The Cost of Costing Treatments Incorrectly: Errors in the Application of Drug Prices in Economic Evaluation Due to Failing to Account for the Distribution of Patient Weight

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A B S T R A C T

Background: The cost of pharmaceuticals dosed by weight or body surface area (BSA) can be estimated in several ways for economic evaluations. A review of 20 recent National Institute for Health and Care Excellence appraisals showed that 17 of them took the mean weight or BSA of patients, 2 costed the individual patient data from trials, and 2 fitted a distribution to patient-level data. **Objectives:** To investigate the estimated drug costs using different methodologies to account for patient characteristics for pharmaceuticals with a weight- or BSA-based posology. The secondary objective was to explore the suitability of general population data as a proxy for patient-level data. **Methods:** Patient-level data were pooled from three clinical trials and used to calculate a hypothetical cost per administration of eight licensed pharmaceuticals, applying the three methods used in recent National Institute for Health and Care Excellence appraisals. The same analysis was performed using data from the Health Survey for England (in place of patient-level data) to investigate the validity of using general population data as a substitute for patient-level data. **Results:** Compared with using patient-level data from clinical trials, the mean patient characteristics (weight or BSA) led to an underestimation of drug cost by 6.1% (range +1.5% to −25.5%). Fitting a distribution to patient-level data led to a mean difference of +0.04%. All estimates were consistent using general population data. **Conclusions:** Estimation of drug costs in health economic evaluation should account for the distribution in weight or BSA to produce accurate results. When patient data are not available, general population data may be used as an alternative.

Keywords: cost-effectiveness, drug costs, health technology appraisal, method of moments, micro-costing.

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Introduction

Cohort-based health economic models typically consider the "average" patient to be a representative of the population of interest. When the posology for the dosing of drugs is based on weight or body surface area (BSA), it is common for the costs of administering a single dose to be based on the weight or BSA of the average patient. Using the characteristics of the average patient, however, does not take into account the distribution seen in the patient population.

We reviewed 60 recent single technology appraisals of the National Institute for Health and Care Excellence, finding 20 with drugs dosed on the basis of weight or BSA when the method of costing is identified. Seventeen of them calculated costs on the basis of the mean weight or mean BSA, two used patient data costed individually, and one used a parametric distribution fitted to patient-level data. In the review, only two academic groups

(Liverpool Evidence Review Group and the School of Health and Related Research) raised the issue of inappropriate costing. This review shows that not only are most analyses using an inaccurate method to estimate drug costs, but this was also rarely challenged by economic assessors. Given drug acquisition costs are often one of the key determinants of cost-effectiveness, accurately estimating these is fundamental to the integrity of economic evaluation in health care.

Our objective was to examine the impact of different methods of costing treatments on the quantification of drug costs per administration of interventions with weight- or BSA-based dosing. To achieve this, we used patient-level data from three clinical trials to calculate the costs of eight drugs on the basis of either weight or BSA. We used three approaches: the parameter mean (termed the parameter mean approach); costing of patients individually and then taking the average cost (trial patient costing); and fitting a parametric distribution to weight or

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BSA and then evaluating the average cost (fitted-distribution costing).

As the trial patient costing and fitted-distribution costing approaches required patient-level data, we replicated the analysis using publicly available general population data to establish whether general population data can be a substitute in the absence of patient-level data.

Methods

Data Sources

Patient-level data from the following three clinical studies were obtained to allow the analysis of different disease areas to enhance the generalizability of our findings: CA184-024, which enrolled 681 patients with advanced melanoma [1]; AI444-040, an open-label trial of 211 patients with chronic hepatitis C [2]; and CA180-034, a dose-ranging study of 670 patients with chronic myeloid leukemia [3]. The data sets were analyzed separately, before being pooled to provide a larger sample size.

The general population data set used in the analysis was derived from the Health Survey for England (HSE), which collects health and demographic data from randomly selected households in England [4]. Only adults aged 31 to 80 years with nonmissing values were included because they represented the pooled clinical trial data set.

Eight drugs that were granted a marketing authorization within the last 5 years were chosen as examples in our analysis: ipilimumab, cabazitaxel, ustekinumab, brentuximab vedotin, cetuximab, clofarabine, panitumumab, and cladribine. These are patented medicines that span a range of disease areas and are dosed using various posologies on the basis of either weight or BSA. The dosing for each of these drugs was taken from the European Summary of Product Characteristics, and prices were taken from the Monthly Index of Medical Specialities (January 2015) (Table 1) [5]. Three of the drugs (ipilimumab, cetuximab, and panitumumab) are available in two linearly priced vial sizes; in our analysis the smaller size was used for simplicity, because the wastage would have been the same if the larger vial was used. When dosing was based on BSA, it was derived from patients' height and weight using the Du Bois formula (the most widely used estimation formula) [6].

Costing Methodologies

The parameter mean approach uses the arithmetic mean of the weight or BSA of the pooled trial data set and calculates the number of vials required to administer each dose for this hypothetical mean patient (rounded up to the nearest whole vial).

The trial patient costing approach involves costing the number of whole vials (and thus the cost) required for each patient, before taking the mean of the individual costs (thus incorporating the distribution in patient characteristics observed in the trial). This approach was used as the reference because it essentially represents the "true" drug cost that would be incurred given the individual characteristics of the trial participants.

Finally, the fitted-distribution approach involves fitting a parametric distribution to the cumulative density of patient weight or BSA. Distribution parameters were estimated using a method of moments technique [7].

Results

The pooled trial data set contained the weight and height of 1326 patients, whereas the HSE data set contained those of 5427 individuals between the ages of 31 and 80 years (inclusive). The results of our analysis were consistent when we analyzed each of the three clinical trials separately and when we pooled the trial data. Here, we focus on the pooled data.

The costs of one administration of each drug using trial patient costing, parameter mean approach, and fitted-distribution costing are presented in Table 2, using the pooled trial data and the HSE data. For all but one of the drugs included (cladribine), the parameter mean approach led to an underestimate of the true drug cost compared with trial patient costing. The scale of error in drug-cost estimation ranged from a 1.5% overestimation of costs with cladribine to a 9.6% underestimation of costs with ustekinumab.

The differences between trial patient costing and fitted-distribution costing were small, ranging from a 0.03% underestimation with ipilimumab to a 0.4% overestimation with ustekinumab.

On comparing the results of trial patient costing with a distribution fitted to HSE data, we found the results to be also consistent, and errors were much smaller than those associated with the parameter mean approach. We found that using the HSE data led to slight overcostings for treatments dosed on the basis of weight and undercostings for treatments dosed on the basis of BSA.

Discussion

The results of the analysis show that using mean patient characteristics (be it weight or BSA) is likely to produce inaccurate

Table 1 – Summary of the drugs included in the analysis.				
Product	Dosing parameter	Dose	Products available (mg)	Cost per vial (£)
Brentixumab vedotin	Weight	1.8 mg/kg	50	2,500
Cabazitaxel	BSA	25 mg/m^2	60	3,696
Cetuximab	BSA	250 mg/m^2	100	178
			500	891
Cladribine	Weight	1.2 mg/kg	10	160
Clofarabine	BSA	52 mg/m^2	20	1,316
Ipilimumab	Weight	3 mg/kg	50	3,750
			200	15,000
Panitumumab	Weight	6 mg/kg	100	379
			400	1,517
Ustekinumab	Weight	<100 kg: 45 mg	45	2,147
		≥100 kg: 90 mg		

BSA, body surface area.

Table 2 – Cost results and percentage impact of adopting alternative methods—including comparison between trial data and general population data.

Product	Trial patient costing (baseline) (£)	Parameter mean approach (£)	Fitted-distribution costing (£)	HSE data fitted distribution (£)	Cost differences relative to observed patients		
					Parameter mean approach (£) (absolute, %)	Fitted-distribution costing (£) (absolute, %)	HSE data fitted distribution (£) (absolute, %)
Brentuximab vedotin	8,273.00	7,500.00	8,270.49	8,343.04	−773.00 (−9.3)	−2.51 (−0.03)	70.04 (0.8)
Cabazitaxel	3,762.90	3,696.00	3,771.61	3,748.80	−66.90 (−1.8)	8.72 (0.23)	−14.09 (−0.4)
Cetuximab	925.56	890.50	925.65	924.34	−35.06 (−3.8)	0.10 (0.01)	−1.21 (−0.1)
Cladribine	1,573.03	1,597.00	1,573.26	1,588.89	23.97 (1.5)	0.23 (0.01)	15.85 (1.0)
Clofarabine	7,085.14	6,580.90	7,086.47	7,075.39	−504.24 (−7.1)	1.33 (0.02)	−9.75 (−0.1)
Ipilimumab	19,414.59	18,750.00	19,408.97	19,592.32	−664.59 (−3.4)	−5.63 (−0.03)	177.72 (0.9)
Panitumumab	1,963.67	1,896.45	1,963.10	1,981.12	−67.22 (−3.4)	−0.57 (−0.03)	17.45 (0.9)
Ustenkinumab	2,375.30	2,147.00	2,384.75	2,377.89	−228.30 (−9.6)	9.45 (0.40)	2.59 (0.1)

HSE, Health Survey for England.

estimates of drug costs—this was consistent for treatments based on both weight and BSA. Subsequent resource allocation decisions could be flawed: either by overestimating costs and rejecting cost-effective technologies or by underestimating costs and accepting cost-ineffective technologies. In our analysis, the parameter mean approach led to costs that were different from the "true" cost (on the basis of patient-level trial data) by more than 3% for six of the eight drugs analyzed.

The impact of inappropriate drug costing is illustrated in the National Institute for Health and Care Excellence technology appraisal TA319 (ipilimumab in previously untreated advanced melanoma), in which the incremental cost-effectiveness ratio was presented using both the fitted-distribution technique and the parameter mean approach. The parameter mean approach resulted in a 4.4% lower cost per dose of ipilimumab, with incremental cost-effectiveness ratios reducing from £47,899 to £45,935 versus dacarbazine and from £28,642 to £20,892 versus vemurafenib (for which incremental differences were lower, making variations in drug cost more influential) [8].

Whether the use of the parameter mean approach underestimates or overestimates the cost of a product depends fundamentally on whether the number of vials required to treat the mean patient is greater or lesser than the mean number of vials required to treat across all patients in the trial. In turn, this depends on the mean patient weight or BSA, the vial size, and the distribution of patient weight or BSA. If the vial size of a drug allows the mean patient to be treated with very little wastage of drug, then the parameter mean approach may likely underestimate the drug cost. In contrast, if the vial size is such that there is substantial wastage in treating the mean patient (as was the case in our analysis for cladribine), then the parameter mean approach may overestimate the drug cost. This, however, also depends on the distribution of weight or BSA. In the data sets we analyzed, there was a right skew in the weight or BSA distributions. For seven of the eight drugs we analyzed, the longer right tail of the distributions meant that the mean number of vials per patient required to treat the population was greater than the number of vials required by the mean patient. This suggests that pharmaceutical companies may at present be basing vial sizes on mean patient weight or BSA, such that there is little wastage when treating the mean patient. This does not necessarily mean that patients at extremes of the distribution are being treated with more wastage; it rather signals that taking account of these patients in cost calculations is likely to increase the quantity of vials estimated to be required when there is a right-skewed distribution, and when the mean patient can be treated with little wastage. Developing methods for identifying how to most efficiently size vials to reduce wastage is a separate question that requires further research.

This analysis focuses only on the cost of one administration of treatment (for simplicity)—any cost differential would be compounded over the duration of treatment. A relatively small costing error per dose could therefore amount to considerable inaccuracy if administration is frequent and continuous. Our analyses, however, are relevant only for treatments that are dosed on a variable scale (according to weight or BSA)—the issue that we have analyzed is not relevant for treatments dosed on a fixed scale because for these treatments there is no distribution to consider.

Use of General Population Data

The primary analyses conducted relied on the availability of patient-level data; the cost estimates using the HSE data set, however, showed results consistent with those of the trial data set. Although the use of HSE data led to slight overcostings for treatments based on weight, and undercostings for treatments

based on BSA, any differences were under 1% in all cases. We suggest that using HSE data is a preferable alternative to the parameter mean approach when patient-level data from relevant trials are not available or accessible.

Estimation of Parameter Distributions

The results of this analysis are less indicative of whether a fitted distribution or the individual patient-level data are optimal. Although the results are similar between the two methods, we would suggest that a distribution would be the most appropriate. A trial is, by definition, only a sample of the eligible patients—unless it is extremely large; it is unlikely to be perfectly representative of the population of interest, particularly concerning the extreme ends of the parameter range. Fitting a distribution would be less sensitive to the inclusion (or exclusion) of outliers in any given sample.

Limitations of the Analysis

The main assumption and limitation of this analysis is that potential vial sharing was not considered. In some markets (e.g., Germany), however, vial sharing is absolutely forbidden, whereas with many new (and niche) treatments, it simply is not practical. For more commonly administered treatments in some markets, there is the potential for a degree of vial sharing to occur if patients are treated in the same center, or if administrations are coordinated. The effect of vial sharing would be to decrease drug wastage (and thus cost) regardless of the costing approach used.

In addition, our analysis has been performed on conditions that affect adults, are not correlated with height or weight, and that have a broadly similar male to female ratio. If a condition is much more prevalent in one sex, is linked to weight, or affects children/adolescents, general population data may need to be further stratified, or alternative data sources sought if patient-level trial data are not available to estimate treatment costs. Alternative analytical techniques may also be required if weight and height were expected to change over time in affected patients. That said, our analysis included three distinct diseases and results were consistent, suggesting that our findings have good generalizability.

Conclusions

Our analysis has demonstrated that for treatments dosed on a variable scale (e.g., by weight or BSA), the use of mean weight or BSA is expected to result in inaccurate estimates of drug costs.

In our analyses, using mean weight or BSA generally led to an underestimation of drug costs. We also found that open access data from the general population can act as a surrogate when patient-level data from relevant trials are not available, and the disease population has no specific characteristics that distinguishes it from the general population.

Whether individual patient-level data are used or a distribution fitted to this, economic models (particularly in health technology assessment) should take into account variability in patient characteristics when costing treatments. Modeling guidelines are not prescriptive regarding the method used for the costing of drugs, which may be an important oversight.

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