To the Editor:

In the January 2015 issue of the Journal, Arnold et al. [1] reported an economic evaluation and concluded that allogeneic hematopoietic cell transplantation (alloHCT) is beneficial and cost-effective for children with sickle cell disease (SCD). When trying to comprehend the article, we encountered several challenges. Here we describe the most prominent ones.

First, the competing alternatives should have been described in more detail. Relevant characteristics of the study participants (ie, of the intervention and control groups) are only poorly stated. In particular, the description of the control subjects lacks clarity. For both clinical studies and economic evaluations, a thorough description of the control group is as important as the description of the intervention group [2].

In the study, the subjects were categorized into 2 main groups, the alloHCT group and the control group. The alloHCT group was further split into 3 subgroups: pre-alloHCT, during alloHCT, and post-alloHCT. The alloHCT group comprised 26 patients. The pre-alloHCT and post-alloHCT groups are reported together, a total of 14 patients with similar demographic and disease characteristics. This seems illogical, because the alloHCT group was followed for 365 days during the alloHCT period. The mean age difference between the pre-alloHCT and post-alloHCT groups should be roughly 1 year. In addition, the authors mention different reasons why patients dropped out or joined both the pre-alloHCT and post-alloHCT groups. Thus, the actual sample sizes and other patient characteristics must have differed.

Only for the alloHCT group is a clear timespan mentioned for which costs and health care utilization data were collected. How long all 3 groups were followed is unclear. Furthermore, it is left open whether controls were matched according to length of stay or other criteria.

Second, the intervention's effectiveness (in this case health-related quality of life [HRQoL] and overall survival) should have been studied and described in a replicable way. This was done in a questionable manner, however. Participants in the post-alloHCT group were questioned about HRQoL using validated instruments. The reported interval between intervention and questioning was extremely long, however (ie, 6 years on average); thus, it is highly likely that recall bias was introduced [3]. Leaving aside the fact that the elicited values likely were not suitable for sound calculations, they were not used for the economic evaluation in any case. Instead, utility scores were based on a “personal communication.” The authors provide no explanation for why they elicited HRQoL values but did not use them in the analysis.

Third, an incremental analysis of costs and consequences of alternatives should have been performed. Although this was formally done, the (statistical) analysis was executed incorrectly.

In their Table 3, Arnold et al. report incremental cost-effectiveness ratios (ICERs) of $287,893, $116,246, $48,788, and $13,904, for days +45, +90, +180, and +365, respectively. ICERs are calculated by differences in costs ($C_1 - C_0$) divided by the differences in effects ($E_1 - E_0$):

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$
Whereas the authors should have obtained incremental costs and effects by subtracting the costs and effects for the intervention and control groups, they obtained the ICERs reported in Table 3 by dividing the median costs of the intervention group by the respective HRQoL utility. Thus, implicitly, the authors assumed that the control group would have no costs and a utility score of 0.

An example for day +45 shows the following calculation:

\[
\frac{204,404 - 0}{0.71 - 0} = 287,893.
\]

This does not seem plausible, for two reasons. On the one hand, costs that are larger than 0 are mentioned for the control group in the Appendix. On the other hand, a utility score of 0 equals death for the EQ-5D [4]. Moreover, the authors show in their Figure 3 that HRQoL utilities did not differ much between the groups. However, this result should be interpreted with caution, because in Figure 3C it appears as if utility ranges exceed 1 (which is not possible by definition). Furthermore, median costs should not be used for this purpose. Cost data are usually highly skewed [5], and thus the mean is the most informative and appropriate measure for the total costs [6,7].

Finally, the authors did not state the basis on which they interpreted their results as being cost-effective. Any (treatment) alternative can be considered “cost-effective” when the ICER is below a certain threshold that one is willing or able to pay for a certain gain in effects. Health economists often refer to this as the “willingness to pay” (WTP) for 1 life year gained in full health (ie, 1 quality-adjusted life year [QALY]). Although there is not one universally accepted WTP, in The Netherlands a threshold value of €20,000 to €80,000 is used [8], whereas in the United Kingdom a value of £20,000 to £30,000 per QALY has been accepted [9]. For the United States, a threshold of US $50,000 to $100,000 per QALY is often mentioned in the medical literature [10].

The authors state a threshold value of US $60,000, but do not clearly indicate that it represents the chosen WTP. The reported total ICER is US $466,830. With none of the currently used thresholds, or even the authors’ own threshold, would this be considered a cost-effective alternative. As a result, the conclusion of the study, as well as the article’s title, are misleading.

Although alloHSCT indeed might be beneficial and cost-effective for children with SCD, the results presented by Arnold et al. are not able support this claim, owing mainly to the impaired methodology used. To derive valid and meaningful conclusions, we offer to jointly reassess the article according to conventional methods for economic evaluation.

ACKNOWLEDGMENTS
Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES
10. Shiroiwa T. International survey on willingness to pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ. 2010;19:422.

Reply to: Using Appropriate Methods in Cost-Effectiveness Analyses: The Case of Allogeneic Hematopoietic Cell Transplantation in Sickle Cell Disease

Staci D. Arnold

Aflac Cancer and Blood Disorders Center, Children’s Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia

In reply:
I greatly appreciate the thoughtful review of Thielen et al [1]. It is the critical appraisal of scientific literature that...