Value Assessment of Orphan Drugs and Treatments for Rare Diseases

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Abstract

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OBJECTIVES: In 1983 the US Orphan Drug Act was passed to facilitate commercialization of drugs to treat rare diseases. The market value for orphan drugs in the US reached $90 billion annually in 2014, with worldwide sales forecast at $176 billion. Payers and policymakers need robust methodology for evaluation of health technology in this growing landscape of expensive treatments for rare diseases. Here I present a systematic review of current practices in value-based evaluation of orphan drugs from a global perspective. I also propose a potential new framework to be developed as new metric for assessing the value of orphan drugs, the Orphan Drug Index Estimate (ODIE). **METHODS:** For the systematic review, searches were conducted in December 2015 in PubMed®, EMBASE®, and Web of Science® databases using the following keywords: orphan drug, rare disease treatment, economics, resource utilization, cost, cost effectiveness, questionnaire, and value. Only references published in English were included.

Manuscripts that solely reported one of the following were excluded: clinical or patient care, policy or legislation on orphan drugs particularly relating to research incentive, opinion or editorial, preclinical studies, drug-development, unrelated to rare diseases or healthcare, reviews other than systematic reviews for health technology assessment. **RESULTS:** A total of 2513 unique references were obtained, and screened by title and abstract according to exclusion criteria. After exclusion, 333 references remained for full evaluation. Of those, an additional 296 were excluded, but 51 additional studies were included from the reference lists of included articles. A total of 88 articles were included in the complete analysis. Overall, the methodology employed for conducting cost-effectiveness assessments followed traditional techniques including decision analysis and Markov modeling techniques. The reported incremental cost effectiveness ratios (ICERs) ranged from dominant treatments to a high of €6.1 million per quality adjusted life year (QALY). Interpretation of the results was more challenging, with 43% of studies reporting ICERs that would not be considered cost-effective under a willingness-to-pay threshold of $50,000 per QALY. In spite of the lack of cost-effectiveness, the majority of authors agreed that since the treatment under review is for a rare condition, there is an obligation to cover the costs. In light of these analyses, there is an evident need for a method of analysis that is more comprehensive than the ICER, and more appropriate for addressing the uniqueness of orphan drugs, including variables related to the rarity and severity of disease, and a broader societal perspective on costs, including societal burden and identifiable opportunity costs. In response, here I propose a potential new metric based on multicriteria decision analysis (MCDA) techniques to provide a more comprehensive evaluation of orphan drugs. **CONCLUSIONS:** There is a global consensus of a need to develop appropriate methodology, analysis techniques, and related policies to address management of expensive treatments. It is not yet clear how best

to evaluate the value of orphan drugs. More thorough evaluation and validation of novel modeling techniques, analytic rationale and proactive policy changes are needed to redefine the status quo of health technology assessment of rare disease treatments. I propose a new metric to overcome some limitations of the ICER in evaluation of rare diseases. Continued research is needed in detailed development of a valid, quantifiable, and reproducible metric; however, the work presented here provides a foundation for the development process.

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1. Introduction

In 1983 the Orphan Drug Act was passed in the United States (US) with the goal of facilitating research, development, and commercialization of drugs to treat rare diseases that had largely been ignored.[1,2] While there has been a clear increase in marketed orphan drugs since passage of the Orphan Drug Act, it is unclear whether it is due entirely to the Act, or if there are other forces at play.[3,4] The impact of the Orphan Drug Act raises many questions of pharmaceutical business practices, the regulatory landscape, and economic impact of orphan drugs in the marketplace.

The Orphan Drug Act is codified in the US Code of Federal Regulations (CFR) Title 21, Part 316 to implement sections 525 through 528 of the Food, Drug and Cosmetic (FD&C) Act.[1] The principal features of the Orphan Drug Act that provide incentives for development and manufacture of drugs for rare diseases include a seven-year market exclusivity period from the time of approval by the US Food and Drug Administration (FDA), and any competitors who wish to market a product that is considered the same as a previously approved orphan drug must demonstrate clinical superiority to be considered for approval.[4] In addition, the Orphan Drug Act allows for tax credits during clinical development, grant support to reduce the financial burden of product development, and exemption of several user fees.[2] Many new drug approval applications are also granted expedited approval or priority review to reduce the timeframe for regulatory approval.[2]

There has been a rapid increase in the number of drugs available for orphan diseases from only 10 FDA approvals for rare diseases between 1972 and 1983, to over 400 orphan drug approvals since the Orphan Drug Act was enacted.[3,4] The number of diseases designated with orphan status has also expanded in part due to biotechnology, technological advances in

molecular biology and diagnostic capabilities, and patient advocacy. There are currently approximately 7000 recognized orphan diseases.[3,4] The definition of an orphan disease in the US is one that affects fewer than 200,000 patients nationwide, but with new technology, even commonplace diseases are being parsed into clusters of orphan diseases.[5] A 2013 analysis found that many common diseases are associated with a large number of orphan drugs due to identification of clinical subgroups. For example, 57 orphan drug designations were for AIDS, a disease affecting an estimated 1.2 million people in the US alone.[4,6]

Criticism has arisen that the Orphan Drug Act may simply be providing a monopolistic market for expensive drugs. The market value for orphan drugs in the US reached approximately $90 billion annually in 2014, with worldwide sales forecast at $176 billion.[7] This accounts for nearly 25% of total drug spending. Development costs for orphan drugs are reported to be approximately half that of non-orphan drugs, with smaller clinical trials and a shorter regulatory review process.[7] The median per-patient cost is nearly 14 times higher for orphan drugs than for non-orphan drugs, and the expected return on investment for approved orphan drugs is estimated to be nearly double that of non-orphan drugs.[8]

While the incentives introduced by the Orphan Drug Act have indeed increased development and marketing of drugs for rare diseases, the escalating costs of these treatments are undermining the affordability of healthcare in the US.[9] There is growing favor among health insurance companies and decision-makers toward more thorough value assessment of pharmaceutical products.[10-12] Robust, well-established tools such as cost-effectiveness, budget impact, and comparative effectiveness analyses are becoming more routinely applied to both new and existing products to describe the clinical, economic, and societal benefits provided by a

treatment. These tools also enable decision-makers to differentiate between competing products, or to determine optimal resource allocation for a given patient population.

While decision analytic tools are becoming more commonplace in all disease categories, the current methodology in interpreting the results of these analyses break down in the face of rare diseases.[13] The current thresholds for acceptance are not always relevant for evaluating orphan drugs. Payers and policymakers need robust methodology for evaluation of health technology in this growing landscape of expensive treatments for rare diseases. Here I present a systematic review of current practices in value-based evaluation of orphan drugs from a global perspective to identify current trends in analysis and interpretation, and to identify areas where improvements could be made. I also propose a new metric for use in evaluating the value of orphan drugs and treatments for rare diseases.

2. Systematic Review

2.1. Objective

This study was conducted to understand the current state of value assessment of orphan drugs and treatments for rare diseases from a global perspective. The primary questions of interest are whether new methodological approaches are being used in economic evaluation of orphan drugs, and how results of economic analyses are interpreted in the setting of rare diseases.

2.2. Methods

2.2.1. Study Criteria

Studies considered for inclusion in this review were primary economic analyses of orphan drugs or treatments for rare diseases. This included cost-effectiveness or cost-utility

analyses used to assess the value of any orphan drugs from any global perspective. Budget impact analyses were excluded from this review to focus on studies that used an evaluation metric such as the incremental cost effectiveness ratio (ICER) that included utility and patient preference information in addition to cost.

2.2.2. Search Strategy

Literature searches were conducted in December 2015 in MEDLINE®, EMBASE®, and Web of Science® databases using the following keywords: orphan drug, rare disease treatment, economics, resource utilization, cost, cost effectiveness, questionnaire, and value. References were initially selected based on the inclusion and exclusion criteria listed in Table 1. **Inclusion and exclusion criteria for evaluated references**. Additional studies were identified through reference lists in relevant publications, and input was solicited from experts in evaluation of pharmaceutical products. All studies were initially screened using information in the title and abstract. Full publications were retrieved for all studies that met the inclusion criteria after title and abstract review.

Table 1. Inclusion and exclusion criteria for evaluated references.

Inclusion Criteria	Exclusion Criteria
• English language publications • Primary economic model • Studies in humans	• Only reporting the following: o Clinical or patient care o Policy or legislation, especially research incentive o Opinion or editorial o Healthcare budget impact o Marketplace repositioning of existing treatments o Preclinical studies o Drug-development o Unrelated to rare diseases o Unrelated to healthcare o Reviews, except systematic reviews

	for health technology assessment that include economic analysis

2.2.3. Data Collection

Abstracts and articles describing cost-effectiveness modeling analyses that met the inclusion criteria (Table 1) were evaluated in their entirety. Each study was summarized and tabulated according to the data fields described in Table 2. Tabulated data were used to identify trends or patterns in any disease states that are favored for analysis, country of analysis or perspective, treatment of interest, results of the analysis, and authors' interpretation of the results (**Appendix A**).

Table 2. Description of data extracted from all studies included in this review.

Data Field	Description
Reference	Author, year, and citation number
Disease	Name or description of the orphan disease under analysis
Drug/Treatment	Name or description of the drug or treatment under analysis
Country/Perspective	Name or description of the country or perspective from which the analysis was conducted
Model Type	Description of the model (e.g. Markov)
Currency	Year and currency used in the analysis
Results	Incremental cost effectiveness ratio reported by the study
Conclusion	Interpretation or conclusion drawn by the authors of the study

2.3. Results

A total of 2,513 unique references were obtained, and screened by title and abstract according to exclusion criteria to identify studies to include in full review. After the initial abstract review, a total of 2,180 articles were excluded, leaving 333 references remaining for full evaluation (Figure 1). During the full article review, an additional 296 were excluded, but 51 additional studies were included from the reference lists of six review articles.[14-19] A total of 88 studies reporting primary economic modeling assessments were included in the final analysis (**Appendix A**).

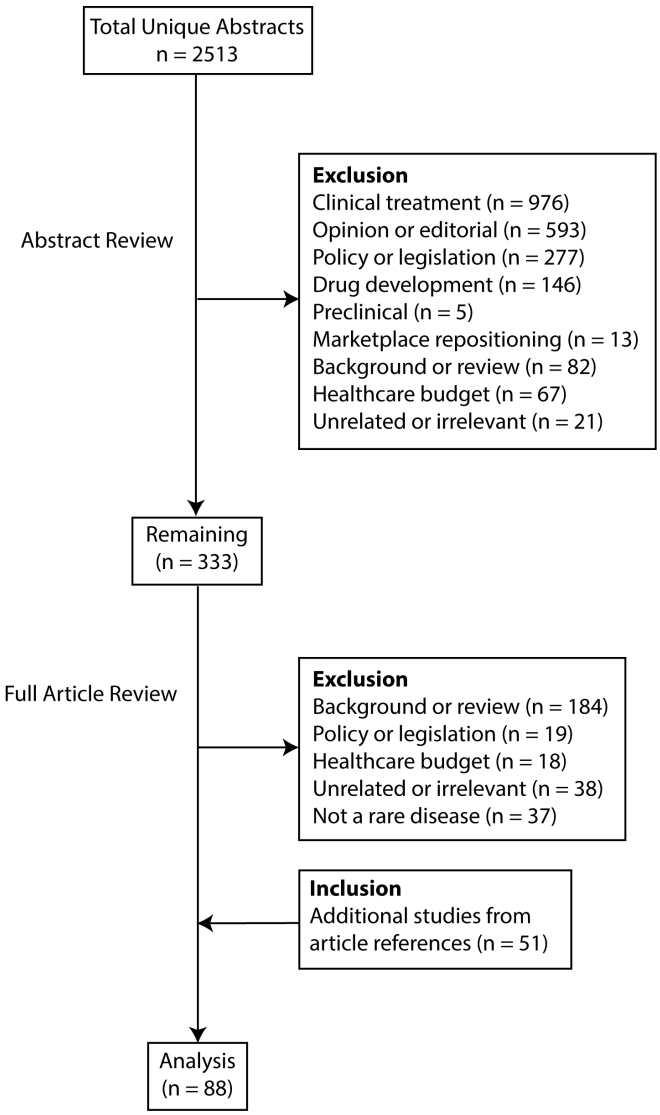

Figure 1. Attrition diagram describing the methodology for study selection.

Of the included articles, 11 were abstracts from conference proceedings, and 77 were published manuscripts from peer-reviewed journals. Articles from 25 countries or perspectives were included (**Table 3**), representing 41 diseases (**Table 4**) and 63 different treatments (**Table 5**). Overall, 44 studies (50%) evaluated cancer treatments. The diseases with the most unique studies were chronic myeloid leukemia (CML, n = 12 references), amyotrophic lateral sclerosis (ALS, n = 6), renal cell carcinoma (n = 6), Crohn's disease (n = 5), gastrointestinal stromal

tumors (n = 4), and multiple myeloma (n = 4). Chronic lymphocytic leukemia (CLL), Fabry disease, Gaucher's disease, hemophilia, head and neck cancer, Lennox-Gastaut syndrome, and osteosarcoma were assessed by three studies each. The remaining 28 disease states were evaluated in only one or two references. The most commonly studied drugs or therapeutic regimens were imatinib (n = 9 references), infliximab (n = 6), and enzyme replacement therapy, interferon-alpha, and riluzole (n = 5 each). Adalimumab, cetuximab, mifamurtied, sorafenib, and sunitinib were assessed in three references each. The remaining 52 treatments were evaluated in only one or two references each.

Table 3. Countries or perspectives with two or more publications represented in this review. Note that these are not mutually exclusive, and one study may conduct an analysis from multiple perspectives.

Country/Perspective*	N	Country/Perspective*	N
Australia	4	Mexico	4
Canada	8	Netherlands	4
China	2	Societal / Payer	3
France	2	Spain	3
Germany	2	United Kingdom	30
Italy	4	United States	20

*Countries with only 1 included reference: Belgium, Cyprus, Czech Republic, Finland, Ireland, Israel, Japan, New Zealand, Serbia, Sweden, Switzerland, Taiwan and Venezuela

Table 4. Number of publications associated with each disease state represented in this review. Note that these are not mutually exclusive, and one study may address more than one disease.

Disease*	N	Disease*	N
ALS	6	Head and neck cancer	3
CLL	3	Hereditary angioedema	2
CML	12	Iron overload	2
Crohn's disease	5	Juvenile idiopathic arthritis	2
Fabry disease	3	Lennox-Gastaut Syndrome	3
GI stromal tumors	4	Renal cell carcinoma	6
Gaucher's disease	3	Multiple myeloma	4
Haemophilia	3	Osteosarcoma	3

*Disease states with only 1 included reference: achalasia, acidemia, acromegaly, acute promyelocytic leukemia, ALK+ lung cancer, burning mouth syndrome, histoplasmosis choroidal neovascularization, cystinosis, hairy cell leukemia, gastric cancer, idiopathic pulmonary hypertension, limbal stem cell deficiency, liver metastases, mesothelioma, soft-tissue sarcoma, drug-resistant tuberculosis, myeloma kidney, paroxysmal nocturnal hemoglobinuria, Pompe disease, pulmonary arterial hypertension, Hodgkin lymphoma, renal transplant, short bowel syndrome, sudden cardiac death in adolescents, variant Creutzfeldt-Jakob disease

Table 5. Number of publications associated with each orphan drug or rare disease treatment represented in this review. Note that these are not mutually exclusive, and one study may address more than one treatment.

Treatment*	N	Treatment	N
Adalimumab	3	Immune tolerance induction	2
Cetuximab	3	Infliximab	6
Dasatinib	2	Mifamurtide	3
Deferasirox	2	Riluzole	5
Enzyme replacement	5	Rituximab	2
IFN-alpha	5	Sorafenib	3
Imatinib	9	Sunitinib	3

*Treatments with only 1 included reference: ablative therapies, abatacept, alemtuzumab, alglucarase, alglucosidase alfa, amisulpride, arsenic trioxide, basiliximab, bedaquiline, bevacizumab, bortezomib, bosentan, botox injection, brentuximab vedotic, certolizumab pegol, clobazam, cysteamine, cytoreductive surgery, eculizumab, EML4-ALK fusion testion + crizotinib, etanercept, everolimus, high cut-off hemodialysis, hydrotherapy, icatibant, laser therapy, lenalidomide, liver transplant, natalizumab, nilotinib, paroxetine, pegvisomant, pemetrexed, pentostatin, plerixafor, prion filtration, prostacyclins, recombinant Factor VIIa, recombinant human IGF-1, rufinamide, screening self-administered icatibant, sertraline, somatropin, stem-cell based product, thalidomide, topical clonazepam, trabectedin, trastuzumab

The methodology employed in all included studies followed traditional analysis techniques based on pharmacoeconomic models for cost-effectiveness or cost-utility, and most were based on standard Markov processes (Table 6).

Table 6. Distribution of modeling methods reported in the included studies.

Model Type	Number of References
Markov	42
Decision Analytic	15
Cost Benefit / Cost Utility	14
Simulation / Survival	12
Other / Not Specified	5

Incremental cost-effectiveness ratios (ICERs) ranged from treatments that were dominant, up to a high of €6.1 million per quality adjusted life year (2009 currency value) for enzyme replacement therapy for Fabry disease. Among all included studies, when a standard cost-effectiveness threshold of $50,000 (£30,000, €40,000) per QALY was applied, a total of 38 studies (43%) reported ICERs that would not be considered cost-effective. When the threshold

was raised to 100,000/QALY (any currency), a total of 21 studies (24%) still failed to achieve cost-effectiveness. Of those with ICERs above 100,000/QALY, the range extended from a low of €102,059/QALY for sorafenib versus best supportive care for renal cell cancer evaluated in Cyprus,[20] to a high of €6.1 million/QALY for enzyme replacement therapy in Fabry disease evaluated in the Netherlands.[21]

Interpretations varied somewhat based on the overall resource limitations of the country or payer. For the high-cost treatments or those with high ICERs, settings that had more resource constraints were more likely to base coverage decisions on a strict willingness-to-pay threshold. Resource rich settings were more likely to conclude that while the treatment may not meet traditional economic thresholds, there is a responsibility to cover treatments for rare diseases, particularly when the overall healthcare budget impact is expected to be manageable due to the small patient population affected by rare diseases.

In light of this systematic review, there is a growing consensus recognizing a need for alternative methods to assess value in the setting of rare diseases, but there is currently limited insight into practical application of any new methodology. To address the need for a new analytical metric, I propose a new approach to value assessment that builds on current techniques with modifications to improve the relevance and interpretability in rare diseases.

3. Orphan Drug Value Assessment

Current methodology for assessing the value of pharmaceutical products is based on robust, validated techniques of decision analysis and health technology assessment;[12] however, the interpretation of results from standard cost-effectiveness evaluations of orphan drugs and treatments for rare diseases is challenging.[13,22] One of the foundations of cost effectiveness

analysis and product comparison is the incremental cost effectiveness ratio (ICER, Eq. 1). This measure enables a cost-based comparison of multiple products across different disease states due to the common factor described by the quality-adjusted life year (QALY). The QALY variable is based primarily on preference-based utilities multiplied by the time spent in a health state for a given health condition.

$$\boldsymbol{ICER = \frac{\Delta\, cost}{\Delta\, QALY}} \qquad \textbf{Eq. 1}$$

The main challenge when applying the ICER to orphan drugs is in the interpretation. The threshold of acceptance (willingness-to-pay) is based on reasonable assumptions that focus on small molecule drugs and treatments for common conditions.[13] In those cases, there is a sufficiently large population affected, and prices have historically been substantially lower, on average, than those observed for orphan drugs.[7] The challenge with orphan drugs under the current framework is in interpreting cost-effectiveness based on the existing thresholds that are derived from the concept of QALY maximization.[13] To be more meaningful for orphan drugs and treatments for rare diseases, the decision metric must be broadened to capture societal preferences, and to include characteristics unique to rare diseases.[12] For example, the rarity of disease, as well as the severity, including mortality, may play an important role in value assessment. There is often a paucity of clinical evidence and experience with the natural history of rare diseases. Clinical trials are often small and do not include randomization in the design due to enrollment size, or randomization may be inappropriate or not feasible for a particular treatment.[12] In many cases the scientific basis of disease pathogenesis or relevant outcomes are poorly understood making clinical evidence difficult to interpret. In an effort to identify a meaningful context for assessing value of orphan drugs and treatments of rare diseases, I propose

a new methodological framework with a metric that deviates from the traditional ICER, but builds on broader concepts of decision analysis.

One approach that is gaining popularity in value assessment is multiple criteria decision analysis (MCDA).[10,11,13,23,24] This encompasses a variety of methodological approaches, with the goal of including the many variables of interest into a single algorithm. The notion of incorporating MCDA into economic analyses is gaining traction, and there are a growing number of reports defining this new framework in the context of healthcare decisions, and in practical application.[10,11,25-30] The framework behind MCDA is in preference weighting or priority ranking of an array of criteria relevant to rare diseases, with the entire weighted outcomes array then compared between treatment options.

While the MCDA methodology is promising, it is not yet clear how to apply it to analysis of multiple products across multiple diseases states, and there is no consensus on the preferred approach to conducting MCDA or how to use it in decision analysis.[24] I propose a new ratio that could be used in the same manner as the ICER in decision analysis, but without reliance on the current, somewhat narrow, framework of willingness-to-pay thresholds.[13] Instead, new decision criteria will be establish to draw the focus toward the quality and clinical performance of the product under analysis from a broader societal perspective to establish a more meaningful measure for comparison. The numerator is an efficacy or effectiveness measure to draw the focus toward the value of a product. This numerator, the quality measure (Q), is based upon MCDA to encapsulate the many relevant variables in orphan drug analysis (**Eq. 2**). Cost is included in the ratio as an essential component for describing value. Here, cost is considered more as 'value' as the measure would extend beyond direct treatment costs to explicitly include societal burden and a measure of opportunity costs. In introducing this new value metric, the goal is to propose a

different paradigm for analysis and to consider assessment under a completely different set of rules than those that govern evaluation with the ICER. I call this new ratio the Orphan Drug Index Estimate (ODIE). Here I describe the process of defining the Q and cost variables for this ratio.

$$\boldsymbol{ODIE = \frac{Q}{cost}} \qquad \textbf{Eq. 2}$$

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recently conferred a task force to develop good-practice guidance on using MCDA in health care decision-making.[10,11] This guidance suggests a sequence of eight steps in defining, developing, implementing, and reporting MCDA results. To the extent feasible, I describe the steps relevant to developing the analytical framework in the context of ODIE.[11] The goal of this description is to frame the metric and describe the process to develop a value assessment tool.

3.1. ODIE Numerator (Q)

3.1.1. Problem Definition

The decision problem we face is the lack of robustness in current value analysis when faced with orphan drugs and treatments for rare diseases. The objective of this new metric, the ODIE, is to provide a mechanism to compare or rank treatment alternatives based on the quality and value of the treatment, as well as the overall societal costs associated with the treatment and the disease. The goal of this framework is to provide a validated, generalized algorithm that can be used for any rare disease treatment to compare alternatives within or across disease states, to help decision makers assess resource allocation within constrained healthcare budgets.

3.1.2. Criteria Selection

The criteria include all factors that stakeholders and experts find relevant for assessing quality and value in the setting of rare diseases. There have been reports in the literature

describing methodology and application of MCDA in healthcare decision analysis,[31] but there is no strong consensus on the preferred approach or interpretation of the results. Perhaps the most visible framework in the literature for assessing rare diseases with MCDA have been developed by an international consortium, the EVIDEM Collaboration.[32] This framework is described as a means for transparently describing the components included in a decision.[29] There are limitations with the EVIDEM framework, particularly due to limited scope and more extensive validation is necessary for the approach to become practical. There is also some redundancy in the factors included in the analysis, particularly related to cost elements, which may bias the results.[27] For example, the framework includes budget impact and cost-effectiveness, which may overlap in the cost variable, and cost-effectiveness may overlap with the patient-specific criteria including patient-reported outcomes. It does introduce a set of criteria, however, that may provide a starting point in developing an MCDA. Table 7 describes the factors I initially identified as important in development of the ODIE. These variables and the results described below are largely arbitrary, and are provided here to describe the process for conducting an MCDA in order to determine the value for Q in the ODIE.

Table 7. Decision criteria expected to be relevant for multicriteria decision analysis of rare diseases.

Factor	Description
Clinical Effectiveness	Magnitude of health improvement compared to other interventions; may include the proportion of patients expected to have improved health, the onset and duration of health gain, and disease-specific improvement in outcomes
Safety	Reduction of short- or long-term adverse events or undesired health effects compared to existing treatment options
Tolerability	Patient tolerability of treatment; may include discontinuation rates or adherence to treatment, discomfort (e.g., injection site reactions), and overall willingness of a patient to participate in treatment
Mortality	Risk of mortality due to the disease process; may capture the change in mortality risk based on treatments under evluation
Disease Severity	Severity of the disease as it relates to morbidity, mortality, and natural history of the disease

Progression Rate	Speed with which the disease reaches an endpoint of morbidity or mortality
Therapeutic Benefit	Assesses the level of benefit of the treatment (e.g. symptom relief, curative)
Rarity of Disease	The size of the population affected (prevalence, incidence)
Unmet Medical Need	Lack of treatment alternatives, or a poor efficacy or safety profile of current care options
Innovation	The level of technological innovation in the treatment,
Patient-Reported Outcomes	Change in outcomes relevant to patients, including health-related quality of life, autonomy, dignity, and convenience of using the treatment
Quality of Evidence	Relevance and overall quality of available studies, including study design, agreement of results between studies, uncertainty, bias, and consistency in evidence reporting
Societal Perspective	Current priorities in healthcare regarding treatment of rare diseases; may include caregiver quality of life

3.1.3. Performance Measures

A relevant means of measuring each factor as it relates to a given condition must be established to assess the evidence. The measures must be relevant for the factor in question. For example, factors that relate to clinical efficacy should be measured based on data presented in clinical trials, while severity of disease can be a more relative measure and is assigned a value on a set scale. For each factor identified above (Table 7), the measurement or scale of assessment is described to provide a practical basis that is relevant for each item of interest (Table 8).

Table 8. Performance measures applied to each relevant factor. Includes efficacy measures from clinical studies, and scales to evaluate items that are more qualitative or relative in nature for the purpose of illustrating the mechanics of conducting the MCDA to calculate the quantity for the ODIE numerator, Q.

Factor	Measurement Scale
Clinical Effectiveness	Outcome of interest. May be Odds Ratio, Relative Risk, Risk Ratio, or other measure of efficacy measured in clinical studies. Focused on clinically important differences informed by both clinicians and patients.
Safety	Safety measures of interest. May be proportion of patients experiencing adverse events, or each event of interest.
Tolerability	Patient tolerability of treatment; may include percent of patients discontinuing treatment, or percent adherence to treatment
Mortality	Risk of death due to disease. Reported as a percentage, the score is determined by subtracting the risk from 100% (e.g., 100% - 20% risk of death = 80)
Disease Severity	Range between mild (e.g., mild discomfort, minimal impact on daily life) and extreme (e.g., completely debilitating, requiring constant caregiver support)

Progression Rate	Time to full disease manifestation (morbidity, mortality)
Therapeutic Benefit	Range between ineffective and curative
Rarity of Disease	Prevalence of disease
Unmet Medical Need	Range between multiple existing treatments and first available treatment
Innovation	Range between old technology and cutting-edge advancement
Patient-Reported Outcomes	Change in PRO or QoL
Quality of Evidence	Estimate based on GRADE criteria[33]
Societal Perspective	Range between treatment unfavored (e.g., minimal burden of disease) and treatment favored (e.g., significant burden of disease)

3.1.4. Scoring Alternatives

To generate a meaningful, and quantifiable result using MCDA, the performance measures must be translated and normalized to a single scale.

3.1.5. Weighting Criteria

In order to use the factors described above, they must be translated into priority weights that could be applied as scaling factors to product data such as clinical safety, efficacy, and patient reported outcomes. The scores that are identified must be validated through stakeholder input. To verify the general preference of stakeholders, a discrete-choice experiment will be conducted such that all pairwise combinations of the factors are presented for the stakeholder to rank by importance. For example, a stakeholder may be given characteristics of a general disease state, and they much choose whether it is more important to consider disease severity or unmet medical need when deciding upon a treatment strategy, or when deciding whether or not to support development or payment of a treatment. Next they would be asked to choose the more important factor between disease severity and safety of the treatment. This would continue through iterations until a relative priority ranking can be established among a variety of stakeholders from varying perspectives. For each stakeholder, each factor will be ranked in order according to preference and assigned a relative weight on a scale from 1 to 100. (Table 9).

Rank order for all stakeholders will be aggregated and the average weight for each factor will be applied as the scaling factor. For example, if the ranks for two stakeholders are as shown in Error! Reference source not found., the average weight for 'Clinical Effectiveness' would be the average of all stakeholder relative weights as follows:

$$Average\ Weight = \frac{w_1+w_2}{n} = \frac{100+85}{2} = 92.5 \qquad \textbf{Eq. 3}$$

where w_1 and w_2 are the relative weights for stakeholder 1 and 2, respectively, and n is the total number of stakeholder weights. These stakeholder weights are then converted to scaling factors to be applied to the performance measures when quantifying the results. The scaling factor is a normalized value that reflects the relative weight of each criteria element. The method for calculating the scaling factor is described in Eq. 4, where the average weight for a factor is divided by the sum of all average weights. Using the factors 'Clinical Effectiveness' the scaling factor is calculated as follows:

$$Scaling\ Factor = \frac{a_i}{\sum_i^n a_i} = \frac{92.5}{718} = 0.128 \qquad \textbf{Eq. 4}$$

where a_i is the average weight for factor i, and n is the total number of factors under consideration.

Table 9. Example for calculating a generalized scaling factor based preference ranking of factors by two independent stakeholders.

Factor	Stakeholder 1		Stakeholder 2		Average Weight	Scaling Factor
	Rank	Relative Weight	Rank	Relative Weight		
Clinical Effectiveness	1	100	3	85	92.5	0.128
Safety	2	93	4	78	85.5	0.119
Tolerability	3	85	6	63	74.0	0.103
Mortality	4	78	2	93	85.5	0.119
Disease Severity	5	70	1	100	85.0	0.118
Progression Rate	6	63	5	70	66.5	0.093
Therapeutic Benefit	7	55	7	55	55.0	0.077
Rarity of Disease	8	48	10	33	40.5	0.056
Unmet Medical Need	9	40	8	48	44.0	0.061

Innovation	10	33	9	40	36.5	0.051
Patient-Reported Outcomes	11	25	11	25	25.0	0.035
Quality of Evidence	12	18	13	10	14	0.019
Societal Perspective	13	10	12	18	14	0.019

3.1.6. Calculating Aggregate Scores

For the sake of illustration, the factors and weights described above (Error! Reference source not found.) will be applied to the clinical characteristics and current treatment strategy for paroxysmal nocturnal hemoglobinuria (PNH), a rare, non-malignant hemolytic anemia. I conducted a systematic review and meta-analysis (**Appendix B**) based on existing literature to identify the clinical benefit of eculizumab (Soliris®) in increasing the number of patients that do not require transfusion, and in decreasing the number of patients that experience a thrombotic event. Based on the specific disease under review, each factor is scored on a scale of one to ten, as described in Table 10 below. The scores discussed here are arbitrary and included only as an example to demonstrate the mechanics of the process, and to describe how to apply the framework in practice.

Table 10. Scoring of each factor based on clinical evidence, pathophysiology, and other relevant data about paroxysmal nocturnal hemoglobinuria.

Factor	**Score**	**Rationale**
Clinical Effectiveness – Transfusion Independence	100	A very large effect size.
Safety	38.5	38.5% patients reported serious adverse events.
Tolerability	80	Fewer than 1% of patients overall discontinued treatment
5-year Mortality	80	Estimated 5-year mortality of approximately 20%.
Disease Severity	50	Patients are able to function normally, but they experience invasive care such as transfusions, and have a high risk for thrombotic events and other morbidity
Progression Rate	50	This is a chronic condition with no overt progression, but the prognosis is only 10-20 years after diagnosis
Therapeutic Benefit	80	Very successful treatment, but does not work 100% of the time
Rarity of Disease	90	Estimated incidence of 1-2:1,000,000. In the US this equates to approximately 350-650 cases

Unmet Medical Need	80	There are treatments available, but they are for managing the consequences of the disease and include packed red blood cell transfusion and anticoagulation therapy. This is the first agent to treat the underlying condition.
Innovation	70	Monoclonal antibody platforms are not new, but targeting a factor in the complement system is novel
Patient-Reported Outcomes	0	PROs were not reported
Quality of Evidence	30	Studies are small, non-randomized, and do not include a comparator. The patient cohorts were all treated with eculizumab and outcomes compared to their reported measures at baseline prior to treatment
Societal Perspective	50	This is an expensive treatment and some are not supportive of paying for treatment; others are supportive of addressing an unmet need

Since the scores in this example can already be mapped to a 100-point scale, the weights can be applied directly to the scores for each factor (Table 11). Scores and weights could also be incorporated into a decision-tree for a visual representation of this analysis.

Table 11. Aggregate scores calculated for each factor based on the quotient of the assigned score, and the preference weights identified from stakeholder input.

Factor	**Score**	**Weight**	**Total Score**
Clinical Effectiveness – Transfusion Independence	100	0.128	12.80
Safety	38.5	0.119	4.58
Tolerability	80	0.103	8.24
Mortality	80	0.119	9.52
Disease Severity	50	0.118	5.90
Progression Rate	50	0.093	4.65
Therapeutic Benefit	80	0.077	6.16
Rarity of Disease	90	0.056	5.04
Unmet Medical Need	80	0.061	4.88
Innovation	70	0.051	3.57
Patient-Reported Outcomes	0	0.035	0.00
Quality of Evidence	30	0.019	0.57
Societal Perspective	50	0.019	0.95
Aggregate			**66.86**

The aggregate score is the sum of the product of score and weight across all factors, *i* (**Eq. 5**).

$$Aggregate\ Score = \sum_{i=1}^{n} s_i \times w_i \qquad \textbf{Eq. 5}$$

where n is the total number of factors in the analysis, s_i is the assigned score for factor i, and w_i is the weight applied to factor i. In this example, the aggregate score is 66.86.

3.1.7. Uncertainty

There is the potential for considerable uncertainty in this analysis, due to the assumptions made when assigning scores and weights to each factor, as well as due to the level of rarity of disease and quality of data available. Therefore, sensitivity analyses must be conducted on the weight for each factor, and the scores assigned to each factor. As this metric is developed further, the scoring algorithm will be refined and validated to produce reliable estimates of product quality (Q) for the numerator of the ODIE. The results will also undergo advanced analysis of uncertainty to identify criteria for which the model is most sensitive.[34] This sensitivity analysis is beyond the scope of this proposal, but will be pursued in the future.

3.1.8. Validation

Validation must be incorporated into each step of this development process.[11] This depends on input from stakeholders, which include decision makers, formulary managers from private payers or institutions, healthcare providers, patients with rare diseases, as well as individuals that confer a perspective of society at large. These stakeholders and other experts will provide input regarding selection of the criteria to be included in the analysis, to ensure the result will be meaningful to support decisions. For each criterion, stakeholder preferences will be recorded to develop a robust model scheme that will appropriately predict priority weights for any rare disease such that the model will be universal and general enough to elicit a confident

estimate of the quality or value of a particular treatment. This will necessarily be an iterative process to test the consistency of responses and results for a cross-section of rare diseases.

3.2. Denominator (cost)

Value, as it pertains to the ODIE denominator, will encompass the expected inputs including drug price and other direct costs of treatment, but may also incorporate broader impacts such as opportunity costs, societal costs, and resource allocation (Table 12). It is important to ensure there is no redundancy in measures used throughout the ODIE analysis, as double counting would bias the results. One means for doing this in the case of the ODIE is to separate cost-related variables into the denominator, while retaining clinical and patient-specific components in the numerator.

Table 12. Factors related to 'cost' in the ODIE metric for assessing value.

Factor	Description
Cost Consequences	Direct costs of the intervention
Other Medical Costs	Medical costs outside the direct costs of the intervention
Non-Medical Costs	Additional costs (e.g., disability, caregiver support, social services, lost-productivity)
Opportunity Costs	Cost of foregone treatments for other diseases and affordability

Direct costs of the intervention can usually be found readily, but assigning costs beyond direct medical costs can be a challenge as those may be obscure and less explicit. For the scope of this example, we will assume the total additional costs attributable to treatment with eculizumab equate to $500,000. Using this measure of cost, and the measure for quality described above, the individual ODIE for eculizumab in increasing transfusion independence in paroxysmal nocturnal hemoglobinuria patients is calculated as follows:

$$ODIE = \frac{Q}{cost} = \frac{66.86}{\$500{,}000} = 0.001337\ per\ dollar \qquad \textbf{Eq. 6}$$

In order to interpret these results, more research is required to validate the analysis, and to identify what ODIE value is meaningful. Since this metric is normalized by the currency of analysis (e.g., dollars), the numerator value then becomes the relevant measure. Once the paradigm of the ODIE is better understood, it would be possible to incrementally compare ODIEs to determine treatments that provide more value per dollar spent. The methodology described here is currently being refined, and the numbers presented are meant only as an example for how the ODIE might be calculated and used in guiding decisions in clinical scenarios. This notion is still in its infancy, but shows promise in value analysis for orphan drugs and treatments for rare diseases where there is currently no robust measure.

4. Discussion

In this study, I conducted a systematic review of the literature to investigate the current methodology employed in pharmacoeconomic evaluation of orphan drugs and treatments for rare diseases. I also propose a new value assessment metric that may be more appropriate for decision analysis of orphan drugs and treatments for rare diseases.

The Orphan Drug Act was in fact developed partly in response to a market failure that took research and development resources away from rare diseases in favor of developing treatments for common diseases considered to be more profitable due to the large market share.[2,3,35] By providing significant incentives, both financial and temporal, the Orphan Drug Act has indeed increased interest and energy in developing treatments for orphan diseases. In fact the revenue associated with orphan drugs is expected to reach $176 billion, and the high prices associated with orphan drugs are creating blockbuster status for many of these products.[7] With prices that are approximately 19 times higher annually for patients receiving treatment with

orphan drugs compared to non-orphan drugs, this increased expenditure reflects resources that are therefore foregone for other goods or services (or drugs). Furthermore, competition is discouraged by Orphan Drug Act as currently written, which invites high prices. A study of competition among generic drug manufacturers showed that by including three competitors, the price for a particular drug is decreased by 32% to 48% compared to the prices the market will bear from a single manufacturer.[36] Presumably competition in orphan drugs will also result in decreased prices.

By incentivizing manufacturers to focus more attention on treating orphan diseases, passage of the Orphan Drug Act did in fact address the lack of interest on the part of the pharmaceutical industry in pursuing orphan drugs and in that way shifted the balance in favor of previously neglected therapeutic areas. The inadvertent result is that manufacturers are justified in charging very high prices for orphan drugs from the belief that the limited market share from a small target population would not result in profitable products;[4] however, with a return on investment nearly double that expected with non-orphan drugs the profitability argument is attenuated by extreme prices.[7] Health plans must allocate their finite resources to provide the most value for customers, and that often means diverting financial resources away from treatment options for non-orphan diseases to pay for orphan treatments, or declining coverage for expensive orphan drugs.[4]

This study has several limitations. First, in the systematic review, an unexpectedly large number of studies were not indexed in the selected databases, and instead were identified from reference lists in systematic reviews and other relevant publications. This suggests there may be additional analyses that were not captured in this review, so while the list of studies presented here is extensive, it may not be exhaustive. For the purpose of this study identifying trends in the

methodology and results for evaluating orphan drugs and treatments for rare diseases, the conclusions are unlikely to be significantly different if a few studies were inadvertently excluded. Second, the ODIE and related definitions are proposals at this point, and have not been fully developed or validated. The purpose was to inspire discourse on how to think differently about value assessment in the rare disease setting. Work is ongoing, but there is a great deal of detail to refine before it can be a viable decision-analysis metric.

5. Conclusion

The Orphan Drug Act was enacted in 1983 to provide incentives to pharmaceutical manufacturers to develop and produce drugs to treat rare diseases. The result was a clear increase in the number of orphan drug approvals for an increased number of orphan diseases. The result has also been a marked increase in the price for these drugs that is quickly overwhelming the economic balance of the already tenuous healthcare system in the US.

There is a global consensus of a need to develop appropriate methodology, analysis techniques, and related policies to address management of expensive treatments. It is not yet clear how best to evaluate the value of orphan drugs. More thorough evaluation and validation of novel modeling techniques, analytic rationale and proactive policy changes are needed to redefine the status quo of HTA relating to rare disease treatments. Here, I propose a new metric that, once validated, could be used to compare orphan drugs across multiple diseases to identify the most beneficial allocation of resources.

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8. Appendix A

Evidence table describing the data reported in studies included in this analysis

Reference	Disease	Drug/ Treatment	Country/ Perspective	Model type	Currency	Results	Conclusion
Ackerman et al, 1999[37]	Amyotrophic lateral sclerosis (ALS)	rhIGF-I	US	Cost effectiveness	1996 US dollars	$67,440/QALY	Treatment is most cost effective in earlier stages of disease or rapidly progressing
Adena et al, 2014[38]	Chronic lymphocytic leukemia (CLL)	rituximab	Australia	Markov	2009 Australian dollars	A$42,906/QALY	Appears to be cost-effective
Beck et al, 2001[39]	Chronic myeloid leukemia (CML)	IFN-alpha vs IFN-alpha + cytarabine vs hydroxyurea	Not specified	Cost effectiveness	US dollars (year not specified)	IFN-alpha vs IFN-alpha + cytarabine: $16,900/QALY; IFN-alpha vs hydroxyurea: $23,700/QALY	Unfavorable cost effectiveness compared to other interventions
Benedict et al, 2010[40]	Lennox-gastaut syndrome (lgs)	rufinamide	UK NHS	Patient level simulation	2006 Pounds Sterling	£2 - £2,151/QALY	Rufinamide had higher total costs than topiramate and lamotrigine, but with better outcomes; the ICER is acceptable.
Benedict et al, 2011[41]	Renal cell cancer	sunitinib, sorafenib, or bevacizumab + iFN-alpha	US and Sweden	Markov	2008 US dollars	sunitinib is dominant	Sunitinib as first-line treatment is cost-effective

Berger et al, 2013[42]	Severe hemophilia A and inhibitors	immune tolerance induction (ITI)	Germany	Markov	Euros (year not specified)	High-dose ITI: average total costs €3,371 million in 18 years, 119.3 bleeds avoided Low-dose ITI: average total costs €2,435 million in 18 years, 90.6 bleeds avoided ITI with risk assessment: average total costs €2.737 million in 18 years, 116.8 bleeds avoided On-demand treatment without ITI: average total costs €1,722 million in 18 years	ITI with risk assessment is cost-saving with comparable outcomes to HD ITI
Beutler et al, 1994[43]	Gaucher's disease	alglucarase	US	Decision analytic	1994 US dollars	$49,000 - $147,000/QALY based on dose	Clinically effective but high cost requires policy to allow access to cost-effective forms
Blackhouse et al, 2012[44]	Crohn's disease (refractory)	infliximab, adalimumab	Canada	Markov	Canadian dollars (year not specified)	Adalimumab vs standard care = $193,305/QALY; Infliximab vs standard care = $222,955/QALY; Moving from adalimumab to infliximab = $451,165/QALY	Not considered cost-effective for refractory Crohn's disease

Brosa et al, 2015[45]	Osteosarcoma	mifamurtide	Spain	Markov	2011 Euros	€33,684/QALY	The ICER is within the range of efficiency defined by NICE, could be considered cost-effective
Brown et al, 2000[46]	Choroidal neovascularization associated with histoplasmosis	laser therapy	US	Markov	1999 US dollars	$4,167/QALY	Appears to be cost-effective
Brown et al, 2008[47]	Head and neck cancer	cetuximab + radiotherapy	Belgium, France, Italy, Switzerland, UK	Patient level simulation	2005 Euros	Belgium: €8,568/QALY France: €10,836/QALY Italy: €7,538/QALY Switzerland: €10,328/QALY UK: €9,144/QALY	Good value alternative
Brown et al, 2013[48]	Multiple myeloma	lenalidomide	UK NHS	Patient level simulation	2011 Pounds Sterling	£30,153/QALY	Cost effective
Chan et al, 2011[49]	Head and neck cancer	cetuximab + radiotherapy	Taiwan	Decision tree	2007 US dollars	$36,992/QALY	Likely cost-effective
Chen et al, 2009[50]	Chronic myeloid leukemia (CML)	imatinib	China	Cost utility	Chinese RMB (year not specified)	RMB 73,674/QALY	Cost effective vs IFN-alpha
Clements et al, 2013[51]	Lennox-Gastaut syndrome (LGS)	clobazam	US	Cost effectiveness	2013 US dollars	clobazam = dominant	May be cost saving
Connock et al, 2006[52]	Fabry disease	enzyme replacement therapy (ERT)	UK NHS	Decision analytic	2003 Pounds Sterling	£252,000/QALY	Exceeds the normal cost-effectiveness threshold, but NHS must provide ERT due to orphan status

Connock et al, 2006[53]	Gaucher's disease	enzyme replacement therapy (ERT)	UK NHS	Markov	2003 Pounds Sterling	£380,000 - £476,000/QALY depending on genotype	Exceeds the normal cost-effectiveness threshold, but NHS must provide ERT due to orphan status
Contreras-Hernandez et al, 2008[54]	Gastrointestinal stromal tumors	Imatinib, sunitinib	Mexico	Markov	2006 US dollars	Sunitinib vs palliatoive care: $46,109/LYG; Sunitinib vs imatinib: dominant	Sunitinib would be cost saving vs imatinib
Cordony et al, 2008[55]	Malignant pleural mesothelioma	pemetrexed + cisplatin vs cisplatin	UK NHS	Cost effectiveness	2004 Pounds Sterling	20,475 - £68,598/QALY	Acceptable cost-effectiveness
Coyle et al, 2014[56]	Paroxysmal nocturnal hemoglobinuria (PNH)	eculizumab	Canada	Markov	2012 Canadian dollars	$4.62 million/LYG, $2.13 million/QALY	Incremental cost that is not justifiable in spite of the fact it is a rare disease
Dalziel et al, 2005[57]	Chronic myeloid leukemia (CML)	Imatinib	UK NHS	Markov	2002 Pounds Sterling	£26,180/QALY (vs IFN-alpha) £86,934/QALY (vs hydroxyurea)	Imatinib may be moderately cost effective vs IFN-alpha, but less cost effective vs hydroxyurea
Djalalov et al, 2014[58]	ALK-positive non-small-cell lung cancer (NSCLC)	EML4-ALK Fusion Testing and first-line crizotinib treatment	Canada	Markov	2012 Canadian dollars	$255,970/QALY (no testing or crizotinib), $250,632/QALY (testing + crizotinib vs standard care)	Likely not cost effective
Eckert et al, 2001[59]	Haemophilia with inhibitors	rfVIIa	Australia	Not specified	Australian dollars (year not specified)	$51,533/QALY	Likely cost effective

Epps et al, 2005[60]	Juvenile idiopathic arthritis	hydrotherapy + physiotherapy (combined) vs physiotherapy (land) alone	UK NHS	RCT with QALY, resource use, and cost outcomes	1999 Pounds Sterling	The combined group had slightly lower mean costs (-£6.91) and lower mean QALYs (-0.0478) vs physiotherapy alone	no evidence to justify costs of adding hydrotherapy
Fordham et al, 2015[61]	Limbal stem cell deficiency	stem cell based product	Italy	clinical trial, methods unclear	Euros (year not specified)	<€40,000/QALY	Cost reduction in the long-term management of LSCD
Ginsberg et al, 1997[62]	Amyotrophic lateral sclerosis (ALS)	riluzole	Israel	Cost benefit analysis	1996 US dollars	$12,013/LYG	Benefits of riluzole clearly exceed costs
Gordois et al, 2003[63]	Chronic myeloid leukemia (CML)	imatinib	UK NHS	Markov	2001 Pounds Sterling	£29,344/QALY (accelerated phase) £42,239/QALY (blast crisis phase)	Considerable health benefits, but considerable cost to the payer vs conventional therapy and palliative care
Gray 1998[64]	Amyotrophic lateral sclerosis (ALS)	riluzole	UK NHS	Cost effectiveness	1997 Pounds Sterling	£45,630/QALY (50mg) £44,890/QALY (100mg)	Not considered cost effective, but considered, due to orphan status
Grima et al, 2011[65]	Myeloma kidney	high cut-off hemodialysis	UK NHS	Decision tree	2009 Pounds Sterling	High cut-off hemodialysis dominated standard hemodialysis.	Dominant
Guest et al, 2009[66]	Hairy cell leukemia	Pentostatin	UK NHS	Markov	2007 Pounds Sterling	<£5,000/QALY	Cost-effective vs cladribine
Hannouf et al, 2012[67]	Head and neck cancer (recurrent or metastatic)	cetuximab	Canada	Markov	2011 Canadian dollars	$386,000/QALY	Not cost-effective in Canada

Helbert et al, 2012[68]	Hereditary Angioedema types I and II	icatibant	UK NHS	Probabilistic cost-utility	Pounds Sterling (year not specified)	Cost saving £592 per attack	Icatibant reduces costs vs C1-INH.
Hens et al, 2012[69]	Burning mouth syndrome	amisulpride, paroxetine, sertraline, topical clonazepam	France, Italy, Netherlands, Spain, UK	Decision tree	2010 Euros	Average coste effectiveness ratios: Amisulpride = €69 - €219; Paroxetine = €61 - €282; Sertraline = €65 - €306; Topical clonazepam = €42 - €157	topical clonazepam was most efficient in all 5 countries
Hornberger et al, 2012[70]	Chronic lymphocytic leukemia	rituximab (added to fludarabine + cyclophosphamide)	US	Decision analytic	US dollars (year not specified)	$23,530/QALY	Cost-effective in previously untreated CLL
Hoyle et al, 2011[71]	Chronic myeloid leukemia (CML, imatinib resistant)	Dasatinib, nilotinib	UK NHS	Survival-based	2010 Pounds Sterling	Nilotinib: dominant (vs imatinib); £104,698/QALY (vs IFN-alpha); Dasatinib: £91,500/QALY (vs imatinib); £277,700/QALY (vs nilotinib); £82,619/QALY (vs IFN-alpha)	High uncertainty in the model. Both nilotinib and dasatinib unlikely to be cost-effective vs IFN-alpha
Hoyle et al, 2010[72]	Renal cell cancer	sorafenib	UK NHS	Decision analytic	2007 Pounds Sterling	£75,398/QALY	May not be cost-effective
Huse et al, 2007[73]	Gastrointestinal stromal tumors	imatinib	US	Cost effectiveness	2005 US dollars	$38,723/QALY	Within the commonly accepted range for life-saving interventions

Imran et al, 2009[74]	Iron overload syndromes	deferasirox	US	Markov	2006 US dollars	$28,255/LYG	Potentially important supplement
Jaisson-Hot et al, 2004[75]	Crohn's disease	infliximab	Third-party payer (country unspecified)	Markov	Euros (year not specified)	€63,700/QALY (episodic reinfusions); €762,245/QALY (maintenance)	May be cost-effective for relapse therapy, but unlikely for maintenance therapy
Johal et al, 2013[76]	Nonmetastatic osteosarcoma	mifamurtide	UK NHS	Markov	2007 Pounds Sterling	£68,734/QALY, £58,737/LYG	Cost-effective option added to standard chemotherapy
Joseph et al, 2009[77]	Multiple myeloma	thalidomide	UK NHS	Markov	Pounds Sterling (year not specified)	£17,002/QALY, £13,346/LYG	Cost-effective added to standard therapy
Kanters et al, 2014[78]	Pompe disease	alglucosidase alfa	Netherlands	Patient level simulation	2009 Euros	€1.0 million/QALY, €0.5 million/LYG	No interpretation
Kattan et al, 1996[79]	Chronic myeloid leukemia (CML)	IFN-alpha	US and Europe	Markov	US dollars (year not specified)	$34,800/QALY	Cost-effective vs hydroxyurea in most clinical scenarios
Knight et al, 2003[80]	Haemophilia with inhibitors	immune tolerance induction (ITI)	UK NHS	Markov	2000 Pounds Sterling	Three ITI protocols vs on-demand (OD) treatment. Malmö dominant; £55,922/QALY (Low-dose); £147,785/QALY (Bonn); £361,657/QALY (Low Dose vs Malmö); £268,337/QALY (Bonn vs Malmö); £244,409/QALY (Bonn vs Low Dose)	The Malmö ITI protocol dominated and is the preferred protocol

Lachaine et al, 2013[81]	Acute promyelocytic leukemia	arsenic trioxide	Canada	Markov	2013 Canadian dollars	$22,219/QALY.	Cost effective, currently the treatment of choice among experts
Leslie et al, 2012[82]	Sudden cardiac death in adolescents	screening	US	simulation models	2010 US dollars	Screening at age 14 = $91,000/LYG; Screening at age 8 = $204,000/LYG	Screening costs are high relative to the benefits
Li et al, 2015[83]	Propionic acidemia (PA) and classical methylmalonic acidemia (MMA)	liver transplant	US	Markov	2014 US dollars	Liver transplant = dominant	Liver transplnat is likely the dominant treatment strategy.
Liberato et al, 1997[84]	Chronic myeloid leukemia (CML)	IFN-alpha	societal (country not specified)	Markov	1995 US dollars	$89,500/QALY	Marginal cost effectiveness
Lindsay et al, 2008[85]	Crohn's disease	infliximab	UK NHS	Markov	2005 Pounds Sterling	£26,128/QALY (luminal disease); £29,752/QALY (fistulizing disease)	8-week maintenance treatment is cost-effective
Look Hong et al, 2014[86]	Metastatic gastrointestinal stromal tumors (GIST)	cytoreductive surgery with tyrosine kinase inhibitor	US	Markov	2012 US dollars	Utility measures were not included. Cost difference between least costly (no surgery) and most costly (surgery for localized progressive disease + imatinib 800mg) was $47,344	Surgery is an economically viable option, but no recommendation on clinical practice; Surgery should not be avoided solely due to economic concerns.
Loveman et al, 2014[87]	Liver metastases	ablative therapies	UK NHS	Survival-based	2009 Pounds Sterling	Dominant to £37,303/QALY	Limited research evidence upon which to base any decisions
Mabasa et al, 2008[88]	Gastrointestinal stromal tumors	imatinib	Canada	Cost effectiveness	2006 Canadian dollars	Can$16,911/LYG	May be cost-effective

McLeod et al, 2009[89]	Iron overload syndromes	deferasirox	UK NHS	Decision tree	2007 Pounds Sterling	Deferasirox vs DFO: Scenario 1 - cost-effective (<£20,000/QALY) until age 6; unlikely to be cost effective (>£30,000/QALY) after age 10; Scenario 2 and 3 - dominant until age 14 years, and then is cost-effective (<£30,000/QALY); Deferasirox vs deferiprone: Scenario 1 - cost-effective until age 6, possibly cost-effective from age 6 to 8, unlikely to be cost effective after age 8; Scenario 2 and 3 - not cost-effective	Short term deferiprone is more cost-effective than deferasirox, and deferasirox is more cost effective than DFO.
Mehta et al, 2004[90]	Multiple myeloma	bortezomib	US	Decision analytic	2003 US dollars	Bortezomib: $45,356/LYG (vs best supportive care); Bortezomib + prior thalidomide: $49,797/LYG (vs best supportive care); Bortezomib without prior thalidomide: $21,483/LYG (vs thalidomide)	Bortezomib is cost-effective and the best value among currently available therapeutic options
Messori 1998[91]	Chronic myeloid leukemia (CML)	IFN-alpha	Societal (country not specified)	Cost effectiveness	US dollars (year not specified)	IFN-alpha: $93,461 - $226,545/LYG	Unselected long-term treatment with IFN-alpha is not cost-effective

Messori et al, 1999[92]	Amyotrophic lateral sclerosis (ALS)	riluzole	Italy	Survival-based	1996 US dollars	$62,609/LYG	Unfavorable or borderline cost-effectiveness
Meza-Torres et al, 2014[93]	Refractory/relapsed hodgkin lymphoma	brentuximab vedotin	Mexico and Venezuela	Markov	US dollars (year not specified)	$38,614/LYG (Mexico); $57,854/LYG (Venezuela)	Cost-effective in Mexico and Venezuela
Migliaccio-Walle et al, 2006[94]	Short bowel syndrome	somatropin	US	Discrete event simulation	2004 US dollars	Cost decrease of $33,789 (year 1), $51,685 (year 2)	Somatropin increases quality of life and results in health care cost saving
Mihajlovic et al, 2013[95]	Metastatic renal cell carcinoma	everolimus (second-line)	Serbia	Markov	2013 Euros	€86,978/QALY	Not likely to be cost-effective
Moore et al, 2007[96]	Fabry disease	enzyme replacement therapy (ERT)	US and Canada	Bootstrap	2005 US dollars	Incremental net benefit = $350,000 over 1 year (upper) and $175,000 over 1 year (lower)	ERT is not cost-effective in the current paradigm
Moore et al, 2009[97]	Acromegaly	pegvisomant	UK NHS	Decision analytic	Pounds Sterling (year not specified)	£81,000/QALY (20 years); £65,000/QALY (40 years)	Not considered cost-effective
O'Connor et al, 2002[98]	Achalasia	Botox injetction, pneumatic baloon dilation, or laproscopic esophagomytomy	US	Markov	1997 US dollars	$1,348/QALY (pneumatic balloon dilation vs Botox); $5,376,750/QALY (laproscopic surgery vs Botox)	Pneumatic dilation is the most cost-effective treatment
Petrou et al, 2014[20]	Renal cell cancer	sorafenib (second-line)	Cyprus	Markov	2012 Euros	€102,059/QALY (vs best supportive care)	Not cost-effective, but orphan status may justify reimbursement on an individual basis for certain patients who meet strict criteria

Punekar et al, 2010[99]	Crohn's disease (pediatric)	infliximab	UK NHS	Markov	2006 Pounds Sterling	£14,607/QALY	8-week maintenance is likely to be cost-effective
Reed et al, 2004[100]	Chronic myeloid leukemia (CML)	imatinib	US	Cost effectiveness	2002 US dollars	$57,103/QALY (AWP drug cost); $46,082/QALY (WAC drug cost)	Cost-effective first-line therapy in newly diagnosed chronic-phase CML vs IFN-alpha + cytarabine
Roman et al, 2012[101]	Pulmonary arterial hypertension (PAH)	prostacyclins (IV epoprostenol, inhaled iloprost, SC terprostinil)	Spain	Markov	2009 Euros	Costs: €132,840 (iloprost), €359,869 (treprostinil), €429,775 (epoprostenol); Efficacy: 1.78 QALY (epoprostenol), 1.74 QALY (iloprost), 1.73 QALY (terprostinil); Prostacyclin + iloprost was dominant vs treprostinil	Epoprostenol was most effective, but iloprost less costly with cost savings of 63% vs treprostinil and 69% vs epoprostenol. Iloprost is dominant vs treprostinil
Rombach et al, 2013[21]	Fabry disease	enzyme replacement therapy (ERT)	Netherlands	Markov	2009 Euros	€6.6 million/years free of end-organ damage; €6.1 million/QALY	Affordability of ERT for Fabry disease is questionable
Scott et al, 2007[102]	Chronic lymphocytic leukemia	alemtuzumab	New Zealand (PHARMAC)	Decision analytic	2006 New Zealand dollars	NZ$46,016/QALY	Third-line treatment with alemtuzumab was less costly than fludarabine + cyclophosphamide + rituximab

Shiroiwa et al, 2011[103]	HER-2 positive Advanced gastric cancer	trastuzumab	Japan	Cost effectiveness	2010 Euros and Japanese Yen	HER-2 positive: JPY 12 million/QALY (€110,000); ICH 2+/FISH+ or IHC 3+ patients: JPY 9.1 million/QALY (€83,000); ICH 3+ only: JPY 6.1 million/QALY (€55,000)	Cost effective for IHC 3+ populations
Soini et al, 2009[104]	Metastatic soft-tissue sarcoma	trabectedin	Finland	Markov	Euros (year not specified)	€38,801 - €46,425/QALY	Cost-effectiveness comparable or superior to cancer drugs for non-orphan conditions
Skrepnek et al, 2005[105]	Chronic myeloid leukemia (CML)	imatinib	US	Markov	2004 US dollars	Imatinib: dominant vs allogenic bone marrow transplant	In most cases imatinib was less costly and more efficacious
Soohoo et al, 1997[106]	Cystinosis	cysteamine	US	Decision tree	US dollars (year not specified)	Cysteamine therapy prior to renal failure decreases lifetime costs per patient by $4000. Medication costs are offset by savings from delaying costly procedures like dialysis or transplant.	Cysteamine improves health outcomes and reduces health care costs
Stewart et al, 2001[107]	Amyotrophic lateral sclerosis (ALS)	riluzole	UK NHS	Survival-based	1999 Pounds Sterling	£39,000/LYG, £58,000/QALY	Authors suggest caution in viewing cost-effectiveness of riluzole.

Tang et al, 2012[108]	Crohn's disease	infliximab, adalimumab, certolizumab pegol, natalizumab	US	Decision analytic	2011 US dollars	Monte Carlo simulation (10,000 cases) showed infliximab was cost-effective in 95.2% of simulations, assuming WTP of $100,000/QALY	Patients with refractory moderate-to-severe Crohn's disease should preferentially receive infliximab as the first biologic
Tavakoli et al, 2001[109]	Amyotrophic lateral sclerosis (ALS)	riluzole	UK NHS	Markov	1998 Pounds Sterling	£20,904/QALY	Riluzole merits supporting
Taylor et al, 2012[110]	Chronic myeloid leukemia (CML, imatinib resistant)	dasatinib	UK NHS	Survival-based	Pounds Sterling (year not specified)	£25,700/QALY	Cost-effective alternative to imatinib dose escalation in refractory patients
Teljeur et al, 2012[111]	Variant Creutzfeldt-Jakob disease	prion filtration of red blood cells	Ireland	Cost effectiveness	2010 Euros	€3.7 million/LYG	Not cost-effective, but with blood product safety there is a possible societal preference for risk reduction
Tenorio et al, 2009[112]	Metastatic renal cell carcinoma	sunitinib	Mexico	Markov	US dollars (year not specified)	PFS = $3,767/QALY OS = $5,669/QALY (vs IFN-alpha alone). Sunitinib likely to be cost-saving vs sorafenib and bevacizumab+IFN-alpha	Cost-effective as first-line treatment vs new agents in mRCC
Tilden et al, 2011[113]	Hereditary Angioedema with C1-INH deficiency	self administered icatibant	Australia	Markov	Austrailan dollars (year not specified)	$71,026/QALY	Reasonable level of cost-effectiveness for an orphan indication

Ungar et al, 2011[114]	Juvenile idiopathic arthritis	etanercept, infliximab, adalimumab, abatacept	Canada	Decision analytic	2008 Canadian dollars	Compared to methotrexate: etanercept = $26,061/QALY; adalimumab = $46,711/QALY; abatacept = $16,204/QALY; infliximab = $31,209/QALY	Biologics are more effective than methotrexate, but at high cost. Long term data are needed to better evaluate the cost effectiveness
van Dussen et al, 2014[115]	Type 1 Gaucher disease	enzyme replacement therapy (ERT)	Netherlands	Markov	2009 Euros	€434,416/year free of end-organ damage; €884,994/QALY	Clinically effective, but low cost-effectiveness (High ICERs) under traditional evaluation is under debate
Vargas-Romero et al, 2013[116]	Osteosarcoma	mifamurtide	Mexico	Markov	US dollars (year not specified)	$56,746.14/LYG; $55,837.7/QALY	Cost-effective in pediatric patients
Vitova et al, 2012[117]	Multiple myeloma and lymphoma	plerixafor (for blood stem cell mobilization)	Czech Republic	Decision tree	Euros (year not specified)	Success rates: POD = 94.9%, SSP = 94.7%, SSNP = 84.7%; Costs: POD = €5,736, SSP = €6,416, SSNP = €4,475; Direct costs per successfully-treated average patient: POD = €6,046, SSP = €6,776, SSNP = €5,641; Cost of first mobilization attempt with G-CSF = €3,905 per patient; Cost of re-mobilization of a poor mobilizer with G-CSF = €4,629,	More cost-effective "on demand" (POD) during early mobilization rather than subsequent re-mobilization

						with plerixafor added = €13,354; total cost of plerixafor used on-demand in a sub-cohort of poor mobilisers was €13,645	
Walters et al, 2001[118]	Renal transplant	basiliximab prophylaxis	healthcare purchaser perspective (multiple countries)	Not specified	1997 US dollars	$4,669/treatment failure	Cost-effective
Warren et al, 2004[119]	Chronic myeloid leukemia (CML)	Imatinib mesylate vs hydroxyurea	UK NHS	Markov	2001 Pounds Sterling	£38,468/QALY	Considerable health benefits, but considerable cost to the payer
Wlodarczyk et al, 2006[120]	Idiopathic pulmonary artery hypertension	bosentan	Australia	Patient level simulation	2001 Australian dollars	$A84,231/LY saved (year 5), $A55,927/LY saved (year 15)	Potentially cost-effective
Wolfson et al, 2014[121]	Multi- and extensively drug-resistant tuberculosis	bedaquiline	Germany	Markov	2014 Euros	€33,357/QALY; €17,915/QALY for extensively drug-resistant	Adding bedaquiline to background anti-TB therapy is cost-effective, and may be cost saving in multi- and extensively drug-resistant TB

Wu et al, 2012[122]	Renal cell cancer	IFN-alpha, interleukin-2, interleukin-2 + IFN-alpha, sunitinib, bevacizumab + IFN-alpha	China	Markov	2011 US dollars	bevacizumab + IFN-alpha = dominated; interleukin-2 + IFN-alpha = dominated; Sunitinib = dominant.	Traditional cytokine therapy is the cost-effective option. In more developed regions of China, sunitinib + patient assistant program may be cost-effective

9. Appendix B

Eculizumab for treatment of paroxysmal nocturnal hemoglobinuria: a systematic review and meta-analysis

9.1. Abstract

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a type of hemolytic anemia caused by loss of regulatory proteins in the complement system. Eculizumab is a monoclonal antibody that binds to C5 to inhibit the terminal complement pathway. Objectives: The aim of this study is to evaluate the clinical efficacy reported in published clinical trials of eculizumab in reducing the number of transfusions required to maintain homeostasis, and in reducing the number of thrombotic events occurring in patients with paroxysmal nocturnal hemoglobinuria. Search Methods: Literature searches were conducted in MEDLINE®, EMBASE®, and Web of Science® databases using the key words paroxysmal nocturnal hemoglobinuria and eculizumab. Studies conducted in children and adults with PNH and published in English were included. Data Collection and Analysis: References were evaluated for inclusion based on title, abstract, then full publication review. Outcomes of interest were the number of patients who were transfusion independent before and after treatment, and the number of thrombotic events reported before and after treatment. A meta-analysis was conducted using Review Manager software. Results: A total of 700 unique references were screened for eligibility. Ten articles initially remained for full evaluation. An additional two references were identified during full article review. Four articles presenting clinical trial data from the same patient sample as those in a long-term extension studies were identified as duplicates and excluded. This left six studies included in the final analysis. Limitations: One major limitation is the low study quality due to small sample sizes and lack of randomization or comparator treatments. Conclusions: Overall, this analysis strongly

favors the use of eculizumab treatment in patients with PNH to reduce the number of transfusions required and to reduce the risk of thrombosis, which is a major cause of morbidity and mortality in this patient population.

9.2. Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a non-malignant type of hemolytic anemia caused by loss of regulatory proteins in the complement system.[123] Complement is a component of immune function and is in a continuous state of activation in PNH resulting in chronic complement-mediated hemolysis of erythrocytes. As a component innate immunity, the complement system is activated by the presence of a pathogen and initiates an amplification cascade to activate the membrane attack complex (MAC), which lyses pathogenic cells.

Patients with PNH suffer from fatigue, hemoglobinuria, dyspnea, abdominal pain, and are at substantial risk of thrombosis, which is the leading cause of death in PNH. It is estimated that the 5-year mortality rate is approximately 35%, and 50% of diagnosed patients die within 10 to 15 years.[124] Eculizumab is a monoclonal antibody that binds to C5 to inhibit the terminal complement pathway. It compensates for the CD59 deficiency, though not the CD55 deficiency, seen in PNH patients. Since eculizumab does not address the CD55 protein deficiency, some PNH patients still experience some extravascular hemolysis, and over half of patients develop a positive direct antiglobulin test due to elevated reticulocytes and mild-to-moderate anemia.

9.3. Objectives

The aim of this study is to evaluate the clinical efficacy reported in published clinical trials of eculizumab in reducing the number of transfusions required to maintain homeostasis, and in reducing the number of thrombotic events occurring in patients with paroxysmal nocturnal hemoglobinuria.

9.4. Methods

9.4.1. Eligibility Criteria

Studies selected for this review included clinical trials conducted to assess eculizumab in children or adults with PNH. Paroxysmal nocturnal hemoglobinuria is a rare disease, so it is reasonable to expect that any clinical trials may not be randomized, placebo controlled, or tested against a comparator; therefore, any study assessing eculizumab in PNH was included regardless of comparator. Studies published solely as an abstract with no corresponding full manuscript were not considered in this analysis. Outcomes of interest included frequency of red blood cell transfusion and the number of thrombotic events occurring after treatment with eculizumab compared to baseline in the same patient population.

9.4.2. Search Methods

Literature searches were conducted in MEDLINE®, EMBASE®, and Web of Science® databases using the following key words: paroxysmal nocturnal hemoglobinuria and eculizumab. Only studies published in English were included in this analysis. Trials conducted in children and adults were included. Exclusion criteria included studies not conducted in humans, review articles other than systematic reviews from which source references could be obtained, and opinion or editorial publications.

9.4.3. Quality Assessment of Studies

All studies included in this analysis were evaluated for quality based on criteria for non-randomized studies. The assessment evaluated the study design based on the choice of comparison group, demographic and clinical equality of any comparison groups, attrition bias regarding how patients who dropped out or were lost to follow-up were reported, prospective design of outcomes and data collection, and limiting risk of selection bias. Risk of bias was also evaluated for each study to identify sources of bias including selection bias, attrition bias, reporting bias, performance bias, and detection bias.

9.4.4. Data Collection and Analysis

References were evaluated for inclusion based on title, abstract, then full publication review. Included references were abstracted and coded according to a standardized format designed for this study. The data of interest to be extracted were number of subjects, median age, percent female, measured hemoglobin at baseline and after treatment, number of subjects who were transfusion independent before and after treatment, and the number of thrombotic events reported before and after treatment. A meta-analysis was conducted based on the outcomes of interest using Review Manager software (RevMan Version 5.1.0, The Cochrane Collaboration).

9.4.5. Summary Measures

Results from each study were pooled and evaluated for heterogeneity with the I^2 statistic. The statistical difference between treatment and no treatment was evaluated with the Z statistic to test for overall treatment effect. Outcome measures were reported as Odds Ratios (OR) and Risk Difference (RD) using both fixed and random effects models. A 95% confidence interval was applied to all outcome measures.

9.5. Results

9.5.1. Study Selection

A total of 1,353 records were retrieved from the database searches, and after removing duplicates, 700 unique references were screened for eligibility based on predefined inclusion criteria (**Figure B-1**). References were screened for eligibility based initially on titles, and a total of 456 records were eliminated. The remaining 244 references were evaluated based on the published abstract, and an additional 236 were excluded leaving 10 articles remaining for full evaluation. An additional two references were identified during full article review that met study criteria and were included in the final review. Upon full manuscript review, only the most recent publications of any particular clinical trial were included, and those reporting preliminary,

interim, or data collected prior to those reported in subsequent studies were excluded in the final analysis. Four articles presenting clinical trial data from the same patient sample as those in a long-term extension studies were identified as duplicates and excluded form the final analysis. This left six clinical trail manuscripts included in the final meta-analysis described here.

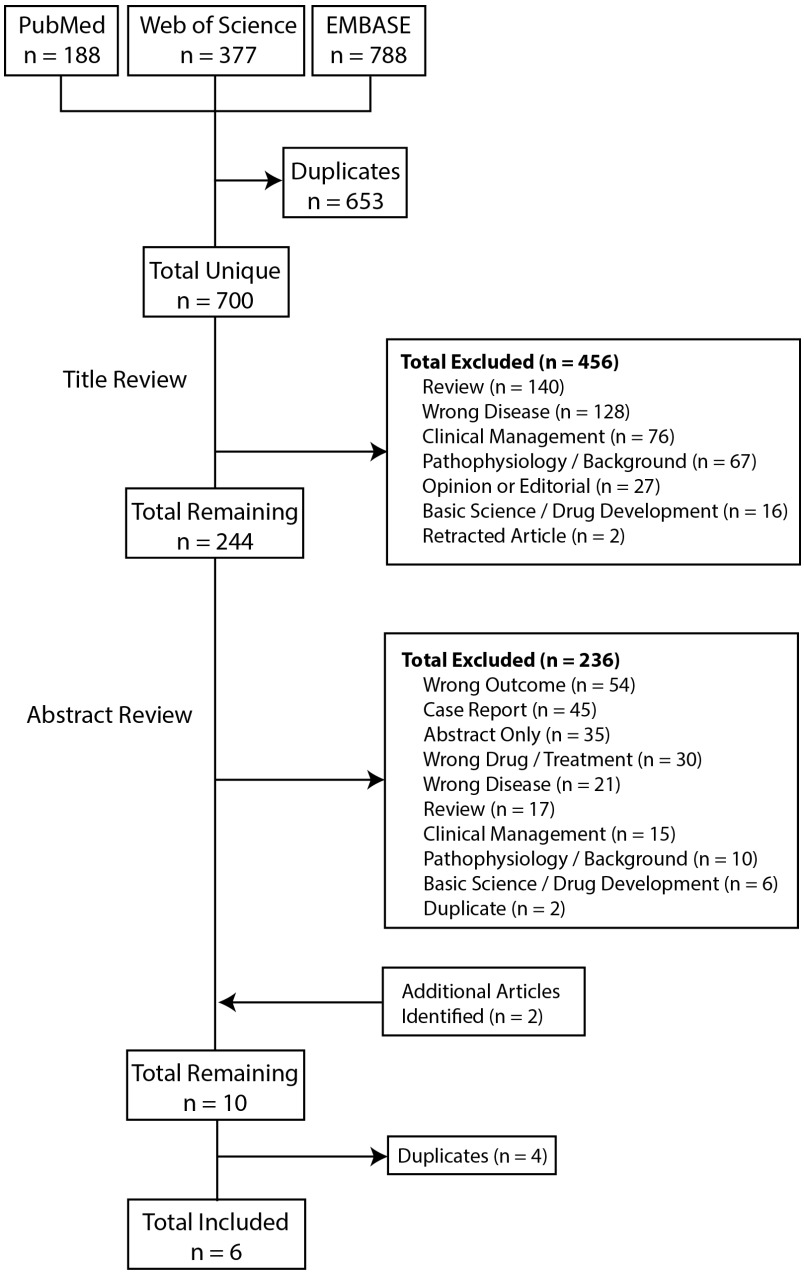

Figure B-1. Attrition diagram describing the study inclusion based on the inclusion criteria.

9.5.2. Study Quality and Risk of Bias

Overall, studies were considered to be of moderate quality, based on the criteria used in this analysis. All study designs were nearly identical. The average score was 10 out of a possible 14 points, with a higher score reflecting a more robust and higher quality study design. Within the constraints of designing studies that are inherently small due to the rarity of disease, the studies were well designed overall. A complete description of the measures and quality assessments for each study are provided in Appendix A. Risk of bias was evaluated for each study and reported in Table B-1.

Table B-1. Assessment of risk of bias in six studies included in this analysis.

Bias	Hillmen 2013	Höchsmann 2012	Kanakura 2013	Kelly 2011	Peffault de Latour 2015	Röth 2011
Selection	X	X	X	X	X	X
Performance	X	X	X	X	X	X
Detection			X		X	X
Attrition			X		X	X
Reporting			X		X	X

Overall, the eligible studies included in this analysis, all had a risk of selection bias primarily due to lack of randomization. In some studies, the patients may be described as a convenience sample coming from a single clinic or practice, or were grouped based on geographic area. There was no blinding in any of the studies, which may result in risk for performance bias; however, as reported, all patients were treated in a similar manner so there are unlikely to be substantial differences in overall care provided. There were no systematic difference is the methods for measuring outcomes, so the risk of detection bias is likely low, and withdrawals from the studies were rare. Since each cohort acted as its own control by comparing baseline measures to the outcomes reported after treatment, there can be no systematic difference in attrition. There was no overt evidence of reporting bias, as all outcomes described in the methodology were reported. It is impossible to know if there is unreported data in these published trials without searching for unpublished data, which was beyond the scope of this

review. Three studies have a very small sample size, which may lead to reporting or detection bias simply by studying too few subjects to identify clinical signals.

9.5.3. Study Characteristics

A total of six studies were included in the final analysis. None of the studies were randomized, and none included a comparator arm. Outcome measures were based on patient characteristics reported prior to treatment with eculizumab, and the same measures observed after treatment. Four studies included complete data for the outcome of interest. One study did not report thrombotic events, and another study did not report measured hemoglobin levels. A complete table listing the data extracted from each study can be found in Appendix B of this report.

9.5.4. Meta-Analysis Results

Data were analyzed for two outcomes: number of patients who were transfusion independent before and after treatment, and number of patients experiencing thrombotic events before and after treatment. The measures were dichotomous and recorded as counts. Odds ratios and risk differences were calculated and used to determine an overall effect estimate.

9.6. Transfusion Independence

Transfusion independence was assessed by the number of individual patients who did not require transfusion with packed red blood cells during the year prior to treatment, and in the most recent year following initiation of treatment with eculizumab.

The odds of transfusion independence were significantly greater after treatment with eculizumab compared to baseline. There was moderate heterogeneity with an I^2 value of 69% ($p = 0.007$); however the odds ratio was statistically significantly different with $p < 0.00001$

favoring eculizumab. **Figures B-2 and B-3** show forest plots for the odds using fixed and random effects, respectively. The total effect estimate has a wider 95% confidence interval when the random effects model was applied, compared to the estimate with fixed effects. A funnel plot of the odds ratio shows a minimal risk of publication bias as each study (open circles) falls roughly within the funnel range. Three of the studies had very small sample sizes of 19, 22, and 27 patients, and therefore the results are less reliable and lie on the perimeter of the funnel plot (**Figure B-4**).

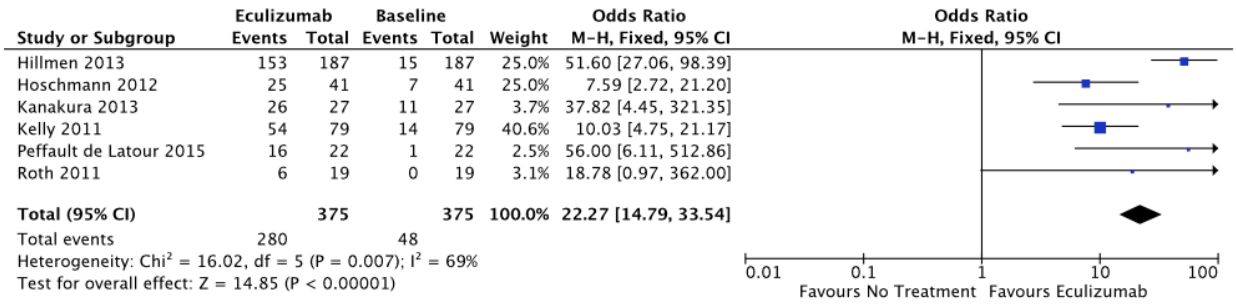

Figure B-2. Forest plot for the odds ratio of transfusion independence before and after treatment with eculizumab, using a fixed-effects model.

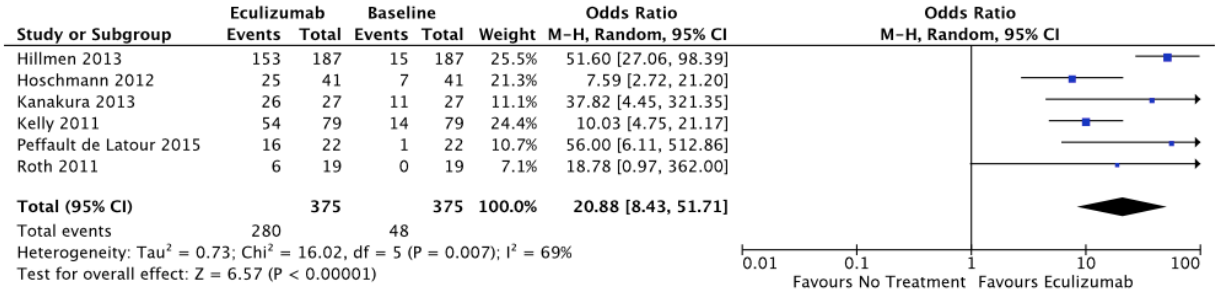

Figure B-3. Forest plot for the odds ratio of transfusion independence before and after treatment with eculizumab, using a random-effects model.

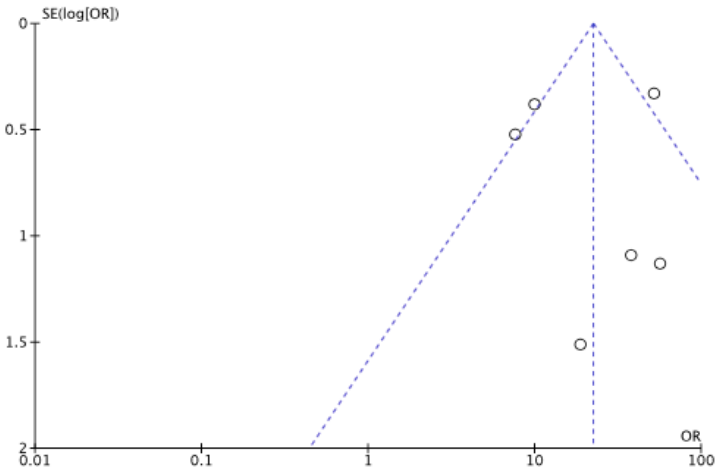

Figure B-4. Funnel plot describing the odds ratio of transfusion independence with eculizumab.

The risk difference of transfusion independence was significantly greater after treatment with eculizumab compared to baseline. In this case the "risk" refers to the positive effect of transfusion independence. There was more heterogeneity when considering the risk difference, with an I^2 value of 81% ($p < 0.0001$). The effect estimate was statistically significantly different with $p < 0.00001$ favoring eculizumab treatment. **Figures B-5 and B-6** show forest plots for the risk difference using fixed and random effects, respectively. The total effect estimate has a wider 95% confidence interval when the random effects model was applied, compared to the estimate with fixed effects.

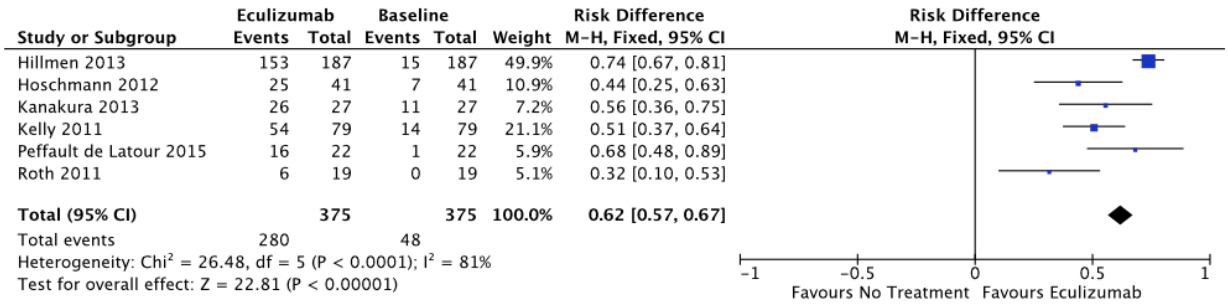

Figure B-5. Forest plot for the risk difference of transfusion independence before and after treatment with eculizumab, using a fixed-effects model.

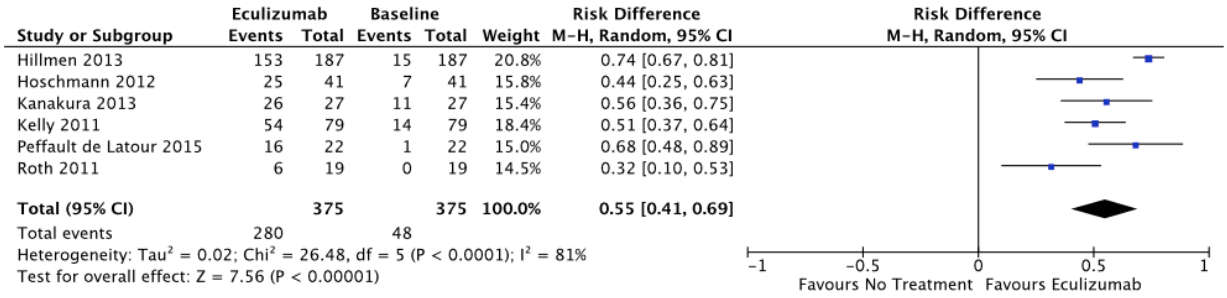

Figure B-6. Forest plot for the risk difference of transfusion independence before and after treatment with eculizumab, using a random-effects model.

9.7. Thrombotic Events

Thrombotic events were assessed by the number of individual patients who experience any thrombosis during the year prior to treatment, and in the most recent year following initiation of treatment with eculizumab. Only four of the six included studies reported thrombotic events.

The odds of a thrombotic event was significantly greater after treatment with eculizumab compared to baseline. There was no heterogeneity with an I^2 value of 0% ($p = 0.92$). The odds ratio was statistically significantly different with $p < 0.00001$ favoring eculizumab. **Figures B-7 and B-8** show forest plots for the odds using fixed and random effects, respectively. There was no difference when using fixed or random effects models. A funnel plot of the odds ratio shows there is no clear risk of publication bias as all four of the studies reporting the outcome of thrombosis are very close to the midline and well within the boundaries of the funnel (**Figure B-9**).

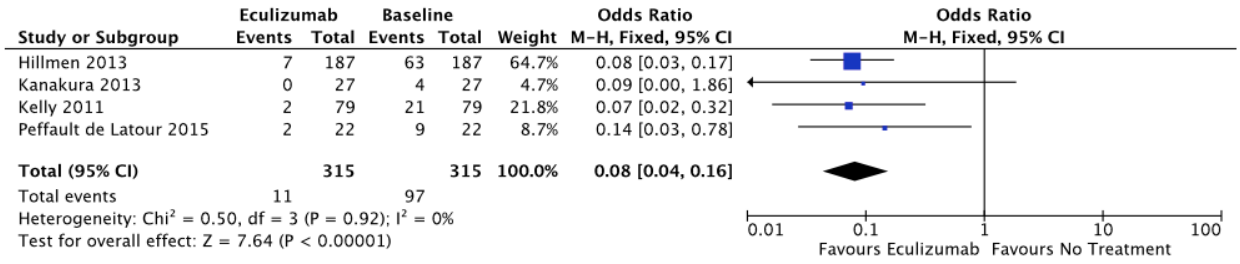

Figure B-7. Forest plot for the odds ratio of thrombotic events before and after treatment with eculizumab, using a fixed-effects model.

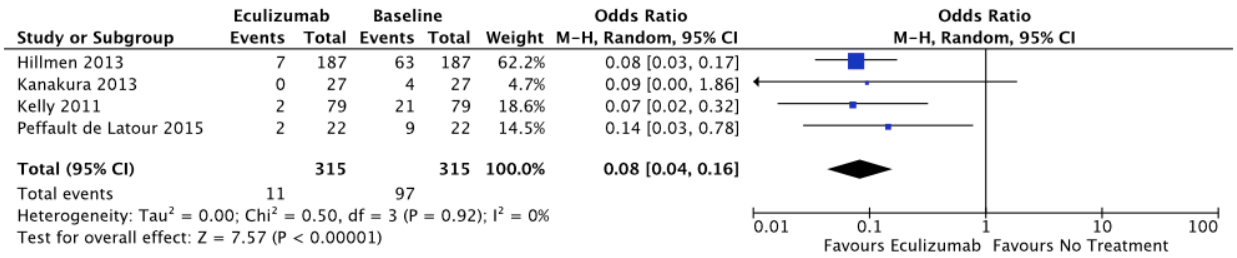

Figure B-8. Forest plot for the odds ratio of transfusion independence before and after treatment with eculizumab, using a random-effects model.

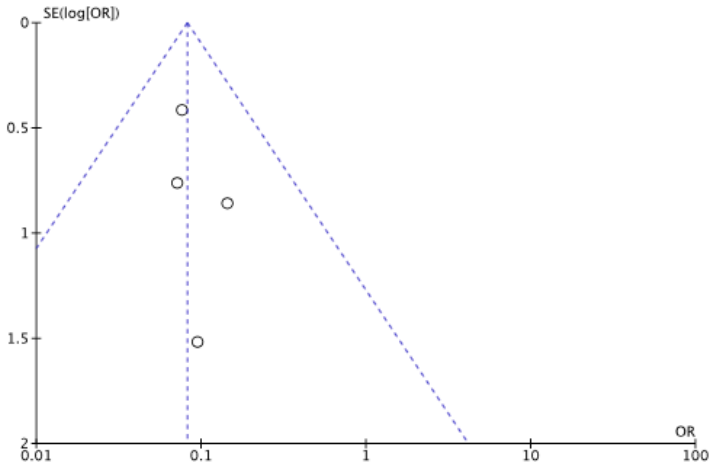

Figure B-9. Funnel plot describing the odds ratio of transfusion independence with eculizumab.

The risk difference of a thrombotic event was significantly less after treatment with eculizumab compared to baseline. In this case the "risk" refers to risk of thrombosis. There was slightly more heterogeneity when considering the risk difference, with an I^2 value of 23% ($p = 0.27$). The overall effect estimate was statistically significantly different with $p < 0.00001$ favoring eculizumab treatment. **Figures B-10 and B-11** show forest plots for the risk difference using fixed and random effects, respectively. There was no difference when using fixed or random effects models.

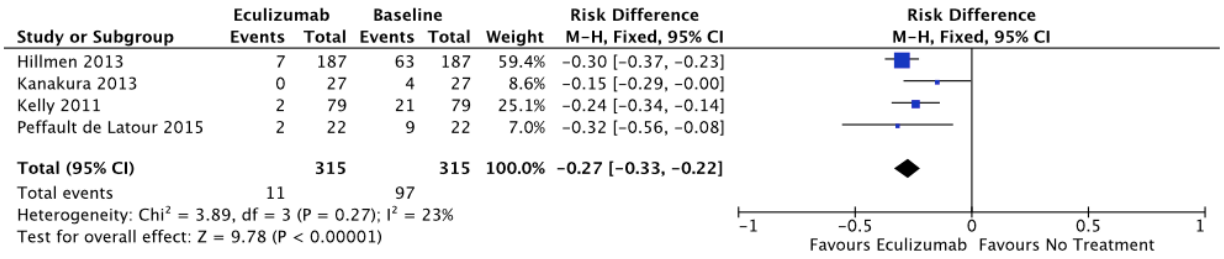

Figure B-10. Forest plot for the risk difference of a thrombotic event before and after treatment with eculizumab, using a fixed-effects model.

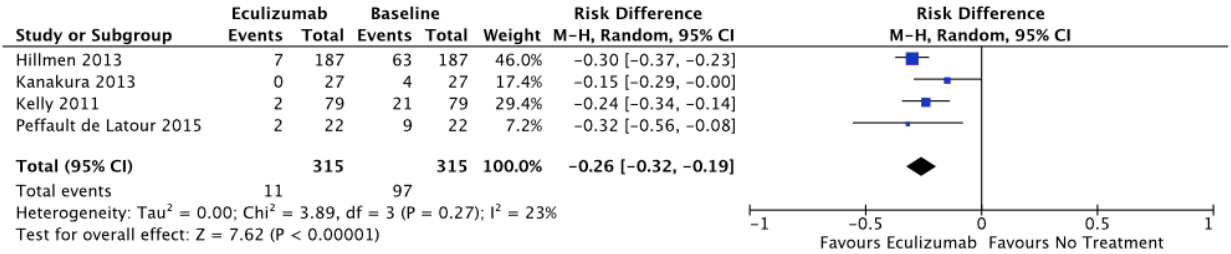

Figure B-11. Forest plot for the risk difference of a thrombotic event before and after treatment with eculizumab, using a random-effects model.

9.8. Discussion

Here I report a systematic review and meta-analysis to describe the efficacy of eculizumab in reducing the transfusion requirements in patients with PNH, and also in reducing the rate of thrombotic events that are among the leading causes of mortality in this patient population. The studies included in this analysis were not randomized controlled trials, but each study compared a cohort of patients with PNH at baseline, with the outcome measures reported after treatment with eculizumab. The results of this meta-analysis show there is a statistically significant increase in the number of patients who were transfusion independent with eculizumab treatment compared to baseline. The results also show a statistically significant decrease in the number of patients experiencing a thrombotic event with eculizumab treatment compared to baseline.

One major limitation to this analysis is the low study quality. The disease under evaluation is rare, so study sample sizes were limited by the number of available patients with PNH. One initial study included a placebo comparator, but the long-term extension of that study did not include comparators, and no other studies included comparator treatments. Instead each patient served as his or her own control in comparing outcome measures reported before and after treatment with eculizumab. Another limitation is the relatively few number of published studies available for analysis. This reflects, in part, the relative newness of the treatment under evaluation, and also the rarity of the disease precludes conducting a large number of trials.

There are a growing number of published case reports or case series describing patient and physician experience in treating PNH with eculizumab. While the clinical trial data is limited due to the rarity of disease and associated challenges of conducting clinical trials with the statistical power to which we have grown accustomed with trials assessing treatments in more common diseases, it may be informative to conduct a meta-analysis or pooled analysis of the individual case reports. This data may not be as robust as would emerge from a controlled clinical trial, but it would likely provide information regarding real-world management of PNH, as well as further description of the natural history of PNH under treatment with eculizumab. Such a study may also alert investigators and practitioners to clinical benefit in standard practice, and may identify safety signals that emerge under typical clinical care.

Overall, this analysis strongly favors the use of eculizumab treatment in patients with PNH to reduce the number of transfusions required and to reduce the risk of thrombosis, which is a major cause of morbidity and mortality in this patient population.

9.9. Appendix B-1. Criteria and results of study quality assessment**.**

REFERENCE: Hillmen et al. Br J Haematol. 2013;162:62-73.

	Questions	*Reviewer comments*	*Score (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
Equal group demographic susceptibility	-Demographics are reported and are similar between groups.	Since each individual acts as his or her own control, there is no difference in demographics	2
Equal group clinical susceptibility	-Doses + durations of treatment are reported and are similar between groups. -Additional medications used are similar between groups.	Dosage regimens were the same for all patients. Use of other medications was not reported	1
Dropout / exclusion analysis	-The same exclusion/inclusion criteria are applied to both groups -Attrition bias: dropout/lost to follow up are reported and do not appear differential.	Only one cohort of patients. There was minimal dropout, and all were reported	2
Adherence monitoring	- How well did patients follow the dosing regimen?	Treatment was delivered by infusion in a clinic so there were no questions of adherence among patients who remained on treatment	2
Outcome assessment	-Outcomes are prospectively defined -Outcomes are assessed by blinded reporters, or other effort to reduce detection bias.	Outcomes were prospectively designed, but there was no blinding	1
Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

Each item is scored using the following scale: 2= adequate and well described; 1= partially adequate or partially described; 0= inadequate or not described. The total quality score for each study is the sum of the individual item scores for that study.

REFERENCE: Höchsmann et al. Vox Sang. 2012;102:159-66.

	Questions	*Reviewer comments*	*Score[1] (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
Equal group demographic susceptibility	-Demographics are reported and are similar between groups.	Since each individual acts as his or her own control, there is no difference in demographics	2
Equal group clinical susceptibility	-Doses + durations of treatment are reported and are similar between groups. -Additional medications used are similar between groups.	Dosage regimens were the same for all patients. Use of other medications was not reported	1
Dropout/ exclusion analysis	-The same exclusion/inclusion criteria are applied to both groups -Attrition bias: dropout/lost to follow up are reported and do not appear differential.	Only one cohort of patients. There was minimal dropout, although 7 deaths occurred, and all were reported	2
Adherence monitoring	- How well did patients follow the dosing regimen?	Treatment was delivered by infusion in a clinic so there were no questions of adherence among patients who remained on treatment	2
Outcome assessment	-Outcomes are prospectively defined -Outcomes are assessed by blinded reporters, or other effort to reduce detection bias.	Outcomes were prospectively designed, but there was no blinding	1
Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

REFERENCE: Kanakura et al. Int J Hematology. 2013;98:406-16.

	Questions	*Reviewer comments*	*Score[1] (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
Equal group demographic susceptibility	-Demographics are reported and are similar between groups.	Since each individual acts as his or her own control, there is no difference in demographics	2
Equal group clinical susceptibility	-Doses + durations of treatment are reported and are similar between groups. -Additional medications used are similar between groups.	Dosage regimens were the same for all patients. Use of other medications was not reported	1
Dropout/ exclusion analysis	-The same exclusion/inclusion criteria are applied to both groups -Attrition bias: dropout/lost to follow up are reported and do not appear differential.	Only one cohort of patients. There was minimal dropout, and all were reported	2
Adherence monitoring	- How well did patients follow the dosing regimen?	Treatment was delivered by infusion in a clinic. The authors reported no patients missed an infusion	2
Outcome assessment	-Outcomes are prospectively defined -Outcomes are assessed by blinded reporters, or other effort to reduce detection bias.	Outcomes were prospectively designed, but there was no blinding	1
Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

REFERENCE: Kelly et al. Blood. 2011;117:6786-92.

	Questions	*Reviewer comments*	*Score[1] (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
Equal group demographic susceptibility	-Demographics are reported and are similar between groups.	Since each individual acts as his or her own control, there is no difference in demographics	2
Equal group clinical susceptibility	-Doses + durations of treatment are reported and are similar between groups. -Additional medications used are similar between groups.	Dosage regimens were the same for all patients. Use of other medications was not reported	1
Dropout/ exclusion analysis	-The same exclusion/inclusion criteria are applied to both groups -Attrition bias: dropout/lost to follow up are reported and do not appear differential.	Only one cohort of patients. There was minimal dropout, and all were reported	2
Adherence monitoring	- How well did patients follow the dosing regimen?	Treatment was delivered by infusion in a clinic so there were no questions of adherence among patients who remained on treatment	2
Outcome assessment	-Outcomes are prospectively defined -Outcomes are assessed by blinded reporters, or other effort to reduce detection bias.	Outcomes were prospectively designed, but there was no blinding	1
Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

REFERENCE: Peffault de Latour et al. Blood. 2015;125:775-83.

	Questions	*Reviewer comments*	*Score[1] (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
Equal group demographic susceptibility	-Demographics are reported and are similar between groups.	Since each individual acts as his or her own control, there is no difference in demographics	2
Equal group clinical susceptibility	-Doses + durations of treatment are reported and are similar between groups. -Additional medications used are similar between groups.	Dosage regimens were the same for all patients. Use of other medications was not reported	1
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Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

REFERENCE: Röth et al. Int J Hematology. 2011;93:704-14.

	Questions	*Reviewer comments*	*Score[1] (0/1/2)*
Comparison group choice	-A clinically comparable (e.g. low risk of selection bias) comparison group is chosen. -Identifies potential confounders + method of addressing (exclusions, analysis)	There is inherent selection bias due to including only PNH patients receiving eculizumab	1
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Prospective design	-The design and data collection is a prospective cohort (+2), a retrospective cohort with well-defined groups (+1) or a cohort with historical controls (0).	The cohort is a combination of retrospective (baseline control measures) and prospective (outcomes after treatment), and were well defined	1
			Total score (10/14)

9.10. Appendix B-2. Data abstraction from six studies included in this analysis.

Reference	N	Female, n (%)	Age	Hemoglobin (Median g/dL)		Transfusion Independence, n (%)		Patients with Thrombosis, n (%)	
			Median (range)	Baseline	Treated	Baseline	Treated	Baseline	Treated
Hillmen et al. Br J Haematol. 2013;162:62-73.[125]	187	106 (54.4)	39.7 (18.3-85.0)	9.37	10.4	15 (8.2)	153 (82.1)	63 (33.7)	7 (3.7)
Höchsmann et al. Vox Sang. 2012;102:159-66.[126]	41	23 (56.1)	40 (18-80)	9.2 (5.0-14.4)	10.3 (5.9-14.9)	7 (17)	25 (61)	NR	NR
Kanakura et al. Int J Hematology. 2013;98:406-16.[124]	27	14 (51.9)	Mean 48.3 (26.8-70.8)	7.9 (SE 0.30)	10.3 (SE 0.41)	11 (40.7)	26 (96)	4 (14.8)	0 (0)
Kelly et al. Blood. 2011;117:6786-92.[127]	79	39 (49.4)	46 (14-84)	NR	NR	14 (19)	54 (72)	21 (26.5)	2 (2.5)
Peffault de Latour et al. Blood. 2015;125:775-83.[128]	22	15 (68)	42 (21-72)	8.2 (SD 1.02)	10.1 (SD 1.02)	1 (4.5)	16 (72.7)	9 (40.1)	2 (9.1)
Röth et al. Int J Hematology. 2011;93:704-14.[129]	19	8 (42)	37 (19-83)	9.2 (7.1-11.3)	10.1 (7.0-12.7)	0 (0)	6 (31.6)	7 (37)	NR