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Published in:
Haemophilia

DOI:
[10.1111/j.1355-0691.2004.00878.x](https://doi.org/10.1111/j.1355-0691.2004.00878.x)

2004

[Link to publication](#)

Citation for published version (APA):

Steen Carlsson, K., Höjgård, S., Lethagen, S., Berntorp, E., & Lindgren, B. (2004). Economic evaluation: what are we looking for and how do we get there? *Haemophilia*, 10(Suppl 1), 44-49. <https://doi.org/10.1111/j.1355-0691.2004.00878.x>

Total number of authors:
5

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Economic evaluation: what are we looking for and how do we get there?

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Summary. The interest in economic evaluation of alternative strategies for haemophilia treatment has increased through the years. Few studies have actually been undertaken, however, and most of them have been simple cost-minimization or cost-effectiveness analyses. From the perspective of the binational project 'Treatment strategies for severe haemophilia – prophylaxis vs. on-demand', the present paper discusses the pros and cons of different methods for economic evaluation and their data requirements. Severe haemophilia is a rare disease

that requires lifelong treatment. In addition, treatment has both short- and long-term effects which are likely to differ between strategies. Accordingly, regardless of the chosen evaluation method, data requirements are non-trivial. Hence, the various problems connected to the generation of data, as well as how they may be addressed, are also discussed.

Keywords: economic evaluation, cost, benefit, haemophilia

Introduction

There is continuing interest in evaluating the two main alternative clotting-factor replacement strategies for severe haemophilia patients: on-demand treatment and long-term prophylaxis. The clinical literature shows that prophylaxis results in fewer bleedings, less problems with joints, less use of special equipment and fewer days lost from work [1–11], but also higher clotting-factor consumption [1,11,12]. The question is then 'Do the superior clinical results justify the greater use of the costly clotting factor?'

Health-economic evaluation methods are well suited to help to answer this question, as they supply tools for a systematic analysis of the costs and benefits of alternative treatments. The starting-point is that all resources (equipment, time, knowledge, etc.) are limited. Thus, choices about their use are always made, either explicitly or implicitly. The aim of an economic evaluation is to demonstrate where resources produce most benefits per Euro spent.

The eminent introduction to economic evaluation of healthcare programmes by Drummond *et al.* has

been used widely and cited since first published in 1987 [13]. Like a cookbook in the culinary field, Drummond *et al.* present each method (the dish to be served), its requirements (the ingredients) and the 'how-to'. However, anyone who has attempted to cook a Béarnaise sauce using vinegar, shallot, tarragon, melted butter and the yolk of egg (i.e. not the semiproduct) knows that the instruction 'add the yolk of egg under heavy stirring' may not always be sufficient to avoid the sauce from curdling. Moreover, even if successful in the preparation of the sauce, putting a lid on it to prevent it from getting cold may also trigger the curdling process.

Economic evaluation may be regarded as similar to preparing a Béarnaise sauce. There are the necessary ingredients but also some potential for variation: for instance, regarding the type of vinegar used. The cooking process needs careful preparation, including the necessary tools and timing. Finally, it needs to be served in the right way. Essential to an economic evaluation is the identification and measurement of costs and benefits of the alternatives, but the results also need to be interpreted correctly.

To investigate the costs and benefits of the on-demand and prophylactic strategies for severe haemophilia a binational project was formed, including the three haemophilia centres in Sweden (where prophylaxis has been standard treatment since the

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1970s) and the haemophilia centre in Norway (where on-demand treatment was standard until the early 1990s). The results will be presented in a series of papers in *Haemophilia*. The intention here is to convey our experience from designing the study and analysing the data, i.e. to go beyond the cookbook instructions and to communicate how we handled the sometimes intricate issues that arose along the way. As such, we hope that this paper will serve as an inspiration and aid to others conducting economic evaluations.

Main courses

The menu of economic evaluation methods contains the following main courses: (a) cost-minimization analysis; (b) cost-effectiveness analysis; (c) cost-utility analysis; and (d) cost-benefit analysis. The same methodological principles for measuring costs apply in all four cases, but they differ in how outcomes are measured. The latter then determines what comparisons that can be made (within disease, between diseases or between healthcare and other sectors in society). Which method is suitable depends on the particular setting and on the objectives of the study.

A *cost-minimization analysis* (CMA) identifies, quantifies and values (in Euros) all relevant resource use and welfare losses when people are not able to work because of the disease. If the outcomes of two treatment alternatives were equal in all relevant aspects, or if the outcome was better in the cheaper alternative, this would be sufficient. The recommendation would be: choose the cost-minimizing strategy.

A *cost-effectiveness analysis* (CEA) compares the costs and outcomes of two or more strategies, when outcomes are different but measured in a single dimension such as life-years gained or reduced number of joint bleedings. The recommendation would be to choose the strategy with the smallest extra cost per life-year gained or joint-bleed avoided. That is, the more costly strategy may still be recommended if it produced sufficiently more of the outcome measure.

A *cost-utility analysis* (CUA) uses a composite outcome measure, while the cost components are the same as for the CEA or CMA. The multidimensional outcomes are aggregated into quality-adjusted life-years (QALYs), which are obtained through eliciting people's utilities in different health states [13,14] and multiplying by the time spent in each health state. The recommendation would be to choose the strategy with lowest cost per QALY gained. That is, again

the more costly strategy may be recommended if it produces sufficiently more QALYs.

A *cost-benefit analysis* (CBA), finally, summarizes outcomes in monetary units, for instance, in dollars or Euros. Monetary values are usually obtained by asking respondents about their willingness to pay (WTP), given that they can only obtain the commodity if their WTP covers the cost of production, and that they would actually lose the opportunity to consume other goods corresponding to their stated WTP [13]. The best alternative would then be the one with the biggest net benefit.

For the choice between prophylaxis and on-demand treatment, a CMA might give sufficient information if prophylaxis, which entails superior clinical outcomes, also had the same or lower costs. Hence, we decided to conduct a CMA first, postponing the decision regarding a more comprehensive analysis. After we found that the clinically superior alternative also was the more expensive strategy, we had to consider the CEA, CUA and CBA as well.

Because the clinical literature indicates that the outcome of haemophilia treatment involves several essential dimensions, the CEA would have been unsuitable for our analysis. We chose the CBA rather than the CUA because the latter is not applicable when an expansion of the healthcare budget may be considered. The gains from using the resources within the healthcare sector then need to be compared to the gains from using them elsewhere, where benefits are typically measured directly in monetary units [15]. Also, the theoretical requirements for measuring people's valuation of health states are less strict for the CBA, as money unlike QALYs can be transferred from one person to another [16].

Ingredients

Costs

In economic evaluations, costs are both resources used that cannot then be used for any other purpose, and welfare foregone because of lost production when people are not able to work. Our first task was to account for the specific characteristics of haemophilia and its treatment and then to identify and quantify the different types of costs both within and outside the healthcare sector.

Haemophilia characteristics (specifics of the ingredients)

First, severe haemophilia requires lifelong treatment, and replacement therapy has both short- and

long-term effects. Hence, to account for the fact that costs and benefits do not occur simultaneously, we used a long period of investigation (1989–99) during which the patient was required to be receiving continuous on-demand or prophylactic treatment, respectively. To analyse even longer-term effects, we collected information on type of treatment, prescribed dose per injection and (for prophylaxis) the frequency of injections from birth to 1988.

Secondly, primary prophylaxis has been the standard treatment in Sweden since the 1970s. Accordingly, the on-demand patients had to be found outside Sweden. As the consequences of treatment may differ depending on the society in which the patient lives, we chose to include on-demand patients from Norway, which has a similar socioeconomic and institutional structure (tax-financed public healthcare and schooling systems, high labour-market participation rates for women, etc.). Thus, although there may be differences between the countries that affect the estimated costs and benefits of treatment, such effects were judged to be small.

Thirdly, severe haemophilia is a rare disease. We therefore included all patients who were on long-term continuous treatment during 1989–99 and born during the years 1939–89. In particular, we wanted to include as many patients as possible in the working ages to explore the effect of treatment choice on labour-market participation. Prophylaxis patients born before 1949 were excluded, however, because this strategy was not available before the 1950s and the older patients would have had too long an initial period without prophylaxis [17]. In Norway, prophylactic treatment was introduced for younger patients in the 1990s. Thus, we excluded patients in Norway born after 1981, as on-demand was not their standard treatment during childhood and adolescence [17]. This sampling difference in age could be handled by various sensitivity analyses of the results where, for instance, we excluded prophylaxis patients born after 1981 and on-demand patients born before 1949.

Physical quantities

Within the healthcare sector doctors' and nurses' visits, telephone consultations, hospitalizations, invasive procedures and the use of clotting-factor were obvious examples of types of resource use that was caused by, and may differ between, the strategies. A second, and more intriguing, category was resource use caused by undesired side-effects of treatment, i.e. the development of inhibitors to clotting factor and the transmission of blood-borne agents (mainly

hepatitis C and HIV). Clearly, they are caused by clotting-factor treatment; however, their effects on resource use might be the same for both strategies. If so, they would be irrelevant to the choice between prophylaxis and on-demand. The critical questions were then: (i) 'Do patients on either treatment have the same risk of incurring the side-effects?'; (ii) 'Does the development of modern medical technologies change the risk of incurring them?' and (iii) 'Do they change the haemophilia treatment *per se*?'.
 First, the risk of contracting any of the side effects does not differ between strategies [8,18–23]. Secondly, modern medical technologies, including the introduction of viral-attenuation methods (mainly heat-inactivation and/or solvent-detergent treatment) to factor VIII concentrates, manage to eliminate the risk of blood-borne agents [23]. Thirdly, the haemophilia treatment *per se* does not change in terms of, for instance, factor dosage or haemostatic drug for patients who have been infected with hepatitis C or HIV [18]. Accordingly, the cost of hepatitis C and HIV can be expected to be equal and therefore irrelevant to the choice between the two strategies.

However, the haemophilia treatment changes for patients who develop inhibitors. In patients developing low-titre inhibitors the dose has to be increased, whereas in patients developing high-titre inhibitors the treatment strategy has to be changed completely, e.g. to infusion of so-called by-passing agents in the case of acute bleeds and/or to implement immune tolerance induction. Nevertheless, this applies under both prophylaxis and on-demand treatments. Hence, we excluded patients who had ever developed inhibitors because neither costs nor benefits can be expected to be representative for the long-term continuous form of either treatment.

Outside the healthcare sector the main type of resource use was days lost from school or work, but also the use of special equipment (cars, wheelchairs, etc.) and adaptations of domiciles. Yet another type of welfare-loss caused by severe haemophilia is premature death. The literature shows no evidence of differences between the strategies in the number of life-years saved (partly, it is too early to say, as replacement therapy was not available before the late 1950s). Nevertheless, during the data generation process we investigated how many patients had died between 1989 and 1999, as well as their causes of death. AIDS caused the majority of deaths and, as argued above, this will be less of a problem in the future. Two on-demand patients of a total of 85 screened and one prophylaxis patient of

a total of 168 screened died from *other* haemophilia-related causes. Although we need more observations to conclude whether this difference is statistically significant, it enabled us to conduct a sensitivity analysis of our estimated costs.

Monetary values

We used Swedish year 2000 prices to convey physical quantities into monetary values. In most cases the prices were market prices (clotting-factor, orthopaedic implants, equipment to compensate for impaired function, adaptations of cars and domiciles and wages). In other cases administrative prices were used (doctors' and nurses' visits, surgical procedures, in-hospital care episodes). A number of considerations then arose.

Some of the clotting-factor brands used in Norway were not marketed in Sweden and some of them used during the first years of the study period had been replaced by newer brands. In these cases we used the price of an equivalent brand conferring with both medical expertise and the manufacturing company.

The costs of days absent from work were calculated using Swedish wages for the employments actually occurring in our material. This implies that we assumed that our sample was representative concerning employments for patients with severe haemophilia, and that Swedish patients receiving on-demand treatment would have had the same types of employment as those found among the Norwegian patients. Days absent from school were assumed not to represent costs if the absence did not imply a risk of delayed graduation.

As most families in both Norway and Sweden own a car, we considered only measures taken to adapt a given car (installation of hand-operated speed and brake controls, extra-powered servo-steering, wheelchair lift, electrically operated driver's seat, etc.) to the needs of the patient.

In the calculation of costs, we used a societal perspective where the resource use in our two populations of patients were considered to be representative for any population of severe haemophiliacs on the same treatment strategies and facing the same institutional setting. Following this approach, we were interested in the expected average annual cost per patient under each treatment strategy. Thus, costs should not be discounted because, from society's perspective, there will always be patients of all ages. Another approach would have been to calculate the present value of lifetime costs for a single patient starting from a specific year, for instance at birth,

which would then require discounting if costs arise at different ages depending on strategy.

Benefits

The benefits of the respective strategies were obtained by asking contingent-valuation [13] questions to a representative sample of the general population. There were three reasons for the choice of respondents. First, even if all patients exhausted their budgets to pay for the treatment, it would probably still not be sufficient to cover the costs of either on-demand or prophylactic treatments. Secondly, the financing of healthcare is typically subject to some kind of insurance (private or social) where the costs are shared. Thirdly, people may be altruistic and willing to pay for haemophilia treatment, even though they will never personally need it, a fact that would have been overlooked by asking patients only about their WTP.

We could not assume that the general population had any prior knowledge about haemophilia. Respondents thus received a letter a few days before the interview with two pages of background information, including a description of the disease, the two treatment strategies and their outcomes. This information was based on our results from the cost analysis and on results in published clinical studies.

Preparing the course

Cost data were generated from hospital casebook records and patient interviews and registered by research nurses at each participating centre. To assure a coherent data generation process and to reduce the potential sources of errors, a new electronic data input form was developed for the project.

The benefit study used telephone interviews. A professional interviewer first read a summary of the premailed letter to help the respondent to recapitulate the issue and then asked the respondent whether he/she would agree to pay a specified amount per year from his/her annual income for prophylaxis, and another specified amount for on-demand treatment. Information on the relevant bid-amounts was obtained from a pilot study.

Cost data were analysed using panel-data regression methods [24] to account for the fact that patients may have different characteristics at different points in time (for instance, present age and frequency or intensity of treatment) and also to account for the possible effects of treatment history on present costs. Benefit data were analysed by means of logistic regressions. Both cost and benefit

analyses were subject to sensitivity analyses, where we examined the effect on the results, for instance, of restricting samples (age-matching in the cost analysis, only first bids in the benefit analysis, etc.).

Serving

The average cost-per-patient estimates were based on successful long-term continuous treatment only, i.e. patients who had ever developed inhibitors were excluded. However, hypothetically, we expect that including patients with inhibitors would have resulted in a lower estimated annual cost for prophylaxis treatment and a higher cost estimate for on-demand treatment, given the changes in treatment when developing inhibitors.

Our results will apply well in many countries, but there should be some caution in using them in countries with large differences in the organization of the healthcare sector or with a radically different average income in the population.

Concluding remarks

Health-economic methods provide tools for the systematic analysis of costs and benefits of alternative healthcare programmes. The results from the analyses will provide information for the resource-allocation process. In other markets, for example for shoes or bicycles, the market price will perform this task. In the healthcare sector, which is characterized typically by third-part financing (private or public insurance), the low or zero user fees do not reflect the full consumer value of what is produced, nor do they cover the actual cost of producing it.

'Cookbooks' on health-economic evaluations [13] guide the investigator in the choice of method and the basic 'how-to' but cannot possibly list all the peculiarities that real life offers. Having an experienced cook at the side when making a Béarnaise sauce will aid the beginner to get onto, and stay, on the right track during the preparation and to make the crucial decisions. However, the experienced cook is also confined to the available ingredients. In the case of an economic evaluation of a healthcare programme, these ingredients must come from the medical experts who can disentangle what are the definitions, contents and consequences of a treatment strategy.

It is our experience that the close multidisciplinary collaboration between health economists and medical experts in our project has brought out the important features of the two treatment strategies for the purpose of economic evaluation. If this is true, our study will provide a good starting point for

decision-makers pondering the pros and cons of prophylactic and on-demand treatment.

Acknowledgements

The authors would like to thank Lilian Tengborn, Anders Glomstein, Sam Schulman, Caroline Ekholm, Christina Follrud, Eva Mattson, Siri Grønhaug, Karin Staffansson, Karin Lindvall and Valbona Meha, Anna Södermark and Doris Näslein for their invaluable work in the project. The authors would also particularly like to thank all the patients in Sweden and Norway who participated in the study. Financial support was received from Aventis Behring GmbH, Bayer, Baxter, Octapharma and the Wyeth/Genetics Institute. However, none of the sponsors were involved in any of the analyses, nor did they influence the conclusions of the research.

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