The application of early HTA in research funding decisions at the Dutch Heart Foundation

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ABSTRACT

The Dutch Heart Foundation (DHF) is a research funder for cardiovascular diseases in the Netherlands. Their goal is to fund research projects aiming to reduce the burden of disease by prevention, minimizing risk factors, and early detection and treatment. Early HTA is a method a research funder can adopt to know the potential impact a research project may have in the future. An early HTA economic evaluation has been conducted in several research projects, to determine the ratio between incremental costs and -effects. An early HTA ethical analysis was retrospectively performed focusing on a project about xenotransplantation, using the Beauchamp and Childress principle model. Six out of nine research projects seem to be suitable to perform an early economic evaluation. The results of the economic evaluations indicates that all six potential interventions resulting from the research projects seem cost-effective, because all ICERs remain below the € 20.000,- p / QALY threshold. The results of the ethical analysis show that there are good reasons for the clinical application of xenotransplantation, however there are found ethical objections with all four principles of the Beauchamp model. This study is explorative, where a lot of uncertainty negatively influences the reliability of the results. The results of this study show that early HTA evaluations are feasible for a large part of the research projects and provide additional information relevant for decision making. We conclude therefore that the DHF could take advantage of implementing early HTA in their funding policy, because this enables the DHF to be better informed about the expected impact of projects that they (will) fund.

INTRODUCTION

In the Netherlands, more than 100 people die of cardiovascular disease (CVD) every day. Furthermore, approximately 1.5 million Dutch people suffer from CVD[1] . CVDs are the leading cause of death globally [2]. In the Netherlands in 2019 a total of 37.433 people died due to CVD, of which 18.208 men and 19.225 women.

The Dutch Heart Foundation (DHF) is a charity research funding organization for CVDs in the Netherlands since 1964. The aim of the DHF is to reduce the CVD burden of disease by prevention, minimizing risk factors, and early detection and treatment of CVD [3]. By research funding and monitoring research projects, the DHF actively stimulates the translation of research results into practice. Because the budget is limited, the DHF aims to fund the most promising research projects, which are expected to result in the highest societal benefits given the costs [4]. Expected societal costs and benefits can be calculated using an Early Health Technology (HTA) approach.

Early HTA is a set of methods to inform stakeholders at an early stage about the potential value of a new medical technology under development. These methods also take into account the uncertainty in this potential value [5,6]. The DHF is interested in whether it is suitable to integrate an early HTA in their funding decisions, through estimating the expected costs and benefits, from a potential intervention resulting from a research project, in an early stage.

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Thereby, early HTA could be used to support the decision which research proposals should or should not be funded.

The expected impact of a health technology studied in the past can be assessed using an early HTA approach. The DHF is interested in the economic (societal) impact as well as the ethical considerations. Ethics is important in itself, but perhaps even more for a research funder as the DHF because of the organization's earmark, which tries to take the interests of their (financial) supporters into account as much as possible. Through these economic and ethical insights derived from early HTA analyses, the DHF aims to review and improve their current research funding policy.

To evaluate whether early HTA can help predict research societal and ethical impact, this study looks back at research projects the DHF funded approximately 30-35 years ago and the impact those studies have generated over the years. To do so nine historical cases were randomly selected and evaluated. An early HTA is conducted for these cases and the results are compared with the actual impact an intervention emerged from these DHF funded project had. One of the research projects funded by the DHF from 1988 till 1991 was case 86.062 *'Xenogeneic heart transplantation; development of effective immunosuppressive regimens in an animal experimental model'*, which will be evaluated in depth and will be the topic of the ethical evaluation.

The main research question this paper tries to answer is: "*What is the added value of early HTA, including economic evaluation and ethical analysis, in making research funding decisions for the DHF*?"

THEORETICAL FRAMEWORK

IMPACT ASSESMENT

The definition of research impact is: "*any type of output from research activities that can be considered a 'positive return' to the scientific community, health systems, patients and society at large*" [7]. For funding bodies it is relevant to map results so that funding bodies can ensure that the output of the research projects they fund is proportional to the input of the investment [8]. In addition to evaluate results, it is also relevant to map out the long-term impact. The long-term impact can provide insights into the diversity and scope of results arising from supporting research and provide a framework for evaluating the results of long-term pilot projects. The Payback Framework is a method to examine the impact of health service research, it is able to facilitate data collection and cross-case analysis by providing a common structure for each case study [9].

HTA

HTA is a set of methods that can be used in funding policy to make decisions between different applications for which funding is requested, in order to maximize value for society given the constrained resources [5,10]. Chapman et al describe that the aim of early HTA is to inform developers "*to avoid investment in devices that could never be cost-effective*", also described as "*fail fast, fail cheap"* according to IJzerman and Steuten[1112] Through a systematic evaluation, HTA measures the medical, social, economic, and ethical impact including intended and unintended effects [13].

COST-EFFECTIVENESS

Due to limited financial resources, it is relevant to achieve maximum health gain with the constrained budget. A (new) intervention is considered cost-effective if it provides health benefits and saves costs, or if the incremental cost-effectiveness ratio (ICER) remains below the relevant Dutch cost-effectiveness threshold [12,14]. The willingness-to-pay threshold (WTP) differs per burden of disease category [15]. In the Netherlands a low burden of disease (Bod) is associated with a proportional shortfall of 0,1-0,4 and has a WTP of €20.000,- per quality adjusted life year (QALY); a moderate BoD is associated with a proportional shortfall of 0,41-0,7 and a WTP of €50.000,- per QALY and a high BoD is associated with a proportional shortfall between 0,71-1 and has a WTP of €80,000,- per QALY [16]. Cost-effectiveness is the standard measure by the Dutch Health Care Institute, which considers it fair to allow cost effectiveness to play an emphatic role in package decisions.

ETHICAL ANALYSIS

In addition to measuring economic impact, impact in terms of ethics also provides valuable information. Advances in medical research leads to critical reflection on conventional beliefs about society's moral obligations in the prevention and cure of diseases [17]. Ethics is a collective term for various

ways of understanding and examining morality [18]. Morality can be defined as norms about right and wrong human behavior that are widely shared and form a stable social consensus [19,20]. Ethical values are intrinsically linked to the development of health technologies [21]. Research policies, such as funding health care for the underprivileged or prohibiting certain topics of biomedical research, usually involve moral considerations. Moral analyses are therefore a relevant part of societally acceptable decision-making [20].

In bioethics three main approaches are distinguished, namely the "principism" of Tom Beauchamp and James Childress, expounded in Principles of Biomedical Ethics (1979), which formalizes four formal with arbitration between these being left to the actors themselves [20]. Second, Tristram Engelhardt's approach, which tends towards a "pluralist and secular ethic", refuses to prioritize any moral approach (whether based on reason, intuition, or religion) in order to allow for a negotiation between the multitude of actors [22]. Third, the casuistic and 'contextualist' model developed by Albert R. Jonsen and Stephen Toulmin, a form of argument used in moral theology [23]. The Beauchamp & Childress Principles of Biomedical ethics model [24] serves as a guideline in this ethical analysis. This framework contains four guiding principles – namely *autonomy*, *non-maleficence*, *beneficence* and *justice* – which serve as categories for ethical dilemmas. Autonomy is the freedom and independency to which patients or test subjects are entitled. Benedicence means that well-being of the patient or society should be promoted. Non-maleficence means that no harm should be done to anyone. Justice means that every person in need should be helped equally. The reflective equilibrium ensures a good balance between the four principles, between a set of beliefs achieved through a process of deliberate mutual adjustment between general principles and particular judgments [25].

PROPORTIONAL REVIEW AND SHARED RESPONSIBILITY

Due to the complexity of the research life cycle, various authorities in the Netherlands are involved in monitoring the components of that cycle. Funders assess research plans in the context of financial support. Medical Ethics Review Committees (METCs) review the elaborated protocols for studies were people are involved. The execution of the research is supervised by the client (institute) and this is supervised by the Care & Youth Inspectorate (IGJ). The RIVM monitors safety aspects of certain research products. During the study, side effects are reported to the Central Committee on Human Research (CCMO) or to the METCs. Each of these parties are charged with the proportional assessment of a specific moment in the life cycle of an investigation. In the Netherlands, a shared responsibility in supervising medical scientific research takes place [26]. For animal testing there is a European directive. All member states of the European Union must incorporate this directive into their national laws and regulations. The following laws are in force in the Netherlands: Animal Testing Act, Animal Testing Decree, Animal Testing Regulation [27].

METHODS

The methods in this study consist of a case study project to understand and provide insight into the impact of research funded by the DHF, an early HTA economic evaluation and an early HTA ethical analysis. It is important to note that this study is explorative, because the application of early HTA for a research funder is a relatively new topic and therefore data collection presents a challenge. In the method section the approaches are further explained.

CASE STUDY APPROACH

For conducting a case study, the Payback Framework is used. This framework is a method to examine the impact of health service research and is able to facilitate data collection and cross-case analysis by providing a common structure for each case study [9]. The method of the Rand Cardiovascular case studies was replicated [28], this is a multinational study investigating the translation and payback of basic biomedical and clinical cardiovascular and stroke research projects [29]. In this case report (86.062) the generated ethical and societal impact was examined. Firstly, data was retrieved from newspaper articles about xenotransplantation via Delpher, related publications from reportages provided by the researchers and correspondence between the researchers of the case and the assessors of the DHF. Also, focused semi-structured interviews were held with the researchers of the case and with people involved into the public debate about xenotransplantation. Research questions were based on the various stages of the Payback Framework. namely, topic identification; inputs to

research; research process; primary outcomes; secondary outcomes; adoption and final outcomes. The researchers were asked what motivation they had and what knowledge and expertise was available. It was discussed how the research process went and with which parties was collaborated. They were also asked to what extent the case has had significance for the research field, policy or legislation. In the end of the interview, respondents were asked to fill in the Pasteurs Quadrant in which the researchers indicated whether the research project has a low-average- high fundamental understanding and a low-average- high consideration of use. The interview lasted about two hours. The conversations were audiotaped. After the recording had started, the respondents were asked whether he or she agreed with the informed consent. Later the audiotape was transcribed, one recording was transcribed by an external company called 'Transcript Online', the other four interviews were transcribed into Excel by one the executors of this study. Important statements from the respondents were highlighted. Then, the text was split up into fragments. Each fragment was labeled. The labels were based on the stages of the Payback Framework and on relevance for ethical and societal impact. The labels were then arranged, combining the results of multiple interviews in one place. Next, open coding was used based on the written case, which answers the research question. Later, the interview reports were sent to the respondents and asked for their feedback. Before finalization of the case study, the respondents receive the draft of the case study and were asked to report any errors they might note.

In this paper was focused on the results related to the economic and ethical evaluation on the case studies. The result of the case report itself were not discussed in detail and is attached in a separate appendix.

SUITABILITY FOR EARLY ECONOMIC EVALUATION

To prepare for early HTA analyses, the suitability of the projects for early HTA, and more specifically for an early economic evaluation, was determined. First, the case study projects were categorized in different development phases (table 1). These phases may influence the suitability for an early economic evaluation. Four development phases were distinguished: '*idea screening'* is the phase where the innovation only consists of an innovative idea; '*concept development*' is when a first version of the innovation is being developed, in the '*pre-market*' phase the product is available but not on the market and in the '*market access'* phase the innovation has entered the market and is used in clinical practice [12]. These research projects were retrospectively analyzed, using an early economic evaluation, to evaluate what the expected cost-effectiveness would have been at the time of the funding decision. The earlier in the development phase, the less data is available on epidemiological numbers, clinical outcomes and costs of the related intervention (figure 1). Therefore, HTAs conducted in such an early development phase result in higher uncertain cost-effectiveness estimates compared to HTAs conducted in later development stages, because more assumptions have to be done. Second, suitability for conducting an early economic evaluation for the case studies selected were assessed using the PICO (patient, intervention, comparator, outcome) [12].

EARLY HTA - ECONOMIC EVALUATION

In this study, economic evaluations were performed following the guideline of the Dutch healthcare institute [30]. The cost utility analysis (CUA) method was used implying that health effects were measured in QALYs and costs in monetary values (€) (table 4, appendix B) [31]. The Excel sheet '*Onderbouwing_Doelmatigheidswinst_ZonMw'* provided by ZonMw was used as guidance, where incidence/prevalence and input on costs and effects is entered, as well as the uptake percentage which indicates to what extent a potential intervention is expected to be implemented in Dutch clinical practice. Input for costs and effects for the CUA were obtained from the Tufts CEA registry, Randomized Clinical Trials (RCTs), Dutch heart registration (DHR) , Open DIS data from the Dutch Healthcare Authority and Dutch hospital tariffs. When data inputs were not available, data inputs on costs and effects were obtained through a targeted literature review, focusing on comparable technologies. A best- and worst-case scenario was used to provide insight into uncertainty surrounding the assumptions. All projects were assessed from a Dutch societal perspective, indicating that all costs and effects were included, regardless of who pays or receives them. Discounting and correction for inflation were not taken into account in the CUA, for pragmatic reasons and to allow for fair comparison between interventions with different expected timing of costs/effects. The Burden of disease per case is

calculated with the iDBC - iMTA Disease Burden Calculator [32].

EARLY HTA - ETHICAL ANALYSIS

The Beauchamp & Childress Principles of Biomedical ethics model was used to provide an ethical reflection on project 86.062 and examine which ethical aspects play a role. Therefore, interviews were held with researchers (n=3) of project 86.062 and leaders of the public debate (n=2) about xenotransplantation. In the interview guide all phases of the Payback Framework were incorporated and the respondents were asked which ethical aspects they considered relevant and what they thought their role was in this at the time of the research (1988-1991). Documentation analysis and literature research has also been performed. The results were presented on the basis of the four principles of the Beauchamp model. Based on these results, recommendations were made who should be responsible at what point for ethical aspects in the research process. Also was recommended what this means for the role of the DHF and how their funding policy may need to be modified to assess research proposals based on the outcomes of the ethical analysis.

SELECTION AND PREPARATION OF SAMPLE

A total of 109 research projects, funded by the DHF between 1985 and 1990, were retrieved from the archive facility. All research projects were related to CVDs. The inclusion criteria for randomization of the cases, were that a project must be scientific, approved, actually performed and that the file could be retrieved from the archive. Exclusion criteria were the presence of a (legal) dispute or a deviant in project duration, projects with a duration shorter then 24 or longer then 36 months were excluded, so that projects have approximately the same size and were therefore more comparable. In order to be able to compare cases sufficiently, the spread in project size was reduced. The grant amount was used as indicator, projects with the 25% smallest and largest grant amounts were excluded. Subsequently the selected projects were categorized into one of the four quadrants, on the y-as pre-clinical or clinical research and on the x-as a low or high consideration of use. All four quadrants were numbered and all projects within a quadrant receive a reference number to allow for easy stratification and randomization. To avoid overlapping and too similar research projects, the projects were also classified according to the type of research and disease category. In the stratification phase, projects were excluded if three projects in a certain category had already been included. After applying the inclusion- and exclusion criteria to the 109 research projects, in the end 42 projects remained from which nine projects were randomly drawn. So after this process the projects were randomly assigned, evenly distributed over the quadrants [33].

RESULTS

DESCRIPTIVES

The nine projects who were randomly drawn, are all non-drug technologies. The projects are classified as follows: relating to fundamental understanding (n= 4), animal experimental model (n=1), diagnostics (n=1) or treatment (n=3) (table 1).

Table 1 Overview of the nine cases funded by the DHF in the period 1985-1990, three research projects are to fundamental to perform an economic evaluation and are grey shaded.

Case	Title	Suitable for early economic evaluation	Type of innovation	Development phase
86.083	Genetics of cardiovascular risk factors	No, too fundamental	Fundamental understanding	Idea screening
86.046	Significance of dopaminergic systems in the central nervous system for the development of hypertension	No, too fundamental	Fundamental understanding	Idea screening
86.021	Changes in self-care in relation to coronary artery bypass surgery: a longitudinal study	Yes	Treatment	Pre market
84.043	Cholesterol synthesis in hepatocytes from hypo and hyper responder rats for nutritional cholesterol	Yes	Animal experimental model	Idea screening

84.082	Regulation of noradrenaline release: pathophysiological and therapeutic aspects of essential hypertension	Yes	Fundamental understanding	Idea screening
85.083	Acute changes in blood pressure when standing up: Physiological and pathophysiological mechanism related to age	Yes	Fundamental understanding	Idea screening
84.074	Quantitative thallium-201 tomography of the heart	Yes	Diagnostics	Pre market
85.113	Heart transplantation in the rat: tolerance induction by means of per and postoperative giving of donor cells in combination with a single injection of Cyclosporine-A (CS-A)	Yes	Treatment	Concept development
86.062	Xenogeneic heart transplantation; development of effective immunosuppressive regimens in an animal experimental model	Yes	Treatment	Concept development

Three of the nine research projects (86.046; 84.042; 85.083) are perceived as too fundamental to conduct an early economic evaluation (table- / figure 1). These projects provide insights that can contribute to future interventions, but it is not yet clear what these interventions will look like or because the project is not focused on a specific disease (area). An attempt was made to fill in the PICO for every project, but for the three projects mentioned earlier little or no data was known about: the amount of patients that are eligible for the intervention, the impact in terms of QALYs and costs related to the intervention. Eventually these three projects are therefore excluded for further analysis.

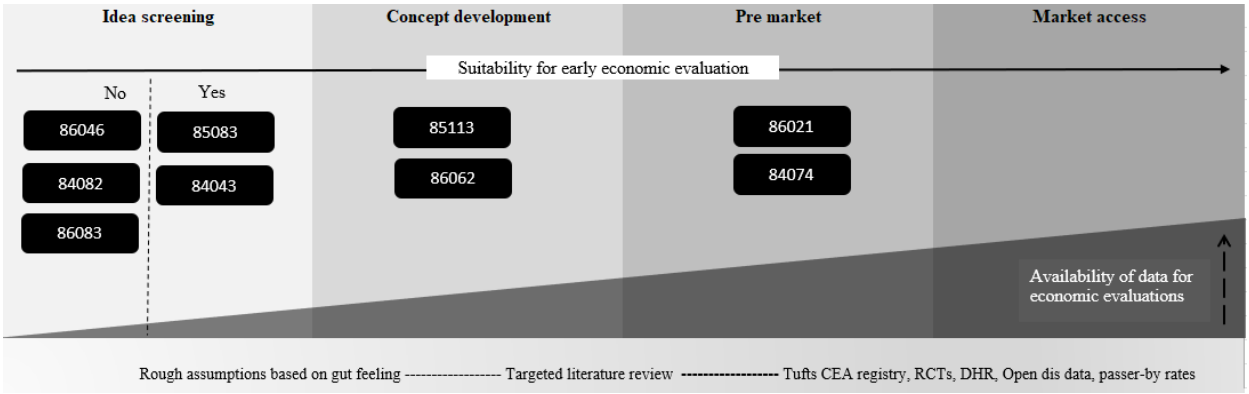

Figure 1 The link between development phases of the research process and the suitability for an economic evaluation based on the availability of epidemiological-, clinical and cost data. The suitability to perform an economic evaluation is indicated by the dotted line, in the idea screening phase.

EARLY HTA - ECONOMIC EVALUATION

The economic evaluations conducted as part of this study have provided insights into the costs and effects associated with standard of care (Soc) and intervention, as well as the ratio between de incremental costs and -effects (ICER) (table 2). The results have indicated that all cases consider interventions which are expected to result in higher QALYs compared to Soc. The potential interventions resulting from case 85.083 and 84.043 show relatively high QALYs (consecutive QALY= 30,2; 51) (table 2). Both potential interventions aimed to gain insight into risk factors of a certain CVD. These insights can then be applied as primary prevention by young patients with an increased heredity risk. Because theses interventions are aimed at a young target group and because the burden of disease is 'low' (table 2), a relatively high life expectancy is expected compared to the other four potential interventions targeting mainly elderly patients (at risk).

Based on the calculations from a societal perspective, it has been found that all potential interventions are expected to result in lower costs compared to Soc, except for the potential

intervention resulting from project 85.113. In this project the effectiveness of two immunosuppressive drugs, to reduce organ rejection by heart transplantations in an animal experimental model, is tested. It turned out that, by adding these immunosuppressives to the transplantation procedure, the procedure is more expensive than Soc, but the QALY gain has increased by 4 (table 2). Also is found, that potential interventions resulting from case 85.113 and 86.062, both in the concept development phase (figure 1), cost more than € 90.000,- while all other potential interventions cost less than € 16.000,-.

Normally, best-worst case analysis provides an interval of the expected cost-effectiveness of the intervention when simultaneously inserting either the most pessimistic or the most optimistic inputs for all model parameters into the health economic evaluation [34]. In this study the base case uptake is based on the extent to which (comparable) interventions, as investigated in the case, have now been implemented in Dutch clinical practice. In the best case, the uptake of the intervention is higher than expected in the base case and vice versa for the worst case (table 2). The broader the best-worst case interval, the higher the uncertainty about the implementation in Dutch clinical practice. The widest range is found in project 86.021 (range: 20% - 70%) where self-care after Coronary artery bypass surgery was tested in a small population in a local hospital in Limburg. However, it was uncertain to what extent this intervention was implemented in Dutch clinical practice. In the case report of this project it also turned out that no broader economic impacts could be identified according to the Payback Framework.

Table 2 Incremental costs and effects per case on patient level, including a best and worst case scenario

Case (description)		Base case			Best case	Worst case	Burden of disease
		Cost (€)	QALY	ICER (€/QALY)	ICER (€/QALY)	ICER (€/QALY)	
				Uptake = 83%	Uptake = 95%	Uptake= 40%	
86.062 Xenotransplantation for patients with severe heart failure	Standard of care	95.432,-	1,7	256,-	289,-	122,-	High
	Intervention	92.773,-	10,4				
				Uptake = 85%	Uptake = 95%	Uptake = 75%	
85.083 Acute blood pressure changes when standing up	Standard of care	376,-	49,3	1.997,-	2.233,-	1.763,-	Low
	Intervention	396,-	49,6				
				Uptake = 45%	Uptake = 70%	Uptake = 20%	
86.021 Self care after coronary artery bypass surgery	Standard of care	12.648,-	5,5	7,-	11,-	3,-	Moderate
	Intervention	12.653,-	5,8				
				Uptake = 80%	Uptake = 90%	Uptake = 70%	
84.043 Identification of cholesterol hyper responders	Standard of care	58.090,-	27,6	4.250,-	4.780,-	3.718,-	Low
	Intervention	50.446,-	29,1				

84.074				Uptake = 86%	Uptake= 95%	Uptake= 75%	
Rotating gamma camera by cardiac catheterization	Standard of care	10.468,-	12,2	2.154,-	2.558,-	2.020,-	High
	Intervention	8.556,-	12,95				
85.113				Uptake = 86%	Uptake= 95%	Uptake= 75%	
Pre- and postoperative donor cells and cyclosporine-a by heart transplantation	Standard of care	158.967,-	10.4	-3.993,-	-4.410,-	-3.482,-	High
	Intervention	168.941,-	13,6				

In this analysis the assumption has been made that the potential interventions do what they were supposed to do. This shows that the calculations have turned out, that all six potential interventions resulting from the research projects seem cost-effective, because all ICERs remain below the € 20.000,- p / QALY threshold (figure 1). Project 85.113 is placed in the north-east quadrant of the ICER plane (figure 1). All five other projects are placed in the south-east quadrant of the ICER plane (figure 2) meaning that intervention is less expensive and gains more QALYs compared to Soc (table 2).

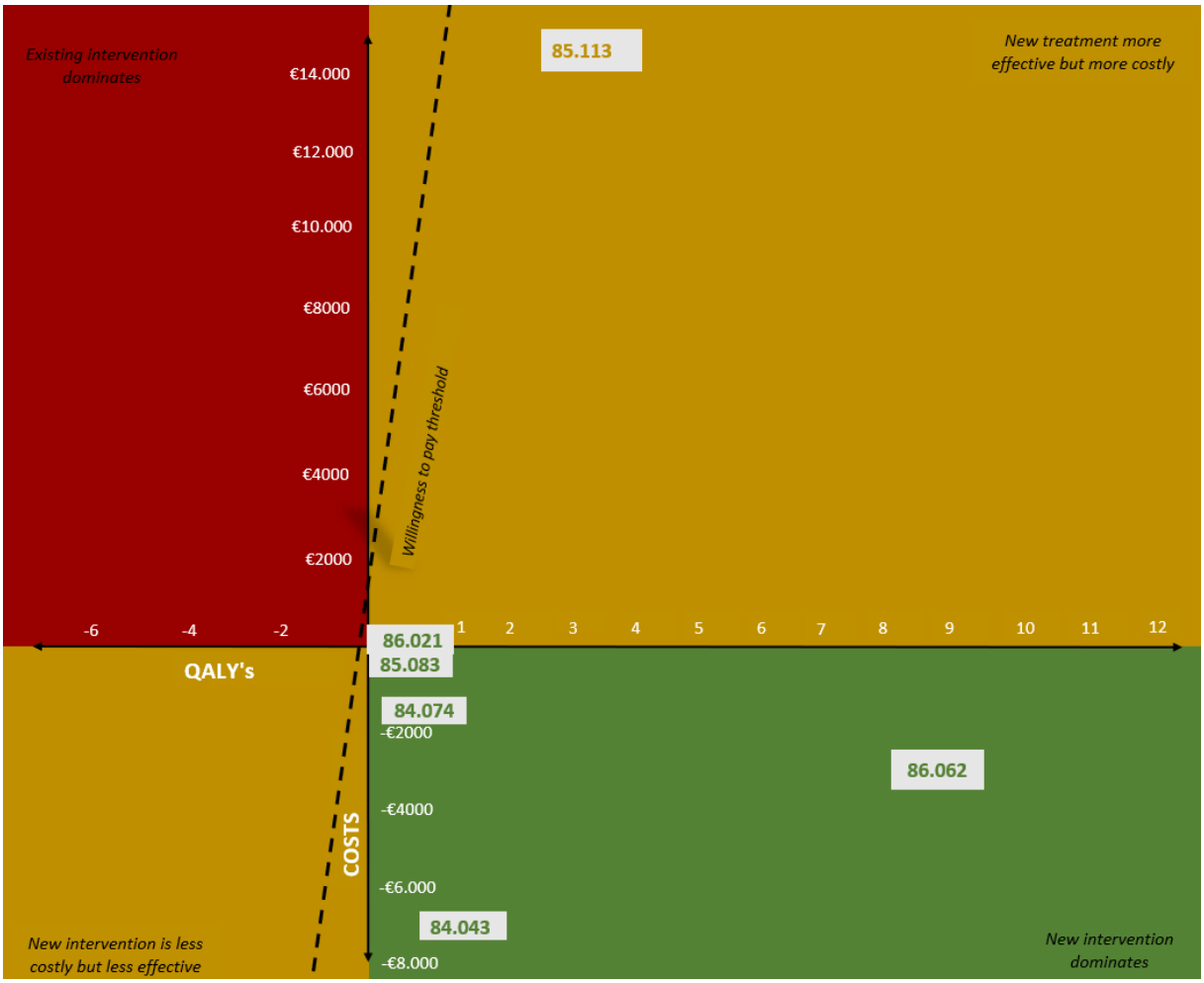

Figure 2 ICER plane based on incremental cost and – effects per patient, Willingness to pay threshold of 20.000 euro per/QALY

An ICER only corporate the ratio of incremental costs and -effects and does not include the size of a population. For a research funder as the DHF it is however interesting to know which research projects reach the highest possible impact in the Dutch population (table 3). The calculations showed that the intervention studied in project 84.043 potentially produces the most health effects for the Dutch society (QALY= 86.340). In contrast the intervention resulting from project 85.113 yields the smallest QALY gain (QALY= 114).

Table 3 Cost effectiveness of cases on patient and on population level; A negative delta cost means that the intervention is more expensive than standard of care

Case	Epidemiology	Patient level		ICER	Population level	
		Δ Costs in €	Δ QALY		Δ Costs in €	Δ QALY
86062	Prevalence 124 per 3,5 year	2.659	8,7	256	78.202	305
85083	Annual incidence 40.000	235	0.1	-1.997	-10.021.210	59.178
86021	Annual incidence 4500	1.889	0,7	1.214	3.825.225	3.150
84043	Annual incidence 60.000	7.643	1,4	4.250	366.910.464	86.340
84074	Annual incidence 65.557	1.912	0,7	2.154	171.463.571	79.589
85113	Prevalence 124 per 3,5 year	-14.973	3,2	-3.993	-456.231	114

EARLY HTA - ETHICAL ANALYSIS

In the ethical analysis, the ethical aspects of case 86.062 (*period:1988-1991*) are studied, to advise the DHF on whether and how ethical considerations should play a role in decision-making about research funding and to provide insight into which stakeholders might be responsible for which aspects at what time in the research process. The ethical aspects relating to case 86.062 (xenotransplantation) are filled in into the four principles of the Beauchamp & Childress Principles of Biomedical Ethics model (figure 3). Substantively meaning that the autonomy of patients or research subjects will be respected. Also, should be strived for a research policy in which only justified interventions are potentially funded. In addition, a research policy must be structured in such a way that the patients or research subjects are not harmed and their well-being should increase.

An important disclaimer is that xenotransplantation of the heart has not yet been implemented in (Dutch) clinical practice. Therefore this ethical analysis contains uncertainties, because it is not yet clear how the xenotransplantation procedure will look like in clinical practice.

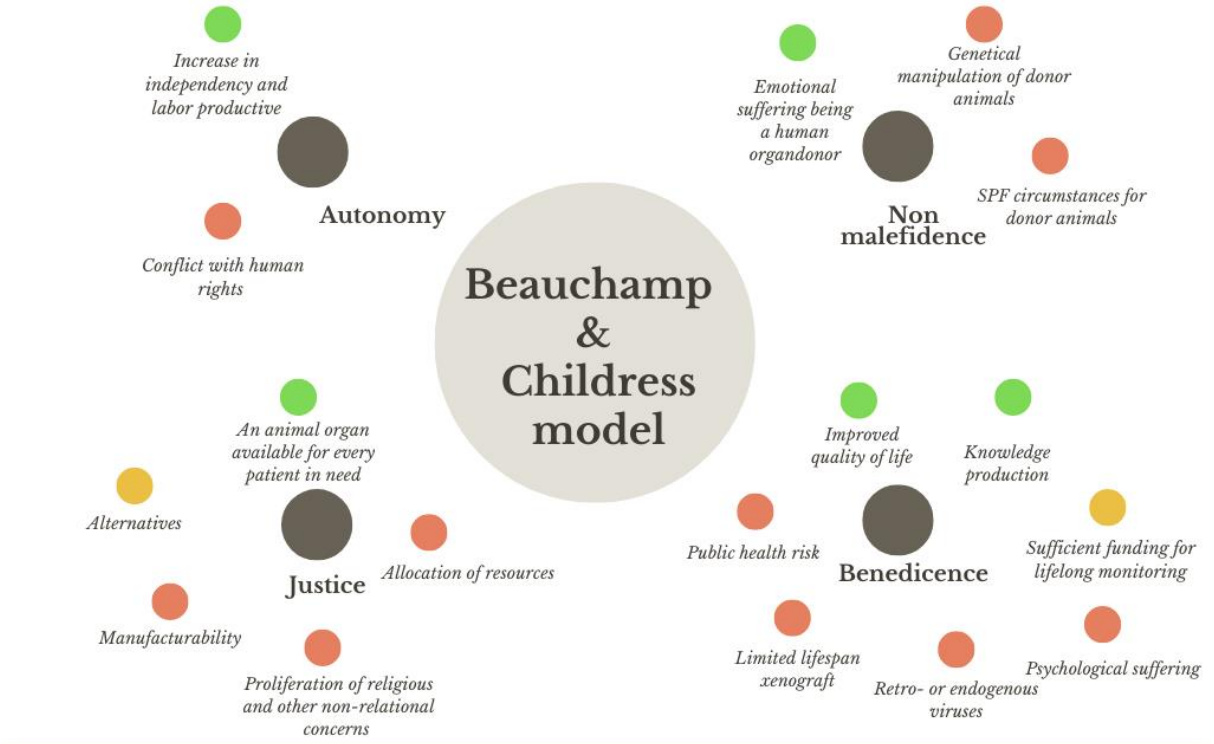

Figure 3 Beauchamp & Childress principles of biomedical ethics model, filled in based on case 86.062. An ethical aspect that positively influences one of the principles is shown in green, an aspects which negatively affects one of the principles is shown in red; and in yellow aspects are shown wherefore attention is required but not directly influence one of the principles in a positive or negative way

Autonomy

Autonomy stands for the freedom and independency to which patients or test subjects are entitled. Generally, after receiving a xenograft the perception is that the autonomy of a patient will be increased [35]. Because the medical condition of a patient has improved, for example, up to 86% of heart transplant patients returned to work after the cardiac event [36].

Non-maleficence

Non-maleficence stands for not harming anyone (in)directly involved in the research. However, the perception dominates that animal welfare of the donor animals is harmed [39]. Literature states that donor animals should live in specific pathogen-free (SPF) laboratories to prevent the development of pathogens, in these laboratories every natural condition is missing [40]. The animals will be frequently checked for possible contamination and

Unfortunately, receiving a xenograft also negatively affects the autonomy of patients, because of the risk of virus transmission a Dutch government committee drew up measures who are in conflict with human rights [37]. To avoid virus transmission, patients should adhere to the following measures: a patient should be quarantined for an indefinite period [38], they should be under lifelong supervision and sexual contacts have to be reported to a public health authority.

genetical manipulation is applied to prevent organ rejection and to eliminate potential viruses [41]. After removing the heart the animal passes away. A study by Paul & Browne indicates that human welfare is often placed above animal welfare [39].

The general perception is that donor animals suffer from genetic manipulation. However, one of the researchers of the project indicated in the interview that the physiology of a donor animal can be affected

by the introduction of a gene, but a donor animal does not suffer psychologically from this procedure.

"Pigs, as laboratory animals, are very well taken care of. Of course, an animal ethics commission has to approve your research, so those things are actually guaranteed by legislation"

Another point promoting non-maleficence was made by one of the interview respondents who indicated that being human organ donor can be a very emotional experience and xenotransplantation can prevent this emotional suffering.

"There are several reasons to try to do a xenotransplantation. When you ask someone to be an organ donor, it makes most people think of death, it's an emotional thought. "

Justice

Justice means that every person in need should be helped equally. Patients with severe heart failure who are on the Eurotransplant waiting list for an allogeneic organ will be offered an animal organ. Currently, only patients with the best match to a allogeneic donor be delighted with an organ. If xenotransplantation will be implemented in Dutch clinical practice and when sufficient xenografts are available, all patients at need will be offered an organ in an equal manner and the Eurotransplant waiting list system will become superfluous.

However, several aspects of the research project are in conflict with the principle *'justice'*. It should be considered if it is justified to use animals organs while the use of human organs (machine perfusion) has not yet been optimized or alternatives (e.g. artificial heart) can also solve the donor shortage. Another question arises whether it is justifiable to already want to perform high-risk research such as xenotransplantation, while fundamental diseases as diabetes still causes high mortality in third world countries [42]. Another ethical dilemma is broadening the indication for xenotransplantation. Currently xenotransplantation is aimed to use as a necessity for patients with severe heart failure, but xenotransplantation can also be applied aimed to increase the fitness of people. Broadening this indication influences the manufacturability of human life [43].

"As a society, we must be careful not to make the indications too broad."

Multiple interview respondents mentioned that ethical concerns about xenotransplantation decreases as the medical condition of a heart failure patient deteriorates. So morality get broadens as soon as the need for a donor organ increases.

"Because doctors know how patients react when there are only a limited number of choices to improve your health or even save your life. Then you just say yes."

Proliferation of religious and other non-relational concerns negatively influences 'justice'. For some people with a Christian point of view xenotransplantation is not justified [42], they advance arguments that xenotransplantation rearrange God's creation and that the God-given boundaries between humans and animals is broken [43].

Benedicence

Beneficence means that well-being of the patient or society should be promoted. The benedicence of a patient is promoted after xenotransplantation, because the medical well-being of severe heart failure patients will be improved considerably (utility + 0,28; life expectancy + 11,5 year) [44]. Even if xenotransplantation would never be applied in (Dutch) clinical practice, all knowledge gained about the immune system, organ rejection etc. would still be useful information for the research field, as the following quote illustrates:

"So a lot of knowledge has been built up around this subject, even if you will never get an organ from an animal in a human"

However, the benedicence of a xenograft patient can be affected if the recipient gets infected with a retro- or endogenous virus [45] and possibly die due to adverse events of xenotransplantation [46]. This virus can pose a threat to public health as it can spread horizontally across a population, infection an unspecified number of people. To enforce to continue the government measures (paragraph '*autonomy*') sufficient budget must be available [47].

"Recently with the transplantation of a pig heart in January 2020 in the United States, it became clear that a pig CMV probably contributed to the death of the recipient of that heart. So I do think that pig viruses can make people sick. But I don't know if that is so easily transferable to another person"

Also, for a patient it might be psychologically difficult to receive an animal organ, because the patient may feel less human or looked at strangely by his or her social contacts [40] [48]. Finally, with the current evidence a xenograft has a limited viability [35], meaning that a xenograft only provides a temporary medical improvement [45].

Other ethical aspects

A fifth category, has been added to ensure a complete ethical analysis, including all relevant ethical aspect related to the case about xenotransplantation. It appeared from the interviews with the researchers that they did think about ethical aspects of their research, but did not have to account for this to stakeholders. They mainly performed transplantation procedures, but left the ethical aspects for ethicists or other involved parties such as an ethics committee, as the following quote illustrates:

"There are many more people who think and work from medical psychology, medical ethics, and who ask these kinds of ethical questions. In that respect we were just a bit of the stupid surgeons, who just want to see if they can make transplants successful. All those other questions are often asked by other people"

Not only the researchers were involved into the xenotransplantation topic at the time, also a public debate was held in the Netherlands (late 90s) to discover the view of Dutch citizens an experts on the clinical application of xenotransplantation. It emerged from the interviews with the leaders of the public debate that experts (e.g. virologists) mentioned that the transplantation field in the Netherlands was not yet ready to take the next step towards transplantation with larger laboratory animals, while the researchers would have taken this step. Another concern that was heard in the public debate was the risk of virus transmission from animals to humans after xenotransplantation. The results of the public debate were presented to the Minister of Health in the year 2000, Borst (D66), she granted the requests and instituted a moratorium on clinical research and clinical application of xenotransplantation [49].

"Finally, the results of the debate were presented to the minister who responded a while later, during the debate she instituted a moratorium. She didn't think you should be arguing about something while you just kept going"

DISCUSSION

FINDINGS

In this study, the added value of an early ethical and economic evaluation as part of HTA has been investigated. It resulted to be an explorative study which indicates that early HTA assessments offer several advantages, but also present methodological challenges [13]. In this study is found that early HTA can be used to systematically evaluate the potential, medical-, economic- and ethical impact of an potential intervention based on the submitted research application by the DHF for a grant

Economic evaluations should preferably be performed in early stages of healthcare innovation development. However, this study showed that early economic evaluations are not possible to perform by some projects in the '*idea screening*' phase, where the related disease area and/or the potential intervention has not yet been defined. In addition, although early HTAs mostly require substantial assumptions, there must be some (preliminary) evidence, regarding incidence or prevalence and on costs and effects of Soc and the (new) intervention, to be used as input for an economic evaluations.

The six projects that were suitable for an early economic evaluation showed that all potential interventions would have been cost effective (ICER < 20.000 QALY) regardless of the WTP threshold. This indicates that also the disorders with a high burden of disease (> 0,71), where a higher WTP threshold applies (€ 80.000 p/QALY), are cost-effective at a threshold of € 20.000/QALY, such as projects 86.062, 87.074 and 85.113. However, because of the exploratory analyses some caveats and nuances are warranted (paragraph 'limitations'). Potential interventions resulting from case 86.062 and 85.113, both in the concept development phase, are extremely more expensive that the other potential interventions. It is unclear whether this fact is due to chance because both projects involve expensive interventions, namely transplantation, or whether the stage in the development process determines the (over)estimation of the costs. Another remarkable finding is that the place on the ICER plane of potential interventions from project 85.083, 84.074 and 86.021 are almost the same (figure 1), meaning that the ratio between incremental costs and effects

are almost equal. While the related proportional shortfall differs per disease investigated in these projects (table 2). A research funder achieves the highest societal impact by preferring projects with a high proportional shortfall and a high incidence or/and prevalence, such as project 84.074. The potential intervention resulting from this project yields the most QALY gain, of this three potential interventions, at population level and contributes to a medical improvement of patients with the highest BoD.

The ethical analysis is based on project 86.062 on xenotransplantation funded by the DHF from 1988 till 1991. The results of the ethical analysis show that there are good reasons for the clinical application of xenotransplantation. Currently in the Netherlands, many patients with organ failure are on the waiting list for a donor organ. These patients have a low quality of life and an increased risk of premature death. They will benefit greatly when receiving a xenotransplant. Despite the patient benefits, this intervention has many conflicting ethical aspects, partly due to the current policy on xenotransplantation, with all four principles of the Beauchamp model. Mainly in the interviews was mentioned that the researchers as well as the DHF have been little till not involved in decision-making on ethical issues. The researchers saw this mainly as the task of ethicists (commissions). However, due to all ethical aspects, a democratic decision has been taken in the Netherlands to impose a moratorium since 2000 which is still valid. If an early ethical analysis had been performed, before funding this project (as part of HTA), the DHF might have been more aware of these ethical dilemmas and better informed in decision-making or could have been more involved in the societal discussion on the regulation of xenotransplantation research. .

In addition, the question remains whether an early ethical analysis should be part of HTA and research funding decisions. In literature is described that it is difficult to integrate ethics into HTA [50]. The current HTA configuration is mainly based on comparing objective and empirically verifiable "facts" [51], while ethics is not empirically verifiable. For nearly 50 years efforts have been made to make ethical analysis part of HTA, but still not successfully integrated [50]. Explanations, mentioned in literature, are that ethicists are professional strangers in HTA and there is also a lack of commonly agreed methodology. Traditional ethical approaches include different methods as: principlenism, casuistry, utilitarianism and coherence analysis [51]. In addition, ethical methodology appears to be flawed, insufficient or inappropriate [50]. Seeing a wide variety of ethical approaches, first consensus has to be created on the suitability of the existing methods [52]. A study by Hoffmann concluded that it is not recommended to integrate an ethical analysis as part of HTA, but to prepare a separate type of ethical evaluation or to change the HTA policy so that ethics will be better integrated [50].

STRENGTHS

A strong point of this analysis is that all research projects included in this paper were carefully stratified and randomly selected so that these projects could be compared with each other. Second, the ethical reflection is based on different input sources such as interviews, document analysis and newspaper articles, providing a complete picture of different perspectives and -opinions of stakeholders. Third, a sensitivity analysis has provided insights into the impact of the uncertainty of the cost-effectiveness estimates, by means of a best-worst case analysis. The ranges are such that both the best and worst case scenarios indicates that the ICER is below the WTP threshold. Resulting in a uncertainty about the size of the ICER, and not so much about whether it is worth funding these projects. Fourth, this retrospective analysis was carried out 30 years after funding, whereby the results of the analysis can be put into perspective. In most retrospective analyses, such a long time frame is not used, e.g. in the RAND study a maximum of 15 to 20 years is included. Fifth, the general fact is that early HTA is playing an increasingly important role in funding decisions, and this study contributed to the integration of early HTA in funding decisions by a research funder as the DHF.

LIMITATIONS

An attempt has been made to collect suitable input data for the economic evaluation, but the execution of the economic evaluations was limited by the lack of available data, so many rough assumptions had to be made about expected effects and -costs of a potential intervention. It was also assumed that the intervention does what it is supposed to do, so the effects were estimated to be relatively high and the costs relatively low, resulting in an overestimation of real situation. In addition, the results of the evaluations are based on different input sources,

which possibly results in an under- or overestimation of true values. Especially the expected utilities and life years gained were surrounded with a lot of uncertainty. For example, in project 86.062 about xenotransplantation, from practice we know that the exact number of patients on the waiting list for a heart transplant is higher than stated on the website of the Dutch transplant foundation, because we know in advance that not all those patients will be eligible for a donor organ and are therefore not even listed on the waiting list. Second, it was difficult to estimate what the costs will be for breeding, raising and maintaining the donor animals. Third, because a xenograft has a limited lifespan this increase the chance of reoperation. The long term medical benefits for a patients are limited due to the shortened lifespan of the xenograft, also additional costs have to be made for a potential reoperation. This negatively influences the ICER. Ideally, effectiveness should be measured empirically to assess true cost-effectiveness, but empirical evidence will become available after a research project has been funded in phase three studies or after market approval, after which phase four studies can be performed, where "real-world" effectiveness is investigated. Also, discounting and correction for inflation are not included in the calculations, due to the explorative nature of this study, although this negatively affects the reliability of the economic evaluations. Discounting would have had a large impact on interventions with large long term effects, compared to interventions where the impact is mainly in the short term. It is in this study also is not defined which projects did result in short or long term impact.

The execution of the ethical analysis is limited by the fact that this analysis was only performed on one case (86.062). This case involves complex ethical aspects and therefore it was difficult to make statements for how many studies such an ethical reflection would be valuable. This study also found that the Beauchamp model itself was limited to just four principles, which were not all-encompassing because some ethical aspects of case 86.062 did not fit well into these principles. A fifth category has been added to cover other relevant ethical issues, regarding the relevance of a code of conduct, which describes the desired attitude and responsibilities of researchers. Also some extra information about the continuation of the project is described regarding regulations and law emerged from this project. This study also did not investigate the way in which ethics currently play a role in funding decisions, it cannot be said whether ethics should be integrated more or differently in the current DHFs funding policy. In literature it was difficult to find relevant articles about the application of early HTA in research funding decisions and thus making it difficult to place the findings of this paper in a broader context of existing initiatives.

FURTHER RESEARCH

Due to the explorative nature of this study, it is recommended to further explore this approach and provide more detailed advice on the integration of early HTA among research funders.

It also might be interesting to look into the relation between the outcomes of an early HTA analysis and the outcomes of the Payback Framework in terms of (long term) impact. Literature also describes that the Payback Framework is a suitable method to asses the impact of (early) HTA projects [59]. The case reports, incorporating the Payback Framework, of all nine cases have already been performed by the DHF. However, every case report has a different focus in terms of impact, e.g.: collaboration, career development, ethics, knowledge development, stakeholders. By doing this, the Payback Framework check whether the results of early HTA actually correspond to practice. By gathering this insight, better substantiated advice can be given about the actual added value of early HTA for a research funder.

IMPLICATIONS FOR PRACTICE

The results of this study show that early HTA evaluations are feasible for a large part of the research projects and provide additional information relevant for decision making. It also is important to realize that cost-effectiveness is one of the package principles that an intervention must meet if the Dutch Health care institution will recommend an intervention to the Dutch Minister of Health to include this intervention into the basic health insurance package. We conclude therefore that the DHF takes advantage of implementing HTA in their funding policy, because the DHF will better informed about the expected impact of projects that they (will) fund. This requires building up expertise within the DHF, for example by setting up a committee or by setting up cooperation with HTA experts. An HTA report can help to identify areas where research is needed [53] by finding gaps in

evidence and then formulate a research question [54]. For example, the National Institute for Health and Care Research (NIHR) a research funder in the UK, requires proposals for new primary research to be justified by existing evidence through systematic evaluations. It is assumed that funders explicitly ask the researchers for information about what already exists and how their research design is based on existing evidence [54].

In the last years the DHF funds more interdisciplinary research projects, where a disease is centralized in a consortium where an interdisciplinary collaboration has been built around. This change has increased the feasibility of HTA, because in a consortium different research routes are examined side by side and HTA can help decide which research routes are the most valuable. However, the implementation of HTA is more complex for interdisciplinary projects [55], because interdisciplinary projects investigates multiple interventions, which can also be in a different development phases.

The results of this study showed that neither the researchers nor the DHF played an active role in ethics at the time of the study (late 1980s). It is not known whether it was really necessary for the DHF to play an more active ethical role, because this dialogue has been conducted extensively and the regulations have developed in it. It is valuable to investigate how this is now addressed in the assessment process of the DHF and how this is now safeguarded at animal experimental commission (DEC) and the medical ethics review committee (METC).

Based on the results of this study, the DHF is recommended to ensure that the researchers are primarily responsible for an active involvement in the ethical implications of their research[56] [57] [58]. Researchers should have a reflective and open attitude to ethical objections from stakeholders (participants, organization, peers, funding agencies, society). The researchers should also strive to minimize harm, treat opponents with respect, strive for a fair distribution of benefits and burdens, give a good assessment of the disadvantages of research to relevant stakeholders and monitor developments that affect ethical aspects of research. If the researchers insufficiently secure the Beauchamp principles, the DHF as research funder would preferably pay more attention to this element in its decision making.

Finally it is important to mention that the concept ‘value’ depends on several factors, which makes it difficult for research funders to paint a complete picture of the value of an intervention using only their own expertise. The interests and needs as the role of relevant stakeholders influence the way value is reasoned. Value claims of medical interventions are by no means always placed in the context of healthcare practice. The DHF also finds it important to spend time and money on career development, knowledge production, contribution to policy etc. It is neither possible nor desirable to reach consensus on the concept of value of interventions. After all, every intervention produces different types of goods. That is why it is important not to hammer out the definition of value, but to keep it open to different perspectives. Broadly exploring and carefully framing the value proposition for specific stakeholders will benefit the intervention. The same can be done for ethics, it is important to look at and talk about ethics application from different perspectives for the further development of the ethical perspective and innovation. Early HTA provides opportunities for early exploration to understand the value of a specific intervention.

CONCLUSION

The added value of early economic evaluations for the DHF are the insights into the possible cost-effectiveness of potential interventions resulting from research projects submitted for funding. By funding projects with the most favorable expected, incremental cost-effectiveness ratio, the greatest societal value will be achieved with limited financial resources. However, early economic evaluations are not suitable for some projects in the *'idea screening phase'*, but this does not mean that the these projects cannot be valuable for the DHF. Thus the application of early HTA for suitable projects is relevant, but cost-effectiveness should not be the only input in a funding decision.

The added value of an early ethical analysis are the insights helping to estimate to fund only research projects that do not conflict with the morality of Dutch citizens and especially the DHF’s financial supporters. Because the public opinion provides important input for Dutch legislation and regulations [60] and if DHF supporters are not in agreement with projects implicating ethical dilemma’s, they may stop their financial support. Based on the ethical analysis in this study it can be concluded that there were many ethical questions at the time of research

86.062 and these were not addressed in the research itself or in the funding decision. As a result, research into xenotransplantation could not be continued after this project, at least not in the Netherlands. There would probably have been an opportunity if the DHF had played an active role in promoting ethical reflection. Ethics can help the DHF form frameworks in making better ethical decisions [43]. An ethical analysis also helps to explore alternatives that cause fewer ethical dilemmas, and thus respond better to ethical objections.

Thus, integrating early HTA into research proposals (and their assessment) by the DHF helps fund innovations that are expected to have the greatest impact, and early HTA also increases the likelihood that promising, cost-effective innovations will reach patients quickly.

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Table 4 Costs per patient: Direct healthcare cost (green)– Indirect healthcare cost (Yellow)– Direct non healthcare cost (red)– Indirect non healthcare cost (orange). * Percentage of number found in literature (most reliable) ** Percentage of number of comparable intervention found in literature (less reliable) * Assumptions based on gut feeling (least realiable)**

<table>
<tr><th colspan="7">Case 86062</th></tr>
<tr><td colspan="7">PICO
P= Patients with severe heart failure, on the waiting list for an donor organ
I= Xenotransplantation
C= Patient on waiting list, following pharmacological treatment, life expectancy is 9 a 10 months
O= Societal costs and effects in QALY’s</td></tr>
<tr><th colspan="2">Epidemiology</th><th colspan="2">Costs</th><th colspan="3">QALYs= utility * life years gained</th></tr>
<tr><td rowspan="11">Prevalence</td><td rowspan="11">124 patients on waiting list (April 2022), average waiting list duration 3,5 year *</td><td>Heart transplantation</td><td>€ 39.655,- *</td><td>Usual care</td><td>0,55 *</td><td>3 *</td></tr>
<tr><td>Preliminary examination with 5 nursing days</td><td>€ 5493,- *</td><td>Intervention</td><td>0,83 *</td><td>12,5 *</td></tr>
<tr><td>Guidance from hospital staff</td><td>€ 24.951,- *</td><td colspan="3" rowspan="9"></td></tr>
<tr><td>Aftercare</td><td>€ 6.206,- *</td></tr>
<tr><td>Diagnostics</td><td>€ 3737,- *</td></tr>
<tr><td>Medical costs current treatment</td><td>€ 23.040,-**</td></tr>
<tr><td>Travel and parking</td><td>€ 25,- **</td></tr>
<tr><td>Productivity loss</td><td>€ 72.280,- **</td></tr>
<tr><td>Euro transplant – waiting list management</td><td>€ 10.000,- ***</td></tr>
<tr><td>Pig breeding and living supply</td><td>€ 4000,- ***</td></tr>
<tr><td>Lifelong monitoring by medical authorities</td><td>€ 3000,- ***</td></tr>
<tr><td colspan="2">https://www.transplantatiestichting.nl/publicaties-en-naslag/cijfers-over-donatie-en-transplantatie/organen-cijfers-afgelopen-maanden</td><td colspan="2">https://www.hartkliniek.com/praktische-informatie/vergoedingen/tarieven & Nza zorgtarieven</td><td colspan="3">https://www.sciencedirect.com/science/article/pii/S0167527313021979?via%3Dihub</td></tr>
<tr><td colspan="7">Case 85083</td></tr>
<tr><td colspan="7">PICO
P= Young people (20-30 year) vs. Elderly people (60-80 year) with orthostatic hypertension
I= Insights into beat-to-beat blood pressure and heart rate changes when standing up and passive tilting
C= Without insights from intervention
O= Societal costs and effects in QALY’s</td></tr>
<tr><th colspan="2">Epidemiology</th><th colspan="2">Costs</th><th colspan="3">QALYs= utility * life years gained</th></tr>
<tr><td rowspan="2">Prevalence</td><td rowspan="2">13,7% in people elder then 60 years *</td><td>GP Visit</td><td>€ 87,- **</td><td>No awareness among children</td><td>0,85 ***</td><td>10 ***</td></tr>
<tr><td>Balance test</td><td>€ 686,33 *</td><td>Informed children due to the</td><td>0,85 5***</td><td>10 ***</td></tr>
</table>

				research project		
		Geriatric exercise therapy	€ 47,61 *			
		Consult clinical geriatrics	€ 238,37 *			
henw.org/artikelen/nhg-standaard-duizeligheid-0 //		https://www.dijklander.nl/praktische-informatie/zorgverzekeraars-en-kosten/passantentarief-als-u-niet-verzekerd-bent#:~:text=Als%20u%20ondanks%20de%20wettelijke,Dit%20is%20het%20zogenaamde%20passantentarief.		https://richtlijnendatabase.nl/richtlijn/duizeligheid_bij_ouderen/duizeligheid_tgv_orthostatische_hypotensie.html		
Case 84074						
PICO **P=** 80 Patients who have undergone cardiac catheterization **I=** Rotating gamma camera with a coupled computer system that allows to determine a three-dimensional perfusion of thallium-201 in the myocardium **C=** Usual care, without rotating gamma camera **O=** Societal costs and effects in QALY's						
Epidemiology		**Costs**		**QALYs= utility * life years gained**		
Incidence	42.147 annual incidence in Belgium (Flanders) * (112.097 in the Netherlands)	Costs spent on CV cause - CCTA (intervention) - SPECT (Soc)	 € 2096,- ** € 2445,- **	Usual care	0,68 *	18 ***
		Outpatient cost - CCTA (intervention) - SPECT (Soc)	 € 1.113,- ** € 1425,- **			
		Drug prescription cost - CCTA (intervention) - SPECT (Soc)	 €582,- ** € 555,- **	Intervention	0,70 ***	18,5 ***
		Non-drug cost - CCTA (intervention) - SPECT (Soc)	 € 531,- ** € 870,- **			
		Inpatient cost - CCTA (intervention) - SPECT (Soc)	 € 982,- ** € 1020,- **			
		Cost spent on non-CV cause - CCTA (intervention) - SPECT (Soc)	 € 2.418,- ** € 2763,- **			
		Productivity loss - CCTA (intervention) - SPECT (Soc)	 € 834,- ** € 1.390,- **			
https://www.zorg-en-gezondheid.be/cijfers-over-cardiale-zorgprogrammas		Coronary computed tomography angiography vs. myocardial single photon emission computed tomography in patients with intermediate risk chest pain: a randomized clinical trial for cost-effectiveness comparison based on real-world cost | European Heart Journal - Cardiovascular Imaging | Oxford Academic (oup.com)		Mapping of the EQ-5D index from clinical outcome measures and demographic variables in patients with coronary heart disease - PMC (nih.gov)		
Case 85113						
PICO						

P= Patients with severe heart failure, on the waiting list for an donor organ

I= Heart transplantation with pre- and postoperative donor cells and cyclosporine-a

C= Usual care, without pre- and postoperative donor cells and cyclosporine-a

O= Societal costs and effects in QALY's

Epidemiology		**Costs**		**QALYs= utility * life years gained**		
Prevalence	124 patients on waiting list (April 2022), average waiting list duration 3,5 year *	Heart transplantation	€39.655,- *	Usual care	0,83 ***	12,5 ***
		Preliminary examination with 5 nursing days	€ 5493,- *	Intervention	0,85 **	16 ***
		Guidance from hospital staff	€ 24.951,- *			
		Aftercare	€ 6.206,- *			
		Medication	€ 1.300,- **			
		Diagnostics	€ 3.738,- *			
		Cyclosporine-a and donor cells	€ 14.973,- **			
		Travel and parking	€ 25,- **			
		Productivity loss	€ 72.280,- **			
		Euro transplant – waiting list management	€ 10.000,- ***			
https://www.transplantatiestichting.nl/publicaties-en-naslag/cijfers-over-donatie-en-transplantatie/organen-cijfers-afgelopen-maanden		Nza zorgtarieven https://www.hartkliniek.com/praktische-informatie/vergoedingen/tarieven		https://www.ntvg.nl/artikelen/harttransplantatie-de-21e-eeuw-de-overleving-wordt-beter		

Case 84043

PICO

P= People at risk for being hyper responder to cholesterol synthesis

I= Developing tests for rapid identification of hyper responders, enabling personalization of nutritional advice **C=** People at risk without nutritional advice

O= Societal costs and effects in QALY's

Epidemiology		**Costs**		**QALYs= utility * life years gained**		
Incidence	60.000 annual *	Statines (cost per patient per year) - 60% use medication of which 89% use statins in Soc group (2% less use in intervention group)	€ 50,- *	Usual care	0,69 **	40 ***
		Ezetimib (cost per patient per year) - 60% use medication of which 10% use Ezetimib in Soc group (2% less use in intervention group)	€ 59,- *	Intervention (Since 1988, the cholesterol level has decreased from 5.8 to 5.4 mm/ mol.)	0,71 **	40,9 ***
		PCSK-9 inhibitors - 60% use medication of which 1% use PCSK-9 in Soc group (2% less	€ 4000,- *			

		use in intervention group)		
		Primary healthcare - 60% use in Soc group - 58% use in intervention group	€ 4000,- ***	
		Nutritional advice - 70% in intervention group	€ 210,- **	
		Combined lifestyle intervention (cost per patient per year) - 20% use in intervention group	€ 1025,- **	
		Productivity loss - Usual care - Intervention	€ 11.120,- € 9.730,-	
https://www.vzinfo.nl/cholesterol		https://www.hartkliniek.com/praktische-informatie/vergoedingen/tarieven https://www.sfk.nl/publicaties/PW/2017/nieuwe-cholesterolverlagers-drijven-medicijnkostenop#:~:text=Ter%20vergelijking%3A%20een%20behandeling%20met,geen%20%E2%82%AC%2050%20per%20jaar. https://www.ahajournals.org/doi/10.1161/01.cir.85.5.1960?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed https://pubmed.ncbi.nlm.nih.gov/17850322/ https://www.heartfoundation.org.au/getmedia/1fce4fbc-1d07-44c5-882d-8d51cf379cd7/EcoCost_Cholest_Summary_WEB.pdf		https://nederlandsehartregistratie.nl/hartenvaatcijfers/wp-content/uploads/2019/12/NHS_Factsheet_Cholesterol_2012.pdf

Case 86021

PICO

P= 60 Dutch born persons admitted for coronary artery bypass surgery (C.A.B.S.) to the academic hospital of the university of Limburg, Maastricht

I= Changes in self care in relation to C.A.B.S.

C= C.A.B.S.without improved perioperative care

O= Societal costs and effects in QALY's

Epidemiology		**Costs**		**QALYs= utility * life years gained**		
Amount of bypass operations per year in the Netherlands	4500 annual *	Operating room per minute	€ 25,- *	Usual care	0,5 **	11 *
		Staff per minute	€ 1,75 *	Intervention	0,53 **	11 *
		Intensive care per hour	€ 50,- *			
		Medium care per day	€ 225,- *			

		Anesthesia per patient - usual care - intervention	** € 1050,- € 1100,-	
		Physiotherapy per patient - usual care - intervention	** € 188,- € 95,-	
		x-ray per patient - usual care - intervention	** € 223,- € 219,-	
		Laboratory per patient - usual care - intervention	** € 420,- € 340,-	
		Cardiology per patient - usual care - intervention	** € 400,- € 380,-	
		Extra actions by nurse after intervention per patient	€ 5,40 **	
medischcontact.nl/nieuws/laatste-nieuws/artikel/bypass-vaak-kosteneffectiever-dan-dotteren.htm		https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-021-06218-5 https://www.medtronic.com/nl-nl/patienten/behandelingen-en-therapieen/behandelingen-kransslagader-aandoening/leven-na-ingreep/periode-na-bypassoperatie.html#:~:text=Hoelang%20u%20in%20het%20ziekenhuis,zes%20weken%20beter%20te%20voelen.		https://www.ntvg.nl/artikelen/overleving-11-jaar-na-een-aorto-coronaire-bypass-operatie