibility of conducting and using Health Technology Assessment in Colombia. The case of severe Hemophilia A. Work in progress. 2013.

3. Fundación de la Hemofilia. Guía de Tratamiento de la Hemofilia. Consenso de Médicos especialistas en Hemofilia de la República Argentina. 1ra Edición. Buenos Aires, Julio de 2011

4. Castro H., Briceño MF., Casas C., Rueda J., The History and Evolution of the Clinical Effectiveness of Haemophilia Type A Treatment: A Systematic Review. Indian J Hematol Blood Transfus. November 2012

5. World Federation of Hemophilia. Report on the Annual Global Survey 2010. December 2011

6. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Systematic Review. 2011. The Cochrane Collaboration.

7. SISMED 2012. Listado de Precios Promedio y Unidades en la cadena de comercializacion de Medicamentos. Enero a Septiembre de 2012.

8. Ministerio de Salud y Protección Social. Resolución 430 de 2013. Listado de enfermedades huérfanas

HOJA DE INFORMACIÓN

Título del proyecto: "**EVALUANDO LA FACTIBILIDAD DE CONDUCIR Y USAR LA EVALUACIÓN DE TECNOLOGÍAS SANITARIAS EN COLOMBIA- El caso de la hemofilia severa tipo A**"

Buen día,

Mi nombre es Héctor Eduardo Castro Jaramillo, soy un médico Colombiano con formación en economía de salud, salud pública y políticas de salud, actualmente estoy finalizando un Doctorado en salud pública y economía de salud con la Universidad de Londres (*London School of Hygiene & Tropical Medicine*) y para poder graduarme y obtener el título correspondiente debo presentar un trabajo original de investigación.

La Evaluación de Tecnologías Sanitarias, es una técnica que tomado fuerza desde finales de los años 70s y que compara los beneficios y costos de diferentes tecnologías en salud. La Evaluación de Tecnologías Sanitarias es utilizada en la actualidad para informar la toma de decisiones en salud en diferentes contextos.

La hemofilia A por su lado, es una enfermedad que afecta a 1 de cada 5.000 a 10.000 hombres en el mundo y en nuestro país se estima que cerca de 2500 personas viven con esta patología (aproximadamente 800 de ellas presentan casos severos de la enfermedad). El tratamiento consiste en reponer el factor de coagulación (FVII) faltante de manera congénita, reestablecer los mecanismos naturales de coagulación y reducir el riesgo de hemorragias que presentan dichos pacientes.

En Colombia el acceso a tratamiento con factores de coagulación ha mejorado en años recientes, no obstante persisten diferencias de acceso entre zonas rurales y urbanas, entre aquellos que tienen EPS y los que no; así mismo la calidad de tratamiento varia de un lugar a otro y hay diferentes formas de tratar la enfermedad que no han sido comparadas plenamente en nuestro medio. Gran parte de la información relacionada con el impacto que tiene el tratamiento en la calidad de vida de los pacientes con Hemofilia proviene de otros países, muchos de ellos con más recursos que el nuestro.

El objetivo del presente estudio es analizar mediante el caso de la Hemofilia severa tipo A como la Evaluación de Tecnologías Sanitarias puede ser usada en nuestro contexto con el fin de identificar la mejor opción de tratamiento, de tal forma que más pacientes de esta y otras patologías puedan beneficiarse del mejor tratamiento disponible y de una manera sostenible. Este estudio requiere recolectar datos relacionados con experiencias y percepciones de aquellos involucrados en la conducción y uso de la Evaluación de Tecnologías Sanitarias en Colombia. Así mismo pudiera requerir información pasada o futura relacionada con la historia clínica, el tipo de tratamiento recibido y la percepción general sobre el estado de salud de los participantes.

En caso de estar interesado en participar lo invito a diligenciar el formato de consentimiento informado en señal de aprobación. Sí a lo largo del estudio tiene preguntas adicionales sobre el proyecto no dude en comunicarlas al investigador principal o a alguna de las personas involucradas, igualmente puede comunicarse al número 310-8226382.

Muchas gracias por su tiempo y disposición al permitir que la investigación científica siga creciendo en nuestro país.

HECTOR EDUARDO CASTRO JARAMILLO MD, MSc, DrPH (cand)

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE
CONSENTIMIENTO INFORMADO

Título del proyecto: "**EVALUANDO LA FACTIBILIDAD DE CONDUCIR Y USAR LA EVALUACIÓN DE TECNOLOGÍAS SANITARIAS EN COLOMBIA- El caso de la Hemofilia severa tipo A**"

Nombre del investigador principal: Héctor Eduardo Castro Jaramillo

Casilla para su inicial

1. Confirmo que he leído y entendido la información de participante proporcionada en el la hoja de información en la fecha _____ para el estudio anotado anteriormente. He tenido la oportunidad de considerar la información, hacer preguntas y estas me han sido contestadas completamente.

2. Entiendo que mi participación es voluntaria y estoy en libertad de retirarme del estudio en cualquier momento, sin necesidad de dar explicaciones, sin que mis derechos legales o mí cuidado en salud (en caso de ser paciente) sean afectados.

3. Así mismo autorizo al investigador principal a grabar, transcribir y analizar las entrevistas a que hubiere lugar con fines puramente académicos.

4. Estoy de acuerdo en hacer parte del estudio mencionado anteriormente

Sí usted es un paciente en tratamiento para Hemofilia A, por favor diligencie la siguiente parte:

5. Entiendo que la información proveniente de mi historia clínica o información recolectada durante el estudio será custodiada por individuos responsables de _____, por autoridades regulatorias o mi EPS, donde sea relevante mi participación en esta investigación. Autorizo a estos individuos a acceder a mi información.

6. Estoy de acuerdo en que le informen a mi médico tratante de que participo en este estudio.

Nombre del participante	Firma	Fecha
_____	_____	_____

Nombre de quien toma consentimiento (Sí difiere de investigador)	Firma	Fecha
_____	_____	_____

Investigador principal	Firma	Fecha
_____	_____	_____

1   copia para el participante; 1 copia para el investigador principal; 1 (original) copia para archivar en el centro de estudio

APENDDIX 10. ETHICAL CONSIDERATIONS

All individuals received an information sheet and consent form in Spanish which explained the objectives of the study, and stressed that their participation was completely voluntary (Appendix 9). Participants were asked to consent to being audio-recorded during the interviews and focus group. When local sources of data were needed to estimate parameters to fill data gaps for insertion into the haemophilia model, participants received a different information sheet and consent form in Spanish, appropriate to their role played in this research.

All forms complied with the London School of Hygiene and Tropical Medicine (LSHTM) ethics approval requirements for non-interventional studies. All documentary, transcript and observation data was anonymised. Interviews and focus group took place in a suitable location for the purpose of this study. Each participant was given a contact number they could call to ask questions about the study after the interviews or focus group were completed. Following transcription, all original audio-recordings were to be stored for a year and then destroyed in December 2014.

VII. REFERENCES

- Aledort, LM 2007, "History of Haemophilia", *Haemophilia*, vol. 13, Suppl. 5, pp. 1-2.
- Aronstam, A, Arblaster, PG, Rainsford, SG, Turk, P, Slattery, M, Alderson, MR, Hall, DE, & Kirk, PJ 1976, "Prophylaxis in hemophilia: a double blind controlled trial", *British Journal of Haematology*, vol. 33, no. 1, pp. 81–90.
- Aronstam, A, Kirk, PJ, McHardy, J, Culver-James, JW, McLEllan, DS, Turk, P, Rainsford, SG & Slattery, M 1977, "Twice weekly prophylactic therapy in haemophilia A, *Journal of Clinical Pathology*, vol. 30, no. 1pp. 65–7.
- Astisagarra, E 2003, *El Método Delphi*, San Sebastian: Universidad de Deusto.
- Awoko, GM. (2001) "Sampling Issues in Qualitative Research", *Nurse Researcher*, vol. 12, no. 1, pp. 7- 19
- Aznar, JA, Magallon, M, Querol, F, Gorina, E, & Tusell, JM 2000, "The orthopaedic status of severe haemophiliacs in Spain", *Haemophilia*, vol. 6 no. 3, pp. 170-6.
- Aznar, JA, Marco, A, Jimenez-Yuste, V, Fernandez-Fontecha, E, Perez, R, Soto, I, Parra, R, Moreno M, Mingot, ME & Moret, A 2012, "Is on-demand treatment effective in patients with severe haemophilia?", *Haemophilia*, vol. 18, no. 5, pp. 738-742
- Baltussen, R & Niessen, L 2006, "Priority-setting of health interventions: the need for multi criteria decision analysis", *Cost-Effectiveness Resource-allocation*, vol. 4, p.14.
- Baltussen, R, Ten Asbroek, AH, Koolman, X, Shrestha, N, Bhattarai, P & Niessen, LW 2007, "Priority-setting using multiple criteria: should a lung health programme be implemented in Nepal?" *Health Policy Planning*, vol. 22, pp. 178–185.
- Bernal, J, Suárez, F 2008, "La carga de la enfermedad genética en Colombia, 1996-2025". *Universidad Medica*, vol. 49, no. 1, pp. 12-28.
- Berntorp, E, Astermark, J, Bjorkman, S, Blanchette, VS, Fischer, K, Giangrande, PLF, Gringeri, A, Ljung, R, Manco-Johnson, MJ, Morfini, M, Kilcoyne, RF, Petrini, P, Rodriguez- Merchan, EC, Schramm, W, Shapiro, A, Van De Berg, HM & Hart, C 2003, "Consensus perspectives on prophylactic therapy for haemophilia: summary statement". *Haemophilia*, vol. 9, Suppl. 1, pp. 1-4.
- Berntorp, E 2009, "Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens", *Haemophilia*, vol. 15, no. 6, pp. 1219-27.
- Birch, S &Gafni, A 1992, "Cost-effectiveness/ utility analyses. Do current decision rules lead us to where we want to be?" *Journal of Health Economics*, vol. 11, pp. 279- 296.
- Birch, S & Gafni, A 1992, "Changing the problem to fit the solution: Johannesson and Weinstein´s (mis) application of economics to real world problems", *Journal of Health Economics*, vol. 12, pp. 469- 76.
- Birch, S & Gafni, A 2002, "On being NICE in the UK: guidelines for technology appraisal for the NHS in England and Wales", *Health Economics*, vol. 11, pp. 185-91.
- Biss, TT, Chan, AK, Blanchette, VS, Iwenofu, LN, Mclimont, M & Carcao MD 2008, "The Use of Prophylaxis in 2663 Children and Adults with Haemophilia: Results of the 2006 Canadian National Haemophilia Prophylaxis Survey." Association of Haemophilia Clinic Directors of Canada (AHCDC); Canadian Association of Nurses in Haemophilia Care (CANHC). *Haemophilia*, vol. 14, no. 5, pp. 923-30.
- Bidlingmaier, C, Knorr, S, Olivieri, M & Kurnik, K 2011, "Mild vs. severe haemophilia A: The dilemma of an underestimated disease", *Journal of Thrombosis and Haemostasis*, vol. 9, p. 694.
- Bohn, RL, Avorn, J, Glynn, RJ, Choodnovskiy, I, Haschemeyer, R. & Aledort, LM 1998, "Prophylactic use of factor VIII: an economic evaluation", *Thrombosis & Haemostasis*, vol. 79, no. 5, pp. 932-937.
- Boer R, Lalla, A, Mathew, P, Preblick R, Pocoski, J 2010, "US cost effectiveness analysis of primary prophylaxis versus on-demand treatment in hemophilia: Design and rationale of a comprehensive model", *Value in Health*, vol. 13, no. 3, Suppl. 3, pp A216.

- Box, GEP & Draper NR 1987, *Empirical Model-Building and Response Surfaces*, Wiley & Sons, United States, p. 424

- Briggs, AH 2001, "Handling uncertainty in economic evaluation and handling results", in MF Drummond & A McGuire (eds), *Economic evaluation in health care, merging theory with practice*, Oxford University Press, Oxford, pp. 162- 80.

- Briggs, AH, Goeree, R, Blackhouse, G & O´Brien, BJ 2002, "Probabilistic analysis of cot-effectiveness models; choosing between treatment startegies for gastroesaphageal reflux disease", *Medical Decision Making*, vol. 22, pp. 290- 308.

- Braun, V & Clarke, V 2006, "Using thematic analysis in psychology", *Qualitative Research in Psychology*, vol. 3, pp. 77-101.

- Britten, N 1995, "Qualitative interviews in medical research", *BMJ,* vol. 311, pp. 251-3.

- Bulfone, L, Younie, S & Carter, R 2009, "Health Technology Assessment: Reflections from the Antipodes", *Value in Health*, vol. 12, Suppl. 2, pp. 1- 5.

- Buse, K, Mays, N & Walt, G 2010, *Making Health Policy*, 2nd Edition, Open University Press, England.

- Buxton, MJ, Drummond, MF, Van Hout, BA, Prince, RL, Sheldon, TA, Szucs & Vray, M 1997, "Modelling in economic evaluation: an unavoidable fact of life", *Health Econ*, vol. 6, no. 3, pp. 217-27.

- Byskov, J, Bloch, P, Blystad, A, Hurtig, AK, Fylkesnes, K, Kamuzora, P, Kombe, Y, Kvåle, G, Marchal, B, Martin, DK, Michelo, C, Ndawi, B, Ngulube, TJ**,** Nyamongo, I**,** Olsen, OE**,** Onyango-Ouma, W, Sandøy, IF**,** Shayo, EH**,** Silwamba, G**,** Songstad, NG & Tuba, M 2009, "Accountable priority-setting for trust in health systems--the need for research into a new approach for strengthening sustainable health action in developing countries", *Health Res Policy Syst*, vol. 7, p. 23.

- Caballero- Uribe, CV 2012, "La crisis del sector salud". *Salud Uninorte*, vol. 28 no. 2, pp. 7- 12.

- Canadian Agency for Drugs and Technologies in Health, CCOHTA to CADTH: our history, http://www.cadth.ca/index. php/en/cadth/corporate-profile/history viewed 15 May 2011

- Capaci, K, Balkan, C, Yilmaz, D, Yilmaz, AY, Kirazli, Y, Durmaz, B & Kavakli, K 2010, "Outcome of joint functions in hemophilic patients: A twelve year retrospective study". *Journal of Rheumatology and Medical Rehabilitation*, vol. 21, no. 2, pp. 29-36.

- Carcao, MD & Aledort LM 2007, "The Round Table Group- prophylaxis in the haemophilia population-optimizing therapy [Report]", *Haemophilia*, vol. 13, no. 3, pp. 227-32.

- Carcao, M, Chambost, H & Ljung, R 2010, "Devising a best practice approach to prophylaxis in boys with severe haemophilia: evaluation of current treatment strategies", *Haemophilia,* vol. 16, Suppl. 2, pp. 4-9.

- Carlsson, M, Berntorp,E, Björkman, S, Lethagen, S, & Ljung, R 1997, "Improved cost-effectiveness by pharmacokinetic dosing of factor VIIII in prophylactic treatment of haemophilia A", *Haemophilia*, vol. 3, pp. 96–101.

- Castro, HE 2011, "Health technology assessment across borders and the role of NICE and NICE international on spreading the message on evidence based health policies", Organisational Policy Analysis Report (DrPH), London School of Hygiene & Tropical Medicine.

- Castro, HE 2012, "Agencias de Evaluación de Tecnologías Sanitarias: ¿Moda o Necesidad", *Revista Via SALUD*- Centro de Gestión Hospitalaria, vol. 16, no. 1, pp. 12- 17.

- Castro, HE, Briceño, MF, Casas, C & Rueda, JD. "The History and Evolution of the Clinical Effectiveness of Haemophilia Type A Treatment: A Systematic Review. Indian Journal of Hematology and Blood Transfusion", viewed May 8 2013, < http://link.springer.com/article/10.1007%2Fs12288-012-0209-0>

- Castro, HE, Briceño, MF, Casas, C & Rueda, JD 2014, "The History and Evolution of the Clinical Effectiveness of Haemophilia Type A Treatment: A Systematic Review", *Indian Journal of Hematology and Blood Transfusion*, vol. 30, no.1, pp. 1-11.

- Centers for Disease Control and Prevention- CDC (eds) 2008, *Summary Report of UDC Activity National: Treatment And Outcome By Severity (Haemophilia)*, Atlanta, Department Of Health And Human Services- Centers For Disease Control And Prevention.

- Centro Nacional para la Prevención de Enfermedades Crónicas y Promoción de Salud 2000, Atlanta, viewed May 30 2013, <http://www.cdc.gov/growthcharts>

- Chalkidou, K, Tunis, S, Lopert, R , Rochaix, L, Sawicki, PT, Nasser, M & Xerri, B 2009, "Comparative Effectiveness Research and Evidence-Based Health Policy: Experience from Four Countries", *The Milbank Quarterly*, vol. 87, no. 2, pp. 339–367.

- Charmaz, K 2002, *Constructing Grounded Theory. A practical guide through qualitative analysis*. Sage.

- Chilcott, J, Tappenden, P, Rawdin, A, Johnson, M, Kaltenthaler, E, Paisley, S, Papaioannou, D & Shippam, A 2010, "Avoiding and identifying errors in health technology assessment models: qualitative study and methodological review". *Health technology assessment*, vol. 14, no. 25, iii-iv, ix-xii, 1-107, DOI 10.3310/hta14250

- Chorba, Tl, Holman, RC, Strine, TW, Clarke, MJ & Evatt, BL 1994, "Changes in longevity and causes of death among persons with haemophilia A", *Am J Hematol*, vol. 45, no. 2, pp. 112-21.

- Claxton, C, Martin, S, Soares, M, Rice, N, Spackman, E, Hinde, S, Devlin, N, Smith, PC & Sculpher, M 2014, *Methods for the Estimation of the NICE Cost Effectiveness Threshold- Final Report. Research Paper 81*. Centre for Health Economics, University of York, UKCHE, York, viewed Jan 13 2014, <http://www.york.ac.uk/media/che/documents/papers/ researchpapers/ CHERP81_methods_estimation_NICE_costeffectiveness_threshold_(Nov2013).pdf>

- Colombian League for Haemophilia/ Liga Colombiana de hemofílicos y otras deficiencias sanguíneas. Secondary data provided to the researcher by its Chair Dr Sergio Robledo Rada, 15 October 2011.

- Colombo, GL, Di Matteo, S, Mancuso, ME & Santagostino, E 2011, "Cost–utility analysis of prophylaxis versus treatment on demand in severe haemophilia A". *Clinico Economics and Outcomes Research*, vol. 3, pp. 55-61.

- Coppola, A, Di Capua, M & De Simone, C 2008, "Primary prophylaxis in children with haemophilia", *Blood Transfusion*, vol. 6, Suppl. 2, pp. s4-s11.

- Crookes, P & Davies, S (eds) 1998, *Research into Practice: Essential Skills for Reading and Applying Research*, Ballière Tindall, in association with the RCN, London.

- Culyer, AJ & Bombard, I 2012, "An Equity Framework for Health Technology Assessments", *Med Decis Making*, vol. 32, no. 3, pp. 428-441.

- Curry, LA, Nembhard, IM & Bradley, EH 2009, "Qualitative and mixed methods provide unique contributions to outcomes research", *Circulation,* vol. 119, pp. 1442-52.

- Daliri, AA, Haghparast, H & Mamikhani, J 2009, "Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran". *International Journal of Technology Assessment in Health Care*, vol. 25, no. 4, pp. 584-587.

- DANE-Departamento Administrativo Nacional de Estadística, Colombia, Bogotá, viewed Aug 4 2014 <http://www.dane.gov.co/index.php/indices-de-precios-y-costos/indice-de-precios-al-consumidor-ipc>

- Darby, SC, Kan, SW, Spooner, RJ, Giangrande, PLF, Hill, F, Hay, C, Lee, CA, Ludlam & Williams, M 2007, "Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV", *Blood*, vol. 110, pp. 815- 825.

- De Charry, LC, Carrasquilla, G & Roca, S 2008, "Equidad en la detección del cáncer de seno en Colombia- Equity regarding early breast cancer screening according to health insurance status in Colombia", *Rev. salud pública*, vol. 10, no. 4, pp. 571- 582.

- Defensoria del Pueblo- Colombia, 2013, Page 110, Bogotá, viewed Sept 30 2013 <http://www.defensoria.org.co/red/anexos/publicaciones/tutelaDerechoSalud2012.pdf>

- De Moerloose, P, Urbancik, W, Van Den Berg, HM & Richards, M 2008, "A survey of adherence to haemophilia therapy in six European countries: results and recommendations", *Haemophilia*, vol. 1, pp. 931–8.

- Diederich, A, Winkelhage, J, Wirsik, N 2011, "Age as a criterion for setting priorities in health care? A survey of the German public view", viewed Feb 16 2014, < http://www.plosone.org/ article/info%3Adoi%2F10.1371%2Fjournal.pone.0023930>

- Dillon, A 2005, cited by O´Donell et al, 2009 "personal communication, Molndal, Sweden, November 2005" in "Health Technology Assessment: lessons learned from around the world—an overview", *Value in health*, vol 12, Suppl. 2, pp. 1098-2015

- Dolan, P, Gudex, C, Kind, P & Williams A 1995, "A social tariff for EuroQoL: Results from a UK general population survey, Discussion paper No 138". Centre for Health Economics, University of York, York, viewed Feb 16 2014 <http://www.york.ac.uk/media/che/documents/ papers/discussionpapers/CHE%20Discussion%20Paper%20138.pdf>

- Dolan, JG 2010, "Multi-Criteria clinical decision support. A primer on the use of multiple criteria decision-making methods to promote evidence-based, patient-centered health care", *Patient*, vol. 3, pp. 229–248.

- Donaldson, C, Currie, G & Milton, C 2002, "Cost-effectiveness analysis in health care: contraindications", *British Medical Journal*, vol. 325, pp. 891- 4.

- Drummond, M & Weatherly, H 2000, "Implementing the Findings of Health Technology Assessments", *International Journal of Technology Assessment in Health care*, vol 16, no. 1 pp. 1-12.

- Drummond, MF, Sculpher, MJ, Torrance, GW, O'Brien, B & Stoddart, GL 2005, *Methods for the economic evaluation of health care programmes*. 3rd ed, Oxford: Oxford University Press, England.

- Drummond MF, Schwartz JS, Jonsson B, Luce BR, Neumann PJ, Uwe Siebert U & Sullivan SD 2008, "Key principles for the improved conduct of health technology assessments for resource-allocation decisions", *Int J Technol Assess Health care*, vol. 24, pp. 244-258.

- Drummond, MF & Sorenson, C 2009, "Nasty or Nice? A Perspective on the Use of Health Technology Assessment in the United Kingdom", *Value in Health*, vol.12, Suppl. 2, pp. S8-S13.

- Drummond, MF, Barbieri, M, Cook, J, Glick, H, Lis, J, Malik, F, Reed, SD, Rutten, F, Sculpher, M & Severens, J 2009, "Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force Report", *Value in Health*, vol. 12, no. 4, pp. 409-18.

- Eddy, D 1990, "Clinical Decision making: from theory to practice. Anatomy of a decision*, JAMA*, vol. 263, pp. 441- 43.

- Eddy, D 2007, "Evidence-based medicine: a unified approach", *Health Aff*airs, vol. 24, pp. 9–17.

- Eddy, D, Hollingworth, W, Caro, J, Tsevat, J, McDonald, K & Wong, J- on Behalf of the ISPOR–SMDM Modeling Good Research Practices Task Force 2012, "Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7", *Value in health*, vol. 15, pp. 843– 850.

- El Colombiano (local press release), Medellin- Colombia, viewed Dec 18 2011 <http://www.elcolombiano.com/BancoConocimiento/L/lo_errores_con_los_que_quedo_el_pos _se_iran_corrigiendo_dijo_el_gobierno/lo_errores_con_los_que_quedo_el_pos_se_iran_corrigi endo_dijo_el_gobierno.asp>

- Elliott, J, Heesterbeek, S, Lukensmeyer, C & Slocum, N 2005, *Participatory Methods Toolkit. A practitioner´s manual*. The Flemish Institute for Science and Technology Assessment (viWTA) and the King Baudouin Foundation.

- El Tiempo (local press release), Bogotá- Colombia, viewed Dec 18 2011 <http://www.eltiempo.com/opinion/editoriales/ARTICULO-WEB-NEW_NOTA_INTERIOR-10869844.html>

- Eichler, HG, Kong, S, Gerth, W, Mavros, P & Jönsson, B 2004, "Use of Cost-Effectiveness Analysis in Health-Care Resource-allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge?", *Value in health*, vol. 7, no. 5, pp. 518- 28.
- Escobar, ML 2005, "Health Sector Reform in Colombia". *Development Outreach*, vol. 22, no. 7, pp. 6-9.
- Evatt, BL 2006, "The tragic history of AIDS in the haemophilia population, 1982-1984", *J Thromb Haemost*, vol. 4, no. 11, pp. 2295-301.
- Farrugia, A, O'Mahony, B, Cassar J 2012, "Health technology assessment and haemophilia, *Haemophilia*, vol. 18, no. 2, pp. 152-157.
- Farrugia A, Cassar J, Kimber, MC, Bansal, M & Balboni, S 2013, "Treatment for life for severe haemophilia A– A cost-utility model for prophylaxis vs. on-demand treatment", *Haemophilia,* vol. 18, no. 5, pp. 828-829.
- Feldman, BM, Pai, M, Rivard, GE , Israels, S, Poon, MC, Demers, C, Robinson,, S, Luke, KH, Wu, JKM, Gill, K, Lillicrap, D, Babyn, P, Mclimont, M & Blanchette VS- on behalf of the association of haemophilia Clinic directors of Canada prophylaxis study group 2006, "Tailored Prophylaxis In Severe Haemophilia A: Interim Results From The First 5 Years Of The Canadian Haemophilia Primary Prophylaxis Study", *J Thromb Haemost*, vol. 4, pp. 1228–36.
- Feldman, B, Funk, S, Bergstrom, BM, Zourikian, N, Hilliard, P, Van der Net, J, Engelbert, R, Petrini, P, Van der berg, H, Manco, M, Rivard, G, Abad, A & Blanchette V 2011, "Validation of the new pediatric joint scoring system from the international haemophilia prophylaxis study group: validity of the heamophilia joint health score", *Arthritis & care*, vol 63, no. 2, pp. 223- 30.
- Fischer, K, Van der Bom, JG, Mauser-Bunschoten, EP, Roosendaal, G, Prejs, R, Grobbee, DE & Van den Berg, HM 2001, "Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy", *Haemophilia,* vol*.* 7, no. 5, pp. 446-52.
- Fischer, K, Van Der Bom, JG, Molho, P, Negrier, C, Mauser-Bunschoten, P, Roosendaal, G, De Kleijn, P, Grobbee, DE & Van den Berg, HM 2002, "Prophylactic versus on-demand treatment strategies for severe haemophilia: A comparison of costs and long-term outcome", *Haemophilia*, vol. 8, no. 6, pp. 745-752.
- Fischer, K & Van Den Berg, M 2003, "Prophylaxis for severe haemophilia: clinical and economical issues", *Haemophilia*, vol. 9, no. 4, pp. 376-81.
- Fischer, K, Grobbee, DE & Van den Berg, HM 2007, "RCTs and observational studies to determine the effect of prophylaxis in severe haemophilia", *Haemophilia*, vol. 13, no. 4, pp. 345-50
- Fischer, K, Valentino, L, Ljung, R, Blanchette, V 2008, "Prophylaxis for severe haemophilia: clinical challenges in the absence as well as in the presence of inhibitors", *Haemophilia*, vol. 14, Suppl. 3, pp. 196-201.
- Florez, CE & Soto, V 2007, "Evolución de la equidad en el acceso a los servicios y estado de salud de la población colombiana 1990 -2005". Universidad de los Andes. Fundación Corona <http://www.asivamosensalud.org/descargas/Presentacion_Equidad_Corona_DNP.pdf>
- Florez, ID, Lugo, LH, Tamayo, ME, Contreras JO, Sierra JM, Acosta JL, Lalinde MI, Granados CM, Lozano JM, Mejía AE, Atehortúa SC, Mejía ME, Ramírez CM & Quintero A- CINETS, Ministerio de Salud y Potección Social, Colciencias 2013, *Guía de Práctica Clínica para la prevención, diagnóstico y tratamiento de la enfermedad diarreica aguda en niños menores de 5 años*, Bogotá-Colombia, viewed Feb 16 2014 <http://www.iets.org.co/reportes-iets/Documentacin%20Reportes/Gu%C3%ADa.Completa.EDA.2013.pdf>
- Franchini, M, Tagliaferri, A & Mannucci, PM 2007, "The Management Of Haemophilia In Elderly Patients". *Clin Interv Aging*, vol. 2, pp. 361–8.
- Garrison, LP, Neumann, PJ, Erickson, P, Marshall, D & Mullins, D 2007, "Using real- world data for coverage and payment decisions: The ISPOR real- world data task force", *Value in Health*, vol. 10, no. 5, pp. 326- 35.

- Geraghty, S, Dunkley, T, Harrington, C, Lindvall, K, Maahs, J & Sek, J 2006, "Practice Patterns In Haemophilia A Therapy – Global progress towards optimal care", *Haemophilia*, vol. 12, no. 75–81.

- Giangrande, PLF &Taylor, S 2002, *Communicating Risk: The Example Of Vcjd. Proceedings Of The World Federation Of Haemophilia Global Forum On The Safety And Risks Of Immunodeficiency, AIDS And Death Supply Of Haemophilia Treatment Products*, Montreal, World Federation Of Haemophilia, p. 39.

- Giangrande, PLF 2004, "Blood Products for Haemophilia Past, Present and Future", *Biodrugs*, vol. 18, no. 4, pp. 225-234.

- Glassman, A, Chalkidou, K, Giedion, U, Teerawattananon, Y, Tunis, S, Bump, J & Pichon- Riviere A 2012, "Priority-setting institutions in health- Recommendations from a Center from Global Development Working Group", *Global Health*, vol. 7, no. 1, pp 13- 34.

- White, G, Rosendaal, F, Aledort, LM, Lusher, JM, Rothschild, C & Ingerslev J 2001, "Definitions in Hemophilia", *Thromb Haemost*, vol. 85, p. 560.

- Glaser, B & Strauss, A, 1965, *Awareness of dying*, Chicago, Aldine.

- Glaser, BG & Strauss, AL 1967, *The Discovery of Grounded Theory* , Glaser, BG & Strauss, AL.

- Glaser, B 1992, *Emergence vs. forcing: Basics of grounded theory analysis*. Mill Valley, California, Sociology Press.

- Goetghebeur, M, Wagner, M, Khoury, H, Levitt, R, Erickson, L & Rindress D 2008, "Evidence and Value Impact on Decision Making- The EVIDEM framework and potential applications", *BMC Health Serv Res*, vol. 8, p. 270.

- Goetghebeur, M, Wagner, M, Khoury, H, Rindress, D, Gregoire, JP & Deal, C 2010, " Combining multicriteria decision analysis, ethics and health technology assessment: applying the EVIDEM decision making framework to growth hormone for Turner syndrome patients", *Cost Eff Resour Alloc*, vol. 8, p. 4.

- Goetghebeur, M, Wagner, M, Khoury, H, Levitt, RJ, Erickson, LJ & Rindress, D 2012, "Bridging health technology assessment (HTA) and efficient health care decision making with multicriteria decision analysis (MCDA): Applying the EVIDEM framework to medicines appraisal", *Med Decis Making*, vol. 32, no. 2, pp.376-88

- Gonzalez-Pier, E, Gutierrez-Delgado, C, Stevens, G, Barraza-Llorens, M, Porras-Condey, R, Carvalho, N, Loncich, K, Dias, RH, Kulkarni, S, Casey, A, Murakami, Y, Ezzati, M & Salomon, JA 2007, "Priority-setting for health interventions in Mexico's System of Social Protection in Health", *Salud Publica Mex*, vol. 49, Suppl. 1, pp. S37-52.

- Goodman, C 2004, *Introduction to Health Technology Assessment*. The Lewin Group, Falls Church, Virginia, USA.

- Gorina, E, Alberca, I, Aznar, JA, Garcia, Talavera, J, Gutierrez, R, Lucia, F, Magallon, M, Moreno, M, Paloma, I, Querol, F, Quintana, M, Rodriguez-Pinto, C, Sedano, C, Tusell, JM & Uranga, M 2002, "Results of an orthopaedic survey in young patients with severe haemophilia in Spain", *Haemophilia*, vol. 8, Suppl. 2, pp. 38-42.

- Gouw, SC, van der Bom, JG, Ljung, R, Escuriola, C, Cid, AR, Claeyssens-Donadel, S, van Geet, C, Kenet, G, Mäkipernaa, A, Molinari, AC, Muntean, W, Kobelt, R,Rivard, G, Santagostino, E, Thomas, A & van den Berg, HM; PedNet and RODIN Study Group 2013, "Factor VIII products and inhibitor development in severe hemophilia A*", N Engl J Med*, vol. 368, no. 3, pp. 231-9.

- Grbich, C 1999, *Qualitative Research in Health: an Introduction*. Thousand Oaks, Sage.

- Green, J and Thorogood, N 2009, *Qualitative methods for health research,* London, SAGE Publications. 2dn edition.

- Gringeri, A, Lundin, B, von Mackensen, S, Mantovani, L & Mannucci, PM, ESPRIT Study Group 2011, "A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study)", *J Thromb Haemost*, vol. 9, no. 4, pp.700-10.

- Guindo, LA, Wagner, M, Baltussen, R, Rindress, D, van Til, J, Kind P & Goetghebeur, M 2012, **"**From efficacy to equity: Literature review of decision criteria for resource-allocation and health care decision making", *Cost Eff Resour Alloc*, vol.10, no. 1, p. 9.
- Ham, C & Robert, G 2003, *Reasonable Rationing. International Experience of Priority-setting in Health care*, Buckingham, Open University Press.
- Hammersley, M 1992, *What's wrong with ethnography?* London, Routledge.
- Hailey, D 2003, "Toward transparency in health tecnology assessment: a check list for HTA reports", *Int J Technol Assess Health Care*, vol. 19, no. 1, pp. 1- 7.
- Heyse, J, Cook, J, & Carides, G 2001, "Statistical considerations in analysing health care resource utilisation and costs data", in MF Drummond and A McGuire (eds), *Economic evaluation in health care, merging theory with practice*, Oxford University Press, Oxford., pp. 213- 35.
- Hilberg, T &Czepa, D 2009, "Cross sectional study to investigate the influence of treatment regimes on the development of haemophilic arthropathy", *Hamostaseologie*, vol. 29, Suppl. 1, pp S77-79.
- Hilgartner, MW 2002, "Current treatment of hemophilic arthropathy", *Current Opinion in Pediatrics*, vol. 14, no. 1, pp. 46-49.
- Hirth, RA, Chernew, ME, Miller E, Fendrick, AM & Weissert, WG 2000, "Willingness to pay for a quality-adjusted life year: in search of standard", *Med Decis Making*, vol. 20, pp. 332–42.
- Hjelmgren, j, Berggren, F & Andersson, F 2001, "Health Economic Guidelines- similarities, differences and some implications", *Value in Health*, vol. 4, pp. 225- 50.
- Hoch, JS, Briggs, AH & William, A 2002, "Something old, something new, something borrowed, something BLUE: a framework for the marriage of health econometrics and cost-effectiveness analysis", *Health Economics*, vol. 11, pp. 415- 430.
- Hutton, J & Benedict, A 2002, "Producing Health Benefits: Cost-Effectiveness of Health and Non-Health Interventions", *MEDTAP® International*, Clinical Excellence- Annual Conference and Exhibition, Birmingham, UK.
- Hyder, A, Corluka, A, Winch, P, El-Shinnawy, A, Ghassany, H, Malekafzali, H, Lim, M, Mfutso-Bengo, J, Segura, E & Ghaffar, A 2011, "National policy-makers speak out: are researchers giving them what they need?", *Health Policy & Planning*, vol. 26, no. 1, pp. 73-82.
- Institute for Quality and Efficiency in Health care, the Institute, viewed 15 May 2011, <http://www.iqwig.de/about-us.21.en.html>
- Inter-American Development Bank- IDB NICE International, Escuela de Gobierno Alberto Lleras Camargo, Universidad de los Andes, Ministerio de la Protección Social, Instituto de Efectividad Clínica Sanitaria de Argentina 2011, Proyecto BID de apoyo al fortalecimiento de los procesos de priorización de salud en Colombia- Componente 2: Estructuración del Sistema de Priorización en Colombia y del Instituto de Evaluación de Tecnologías.
- Jacob, R & McGregor, M 1997,"Assessing the Impact of Health Technology Assessment." *International Journal of Technology Assessment in Health care*, vol 13, no. 1, pp 68-80.
- Jewell, C & Bero, L 2008, "Developing good taste in evidence: facilitators of and hindrances to evidence informed health policymaking in state government", *The Milkbank Quarterly*, vol. 86, pp. 177- 208
- Johannesson, M 1992, "The Australian Guidelines for subsidisation of pharmaceuticals: the road to cost-effective prescribing?", *Pharmacoeconomics*, vol 2, pp. 355–62, 422–6.
- Johannesson, M & Weinstein, MC, 1993, "On the decision rules of cost-effectiveness analysis", *Journal of Health Economics*, vol. 12, pp. 459- 67.
- Keen, J 2006, "Using case studies in health services research and health policy", in C Pope & N Mays (eds), *Qualitative Research in Health care* (3rd ed), Oxford, Blackwell.
- Kempton, C, Valluri, S, Reding, M, Lissitchkov, T, Goranov, S, Gercheva, L, Rusen, L, Ghinea, M, Uscatescu, V, Rescia, V, Hong, W & Manco-Johnson M 2012, "Regional differences in baseline patient-reported outcomes in a randomized, controlled, prospective trial of secondary prophylaxis VS on-demand treatment in patients with severe hemophilia A, *Haemophilia*, vol. no. 18, p. 25.

- Kendall, J 1999, "Sibling accounts of ADHD", *Family Process*, vol. 38, no. 1, pp. 117-136.
- Kanavos, P & Angelis, A, 2013, "Multiple Criteria Decision Analysis for Value Based Assessment of New Medical Technologies: A Conceptual Framework. Working Paper No: 33/2013" LSE Health London School of Economics and Political Science, London, viewed 11 Feb 2014, <http://www.lse.ac.uk/LSEHealthAndSocialCare/pdf/LSEHealthworkingpaperseries/LSEH-WP33_final.pdf>
- Key, NS, Aledort, LM, Beardsley, D, Cooper, HA, Davignon, G, Ewenstein, BM, Gilchrist, GS, Gill, JC, Glader, B, Hoots, WK, Kisker, CT, Lusher, JM, Rosenfield, CG, Shapiro, AD, Smith, H &Taft E 1998, "Home Treatment Of Mild To Moderate Bleeding Episodes Using Recombinant Factor VIIa (Novoseven) In Haemophiliacs With Inhibitors", *Thromb Haemost,* vol. 80, pp. 912–8.
- Kirk, J & Miller, M 1986, "Reliability and validity in qualitative research", in J Kirk & M Miller (eds), *Qualitative research methods series No 1*. London: Sage.
- Knight, C, Jones, ML, Paisley, S & Wight, J 2003, "Economic modelling of different treatment strategies for severe haemophilia A with high- responding inhibitors", *Haemophilia*, vol. 9, no. 4, pp. 521- 40.
- Kottak, C 2006, *Mirror for Humanity*, McGraw-Hill, New York, p. 47.
- Krueger, R & Casey, MA 2002, *Fous groups: a practical guide for aplied research*, 3rd edition. Thousand Oaks- CA, Sage
- Kuntz, K & Weinstein, MC 2001, "Modelling in economic evaluation", in MF Drummond and A McGuire (eds), *Economic evaluation in health care, merging theory with practice*, Oxford University Press, Oxford., pp. 154-60.
- Kurnik, K, Bidlingmaier, C, Engl, W, Chehadeh, H, Reipert, B & Auerswald, G 2010, "New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development", *Haemophilia*, vol. 16, pp. 256–62.
- Lalezari, S, Coppola, A, Lin, J & Enriquez, M. 2011, "Subgroup analyses of annualized number of bleeds with three-times-per-week prophylaxis with rFVIII-FS", *Journal of Thrombosis and Haemostasis*, vol. 9, p 373.
- Larsson, SA 1985, "Life Expectancy Of Swedish Haemophiliacs, 1831-1980", *Br J Haematol*, vol. 59, no. 4, pp. 593-602.
- Laupacis, A, Feeny, D, Detsky, AS, Tugwell, PX 1992, "How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations", *Can Med Assoc J*, vol. 146 no. 473–81.
- Laupacis, A, Bourne, R, Rorabeck, Feeny, D, Wong, C, Tugwell, P, Leslie, K & Bullas, R 1993, "The effect of elective total hip replacement on health-related quality of life", *J Bone Joint Surg Am*, vol.75, no. 11, pp. 1619–1626.
- Lee, Ca 2009, "The Best Of Times, The Worst Of Times: A Story Of Haemophilia", *Clin Med*, vol. 9, no. 5, pp. 453-8.
- Lindblom, CE 1959, "The Science of Muddling Through", *Public Administrative Review*, vol. 19, pp. 79-88.
- Linstone, HA & Turoff, M 1975, *The Delphi method: techniques and applications*. Reading, Mass: Addison-Wesley Pub. Co., Advanced Book Program.
- Lippert, B, Berger, K, Berntorp, E, Giangrande, P, van Den Berg, M, Schramm, W & Siebert, U 2005, "Cost effectiveness of haemophilia treatment: A cross-national assessment", *Blood Coagulation and Fibrinolysis*, vol. 16, no. 7, pp. 477-485.
- Littlejohns, P 2002, "Does NICE have a threshold? A response", in A Towse, C Pritchard & Devlin N (eds), *Cost-Effectiveness Thresholds*: *Economic and Ethical Issues*. London, King's Fund and Office of Health Economics.
- Ljung, R 2007, "The Risk Associated With Indwelling Catheters In Children With Haemophilia", *Br J Haematol*, vol. 138, pp. 580–6.

- Loomes, G 2002, "Valuing life years and QALYs: transferability and convertibility of values across the UK public sector", in A Towse, C Pritchard & N Devlin (eds), *Cost-Effectiveness Thresholds: Economic and Ethical Issues*. London: King's Fund and Office of Health Economics.
- Lorio, A, Marchesini, E, Marcucci, M, Stobart, K & Chan, AK, 2011, "Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B", *Cochrane Database Syst Rev.*, Sep vol. 7, no. 9
- Lusher, JM 2000, "Factor VIII Inhibitors with Recombinant Products: Prospective Clinical Trials", *Haematologica*, vol. 85, Suppl. 10, pp. 2-6
- Makris, M, Garson, JA, Ring, CJ, Tuke, PW, Tedder, RS & Preston, FE 1993, "Hepatitis C Viral RNA In Clotting Factor Concentrates And The Development Of Hepatitis In Recipients", *Blood,* vol. 81, no. 7, pp. 1898-902.
- Mannucci, PM & Tuddenham, EG 2001, "The Haemophilias - from royal genes to gene therapy", *N Engl J Med*, vol. 344, no. 23, pp. 1773-9.
- Mannucci, PM 2003, "AIDS, Hepatitis and Haemophilia in the 1980s: memoirs from an insider", *J Thromb Haemost*, vol. 1, no. 10, pp. 2065-9.
- Mannucci, PM 2006, "International Clinical Experience with Plasma-Derived Factor VIII And IX Concentrates", *Haematologica*, vol. 91, Suppl. 3, pp. 26–31.
- Mays, N & Pope, C 2000, "Qualitative research in health care Assessing quality in qualitative research", *BMJ*, vol. 320, pp. 50–2.
- Morfini, M, Mannucci, PM, Mariani, G, Panicucci, F, Petrucci, F, Baicchi, U, Capitanio, A, Ferrini, PL & Mandelli, F 1976, "Evaluation of prophylactic replacement therapy in haemophilia B", *Scandinavian Journal of Haematolog*, vol. 16, no. 1, pp. 41–7.
- Nord, E 1996, "Health status index models for use in resource-allocation decisions: A critical review in the light of observed preferences for social choice", *International Journal of Technology Assessment in Health Care*, vol. 12, pp. 31- 44.
- Manco-Johnson, MJ, Abshire, TC, Shapiro, AD, Riske, B, Hacker, M, Kilkoyne, R, Ingram, D, Manco-Johnson ML , Funk S, Jacobson L, Valentino LA, Hoots K, Buchanan GR, DiMichele D, Recht, M, Brown, D, Leissinger, C, Bleak, S, Cohen, A, Mathew, P, Matsunga, A, Madeiros, D, Nugent, D, Thomas, G, Thompson, A, McRedmond, K, Soucie, M & Austin H" 2007, "Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia", *New England Journal of Medicine*, vol. 357, pp. 535- 544.
- McGregor, M 1994, "Can our health services be saved by technology evaluation? The Quebec Experience", *Clin Invest Med*, vol. 17, no. 4, pp: 334-342.
- Miller, DK & Homan, SM 1994, "Determining transition probabilities: confusion and suggestions", *Med Decis Making*, vol. 14, no. 1, pp. 52-8.
- Miners, A, Sabin, C, Tolley, K & Lee, C 2002, "Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia", *PharmacoEconomics*, vol. 20, no. 11, pp 759-774.
- Miners, A 2009, "Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A", *Haemophilia*, vol 15, no. 4, pp. 881-87.
- Miners, AH 2013, "Economic evaluations of prophylaxis with clotting factor for people with severe haemophilia: why do the results vary so much?", *Haemophilia*, vol. 19, no. 2, pp. 174-180.
- Mingot, ME, Heiniger, AI, Garcia, M & Fernandez, JA 2009, "Impact of FVIII product change in severe haemophilia A patients previously treated with plasma-derived FVIII", *Journal of Thrombosis and Haemostasis*, vol. 7, Suppl. 2, p. 1124.
- Ministerio de Protección Social- Colombia 2010, "Guía Metodológica para la elaboración de Guías de Atención Integral en el Sistema general de Seguridad Social en Salud Colombiano", viewed April 30 2014, < http://www.minsalud.gov.co/salud/Documents/ Gu%C3%ADa% 20Metodol%C3%B3gica%20para%20la%20elaboraci%C3%B3n%20de%20gu%C3%ADas.pdf>
- Ministerio de la Protección Social- Colombia 2011, viewed 13 December 2012, <http://www.minproteccionsocial.gov.co/>

- Ministerio de Salud y Protección Social. Public declaration from Minister Beatriz Londoño, viewed 29 February 2012, <http://www.minproteccionsocial.gov.co/Paginas/_Super%20Salud%20deber%C3%A1%20tener%20registro%20de%20quejas%20y%20reclamos%20de%20pacientes%20con%20enfermedades%20huerfanas.aspx>.

- Miot, J, Wagner, M, Khoury, H, Rindress, D & Goetghebeur, MM 2012, "Field testing of a multi criteria decision analysis (MCDA) framework for coverage of a screening test for cervical cancer in South Africa", *Cost Effectiveness and Resource-allocation*, vol. 10, no. 2, doi:10.1186/1478-7547-10-2.

- Mocroft, A, Ledergerber, B, Katlama, C, Kirk, O, Reiss, P & D'arminio, MA 2003, "Decline in the AIDS and death rates in the eurosida study: an observational study", *Lancet*, vol. 362, no. 9377, pp. 22-9.

- Morrison, DS & Batty, GD 2009, "The advantages of being called NICE: a systematic review of journal articles using the acronym for the National Institute for Health and Clinical Excellence", *J Public Health*, vol. 31, no. 127–30.

- Morse, J.M. & Field, P.A 1996, *Nursing Research: The Application of Qualitative Approaches*. Basingstoke, Macmillan.

- Murphy, E, Dingwall, R, Greatbatch, D, Parker, S & Watson P 1998, "Qualitative research methods in Health Technology Assessment: A review of the literature", *Health Technology Assessment*, vol. 2, no. 16, iii-ix, pp. 1-274.

- National Institute for Health and Clinical Excellence 2008, *Guide to the methods of technology appraisal*, London, UK.

- National Institute for Health and Care Excellence and NICE international, London, UK, viewed 15 December 2011,

- <http://nice.org.ok/aboutnice/niceinternational/niceinternational.jsp>

- NICE international 2011, *An institutional framework for priority-setting in Colombia: A blueprint for action, Drafts of blueprint and white paper for IETS*, London, UK.

- National Institute for Health and Clinical Excellence 2001, *Discounting of health benefits in special circumstances*, University of Birmingham, viewed 20 May 2013, <http://www.nice.org.uk/media/955/4F/Clarification_to_section_5.6_of_the_Guide_to_Methods_of_Technology_Appraisals.pdf. 2011>

- Nilsson, M, Berntorp, E, Lofqvist, T & Pettersson, H 1992, "Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B", *Journal of Internal Medicine*, vol. 232 no. 1, pp. 25-32.

- Noone D, Mahony, O & Prihodova, L 2011, "A survey of the outcome of prophylaxis, on-demand or combined treatment in 20-35 year old men with severe haemophilia in four European countries", *Haemophilia*, vol. 17, pp. 842–3

- Noticiero del llano- Southwest regional news Colombia, "Familias que tienen enfermos de hemofilia, venden los medicamentos a las EPS, por ser de alto costo", 2013, viewed April 29 2014 <http://www.llanera.com/?id=16281>

- OANDA currency converter, viewed 15 July 2011, 16 May and 12 July 2013. <www.oanda.com>

- O'Donnell, JC, Sissi, V, Pashos, CL, Miller, DW & Smith, MD 2009, "Health Technology Assessment: Lessons Learned from Around the World- an Overview", *Value in health*, vol. 12 Suppl. 2, pp. 1098-2015.

- O'Mahony, B 2011, "Hemophilia societies: challenges and development". *Hemophilia organization development*, vol. 1, pp. 1- 24

- Oldenburg J, Dolan, G & Lemm, G 2009, "Haemophilia Care Then, Now And In The Future", *Haemophilia*, vol. 15, Suppl 1, pp. 2-7.

- Oldenburg, J, Zimmermann, R, Katsarou, O, Theodossiades, G, Zano, E, Niemann, B, Kellermann, E & Lundin, B 2012, "Diagnostic, cross-sectional evaluation of joint status using

magnetic resonance imaging in patients with severe hemophilia a: Biomarker analysis, *Haemophilia*, vol. 18, pp 124-125.

• Oliver, S, Milne, R, Bradburn, J, Buchanan, P, Kerridge, L, Walley, T & Gabbay, J, 2001,"Involving consumers in a needs-led research programme: A pilot project", *Health Expectations*, vol. 4 no. 1, pp. 18-28.

• Olivieri, M, Kurnik, K, Pfluger, T & Bidlingmaier, C 2012, "Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis", *Haemophilia*, vol. 18, no. 3, pp. 369-374.

• Pan American Health Organization – PAHO, Regional Health Report 2008, Washington, viewed November 15 2011, http://www.paho.org/hq/index.php?option=comcontent &view=category& layout= blog&id=2394&Itemid=2395&lang=en

• Patton, M 2002, *Qualitative research and evaluation methods,* Thousand Oaks, Sage.

• Perez- Bianco, P , Berges, A, Soto, V, Linares, A, Krishnan, S, Xiong, Y, Aguilar, L, Gomez, J, Arvizu, J & Brabata, C 2012, "Association of prophylaxis regimen with FVIII and treatment outcomes in Latin America patients", *Haemophilia*, vol. 18, p. 143.

• Perry, F, Garcia, O, Diaz, S, Guzman, L, Ángel, J, Lehmann, C, Sánchez, J, Poveda, C, Alba, M, Sierra, F, Peña, E, González, A, Medina, E, Rosas, ML, Martín, H, Sánchez, R, Moreno, M, López, MC, Murillo, R, Rossi, F, Acosta, B, Cabarcas, M, Zea, D, Torres, L, Serrano, C, Rugeles, J, Moran, D, Arango, N, Cuello, J, Mejía, A, Carvajal , A, Ayala, LE, García, D, García MP, Ortegón, M, Gamboa, O, Muñoz, A, Lozano, T, Gamboa, C, León, E & Gil, A- Instituto Nacional de Cancerología ESE, Instituto Nacional de Cancerología, Ministerio de Salud y Potección Social, Colciencias 2012, *Guía de Práctica Clínica para la detección temprana, tratamiento integral, segumiento y rehabilitación del Cáncer de Mama*, Bogotá- Colombia, viewed 24 February 2014 <http://www.minsalud.gov.co/Documentos%20y%20Publicaciones/Gu%C3%ADa%20de20Pr%C3 %A1ctica%20Cl%C3%ADnica%20%20de%20Cancer%20de%20Mama%20versi%C3%B3n%20comp leta.pdf>

• Petrini, P 2007, "Identifying And Overcoming Barriers to Prophylaxis In The Management Of Haemophilia", *Haemophilia*, vol. 13, Suppl. 2, pp. 16–22.

• Pichon-Riviere, A, Ceballos, RM & Briones, E 2009, "Health technology assessment in Latin-America and the Caribbean, facilitators and barriers for international collaboration: A survey-ISPOR 12th Annual European Congress Paris France. Conference", *Value in Health*. Vol. 12, no. 7, A488.

• Pinchon- Riviere, A, Augustovski, F, Rubinstein, A, Garcia Marti, S, Sullivan, SD & Drummond, MF 2010, "Health technology assessment for resource-allocation decisions: are key principles relevant for Latin America?", *Int J Technol Assess Health care*, vol 26, no. 4, pp. 421-7.

• Phillips, Z, Ginnelly, L, Sculpher, M, Claxton, K, Golder, S, Riemsma, R, Woolacott, N & Glanville, J 2004, " A review of guidelines for good practice in decision- analytic modeling in health technology assessment", *Health Technology Assessment*, vol. 8, no. 36, pp. 1- 158.

• Pluye, P, Grad, RM, Levine, A & Nicolau, B 2009, "Understanding divergence of quantitative and qualitative data (or results) in mixed methods studies", *International Journal of Multiple Research Approaches*, vol. 3 , no. 1, pp. 58- 72

• Porter, K, Babiker, A, Bhaskaran, K, Darbyshire, J, Pezzotti, P, Porter, K, Walker, AS & CASCADE Collaboration 2003, "Determinants Of Survival Following HIV-1 Seroconversion After The Introduction Of HAART", *Lancet,* vol . 362, no. 9392, pp. 1267-74.

• Ragni, MV, Tegtmeier, GE, Levy, JA, Kaminsky, LS, Lewis, JH, Spero, JA 1986, "AIDS retrovirus antibodies in haemophilia cases treated with factor VIII or factor IX concentrates, cryoprecipitate, or fresh frozen plasma: prevalence, seroconversion rate, and clinical correlations", *Blood*, vol. 67, no. 3, pp. 592-5.

• Rajan, A, Gutierrez-Ibarluzea, I & Moharra, M 2011, "Addressing issues in health technology assessment promotion: Motives, enablers, and barriers", *International journal of technology assessment in health care*, vol. 27, no. 1, pp. 55-63.

- Rayan, M & Gerard, K 2003, "Using discrete choice experiments to value health care programmes: current practice and further research reflections", *Applied Health Economics and Health Policy*; vol. 2, pp. 55- 64.

- Rawlins, MD, 1999 "In pursuit of quality: the National Institute for Clinical Excellence", *Lancet*, vol. 353, pp. 1079–82.

- Rawlins, MD & Culyer AJ 2004, "The National Institute for Clinical Excellence and its value judgments", *BMJ*, vol. 329, pp. 224–27.

- Rawlins, MD 2005, "5 NICE years", *Lancet*. Vol. 365, pp. 904–08.

- Reason, J 1990, *Human Error,* Cambridge University Press. Ashgate

- Reipert, BM, van den Helden, PMW, Schwarz, HP & Hausl, C 2007, "Mechanisms of action of immune tolerance induction against factor VIII in patients with congenital haemophilia A and factor VIII inhibitors", *Br J Haematol*, vol. 136, pp. 12–25.

- Risebrough, NA, Oh, P, Blanchette, V, Curtin, J, Hitzler, J & Feldman, BM 2008, "Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A", *Haemophilia*, vol. 14, pp. 743-752.

- Robinson, A, Loomes, G & Jones- Lee, M 2001, "Visual analogue scales, standard gambles and relative risk aversion", *Medical decision making*, vol. 21, pp. 17-27.

- Roehrig, C & Kargus, K 2003, *Health Technology Assessment in Canada and the G-7 Countries: A Comparative Analysis of the Role of HTA Agencies in the Decision Making Process*, Health care System Division/ Division du Système de soins de santé. Working Paper/ Document de Travail. Health Canada <http://www.hc-sc.gc.ca>

- Rodriguez-Merchan, EC, Jimenez-Yuste, V, Aznar, JA, Hedner, U, Knobe, K, Lee CA, Ljung, R, Querol, F, Santagostino, E, Valentino, LA & Caffarini, A 2011, "Joint protection in haemophilia", 2011, *Haemophilia*, vol. 17, Suppl. 2, pp. 1-23.

- Rosenau, P 2000, "Managing Medical Technology: Lessons for the United States from Quebec and France", *International Journal of Health Services*, vol. 30, no. 3, pp. 617-639.

- Royal, S, Schramm, W, Bertntorp, E, Giagrande, A, Ludlam, C, Kronker, B, Szucs, T 2002, "Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients", *Haemophilia*, vol. 8, no. 1, pp. 44-50.

- Saari, DG 2000, "Mathematical Structure of Voting Paradoxes: II. Positional Voting". *Journal of Economic Theory,* vol, 15, no. 1.

- Sanchez, R & Jaramillo, LE 2009, "Metodología de calificación y resumen de las opiniones dentro de consensos formales", *Rev Colomb Psiquiat*, vol. 38, no. 4, pp. 777-85.

- Sculpher, M, Fenwick, E & Claxton, K 2000, "Assessing the quality in decision- analytic cost-effectiveness models- A suggested framework and example of application", *Pharmacoeconomics*, vol. 17, pp. 461- 77.

- Scharrer, I, Bray, GL & Neutzling, O 1999, "Incidence of Inhibitors in Haemophilia A Patients- a Review of Recent Studies of Recombinant and Plasma-derived Factor VIII Concentrates", *Haemophilia*, vol. 5, pp. 145-54.

- Schutz, A 1964, *Studies in social theory*, The Hague, Martinius Nijhoft

- Schutz, A 1970, *On phenomenology and social relations,* Chicago, Universisty of Chicago Press.

- Senior, JM, Lugo, LH, Acosta, N, Acosta, JL, Díaz, J, Osío, O, Plata, JA, Saldarriaga, CI, Trespalacios, EJ, Toro, JM, Pastor, MP, Ciapponi, A, Mejía, AE, Atehortúa, S, Ceballos, M, Mejía, ME & Ramírez, C, Universidad de Antioquia, Ministerio de Salud y Potección Social, Colciencias 2013, *Guía de Práctica Clínica para el Síndrome coronario Agudo*, viewed 25 Feb 2014 <http://scc.org.co/wp-content/uploads/2013/07/GPC-SCA-Guia-para-Usuarios-MPS-Colciencias-UdeA.pdf>

- Shekelle, PG, Ortiz, E, Rhodes, S, Morton, SC, Eccles, MP, Grimshaw, JM & Woolf, S 2001, "Validity of the Agency for Health care Research and Quality Clinical Practice Guidelines: how quickly do guidelines become outdated?", *JAMA*, vol. 286 pp. 1461–67.

- Silva, ML, Spath, HM, Moumjid NF 2010, "The use of economic evaluations in decision-making at macro level: A literature review"- Conference: ISPOR 13th Annual European Congress Prague Czech Republic, *Value in Health*, vol. 13, no. 7, A248.
- Simon, HA 1957, *Administrative Behaviour*, 2nd edition, Macmillan, New York.
- SISIMED- Sistema de información de Precios de Medicamentos, viewed August 15 2013, http://www.minsalud.gov.co/salud/Paginas/Documentaci%C3%B3nyServicios-SISMED.aspx
- Smith, PS, Teutsch, SM, Shaffer, PA, Rolka, H & Evatt, B 1996, "Episodic versus prophylactic infusions for hemophilia A: a cost-effectiveness analysis", *Journal of Pediatrics*, vol. 129, no. 3, pp. 424-431.
- Stachnik, J 2010, "Haemophilia: Etiology, Complications, and Current Options in Management", *Formulary*. Vol. 45, no. 7, p. 218.
- Stafinski, T, Menon, D, Philippon, DJ & McCabe, C 2011, "Review article. "Health Technology Funding Decision-Making Processes around the World, the Same, Yet Different", *Pharmacoeconomics*, vol. 29, no. 6, pp. 475-495.
- Saulyte, TS, Ingerslev J & Rageliene, L 2010, " Utility of the Haemophilia Joint Health Score in study of episodically treated boys with severe haemophilia A and B in Lithuania", *Haemophilia*, vol. 16, no. 3, pp. 479-486.
- Steen Carlsson, K, Höjgård, S, Lethagen, S, Lindgren, A, Berntorp, E & Lindgren, B 2004, "Willingness to pay for on-demand and prophylactic treatment for severe haemophilia in Sweden", *Haemophilia*, vol. 10, no. 5, pp. 527-541.
- Tagliaferri, A, Rivolta, G, Coppola, A, Rivolta, GF, Santoro, C, Rossetti, G, Feola, G, Zanon, E, Dragani, A, Iannaccaro, P, Radossi, P & Mannucci, PM 2008, "Effects of secondary prophylaxis started in adolescent and adult haemophiliacs", *Haemophilia*, vol. 14, no. 5, pp. 945-51.
- Tanios, N, Wagner, M, Tony, M, Baltussen, R, van Til, J, Rindress, D, Kind, P & Goetghebeur MM 2013, "International Task Force on Decision Criteria Which criteria are considered in health care decisions? Insights from an international survey of policy and clinical decision-makers", *J Technol Assess Health Care*, vol. 29, no. 4, pp. 456-65.
- Tony, M, Wagner, M, Khoury, H, Rindress, D, Papastavros, T, Oh, P & Goetghebeur, MM 2011, "Bridging health technology assessment (HTA) with multicriteria decision analyses (MCDA): field testing of the EVIDEM framework for coverage decisions by a public payer in Canada", *BMC Health Serv Res*, vol. 11, p. 329.
- Torrance, GW 1976, "Social preferences for health states: An empirical evaluation of three measurement techniques", *Socioeconomic planning sciences*, vol. 10, pp. 129- 36.
- Torrance, GW, Boyle, MH & Horwood, SP 1982, "Application of multi- attribute utility theory to measure social prefernces for health states", *Operations research*, vol. 30, pp. 1043-9.
- Torrance, GW, Feeny, DH, Furlong, WJ, Barr, RD, Zhang, Y & Wang, Q 1996, "Multi- attribute utility function for a comprehensive health status classification system: Health Utility Index mark2", *Medical care*, vol. 34, pp. 702-22.
- Torrance, GW, Feeny DH & Furlong WJ 2001, "Visual analogue scales: do they have a role in the measurement of preferences for health states?", *Medical decision making*, vol. 21, no. 329-34.
- Towse, A & Pritchard, C 2002, "Does NICE have a threshold? An external view", in A Towse, C Pritchard C, & N Devlin N (eds), *Cost-Effectiveness Thresholds. Economic and Ethical Issues*., London, King's Fund and Office of Health Economics.
- Towse, A & Buxton, M 1978, "Three challenges to achieving better analysis for better decisions: generalisability, complexity and thresholds". *OHE briefing,* no. 42, pp. 1–13.
- Trend, M, 1978, "Reconciliation of qualitative and quantitative-analyses - Case-study", *Human Organization,* vol. 37, no. 4, pp. 345-354.
- Triemstra, M, Roosendaal, FR, Smit, C, van Der Ploeg, HM & Briet, E 1995, "Mortality In Patients With Haemophilia . Changes in a Dutch Population from 1986 to 1992 and 1973 To 1986", *Ann Int Med,* vol. 123, pp. 823–7.

- Tunis, SR 2007, "Reflections on science, judgment, and value in evidence-based decision making: a conversation with David Eddy", *Health Aff (Millwood)* vol. 26, pp. 500–515.

- Ubel, PA, Loewenstein, G, Schwarz, N & Smith, D 2005, "Misimagining the unimaginable: the disability paradox and health care decision making", *Health Psychol*, vol. 24, Suppl. 4, pp. S57–62.

- Unidad Administrativa Especial- Comisión de Regulación en Salud- CRES 2012, "Metodología para la determinación de los criterios y categorías para la priorización de tecnologías en salud en el proceso de actualización del POS". Documento técnico proyecto POS – UPC 2012 – 2013. subdirección técnica – Bogotá, Colombia, viewed 18 February 2013, <http://www.cres.gov.co/Portals/0/Convocatoria%20Participaci%C3%B3n%20Ciudadana%202012.pdf>

- Van Der Poel, CL, Reesink, HW, Mauser-Bunschoten, EP, Kaufmann, RH, Leentvaar-Kuypers, A, Chamuleau, RA, Schaasberg, W, Bakker, E, Exel-Oehlers, PJ, Theobalds, I, Van Boven JJP, Cameron, A & Lelie PN 1991, "Prevalence Of Anti-HCV antibodies confirmed by recombinant immunoblot in different population subsets in the Netherlands", *Vox Sang*, vol. 61, no. 1, pp. 30-6.

- Van Den Berg, HM, Fischer, K & Van Der Bom, JG 2003, "Comparing outcomes of different treatment regimens for severe haemophilia", *Haemophilia*, vol. 9, Suppl. 1, pp 27-31.

- Van Dijk, K, Fischer, K, van der Bom, JG, Grobbee, DE & van den Berg, HM 2005, "Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed", *Haemophilia*, vol. 11, no. 5, pp. 438-43.

- Van Manen, M 2001, '*Phenomenology' Course Handbook*. QHR 2001 Post-Workshop B., Ewha Women's University, Seoul.

- Varela-Lema L, Merino, GA, Garcia, ML, Martinez, MV, Triana, EG & Mota TC 2011, "Requirements for and expectations of health technology assessment in Galicia (Spain). A qualitative study from the perspective of decision-makers and clinicians. <Demandas y expectativas de la evaluación de tecnologías sanitarias en Galicia. Analisis cualitativo desde la perspectiva de decisores y clínicos", *Gaceta Sanitaria*, vol. 25, no. 6, pp 454-460.

- Vdovin, VV, Andreeva, TA, Chernova, TA, Perina, FG, & Maas-enriquez, M, Rauchensteiner, S 2011, "The Russian children study: A prospective study to evaluate the effect of rFVIII-fs in different prophylactic regimens on frequency of bleeding events and development of arthropathy in a previously treated and minimally treated haemophilia A paediatric population", *Haemophilia*, vol. 17, no. 2, p 360.

- Weinstein, MC 1995, "From cost-effectiveness ratios to resource-allocation: where to draw the line?", in FA Sloan, (ed.), *Valuing Health care: Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies*. New York: Cambridge University Press.

- Wilensky, G 2006, "Developing a centre for comparative effectiveness information", *Health Aff*, vol. 25, pp. 572–85.

- Wilkinson, E 2009, *Talking NICE around the globe*, BBC News, viewed 16 Feb 2009, <http://news.bbc.co.uk/1/hi/health/7830744.stm>

- Windyga, J, Stefanska, E, Lopaciuk, S, Juszynski, A, Wozniak, D & Strzelecki, O 2005, "The orthopaedic status of a selected severe haemophilia group/ Stan narzadu ruchu w wybranej grupie chorych na ciezka hemofilie", *Polskie archiwum medycyny wewntrznej*, vol. 113, no. 6, pp 562-569.

- Wong, T & Recht, M 2011, "Current options and new developments in the treatment of Haemophilia", *Drugs*, vol. 7, no. 3, pp. 305-20.

- World Health Organization – WHO 2007, *World Health Statistics*. World Health Organization. Geneva Switzerland.

- Xu, K, Evans, DB, Kawabata, K, Zeramdini, R, Klavus, J & Murray, CJ 2003, "Household catastrophic health expenditure: a multicountry analysis", *Lancet*, vol. 362, pp. 111–17.

- Youngkong, S, Kapiriri, L & Baltussen, R 2009, "Setting priorities for health interventions in developing countries: a review of empirical studies", *Trop Med Int Health*, vol. 14, pp. 930– 939.

- Zwart-van Rijkom, J, Leufkens, H, Busschbach, J, Broekmans, A & Rutten, F 2000, "Differences in Attitudes, Knowledge and Use of Economic Evaluations in Decision-Making in The Netherlands: The Dutch Results from the EUROMET Project", *Pharmacoeconomics*, vol. 18, no. 2, pp. 149-160.