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Making economic evaluations more helpful for treatment choices in haemophilia

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Abstract

Aim: Poorly conducted economic evaluations have the potential to mislead both clinicians, leading to inappropriate treatment choices, and payers who must decide on the reimbursement of treatment costs. This paper reviews the methods used in economic evaluations in haemophilia and proposes standards for conducting and reporting such evaluations in the future.

Methods: A systematic review of economic evaluations in haemophilia published since 2008 was conducted. The reporting and methods of the studies were assessed using the recently published Consolidated Health Economic Evaluation Reporting Guidelines (CHEERS) checklist. The key methodological deficiencies in the studies were recorded.

Results: Twenty-one studies met the inclusion criteria, classified as follows: prophylaxis vs. treatment on-demand (five studies); use of bypassing therapy (six); immune tolerance induction (four); and other topics (six). In general, the quality of reporting was good. However, it was poorest for the CHEERS item of patient heterogeneity, with most studies lacking discussion of heterogeneity in the patient population. The main recurring methodological deficiencies were the evaluation of single episodes of care rather than entire treatment strategies; inadequate control for confounders when comparing treatment options; the frequent use of expert opinion to determine drug doses and treatment patterns; lack of consideration of patient heterogeneity; failure to identify patient subgroups; and the inadequate exploration of uncertainty in estimates.

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49 **Conclusions:** A set of twelve standards for future reporting and conduct of economic
50 evaluations within haemophilia is proposed, with the objective of making such
51 evaluations more relevant and reliable for those making treatment and
52 reimbursement decisions in the future.

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Introduction

Treatment decisions remain the sole responsibility of clinicians, yet increasing pressures on healthcare resources have a direct impact on healthcare funders and clinicians. Patients may also be concerned about treatment costs if they face substantial user charges. Hence, clinicians are increasingly requested to consider the cost/benefit ratios of different therapies.

Studies assessing the costs and consequences of healthcare treatments and programmes are known as economic evaluations [1], and a substantial body of empirical economic studies now cover all branches of healthcare [2]. For these studies to be helpful to clinicians and patients, they must be both relevant (i.e. address appropriate treatment choices) and reliable (i.e. have a sound methodology). Comprehensive and transparent reporting is particularly important to assess whether a given study is methodologically sound.

Several systematic reviews have indicated that economic evaluations in haemophilia often have substantial methodological deficiencies. In a systematic review of 12 studies on bypassing agents (used to treat haemophilia with inhibitors), the authors concluded that economic models based on different sources of data produced fairly similar and robust results, but ideally a systematic approach should be used to identify the relevant data [3]. In another review of 11 studies of bypassing agents, Hay and Zhou concluded that crucial assumptions about treatment efficacy and dosing drove the reported findings. Further, eight of nine company-sponsored studies favoured the

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company's product; the two existing head-to-head clinical studies did not support superior efficacy for either product [4].

In a review of 11 prophylaxis studies, the authors observed that reported cost-effectiveness ratios for prophylaxis varied greatly [5]. They ranged from dominance over on-demand treatment (i.e. superior efficacy and lower cost) to over €1 million per additional quality-adjusted life-year (QALY) gained if prophylaxis replaces on-demand treatment after a bleed [5]. The conclusion was that the studies exhibited considerable methodological differences and that it would be preferable if analysts adhered to established conventions when conducting and reporting economic evaluations. Finally, in a literature review on prophylaxis vs. on-demand treatment, using strict inclusion/exclusion criteria (only five studies were reviewed), authors concluded that further economic evaluations are required, reflecting the clinical reality and consumption of resources in each country [6].

Poorly conducted economic evaluations have the potential to mislead clinicians and lead to inappropriate treatment choices. Recently, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) became available [7]. CHEERS, comprising a 24-item checklist focusing on the quality of reporting, was developed using CONSORT methodology [8] and is endorsed by several health services research journals. The CHEERS guidelines build on the earlier Drummond *et al.* checklist [9] used in three of the four reviews cited above, therefore representing an improved assessment tool.

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The reporting items in the CHEERS checklist reflect the key methodological features of economic evaluation (Table 1), including study objectives, patient population, compared treatment alternatives, relative effectiveness of different treatments, associated resource consumption and relative treatment costs. The checklist also covers details of the methodology employed, such as the time horizon considered, discounting of future costs and benefits, characterization of uncertainty in parameter estimates and consideration of patient population heterogeneity due, for example, to different disease severities. Furthermore the checklist distinguishes between economic evaluations conducted alongside an individual clinical study (e.g. randomized controlled trial [RCT]) and evaluations conducted using a decision-analytic model, where data from a variety of sources are synthesized and analysed.

[Table 1 about here]

This paper aims to (i) use CHEERS to assess the quality of reporting in more recent economic evaluations in haemophilia; (ii) describe common methodological deficiencies in greater detail; and (iii) propose standards for conducting and reporting future economic evaluations. It is hoped that the use of these standards will make economic evaluations more helpful to clinicians when making treatment choices, and to payers making reimbursement decisions.

Methods

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We conducted a systematic review of economic evaluations in haemophilia, identifying all studies published since 2008. This covered all studies other than those included in the early review by Knight *et al.* [3] and focused on more recent practices in economic evaluation. Electronic databases (MEDLINE and Embase) were searched on November 25th, 2015. The search terms and PRISMA diagram are shown in Appendix 1 (available online). All identified hits were captured and duplicates were removed. Titles and abstracts were screened to determine whether full-text articles should be retrieved and reviewed for eligibility. Eligibility criteria included disease area (haemophilia, all types), patient group (human, adults and children), language (English), year of publication (2008 and later) and document type (journal article). Reasons for excluding articles were recorded. Conference abstracts were excluded as these provide insufficient detail to judge the reporting quality of studies.

Identified studies were assessed by two reviewers (NH and MD) using the CHEERS checklist. Any differences of opinion were resolved between the two reviewers to obtain a summary of reporting standards of the included studies.

Results

Twenty-one economic evaluations met our inclusion criteria and were grouped under the following topics: prophylaxis vs. treatment on demand (five studies) [10–14]; bypassing therapy use (six studies) [15–20]; immune tolerance induction (four studies) [21–24]; and other topics within haemophilia (six studies) [25–30]. Details of the

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CHEERS assessments for the 15 studies discussing the three main topics are given in Appendix 2 (available online) and described below. The remaining six studies on 'other topics' were not assessed by CHEERS but are discussed briefly below.

Quality of reporting

The CHEERS assessment results are summarized in Table 2. Overall, the quality of reporting was good. The majority of studies (12) used a decision-analytic model and three were conducted alongside a single clinical study, although none of these were RCTs. Reporting quality was poorest for patient heterogeneity: few studies discussed the importance of patient characteristics or defining subgroups. The procedure for discounting future costs and benefits was inadequately reported in 10/15 studies, although some were based on a time horizon of <1 year and discounting would therefore not be relevant. In seven studies with a time horizon of >1 year, the reporting standard was not met in four. In decision-analytic modelling studies, characterization of uncertainty is particularly important; although this was done in the majority of modelling studies, the ranges of the parameter estimates used in the sensitivity analyses were not always adequately reported and a probabilistic sensitivity analysis was not always conducted. An example of a study following the correct approach is that by Earnshaw *et al.* (2015) [24]. Finally, although the treatments being compared were almost always reported, the reasons for choosing the comparator treatment were rarely given. The CHEERS guidelines state that the choice of comparators should always be justified.

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[Table 2 about here]

Based on the reporting of the studies, identified methodological weaknesses are discussed for the three main groups of studies below.

Prophylaxis vs. treatment on demand

In the review of economic evaluations of prophylaxis, key reasons identified for result variability included different definitions of 'prophylaxis', differences in the choice of time horizon, estimates of treatment effect, clotting factor unit cost and discount rates [5]. As four of the five studies [10–14] in the current review included the most recent studies in the Miners review [5], plus one more recent study, many of the same issues arise.

Most authors studied primary prophylaxis vs. on-demand treatment, although one study reported secondary prophylaxis. The quality of reporting varied, but it was clear that the prophylactic regimen details differed from one another. However, not all authors specified when prophylaxis was initiated, the duration and frequency of infusions, or whether there was dose escalation or change in regimen with increasing patient age. Given that the costs of clotting factor represent a large percentage of total treatment costs, it is important that the dosage and unit cost are clearly reported.

For published economic evaluations, the convention is to report the official list prices of drugs and the average unit cost estimates for other resource items (e.g. cost of a

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hospital episode). These prices have the advantage of being publicly available and verifiable. However, prices can vary across healthcare institutions in a given jurisdiction and across healthcare systems within or between countries. Therefore, it is important that the published study users check whether the prices used apply in their institution, and that they explore what implications any price differences might have for the results. It is therefore helpful if analysts report a sensitivity analysis, in which the values for the key parameters, such as unit costs, are changed in order to assess their impact on the overall study results.

In the earlier review, it was noted that the differing time horizons between studies could have a major impact on study results [5]. As lifetime therapy is needed for haemophilia, a lifelong time horizon should ideally be used to cover the costs of treating adults with clotting factor, averted surgical costs and the longer-term benefits of preventing bleeds. A lack of long-term clinical data is often used to justify shorter time horizons, since extrapolation of data to the longer time period required would introduce uncertainty into the estimates. Normally, economic evaluations use long-term observational studies, such as case series and registries [1], to inform this extrapolation, but this approach is not typically used in the haemophilia literature.

All of the studies on prophylaxis vs. on-demand treatment discounted future costs and benefits, as commonly recommended [1]. The discount rates used varied between studies, often according to local methods guidelines relevant to where the study was conducted, but were in the range of 3–6% per annum. Discounting reduces the

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quantitative importance of costs and benefits occurring in the future, and therefore also reduces some of the uncertainty introduced by extrapolation.

As patient quality of life (QoL) would be expected to differ between similar patients treated with primary prophylaxis vs. on-demand treatment, this is likely to be an important factor in economic evaluations for haemophilia. Such pure comparisons are rarely done in trials, and secondary prophylaxis carries with it reasons for initiation including frequent bleeding, pain and functional impairment that suggest at least adults on prophylaxis are likely to have worse initial health-related QoL. In economic evaluations, QoL is normally reflected in the utility value applied to calculate the QALYs gained. Many of the reviewed studies followed this approach, but most used utility values from the existing literature, sometimes estimates from a different country. If the study result is not very sensitive to the utility values used, this may suffice. However, consideration should be given to collecting utility data in future clinical studies, using a widely used generic instrument such as EQ-5D. In addition, consideration should be given to developing algorithms to map from any descriptive QoL data typically collected in clinical studies in haemophilia, in order to derive QALY estimates..

Although most of the studies were concerned with the treatment of people with 'severe' haemophilia with or without inhibitors, there was very little discussion of patient population heterogeneity (e.g. in disease severity), or whether this would affect treatment effectiveness or cost. Finally, most studies focused on costs borne by

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239 the healthcare system, probably because concerns about healthcare costs are often
240 the motivation for conducting such economic evaluations. However, one might expect
241 that prophylaxis and on-demand treatment have different impacts on the patient's
242 family or their activities in school or work. These impacts would be worth exploring
243 further, especially given the difference in cost between the two regimens.
244
245 *Use of bypassing therapy*
246 All six studies reviewed [15–20] examined the comparative cost or cost-effectiveness
247 of the two available bypassing agents, recombinant activated factor VII (rFVIIa) and
248 plasma-derived activated prothrombin complex concentrate (pd-aPCC). One of the
249 main weaknesses in these published economic evaluations stems from the lack of
250 adequate comparative clinical trials. Only two small head-to-head trials have been
251 conducted, with contradictory results [31, 32]. As a result, the published economic
252 studies rely mainly on observational data, from either small single-arm studies or
253 clinical series, with or without attempts to address potential confounders. The
254 extensive use of single-arm studies is problematic, as is the selective use of data from
255 small studies, or comparisons of small prospective studies with real world data that
256 includes combinations of regimens (e.g. on demand with post-haemostatic
257 prophylaxis) [33]. One approach to overcoming these problems is to assume
258 equivalent efficacy of the two therapies [17], reducing the economic study to a cost-
259 minimization analysis. However, this approach would be overly simplistic if there were
260 important differences between the therapies.
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An alternative approach is to produce a summary estimate of relative clinical effect by undertaking a meta-analysis, including the single-arm observational studies [34]. A major issue in summarizing data from such studies is controlling for potential sources of confounding. Treur *et al.* attempted this by performing a Bayesian meta-regression [35].

In addition, there is uncertainty concerning the equivalence of the doses of the two therapies, either because of variations in patient weight or the number of infusions of rFVIIa and pd-aPCC required to achieve haemostasis, the type or severity of bleeds treated, or differences in the type of data cited (real world compared with clinical trial). In their sensitivity analysis, Hay and Zhou highlight that pd-aPCC would not be the lower cost therapy if the rFVIIa dose was assumed to be two infusions per line or episode of therapy, rather than three (as in their base-case analysis) [17]. Furthermore, some studies consider the comparative costs of treating a single bleed, but those considering multiple treatment events have to estimate the probability of treatment switching or augmentation. Many of the studies use estimates from either the literature or expert opinion without providing details of the search methods used or justifying why those particular sources are the most appropriate. This is potentially problematic given that the results of studies are often very sensitive to these parameters.

Ideally, these issues could be resolved by conducting a long-term clinical trial in which patients are randomized to first-line treatment with one of the bypassing agents, with

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subsequent treatments being determined by physicians as they would in normal clinical practice. One could then observe a series of treatment decisions over time for equivalent patients who differ only in the initial random assignment of therapy. However, RCTs can be difficult to conduct and analyse, although they have formed the basis for cost-effectiveness assessments in other therapeutic areas [36, 37]. Given the small percentage of haemophilia patients developing inhibitors, such a trial is unlikely to be feasible. Therefore, the very small sample sizes available in the inhibitor segment increase the risk of selection bias when performing evaluations. Transparency thus becomes especially important when reporting results and stating conclusions.

If a RCT cannot be conducted, a second-best approach is to establish a registry of patients who are treated with differing bypassing agents and then analyse the data, adjusting for known and unknown confounders. The main problems here lie in having enough data on possible confounders to make the adjustments, through either multivariable regression or propensity scoring, and in needing an approach to deal with unknown confounders. The approach favoured in many economic analyses is to use an instrumental variable (IV) in the regression analysis [38]. An IV is a variable that does not itself belong in the explanatory equation, but is correlated with patients' treatment allocation based on other covariates, but not correlated with treatment outcome. For example, in an evaluation of diabetes treatment, Prentice *et al.* used variation in physician prescribing (i.e. frequency of use of one drug vs. another) as an IV, since these prescribing variations would influence treatment while being effectively

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307 random with respect to patient risk and other potential influences on treatment
308 outcome [39].
309
310 However, many of the registries established in haemophilia are unable to inform
311 estimates of relative treatment effect, since all the patients enrolled are treated with
312 the same therapy. Although some good patient registries do exist, such as the one in
313 the United Kingdom (www.ukhcdo.org), they often have inadequate detail to adjust
314 for potential confounders or data on treatment patterns to facilitate an accurate
315 costing of different treatments. The methodological and practical issues in establishing
316 a registry that facilitates economic evaluations should be investigated. An important
317 issue in the design of future registries and other clinical studies is the standardization
318 of definitions for terms such as 'joint bleeds' and 'target joints', to more easily enable
319 comparisons between studies [40]. Further, it needs to be clear whether the
320 information captured about administration relates to bleed treatment or is being
321 administered as post-haemostatic prophylaxis. This becomes more complicated in the
322 situation of capturing breakthrough bleed treatment during bypassing agent
323 prophylaxis, where it becomes even less clear when bleed treatment ends and
324 prophylaxis *per se* resumes.
325
326 *Immune tolerance induction*
327 All four of the reviewed studies considered alternative strategies for treating patients
328 with inhibitors [21–24]. These strategies included prophylaxis or on-demand treatment
329 with a bypassing agent, low- and high-dose immune tolerance induction (ITI) regimens

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and ITI treatment based on risk assessment. While all the studies modelled treatments and outcomes over time, the reported time horizon varied between 1–1.5 years and a lifetime, often with no justification given for the time horizons chosen. All studies recognized patient population heterogeneity, noting that patients could be 'high risk' or 'low risk' of anamnestic response, but the extent to which patient heterogeneity could impact the cost-effectiveness of the various strategies was explored to differing degrees.

For bypassing therapy, little or no head-to-head clinical data compared the various treatment strategies particularly during ITI, and some synthesis of data from different sources was required. The various studies differed in the robustness of their literature reviews, which were not always systematic. Some of the uncertainties found in the literature on bypassing agents (e.g. doses required) also carry over into the literature on ITI.

One additional feature of this body of literature is the use, in some studies, of QALYs as the main outcome for the economic evaluation. This is more consistent with the broader literature on economic evaluation and in keeping with many of the formal methods guidelines that exist in various jurisdictions. In principle, this approach is relevant for many of the haemophilia treatment choices, as differences in bleeding frequency or the care setting are likely to impact patient QoL. However, the literature on utility values for people with haemophilia is itself quite limited, especially as many

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patients are children or adolescents. The generation of utility values for this patient population should be considered.

As observed in the literature on prophylaxis and bypassing therapy, various uncertainties in economic analyses of ITI exist. Extensive use of sensitivity analyses is therefore advisable in order to help the users of studies appreciate the impact these uncertainties have on the relative cost-effectiveness of therapies. Furthermore, estimates of the success rates of ITI fail to account for reoccurrence of inhibitors.

Other clinical topics in haemophilia

Six studies evaluating other haemophilia therapeutic options were identified, covering a wide range of topics: home-based care [28], screening for intracranial haemorrhage in neonates with haemophilia [29], high vs. standard initial doses of rFVIIa [30], pd-aPCC vs. rFVIIa in haemophilia patients with inhibitors undergoing major orthopaedic surgeries [26] and major knee surgery with rFVIIa in patients with high-titre inhibitors [25]. The literature review also identified one other study on bypassing therapy, which is interesting in that it uses a pre- and post-treatment design, but only examines the impact of a single bypassing agent in three patients [27]. Because of the diversity of topics, these six studies were not analysed using the CHEERS checklist, but were assessed to determine whether they offered any other methodological insights. Three points merit more discussion.

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First, a study of home-based care utilized a *de novo* survey of 105 patients to generate utility estimates of home- and hospital-based care [28]. Potential differences in convenience offered to patients and their families by different treatments is an important area [41] that deserves more attention in the published literature.

Second, in the study of rFVIIa in knee surgery [25], utility values were generated using the EuroQoL 5-dimension, a generic utility instrument widely used across several therapeutic areas and favoured by some decision-makers [42]. However, this study was predominantly about knee surgery, not treatment of haemophilia *per se*, so the health state values generated may not have relevance to other economic evaluations in haemophilia.

Finally, the study comparing high and standard initial doses of rFVIIa used registries to collect data on the frequency of bleeds and the resulting treatment patterns [30]. While statistical adjustments were made for patient characteristics through multivariate analysis, this was restricted owing to the limited nature of the data recorded in the registry.

Future developments in treatments for haemophilia

There are several developments in haemophilia treatment for which no published economic evaluations were available at the time of this review. Extended half-life clotting factor products might change the way in which treatment is approached. Patients may be able to reduce injection frequency while maintaining high trough

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levels to protect against bleeds, particularly in the case of Factor IX. Therefore, the use of other resources, such as hospital and physician visits, could be reduced. Innovative molecules like monoclonal antibodies or FVIII mimetics can change the treatment paradigm with new mechanisms of action and easier methods of administration, such as subcutaneous injection. If successful, these alternatives may improve the treatment and lives of haemophilia patients, whereas gene therapy, when feasible, will remove the risk of bleeding completely. In order to justify the expected higher costs of these new therapies, the methods of economic evaluation need to be equal to the task of accurately assessing cost-effectiveness. In addition, expensive new health technologies (e.g. gene therapy) may require the development of new methods of reimbursement [43], which will also need to be informed by economic evaluation.

Discussion

The existing literature on the economic evaluation of haemophilia treatments has several recurring methodological deficiencies. These include uncertainties about the relative efficacy of treatments, lack of clarity on the doses required or used in practice and the analysis of individual treatment episodes rather than whole therapeutic strategies, with inadequate description and analysis of treatment switches. Therefore, the results of most published studies are subject to considerable uncertainty and, without an extensive sensitivity analysis, the results should be treated with caution.

The first step to improvement is to ensure that studies are reported thoroughly and systematically, using the CHEERS reporting standard. This is imperative to allow the

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quality of the methods used to be judged and to identify key assumptions that impact the study results. For this reason, we excluded conference abstracts and posters from our review, as they do not allow enough space to explain methods thoroughly and therefore provide an inadequate basis for making treatment choices or reimbursement decisions.

In addition, it is necessary to develop some methodological standards for studies in haemophilia, based on the general methodological principles of economic evaluation [1]. We propose some aspirational standards in Table 3 that may not always be attainable. For example, whereas long-term studies are often desirable, they may not be possible if the treatment of interest has been only recently introduced, or if the main interest of decision-makers is short-term budgetary impact.

[Table 3 about here]

However, the implementation of these standards would improve the quality of the published literature, enabling a higher level of confidence in the study results and an understanding of the basis for competing claims. Given the difficulties in conducting definitive clinical studies, there will always be considerable uncertainties. Therefore, item #10 of our proposed standards, the characterization of uncertainty, is particularly important, as is item #12, which advocates discussing the main study limitations and why the results may differ from those of other published studies investigating the same treatment strategies.

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Other items might be particularly important to a physician deciding on the choice of treatment for a particular patient. These could include item #7, concerning the assessment of health outcomes in QoL, and item #11, which deals with patient convenience and preferences and the broader impact the disease and its treatment has on families.

Conclusions

The growing literature on the economic evaluation of haemophilia treatments reflects increasing concerns about rising healthcare costs. Although the quality of reporting in studies is generally good, several recurring methodological weaknesses exist. Given that economic evaluations are likely to become more important as new treatments are developed, there is a need for improved methodological standards. By identifying examples of poor methodology, and offering suggestions for improvement, it is hoped that this paper will help to make studies more relevant and reliable for future treatment and reimbursement decisions.

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References

1 Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: 4th edition. Oxford University Press: Oxford, 2015.

2 Greenberg D, Rosen AB, Wacht O, Palmer J, Neumann PJ. A bibliometric review of cost-effectiveness analyses in the economic and medical literature: 1976-2006. *Med Decis Making* 2010; **30**: 320–7.

3 Knight C, Danø AM, Kennedy-Martin T. A systematic review of the cost-effectiveness of rFVIIa and APCC in the treatment of minor/moderate bleeding episodes for haemophilia patients with inhibitors. *Haemophilia* 2009; **15**: 405–19.

4 Hay JW, Zhou ZY. Systematic literature review of economics analysis on treatment of mild-to-moderate bleeds with aPCC versus rFVIIa. *J Med Econ* 2011; **14**: 516–25.

5 Miners AH. Economic evaluations of prophylaxis with clotting factor for people with severe haemophilia: why do the results vary so much? *Haemophilia* 2013; **19**: 174–80.

6 Unim B, Veneziano MA, Boccia A, Ricciardi W, La Torre G. Haemophilia A: pharmacoeconomic review of prophylaxis treatment versus on-demand. *Scientific World Journal* 2015; **2015**: 596164.

7 Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013; **16**: 231–50.

CONFIDENTIAL DRAFT

8 Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med* 2010; **7**: e1000217.

9 Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; **313**: 275–83.

10 Risebrough N, Oh P, Blanchette V, Curtin J, Hitzler J, Feldman BM. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A. *Haemophilia* 2008; **14**: 743–52.

11 Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. *Haemophilia* 2009; **15**: 881–7.

12 Daliri AA, Haghparast H, Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran. *Int J Technol Assess Health Care* 2009; **25**: 584–7.

13 Colombo GL, Di Matteo S, Mancuso ME, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clinicoecon Outcomes Res* 2011; **3**: 55–61.

14 Farrugia A, Cassar J, Kimber MC, Bansal M, Fischer K, Auerswald G *et al.* Treatment for life for severe haemophilia A - A cost-utility model for prophylaxis vs. on-demand treatment. *Haemophilia* 2013; **19**: e228–38.

15 Steen Carlsson K, Astermark J, Donfield S, Berntorp E. Cost and outcome: comparisons of two alternative bypassing agents for persons with haemophilia A complicated by an inhibitor. *Thromb Haemost* 2008; **99**: 1060–7.

CONFIDENTIAL DRAFT

16 You CW, Lee SY, Park SK. Cost and effectiveness of treatments for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Korea. *Haemophilia* 2009; **15**: 217–26.

17 Hay JW, Zhou ZY. Economical comparison of APCC vs. rFVIIa for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. *Haemophilia* 2011; **17**: e969–74.

18 Salaj P, Penka M, Smejkal P, Geierova V, Ovesná P, Brabec P *et al.* Economic analysis of recombinant activated factor VII versus plasma-derived activated prothrombin complex concentrate in mild to moderate bleeds: haemophilia registry data from the Czech Republic. *Thromb Res* 2012; **129**: e233–7.

19 Jimenez-Yuste V, Núñez R, Romero JA, Montoro B, Espinós B. Cost-effectiveness of recombinant activated factor VII vs. plasma-derived activated prothrombin complex concentrate in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors in Spain. *Haemophilia* 2013; **19**: 841–6.

20 Villarrubia R, Oyagüez I, Álvarez-Román MT, Mingot-Castellano ME, Parra R, Casado MA. Cost analysis of prophylaxis with activated prothrombin complex concentrate vs. on-demand therapy with activated factor VII in severe haemophilia A patients with inhibitors, in Spain. *Haemophilia* 2015; **21**: 320–9.

21 Odeyemi IA, Danø AM. Optimising immune tolerance induction strategies in the management of haemophilia patients with inhibitors: a cost-minimisation analysis. *Curr Med Res Opin* 2009; **25**: 239–50.

CONFIDENTIAL DRAFT

22 Rasekh HR, Imani A, Karimi M, Golestani M. Cost-utility analysis of immune tolerance induction therapy versus on-demand treatment with recombinant factor VII for hemophilia A with high titer inhibitors in Iran. *Clinicoecon Outcomes Res* 2011; **3**: 207–12.

23 Berger K, Schopohl D, Eheberg D, Auerswald G, Kurnik K, Schramm W. Treatment of children with severe haemophilia A and inhibitors: a health economic evaluation for Germany. *Klin Padiatr* 2013; **225**: 152–8.

24 Earnshaw SR, Graham CN, McDade CL, Spears JB, Kessler CM. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. *Haemophilia* 2015; **21**: 310–9.

25 Ballal RD, Botteman MF, Foley I, Stephens JM, Wilke CT, Joshi AV. Economic evaluation of major knee surgery with recombinant activated factor VII in hemophilia patients with high titer inhibitors and advanced knee arthropathy: exploratory results via literature-based modeling. *Curr Med Res Opin* 2008; **24**: 753–68.

26 Bonnet PO, Yoon BS, Wong WY, Boswell K, Ewenstein BM. Cost minimization analysis to compare activated prothrombin complex concentrate (APCC) and recombinant factor VIIa for haemophilia patients with inhibitors undergoing major orthopaedic surgeries. *Haemophilia* 2009; **15**: 1083–9.

27 Mirbehbahani N, Jahazi A. Different treatment strategies for Haemophilia A with Low Inhibitor. *Pak J Med Sci* 2011; **27**: 229–32.

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28 Pattanaprateep O, Chuansumrit A, Kongsakon R. Cost-utility analysis of home-based care for treatment of Thai hemophilia A and B. *Value Health Reg Issues* 2014; **3C**: 73–8.

29 Malec LM, Sidonio RF Jr, Smith KJ, Cooper JD. Three cost-utility analyses of screening for intracranial hemorrhage in neonates with hemophilia. *J Pediatr Hematol Oncol* 2014; **36**: 474–9.

30 Salaj P, Kubes R, Cetkovsky P, Capova I, Penka M, Ovesná P *et al*. Economic evaluation of rFVIIa high initial dose compared to rFVIIa standard initial dose in patients with haemophilia with inhibitors using the Czech HemoRec registry. *Thromb Res* 2014; **133**: 162–7.

31 Astermark J, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J, Berntorp E; FENOC Study Group. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood* 2007; **109**: 546–51.

32 Young G, Shafer FE, Rojas P, Seremetis S. Single 270 μg kg^{-1}-dose rFVIIa vs. standard 90 μg kg^{-1}-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. *Haemophilia* 2008; **14**: 287–94.

33 Mehta DA, Oladapo AO, Epstein JD, Novack AR, Neufeld EJ, Hay JW. A Budget Impact Model of Hemophilia Bypassing Agent Prophylaxis Relative to Recombinant Factor VIIa On-Demand. *J Manag Care Spec Pharm* 2016; **22**: 149–57.

34 Zhou ZY, Hay JW. Efficacy of bypassing agents in patients with hemophilia and inhibitors: a systematic review and meta-analysis. *Clin Ther* 2012; **34**: 434–45.

CONFIDENTIAL DRAFT

35 Treur MJ, McCracken F, Heeg B, Joshi AV, Botteman MF, De Charro F, Van Hout B. Efficacy of recombinant activated factor VII vs. activated prothrombin complex concentrate for patients suffering from haemophilia complicated with inhibitors: a Bayesian meta-regression. *Haemophilia* 2009; **15**: 420–36.

36 Simon GE, VonKorff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, Wagner EH. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs tricyclic antidepressants. *JAMA* 1996; **275**: 1897–902.

37 Oster G, Borok GM, Menzin J, Heys JF, Epstein RS, Quinn V *et al*. A randomized trial to assess effectiveness and cost in clinical practice: rationale and design of the Cholesterol Reduction Intervention Study (CRIS). *Control Clin Trials* 1995; **16**: 3–16.

38 Wooldridge, J. M. 2010. Econometric Analysis of Cross Section and Panel Data. MIT Press, Cambridge MA.

39 Prentice JC, Conlin PR, Gellad WF, Edelman D, Lee TA, Pizer SD. Capitalizing on prescribing pattern variation to compare medications for type 2 diabetes. *Value Health* 2014; **17**: 854–62.

40 Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van Den Berg HM, Srivastava A, for the Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost* 2014; **12**: 1935–9.

41 Higgins A, Barnett J, Meads C, Singh J, Longworth L. Does convenience matter in health care delivery? A systematic review of convenience-based aspects of process utility. *Value in Health* 2014; **17**: 877–87.

CONFIDENTIAL DRAFT

42 National Institute of Health and Care Excellence. Guide to the processes of technology appraisal. London, NICE, September 2014. Available at http://www.nice.org.uk/article/pmg19. Accessed 3 February 2016.

43 Edlin R, Hall P, Klemens W, McCabe C. Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? *Value Health* 2014; **17**: 438–44.

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618 **Table 1.** CHEERS checklist–items to include when reporting economic evaluations of health

619 interventions (*reproduced from Husereau et al., 2013* [7]).

Section/item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as 'cost-effectiveness analysis' and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	_____
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	_____
		Present the study question and its relevance for health policy or practice decisions.	_____
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	_____
Study perspective	6	Describe the perspective of the study and relate this to the	_____

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		costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	*Single study–based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____
	11b	*Synthesis-based estimates*: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	_____
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	_____
Estimating resources and costs	13a	*Single study–based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to	_____

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		approximate to opportunity costs.	
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	_____
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	_____
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.	_____
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g. half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	_____
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons	_____

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		or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	_____
Characterizing uncertainty	20a	*Single study–based economic evaluation*: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	_____
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	_____
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	_____
Discussion			
Study findings, limitations, generalizability and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	_____
Other			

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Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other nonmonetary sources of support.	_____
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	_____

Note. For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

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625 **Table 2.** Reporting standards in the included studies.

CHEERS reporting item		Studies meeting the standard		
		Yes	No	Not applicable
1	Title	14	1	
2	Abstract	13	2	
3	Background and objectives	15		
4	Target population and subgroups	14	1	
5	Setting and location	14	1	
6	Study perspective	15		
7	Comparators	13	2	
8	Time horizon	12	3	
9	Discount rate	5	10	
10	Choice of health outcomes	14	1	
11a	Measurement of effectiveness *(single study-based estimates)*	2	1	12
11b	Measurement of effectiveness *(synthesis-based estimates)*	6	6	3
12	Measurement and valuation of preference-based outcomes	5	1	9
13a	Estimating resources and costs *(single study-based economic evaluation)*	1	2	12
13b	Estimating resources and costs *(model-based economic evaluation)*	9	3	3
14	Currency, price date and conversion	12	3	
15	Choice of model	11	1	3
16	Assumptions	11	1	3
17	Analytic methods	14	1	
18	Study parameters	9	6	
19	Incremental costs and outcomes	13	2	
20a	Characterizing uncertainty *(single study-based economic evaluation)*	2	1	12

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20b	Characterizing uncertainty *(model-based economic evaluation)*	9	3	3
21	Characterizing heterogeneity	6	9	
22	Study findings, limitations, generalizability and current knowledge	11	4	
23	Source of funding	15		
24	Conflicts of interest	12	3	

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629 **Table 3.** Proposals for methodological standards for economic evaluations in haemophilia.

1. *Compare alternative treatment strategies over time, not individual episodes of care, such as the treatment of individual bleeds.*
2. *Assess cost-effectiveness over a long time horizon, preferably a lifetime, but also consider shorter periods of time if there are uncertainties in the longer term projections.*
3. *Base the economic evaluation on a systematic review to obtain estimates of the key clinical parameters, and clearly identify the inclusion and exclusion criteria.*
4. *If head-to-head clinical studies are not available to estimate relative treatment effect and observational data are used, employ an analytic strategy to adequately adjust for observed differences, such as differences in study populations and non-observed confounders. Crude comparisons of treatment effects in single-arm studies should be avoided.*
5. *Base drug doses and other treatment patterns on observed data; rely on expert opinion or assumptions only as a last resort.*
6. *Consider the probable heterogeneity in the patient population and include relevant subgroup analyses of cost-effectiveness.*
7. *Use a generalizable measure of benefit in the economic study (e.g. for a measure of health gain, use QALYs).*
8. *Clearly identify all sources of, and values for, unit costs/prices and present these separately from the quantities of resources estimated from the treatment patterns.*

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9. *Discount future costs and effects at the relevant discount rate for the jurisdiction(s) where the economic study is conducted.*

10. *Adequately characterize the uncertainty in parameter estimates by using probabilistic sensitivity analysis. Additionally, present univariate analyses if these are useful for explaining the impact of key structural assumptions.*

11. *Consider other factors alongside cost-effectiveness, including patient convenience and preferences and the broader impact of the disease and its treatment on families.*

12. *Discuss the main weaknesses in the study and explain how and why the results differ from other published studies of the treatment strategies being examined.*

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Appendix 1

Search strategy and PRISMA flow diagram

The following databases were searched, using the search engine ProQuest: MEDLINE (1946–current) and Embase (1947–current). The search terms are shown in Table A1.1. After removal of duplicates, articles were assessed for eligibility according to the criteria in Table A1.2, in two rounds (first round: inclusion or exclusion based on the screening of title and abstract only; second round: assessment of full text). Reference lists of the selected articles and of key review papers were reviewed for potentially relevant records that might not have been identified by the database search. The PRISMA flow diagram of the search is shown in Figure A.1.

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Table A1.1. Search terms for identifying economic evaluations in haemophilia in MEDLINE and Embase.

Topic	#	Search term
Economic evaluation	1	ti,ab('cost effectiveness' OR 'economic evaluation' OR 'cost analysis' OR 'cost utility' OR 'cost benefit?' OR 'economic analysis' OR 'pharmaco economic?' OR (economic near model*) OR 'decision model*' OR 'economic study' OR 'cost-effectiveness' OR 'economic-evaluation' OR 'cost-analysis' OR 'cost-utility' OR 'cost-benefit?' OR 'economic-analysis' OR 'pharmaco-economic?' OR 'decision-model*' OR 'economic-study')
Disease	2	ti,ab(hemophilia OR haemophilia OR 'Factor VIII Deficiency' OR 'Congenital Factor 8 Deficiency' OR 'Factor VIII Deficiency' OR 'Congenital Factor VIII Deficiency')
Economic evaluations in haemophilia	3	#1 AND #2

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649 **Table A1.2.** Eligibility criteria used in the search for economic evaluations in haemophilia.

Topic	Inclusion criteria	Exclusion criteria
Disease	Haemophilia, all types	Other diseases
Patient population	Adult and paediatric	Non-human
Treatment	Treatments, procedures, care programmes in haemophilia	Other
Economic evaluation	Cost-utility, cost-effectiveness, cost-minimization studies	Other
Document type	Journal articles with original economic analyses comparing treatments, procedures or care programmes in haemophilia	• Conference abstracts • Review articles • Letters or editorials that comment on results of an original article • Case studies (i.e. a report based on only one patient)
Language	English	Other language
Year of publication	Published in or after 2008	Published before 2008

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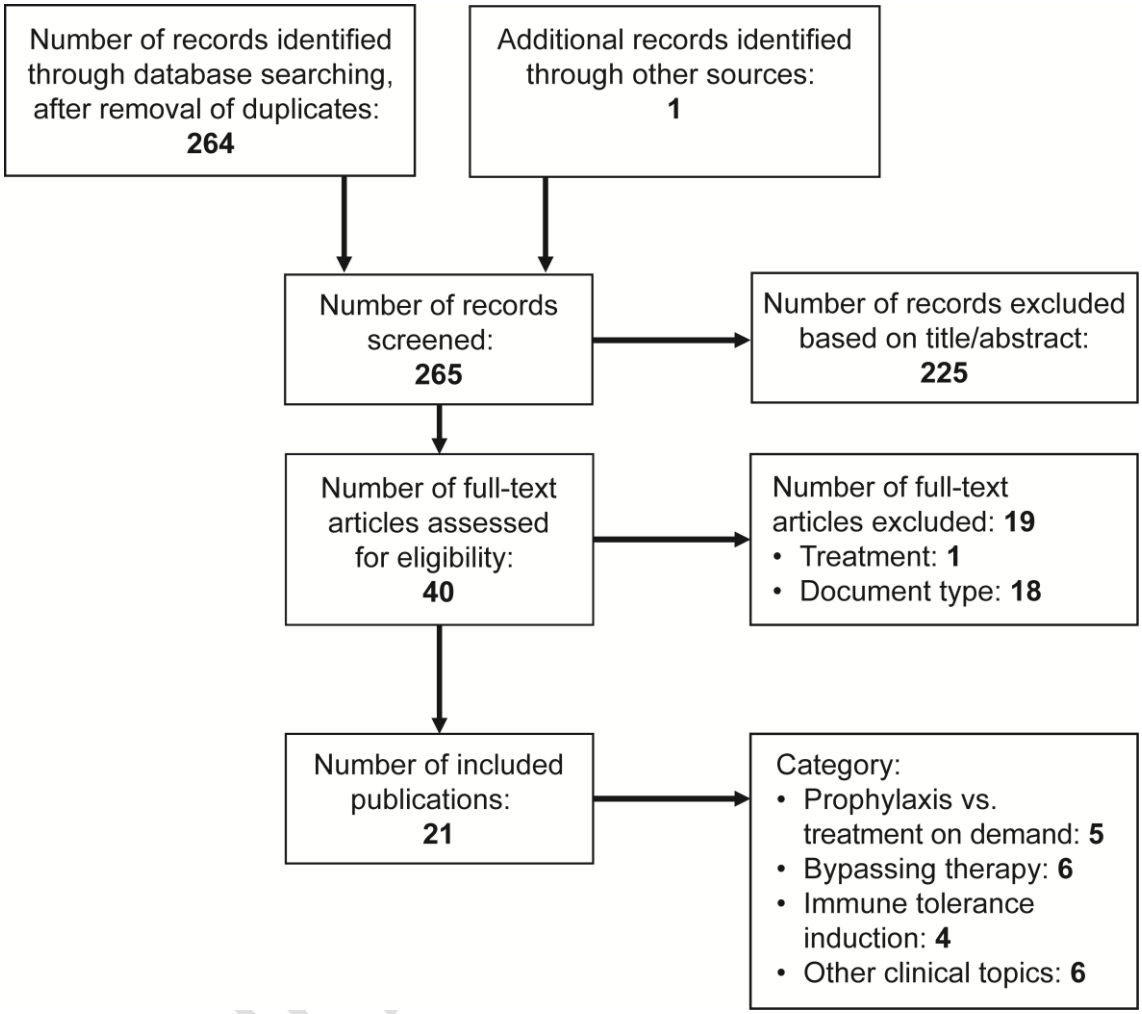
653 **Fig. A.1.** PRISMA flow diagram.



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