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1 **Making economic evaluations more helpful for treatment**

2 **choices in haemophilia**

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17

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21 **Keywords:** bypassing therapy, cost-effectiveness analysis, haemophilia,
22 immune intolerance induction, methodological standards, prophylaxis.

23

24

Abstract

25

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

31

32 **Methods:** A systematic review of economic evaluations in haemophilia published since
33 2008 was conducted. The reporting and methods of the studies were assessed using
34 the recently published Consolidated Health Economic Evaluation Reporting Guidelines
35 (CHEERS) checklist. The key methodological deficiencies in the studies were recorded.

36

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

48

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.

53

54

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55 **Introduction**

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

61
62 Studies assessing the costs and consequences of healthcare treatments and
63 programmes are known as economic evaluations [1], and a substantial body of
64 empirical economic studies now cover all branches of healthcare [2]. For these studies
65 to be helpful to clinicians and patients, they must be both relevant (i.e. address
66 appropriate treatment choices) and reliable (i.e. have a sound methodology).
67 Comprehensive and transparent reporting is particularly important to assess whether a
68 given study is methodologically sound.

69
70 Several systematic reviews have indicated that economic evaluations in haemophilia
71 often have substantial methodological deficiencies. In a systematic review of 12
72 studies on bypassing agents (used to treat haemophilia with inhibitors), the authors
73 concluded that economic models based on different sources of data produced fairly
74 similar and robust results, but ideally a systematic approach should be used to identify
75 the relevant data [3]. In another review of 11 studies of bypassing agents, Hay and
76 Zhou concluded that crucial assumptions about treatment efficacy and dosing drove
77 the reported findings. Further, eight of nine company-sponsored studies favoured the

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

80

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

92

93 Poorly conducted economic evaluations have the potential to mislead clinicians and
94 lead to inappropriate treatment choices. Recently, the Consolidated Health Economic
95 Evaluation Reporting Standards (CHEERS) became available [7]. CHEERS, comprising a
96 24-item checklist focusing on the quality of reporting, was developed using CONSORT
97 methodology [8] and is endorsed by several health services research journals. The
98 CHEERS guidelines build on the earlier Drummond *et al.* checklist [9] used in three of
99 the four reviews cited above, therefore representing an improved assessment tool.

100

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

112

113

114 [Table 1 about here]

115

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

122

123 **Methods**

124 We conducted a systematic review of economic evaluations in haemophilia, identifying
125 all studies published since 2008. This covered all studies other than those included in
126 the early review by Knight *et al.* [3] and focused on more recent practices in economic
127 evaluation. Electronic databases (MEDLINE and Embase) were searched on November
128 25th, 2015. The search terms and PRISMA diagram are shown in Appendix 1 (available
129 online). All identified hits were captured and duplicates were removed. Titles and
130 abstracts were screened to determine whether full-text articles should be retrieved
131 and reviewed for eligibility. Eligibility criteria included disease area (haemophilia, all
132 types), patient group (human, adults and children), language (English), year of
133 publication (2008 and later) and document type (journal article). Reasons for excluding
134 articles were recorded. Conference abstracts were excluded as these provide
135 insufficient detail to judge the reporting quality of studies.

136
137 Identified studies were assessed by two reviewers (NH and MD) using the CHEERS
138 checklist. Any differences of opinion were resolved between the two reviewers to
139 obtain a summary of reporting standards of the included studies.

140

141

142 **Results**

143 Twenty-one economic evaluations met our inclusion criteria and were grouped under
144 the following topics: prophylaxis vs. treatment on demand (five studies) [10–14];
145 bypassing therapy use (six studies) [15–20]; immune tolerance induction (four studies)
146 [21–24]; and other topics within haemophilia (six studies) [25–30]. Details of the

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

150

151 *Quality of reporting*

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

169

170 [Table 2 about here]

171

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

174

175 *Prophylaxis vs. treatment on demand*

176 In the review of economic evaluations of prophylaxis, key reasons identified for result
177 variability included different definitions of 'prophylaxis', differences in the choice of
178 time horizon, estimates of treatment effect, clotting factor unit cost and discount rates
179 [5]. As four of the five studies [10–14] in the current review included the most recent
180 studies in the Miners review [5], plus one more recent study, many of the same issues
181 arise.

182

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

190

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

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

201

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

211

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

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

218

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

234

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

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.

261

262 An alternative approach is to produce a summary estimate of relative clinical effect by
263 undertaking a meta-analysis, including the single-arm observational studies [34]. A
264 major issue in summarizing data from such studies is controlling for potential sources
265 of confounding. Treur *et al.* attempted this by performing a Bayesian meta-regression
266 [35].

267

268 In addition, there is uncertainty concerning the equivalence of the doses of the two
269 therapies, either because of variations in patient weight or the number of infusions of
270 rFVIIa and pd-aPCC required to achieve haemostasis, the type or severity of bleeds
271 treated, or differences in the type of data cited (real world compared with clinical
272 trial). In their sensitivity analysis, Hay and Zhou highlight that pd-aPCC would not be
273 the lower cost therapy if the rFVIIa dose was assumed to be two infusions per line or
274 episode of therapy, rather than three (as in their base-case analysis) [17].

275 Furthermore, some studies consider the comparative costs of treating a single bleed,
276 but those considering multiple treatment events have to estimate the probability of
277 treatment switching or augmentation. Many of the studies use estimates from either
278 the literature or expert opinion without providing details of the search methods used
279 or justifying why those particular sources are the most appropriate. This is potentially
280 problematic given that the results of studies are often very sensitive to these
281 parameters.

282

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

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

294
295 If a RCT cannot be conducted, a second-best approach is to establish a registry of
296 patients who are treated with differing bypassing agents and then analyse the data,
297 adjusting for known and unknown confounders. The main problems here lie in having
298 enough data on possible confounders to make the adjustments, through either
299 multivariable regression or propensity scoring, and in needing an approach to deal
300 with unknown confounders. The approach favoured in many economic analyses is to
301 use an instrumental variable (IV) in the regression analysis [38]. An IV is a variable that
302 does not itself belong in the explanatory equation, but is correlated with patients'
303 treatment allocation based on other covariates, but not correlated with treatment
304 outcome. For example, in an evaluation of diabetes treatment, Prentice *et al.* used
305 variation in physician prescribing (i.e. frequency of use of one drug vs. another) as an
306 IV, since these prescribing variations would influence treatment while being effectively

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

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

337

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

344

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

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

354

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

360

361 *Other clinical topics in haemophilia*

362 Six studies evaluating other haemophilia therapeutic options were identified, covering
363 a wide range of topics: home-based care [28], screening for intracranial haemorrhage
364 in neonates with haemophilia [29], high vs. standard initial doses of rFVIIa [30], pd-
365 aPCC vs. rFVIIa in haemophilia patients with inhibitors undergoing major orthopaedic
366 surgeries [26] and major knee surgery with rFVIIa in patients with high-titre inhibitors
367 [25]. The literature review also identified one other study on bypassing therapy, which
368 is interesting in that it uses a pre- and post-treatment design, but only examines the
369 impact of a single bypassing agent in three patients [27]. Because of the diversity of
370 topics, these six studies were not analysed using the CHEERS checklist, but were
371 assessed to determine whether they offered any other methodological insights. Three
372 points merit more discussion.

373

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

378

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

385

386 Finally, the study comparing high and standard initial doses of rFVIIa used registries to
387 collect data on the frequency of bleeds and the resulting treatment patterns [30].

388 While statistical adjustments were made for patient characteristics through
389 multivariate analysis, this was restricted owing to the limited nature of the data
390 recorded in the registry.

391

392 *Future developments in treatments for haemophilia*

393 There are several developments in haemophilia treatment for which no published
394 economic evaluations were available at the time of this review. Extended half-life
395 clotting factor products might change the way in which treatment is approached.

396 Patients may be able to reduce injection frequency while maintaining high trough

397 levels to protect against bleeds, particularly in the case of Factor IX. Therefore, the use
398 of other resources, such as hospital and physician visits, could be reduced. Innovative
399 molecules like monoclonal antibodies or FVIII mimetics can change the treatment
400 paradigm with new mechanisms of action and easier methods of administration, such
401 as subcutaneous injection. If successful, these alternatives may improve the treatment
402 and lives of haemophilia patients, whereas gene therapy, when feasible, will remove
403 the risk of bleeding completely. In order to justify the expected higher costs of these
404 new therapies, the methods of economic evaluation need to be equal to the task of
405 accurately assessing cost-effectiveness. In addition, expensive new health technologies
406 (e.g. gene therapy) may require the development of new methods of reimbursement
407 [43], which will also need to be informed by economic evaluation.

408

409 **Discussion**

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

417

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

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

425

426 In addition, it is necessary to develop some methodological standards for studies in
427 haemophilia, based on the general methodological principles of economic evaluation
428 [1]. We propose some aspirational standards in Table 3 that may not always be
429 attainable. For example, whereas long-term studies are often desirable, they may not
430 be possible if the treatment of interest has been only recently introduced, or if the
431 main interest of decision-makers is short-term budgetary impact.

432

433 [Table 3 about here]

434

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

443

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

449

450 **Conclusions**

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

459

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470 systematic review, undertook the analysis and contributed to the writing of the
471 manuscript. US contributed to the design of the study and to the writing of the
472 manuscript. PG acted as clinical consultant to the study and contributed to the writing
473 of the manuscript.

474

475

476

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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	_____

		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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____
	11b	<i>Synthesis-based estimates:</i> 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	<i>Single study-based economic evaluation:</i> 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	_____

		approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> 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	_____

		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	<i>Single study–based economic evaluation:</i> 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	<i>Model-based economic evaluation:</i> 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			

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.	_____

620 *Note.* For consistency, the CHEERS statement checklist format is based on the format of the CONSORT
621 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 (<i>single study-based estimates</i>)	2	1	12
11b Measurement of effectiveness (<i>synthesis-based estimates</i>)	6	6	3
12 Measurement and valuation of preference-based outcomes	5	1	9
13a Estimating resources and costs (<i>single study-based economic evaluation</i>)	1	2	12
13b Estimating resources and costs (<i>model-based economic evaluation</i>)	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 (<i>single study-based economic evaluation</i>)	2	1	12

20b	Characterizing uncertainty (<i>model-based economic evaluation</i>)	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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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.*

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.*

630

631

632 **Appendix 1**

633

634 **Search strategy and PRISMA flow diagram**

635

636 The following databases were searched, using the search engine ProQuest: MEDLINE
637 (1946–current) and Embase (1947–current). The search terms are shown in Table A1.1.

638 After removal of duplicates, articles were assessed for eligibility according to the
639 criteria in Table A1.2, in two rounds (first round: inclusion or exclusion based on the
640 screening of title and abstract only; second round: assessment of full text). Reference
641 lists of the selected articles and of key review papers were reviewed for potentially
642 relevant records that might not have been identified by the database search. The
643 PRISMA flow diagram of the search is shown in Figure A.1.

644

645 **Table A1.1.** Search terms for identifying economic evaluations in haemophilia in MEDLINE and
 646 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

647

648

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

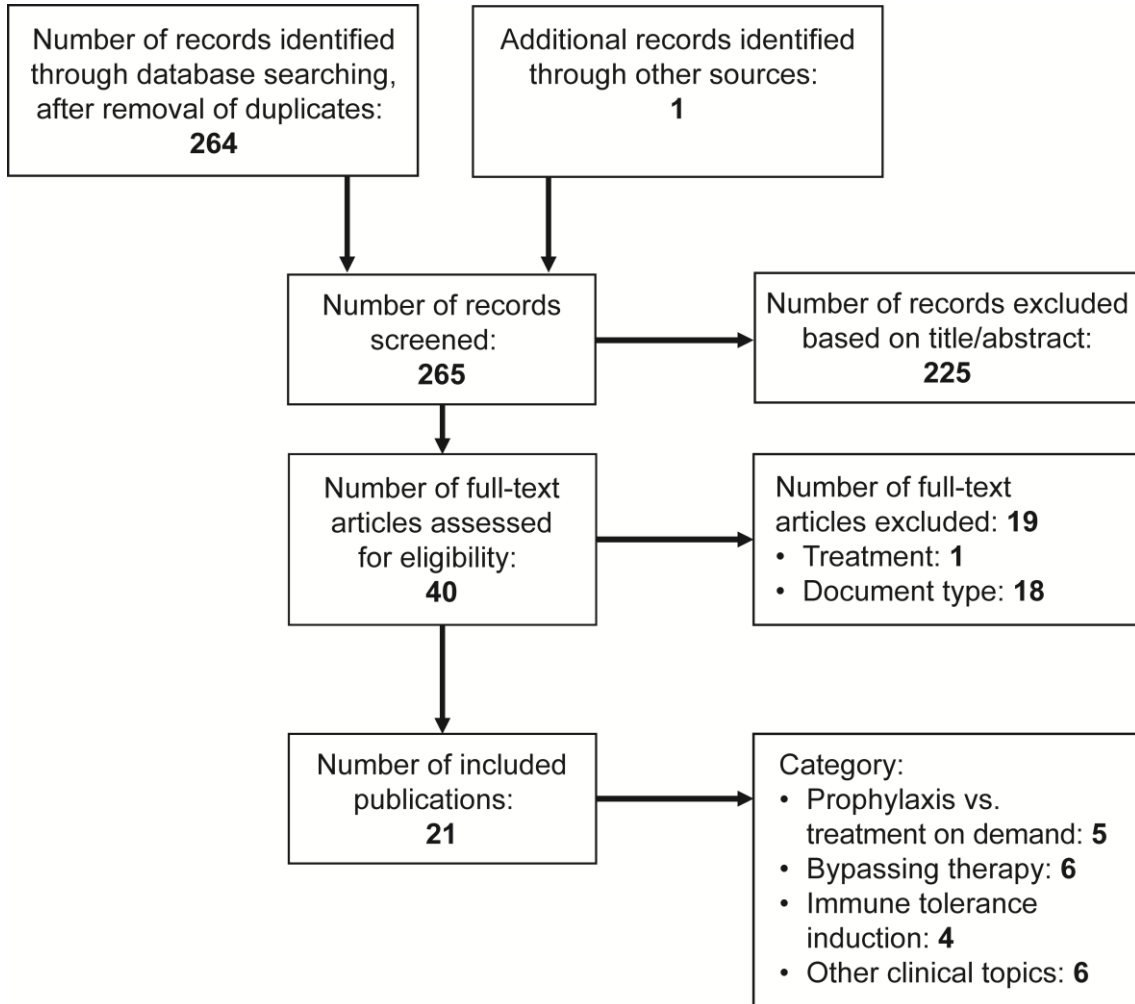
Topic	Inclusion criteria	Exclusion criteria
Disease	Haemophilia, all types	Other diseases
Patient population	Adult and paediatric	Non-human
Treatment	Treatments, procedures, care programmes in haemophilia	Other
Economic evaluation	Cost-utility, cost-effectiveness, cost-minimization studies	Other
Document type	Journal articles with original economic analyses comparing treatments, procedures or care programmes in haemophilia	<ul style="list-style-type: none"> • 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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