Estimating the Costs of Adverse Events in Economic Models: Is There a "Right" Approach?

William Wong, MS, PharmD, Genentech Inc, San Francisco, CA, USA; **Josh Carlson, PhD, MPH**, University of Washington, Seattle, WA, USA; and **Martin Cloutier, MSc**, Analysis Group, Montreal, QC, Canada

There is heterogeneity in approaches to estimating the cost of adverse events for economic models with no apparent standard. Two common methods include a guidelines-based approach and claims-based approach, but potentially may provide vastly different estimates.

Estimates of adverse event (AE) costs are an important input into economic models and their inclusion has been outlined in modeling best practices guidelines such as the *ISPOR Task Force Report on Budget Impact Analyses.*[1] While the guidelines have emphasized the importance of inclusion, there has been no consensus recommendation on the most appropriate approach to estimating AE costs. The key data input needs for all estimates of AE costs include:

- Probability: Frequency of AE over a defined period
- Unit cost: Cost per episode of care associated with the event

The probability multiplied by the unit cost is the expected (average) cost per patient.

IDENTIFYING A PROBABILITY OF AN AE

The probability of an AE is commonly derived from clinical studies, where incidence is typically reported (an important assumption to note is that this assumes that the event occurred only once while under treatment). As the severity of an AE may indicate the level of resource intensity required to treat that AE, this is an important factor to consider when determining the appropriate incidence to include in a model (eg, incidence of grade 3 or 4 AEs vs incidence of any grade AEs). Furthermore, given that there can be variation in the methodology to estimate the unit cost of the adverse event, the method by which the unit cost was derived should also be considered when determining the appropriate incidence of the AE, as these should be consistent with each other (ie, if the unit cost was derived from only severe AEs, then it may be most appropriate to use the severe AE event).

Identifying the Cost of an AE: Common Limitations With Existing Literature Estimates

Sources of the unit cost may include:

- Literature
- Micro-costing approach
- Guidelines/clinical consensus-based approach
- Claims-based approach

While utilizing existing literature may be the most convenient, the objectives of AE cost studies vary and may not align with the goal of incorporation of these estimates into an economic model. Potential limitations to consider include generalizability issues, recency of the data, inclusion of treatment costs, and reporting of overall cost (rather than the incremental cost of the adverse event). Additionally, a single study may not have all adverse events required for a model, hence multiple studies with varying methodologies may be required, adding heterogeneity to the estimates.

Guidelines/Clinical Consensus-Based Approach

The guidelines/clinical consensus-based approach leverages existing clinical management guidelines and clinical expert recommendations to estimate the cost of the adverse event. Key decisions include the selection of AEs (ie, grade/severity, treatment-related, frequency above a certain threshold) and the treatment assumptions per AE (types and frequencies of medical resource utilization). There is no consensus as to which AEs to include but we suggest focusing on grade 3+ or severe AEs with a frequency above 5% for any included intervention as a good starting point, as these are most likely to require healthcare resources and have a meaningful impact on the results (note that if you include an AE for one intervention the same AEs should be included for the other interventions even if below the frequency threshold).

While the guidelines have emphasized the importance of inclusion, there has been no consensus recommendation on the most appropriate approach to estimating AE costs.

Examples of this approach using CMS physician fee schedules in oncology are given in the table below. This approach has several strengths including strong clinical validity and it is less time/resource >

intensive than some other approaches. The main limitation to this approach, however, is the potential to miss costs and the inability to account for variation in care across practices or AE management.

Grade 3/4 Toxicity	Management Assumptions	Total Cost
Fatigue	One outpatient visit ($146)	$146
Neutropenia	4 administrations of pegfilgrastim by subcutaneous injection (4 x [$4,685 + $25]) + 10% of patients have: ER visit ($176), 3-day hospital stay ($9837), primary physician consultation each day ($138 + $73 + $73), specialist visit each day (3 x $203)	$19,933
Thrombo-cytopenia	2 units of platelet transfusion ($6,427) + ER visit ($176) required 25% of time	$6472
Anemia	One outpatient visit ($146) + CBC Test ($0) + 50% of patients treated with 40,000 units of epoetin weekly for 8 weeks (20 x $30/2000 units x 8 weeks = $4800)	$2577

CLAIMS-BASED APPROACH

This data source leverages large real-world databases to estimate costs and may include multiple AEs from multiple conditions (improving consistency in estimates across AEs). This approach may entail different study designs, including a pre-defined management approach or an episode-based approach.

The predefined management approach is like that of the guidelines-based approach in that it leverages clinical expertise to define the management of the AE; however, the cost of that resource use is derived from real-world claims data (as opposed to fixed reimbursement rates for services). While this accounts for some potential variation in reimbursement rates, it may not capture the entire economic burden associated with the adverse event.

Given the differences in approaches, the estimates for a given AE may be vastly different depending on the methodology.

Alternatively, an episode-based approach attempts to capture a more holistic picture of the economic burden through matching treatment episodes with similar characteristics with and without the AE of interest. This approach allows a more comprehensive estimate of costs, including the impact that AEs may have on other conditions and increased costs in the event of multiple AEs/conditions. An additional strength is that no assumption about the AE management behavior is made.

Limitations to the claims-based approach include being limited to AEs requiring resource utilization, lack of information on the severity of an AE, and it is more time and resource intensive than the guidelines-based approach.

Example: Comparison of Estimates in Oncology

Given the differences in approaches, the estimates for a given AE may be vastly different depending on the methodology. Table 2 shows some common AEs in oncology estimated by the episode-based claims analysis approach[2] compared to the guidelines-based method (using Medicare Physician Fee Schedule, Diagnostic). While some estimates are very close, such as pneumonia or thrombocytopenia, others are vastly different such as in the case of neutropenia.

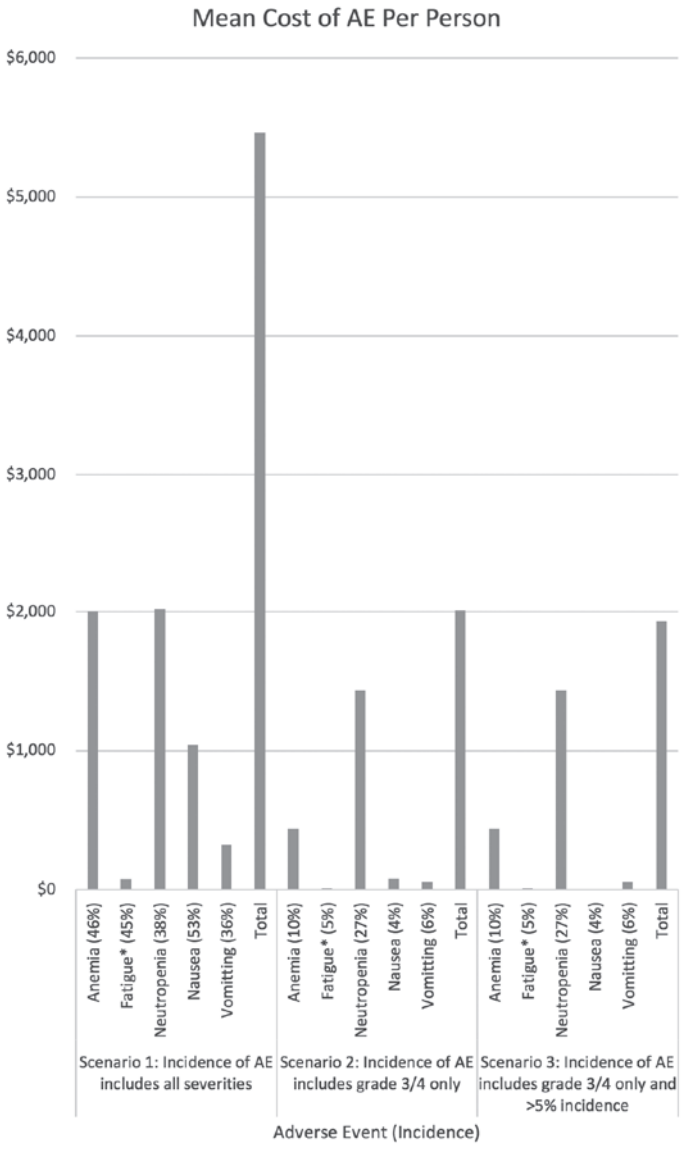
Study AE	Claims Analysis Cost (Incremental Cost per Episode)	Guidelines-Based Cost of AE	Difference
Vomiting	$895	$489	$406
Nausea	$1965	$146	$1819
Anemia	$4353	$2577	$1776
Neutropenia	$5321	$19,933	($14,612)
Thrombo-cytopenia	$6325	$6472	($147)
Pneumonia	$9941	$9808	$133
Fatigue	Not Estimated	$167	N/A

Example: Application of Estimates to Oncology Model

Adverse event cost estimates should be consistent with the AE probabilities utilized and subsequently the total costs related to AEs. When applying claims analysis-based estimates, an assumption regarding the similarity in severity of AEs observed in claims and the source of the AE rates must be made. For example, Figure 1 demonstrates how the assumption of AE severity within claims data may impact the overall costs of AEs. Given that all observed AEs in claims require resource utilization, application of claims-based estimates to all AEs regardless of severity may result in an overestimate of the AE costs that normally may be expected to be less costly, such as nausea (Figure 1: Scenario 1). Alternatively, it may be more appropriate to assume that the observed AEs are like more severe AEs, such as grade 3 or 4 in this example of oncology (Figure 1: Scenario 2). Furthermore, simplifying assumptions may be appropriate, such as utilizing an incidence rate cut-off, especially when the expected impact is minimal (Figure 1: Scenario 2 vs. Scenario 3).

When further considering the impact of these variabilities on the incremental cost-effectiveness ratio (ICER), the cost of the intervention itself is an important factor. Using the same scenarios in Figure 1, Table 3 demonstrates how the variability in intervention costs may impact the ICER. When the difference in intervention costs are small, differences in estimates of the AE costs (Scenario 1 vs 3) resulted in the largest percentage change in ICER. Conversely, large differences in intervention costs resulted in minimal impact of the ICER. These observations imply

that where interventions are costlier and hence differences in costs are potentially larger, the cost of the AEs will have less impact than when considering interventions where the AE costs are a larger proportion of the overall cost of the intervention. While this example utilizes the scenarios outlined above, similar outcomes would be expected using scenarios where different methodologies are utilized, which result in different unit costs of AEs (ie, claims-based estimates vs. guidelines-based estimates). Lastly, when examining scenario 2 vs 3, as in Figure 1, we see that simplifying assumptions may result in minimal impact, indicating that this approach potentially may be appropriate.



*For AEs with no claims data, a guidelines-based approach is used.

CONCLUSION

Guideline-based and claims-based approaches may provide different estimates of AE costs and which can potentially have a large impact on ICER estimates, depending on the circumstances. Given the strengths and limitations of both, applying a combination of both approaches may be optimal when applying estimates to economic models (ie, using a claims-based approach and supplementing with a guidelines-based approach where estimates from the claims data are not available/feasible). When choosing a method, the detail and precision needed to estimate the AE costs based on the likely impact on the outcomes of the model needs to be balanced with the effort required to estimate them accurately. In oncology models, we have found that applying claims-based estimates combined with guidelines-based estimates for AEs with a greater incidence than 5% can be a practical approach.

*Table 3: Impact of Difference in Drug Costs on Incremental Cost-Effectiveness Ratio**

	Incremental Cost-Effectiveness Ratios (ICERs)			Difference in ICER (%)	
Difference in drug costs	Scenario 1: $4268 difference in average AE costs per person[1]	Scenario 2: $1794 difference in average AE costs per person[1]	Scenario 3: $1717 difference in average AE costs per person[1]	Scenario 1 vs 3	Scenario 2 vs 3
0	$21,340	$8970	$8580	59.8	4.3
$100	$21,840	$9470	$9080	58.4	4.1
$1000	$26,340	$13,970	$13,580	48.4	2.8
$10,000	$71,340	$58,970	$58,580	17.9	0.7
$20,000	$121,340	$108,970	$108,580	10.5	0.4
$30,000	$171,340	$158,970	$158,580	7.4	0.2
$40,000	$221,340	$208,970	$208,580	5.8	0.2
$50,000	$271,340	$258,970	$258,580	4.7	0.2

*Assume difference in QALY of 0.2. ICER = (△ treatment costs + △AE costs) / (△ QALY). Example: ($100+$4268)/ (0.2) = $21,840.

[1] Assumes 50% reduction in AE incidence between treatment groups in each scenario: $\sum(probability\ of\ AE \times unit\ cost)_i - \sum(probability\ of\ AE \times 0.5 \times unit\ cost)_i$; *where i=each AE in scenario.*

REFERENCES

1. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014;17(1):5-14.

2. Wong W, Yim YM, Kim A, et al. () Assessment of costs associated with adverse events in patients with cancer. PLoS ONE. 2018;13(4): e0196007.

ADDITIONAL INFORMATION

The preceding article is based on a presentation from ISPOR 2018. For more information, go to https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2018.