



ESTIMATING THE COST OF ADVERSE EVENTS IN ECONOMIC MODELS

A discussion of guidelines-based and claims-based approaches



INTRODUCTION

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OUTLINE

- Background
- Overview of approaches to estimating adverse event (AE) costs
- Main challenges for oncology
- Guidelines/Clinical consensus-based approach
- Claims-based approach
- Manufacturer perspective
 - Importance of robust estimates
 - Comparison of guidelines-based versus claims-based approaches
 - Potential applications and recommendations
- Conclusion

BACKGROUND

- Modeling best practices guidelines have stated the importance of inclusion of all relevant costs, including AEs
- However, there has been no consensus on the most appropriate approach to estimating the cost of AEs





BACKGROUND

- Variety of approaches to generating cost estimates for AEs in economic analyses
- Key data needs:
 - Rate: Frequency of adverse event over defined time period
 - Unit Cost: Cost per episode of care associated with event
- Rate X Unit Cost = Expected (average) cost per patient
- General principle:
 - Juice must be worth the squeeze



BACKGROUND

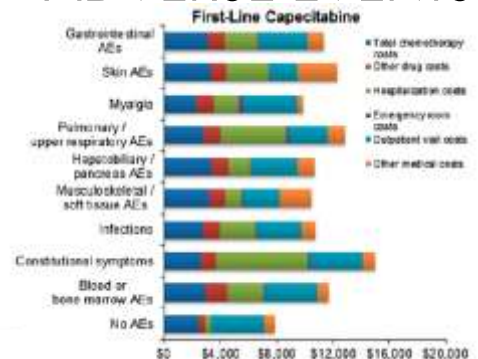
- While prevalence of AEs is commonly derived from clinical trials (which are representative of a select patient population), costs of AEs can be derived from a number of different sources/approaches
 - Sources/approaches may include:
 - Literature
 - Micro-costing approach
 - Guidelines/Clinical consensus-based approach
 - Claims-based approach
- ← Focus for today

OVERVIEW OF APPROACHES

| Approach | Data | Main strengths | Main limitations |
|-------------------------------------|---|---|---|
| Literature | <ul style="list-style-type: none"> Systematic literature review | <ul style="list-style-type: none"> Peer-reviewed evidence | <ul style="list-style-type: none"> Combines different methodologies for estimates |
| Micro-costing | <ul style="list-style-type: none"> Costs assigned to HRU (e.g., EMR) | <ul style="list-style-type: none"> Detailed | <ul style="list-style-type: none"> Time/Resource intensive May not be generalizable |
| Guidelines/Clinical consensus-based | <ul style="list-style-type: none"> Clinical expert opinion Guidelines Merck manual Peer reviewed literature | <ul style="list-style-type: none"> Clinical validation (i.e., matching severity in trial) Less time/resource intensive compared to claim-based approach | <ul style="list-style-type: none"> Potential to miss some costs Not reflective of variation in care across practices |
| Claims-based | <ul style="list-style-type: none"> Retrospective databases | <ul style="list-style-type: none"> Costs may not be limited to AE management (e.g., include costs resulting from potential treatment delay/disruption) Large sample size from real-world setting (more generalizable) | <ul style="list-style-type: none"> Limited to AEs requiring health resource utilization Costs related to AEs cannot be perfectly distinguished from disease-related costs |

CURRENT LITERATURE ON COST OF ADVERSE EVENTS

- Existing publications have limitations which may prevent incorporation into economic modeling
 - Inclusion of treatment costs
 - Overall costs versus incremental costs
 - Studies may not be generalizable
 - Variations in methodologies
 - Costs limited to AE management only, which may not represent the actual economic burden resulting from an AE during a cancer treatment episode



The Oncologist 2014;19:901-908



QUESTION FOR AUDIENCE

Which method do you currently/would you use?

1. Literature
2. Micro-costing approach
3. Guidelines/Clinical consensus-based approach
4. Claims-based approach
5. Other

GUIDELINES/CLINICAL CONSENSUS APPROACH – ONCOLOGY FOCUS

Josh Carlson
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MAIN CHALLENGES FOR ONCOLOGY

- Innovative cancer treatments have increased the demand for economic models to inform decision makers in managing their health care budget
- Considering that AEs may disrupt planned cancer treatment, resulting in serious clinical consequences for patients and in an increased disease and economic burden, a comprehensive assessment of cancer care costs should go beyond cancer therapy costs and consider the economic burden associated with AEs



MAIN CHALLENGES FOR ONCOLOGY

- Published data on the real-world costs of AEs in cancer are limited:
 - Specific AEs
 - Treatments/drug classes
 - Cancer types
- These limitations may be difficult to reconcile in economic models due to discrepancies in the methodology used by different sources for different AEs and cancer types

MAIN CHALLENGES FOR ONCOLOGY

- CTCAE grading – which to include?

| Grade | Description |
|---------|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death |

ADL: Activities of daily living

| Adverse Reaction | All Grades (%) | Grades 3-4 (%) |
|---|----------------|----------------|
| General | | |
| Fatigue ^a | 52 | 9 |
| Peripheral edema ^a | 37 | 5 |
| Fatigue ^b | 14 | 0.8 |
| Gastrointestinal | | |
| Diarrhea ^a | 24 | 4 |
| Nausea | 22 | 2 |
| Vomiting | 19 | 0.9 |
| Constipation | 13 | 1 |
| Abdominal pain ^a | 13 | 0.9 |
| Musculoskeletal and Connective Tissue | | |
| Decreased appetite ^a | 28 | 0 |
| Neurological and Cognitive Dysfunction | | |
| Headache pain | 18 | 1 |
| Arthralgia | 13 | 0 |
| Site and Subcutaneous Tissue | | |
| Pruritus | 18 | 0.6 |
| Foot ^a | 17 | 0.9 |
| Infections | | |
| Upper respiratory ^a | 17 | 0 |
| Respiratory, Thoracic, and Mediastinal | | |
| Cough ^a | 18 | 0 |
| Dyspnea ^a | 12 | 0 |

MAIN CHALLENGES FOR ONCOLOGY

- Selection of AEs
 - Guidelines recommend inclusion of all relevant AEs
 - Inclusion of all AEs requires additional data and model assumptions/complexity
 - Data may not be available for all relevant comparators (i.e., breakdown of incidence by each CTCAE grade)
 - Additional differentiation of costs between different grades
 - Practical approach may be to include only high resource (grade 3 or 4) AEs above a given incidence

GUIDELINES/CLINICAL CONSENSUS-BASED APPROACH

- Obtain rates of AEs from clinical trial data:
 - Individual trial or pooled data
- Select which AEs to include:
 - Grade
 - Serious
 - Treatment-related
 - Above a certain frequency (e.g., >5%)
- Develop treatment assumptions per included AE
 - Types and frequencies of medical resource utilization
 - Validate with clinical experts
- Assign unit costs per resource type (e.g., CMS reimbursable rates)
- Multiply rates X cost per AE and sum = average AE cost per patient

SOURCES OF DATA

- Potential sources of guidelines in AE management:
 - Merck Manual
 - Guidelines
 - Clinical expert opinion
 - Peer-reviewed literature



METHODS: MANAGEMENT OF AES - EXAMPLES

| 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)) + <u>10%</u> 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 |
| Thrombocytopenia | 2 units of platelet transfusion (\$6,427) + ER visit (\$176) required <u>25%</u> of time | \$6,472 |
| Anemia | One outpatient visit (\$146) + CBC Test (\$0) + <u>50%</u> of patients treated with 40,000 units of epoetin weekly for 8 weeks (20 x \$30/2000 units x 8 weeks = \$4,800) | \$2,577 |

Considerations:

- Medication use
- Procedures
- Distribution of management in outpatient vs. inpatient

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METHODS: MANAGEMENT OF AES- EXAMPLES

| Grade 3/4 Toxicity | Management Assumptions | Total Cost | AE Incidence | Cost of AE per person |
|--------------------|--|------------|--------------|-----------------------|
| Fatigue | One outpatient visit (\$146) | \$146 | 10% | \$14.60 |
| Neutropenia | 4 administrations of pegfilgrastim by subcutaneous injection (4 x (\$4,685 + \$25)) + <u>10%</u> 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 | 5% | \$996.65 |
| Thrombocytopenia | 2 units of platelet transfusion (\$6,427) + ER visit (\$176) required <u>25%</u> of time | \$6,472 | 2% | \$129.44 |
| Anemia | One outpatient visit (\$146) + CBC Test (\$0) + <u>50%</u> of patients treated with 40,000 units of epoetin weekly for 8 weeks (20 x \$30/2000 units x 8 weeks = \$4,800) | \$2,577 | 5% | \$128.85 |
| Total: | | | | \$1,269.54 |



STRENGTHS

- Clinical validation
- Can cost out AEs which may not be observable in real-world data (i.e., self limiting adverse events)
- Estimates reflect trial based rates that match trial based outcomes
- Less time and resource intensive
 - Need to balance the detail and precision needed for an input, based on the likely influence on model outcomes, with the "effort required to measure or value them accurately"
 - Drummond et al.



LIMITATIONS

- Potential to miss some costs
- Not reflective of variation in care across practices
- May not account for variation in outcomes of AE management

CLAIMS-BASED APPROACH

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DATA SOURCE

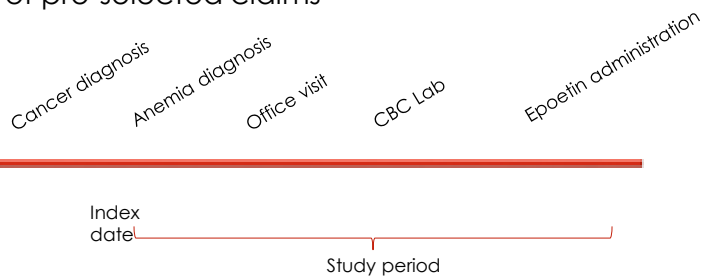
- Desired characteristics:
 - Large and representative data to allow generalizability
 - Both medical and pharmacy data to capture costs across different sites of care
 - Data on costs rather than charges

CLAIMS-BASED POTENTIAL APPROACHES

- Pre-defined management approach
- Episode-based approach

PRE-DEFINED MANAGEMENT APPROACH

- Identify expected resource use of management of AE based on clinical expertise
- Estimate costs of pre-selected claims



*May not represent the actual economic burden resulting from an AE during a cancer treatment episode (e.g., costs resulting from potential treatment delay/disruption)

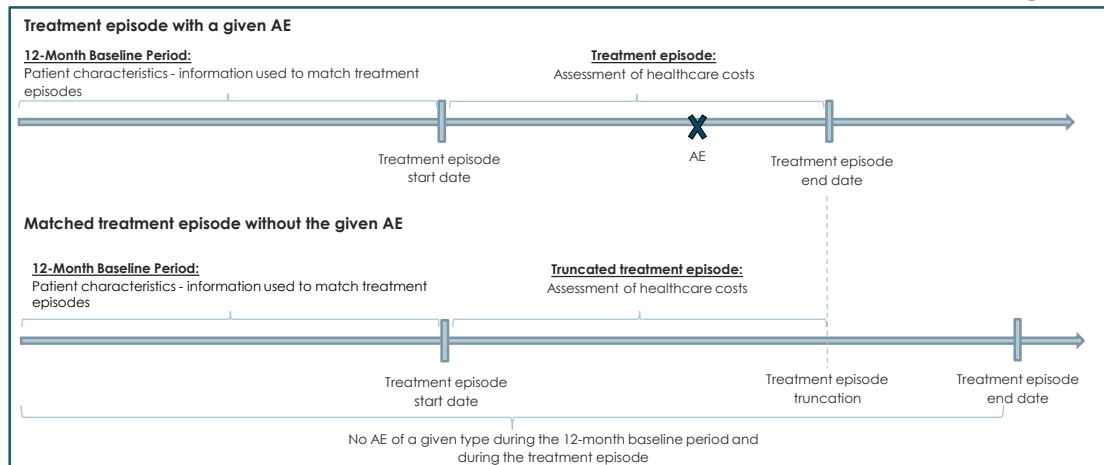
EPISODE-BASED APPROACH: EXAMPLE



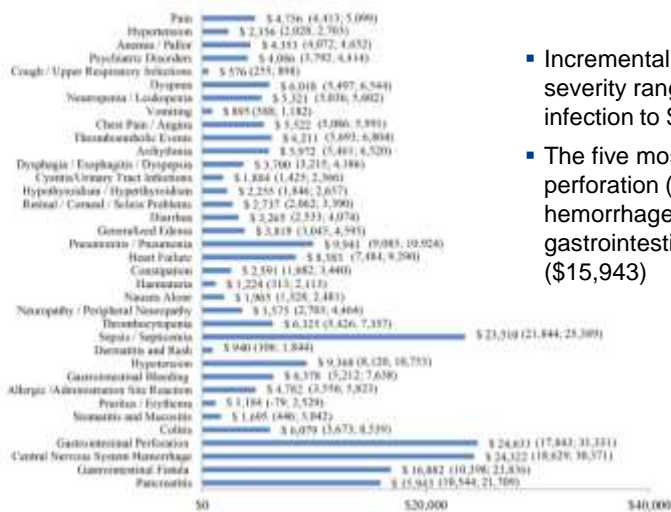
METHODS – MATCHED TREATMENT EPISODE

- Treatment episodes with a given AE were matched to similar treatment episodes without the given AE in order to assess the incremental costs associated with the AE during cancer treatment episodes
- All costs were considered without assumptions on particular AE management behaviors
- Assumption: incremental cost attributable to the AE and not the disease (e.g., similar disease characteristics across matched episodes)

METHODS

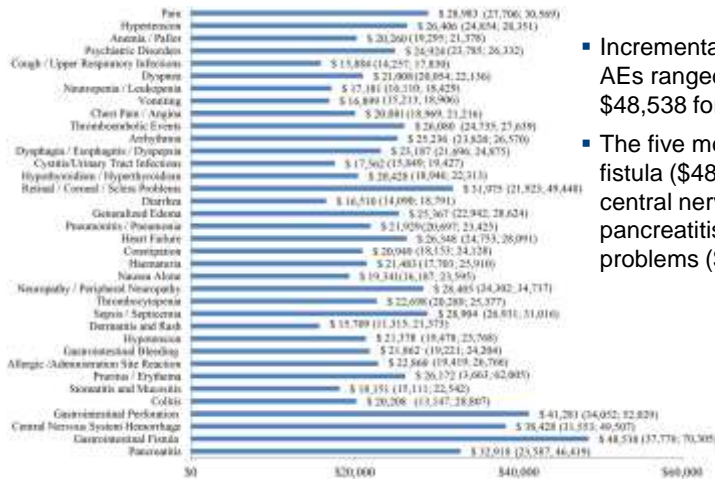


RESULTS



- Incremental healthcare costs associated with AEs of any severity ranged from \$576 for cough/upper respiratory infection to \$24,633 for gastrointestinal perforation
- The five most costly AEs were gastrointestinal perforation (\$24,633), central nervous system hemorrhage (\$24,322), sepsis/septicemia (\$23,510), gastrointestinal fistula (\$16,882), and pancreatitis (\$15,943)

RESULTS – SEVERE AES (HOSPITALIZATION)



- Incremental healthcare costs associated with severe AEs ranged from \$15,709 for dermatitis and rash to \$48,538 for gastrointestinal fistula
- The five most costly severe AEs were gastrointestinal fistula (\$48,538), gastrointestinal perforation (\$41,281), central nervous system hemorrhage (\$38,428), pancreatitis (\$32,918), and retinal/corneal/sclera problems (\$31,975)

STRENGTHS

- No assumptions about AE management behaviors
- Comprehensive, including:
 - impact that AEs may have on other conditions
 - increased costs in the event of multiple AEs/conditions
 - costs resulting from potential treatment delay/disruption
- Large sample size from real-world setting (more generalizable)
- Multiple AEs for multiple underlying conditions can be assessed with a consistent approach




LIMITATIONS

- Limited to AEs requiring medical services
 - may be associated with higher costs
 - no staging hence inherent assumptions about severity
- More time and resource intensive compared to guidelines-based approach
- Costs related to AEs cannot be perfectly distinguished from disease-related costs
 - potential for double counting when included in a model
- Difference may exist between trial population used to inform AE rates and real-world sample used to inform AE-related costs

MANUFACTURER PERSPECTIVE AND COMPARISON OF APPROACHES

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SUMMARY OF GUIDELINES-BASED VERSUS CLAIMS-BASED APPROACHES

| | Guidelines/Clinical consensus-based | Claims-based (episode-based) |
|----------------------------|-------------------------------------|--|
| Clinical validation | Based on expert opinion | No disease stage – assumption on severity |
| Self-limiting AEs captured | Yes | Potentially challenging |
| Practice variations | Less generalizable | More generalizable |
| Resource intensity | Less | More |
| Costs captured | Related to AE management only | More comprehensive, however may be difficult to distinguish from disease costs |

WHY IS HAVING ROBUST ESTIMATES IMPORTANT?

- Draft guidance from FDA has clarified standards for what it considers “competent and reliable scientific evidence” (CARSE) and supports the Use of Current Good Research Practices from Authoritative Bodies Such as ISPOR
- Section 502(a) states that HCEI shall not be considered false or misleading if, among other things, it is “based on competent and reliable scientific evidence.” **FDA considers HCEI to be based on CARSE if the HCEI has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results. In evaluating whether the amount and type of evidence that forms the basis for a particular communication of HCEI meets the generally-accepted scientific standards for such information, FDA will consider the merits of existing current good research practices for substantiation developed by authoritative bodies (e.g., International Society for Pharmacoeconomic and Outcomes Research (ISPOR), Patient-Centered Outcomes Research Institute)**



ISPOR PRINCIPLES OF GOOD PRACTICE (BUDGET IMPACT)

- Costs of managing any side effects or complications should also be included in the cost of the current and new intervention mix as a separate item. The rates of adverse events should be derived from product labels or publications for all interventions in the treatment mix..... **If published studies of the adverse event costs are not available, treatment algorithms should be developed in consultation with physicians who treat each condition and local unit costs for the health care services should be applied.**

1. Sullivan SD et al. Value in Health 17 (2014) 5- 14. <https://www.ispor.org/budget-impact-health-study-guideline.pdf>

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COMPARISON OF GUIDELINES-BASED VERSUS CLAIMS-BASED FINDINGS

| Study AE | Claims Analysis Cost (Incremental Cost Per Episode) | Guidelines-based cost of AE | Difference |
|------------------|---|-----------------------------|------------|
| Vomiting | \$895 | \$489 | \$406 |
| Rash | \$940 | \$132 | \$808 |
| Stomatitis | \$1,695 | \$1,241 | \$454 |
| Nausea | \$1,965 | \$146 | \$1,819 |
| Hypertension | \$2,356 | \$211 | \$2,145 |
| Constipation | \$2,591 | \$396 | \$2,195 |
| Diarrhea | \$3,265 | \$1,033 | \$2,232 |
| Neuropathy | \$3,575 | \$108 | \$3,467 |
| Peripheral edema | \$3,819 | \$859 | \$2,960 |
| Anemia | \$4,353 | \$2,577 | \$1,776 |
| Neutropenia | \$5,321 | \$19,933 | (\$14,612) |
| Dyspnea | \$6,018 | \$4,714 | \$1,304 |
| VTEs | \$6,211 | \$10,505 | (\$4,294) |
| Thrombocytopenia | \$6,325 | \$6,472 | (\$147) |
| GI Hemorrhage | \$6,378 | \$9,196 | (\$2,818) |
| Pneumonia | \$9,941 | \$9,808 | \$133 |
| GI Perforation | \$24,633 | \$12,685 | \$11,948 |

APPLICATION OF RESULTS TO MODEL (OPTION 1)

Cost of AE per Person = Cost Per Episode × Incidence of AE (All Grades)

Assumption: AEs observed in claims analysis are reflective of all Grades

| | Cost per Episode | Incidence of AE (all Grades) | Cost of AE per person |
|-------------|------------------|------------------------------|-----------------------|
| Anemia | \$4,353 | 12.2% | \$531 |
| Fatigue* | \$167* | 42.7% | \$71 |
| Pneumonitis | \$9,941 | 3.5% | \$348 |
| Diarrhea | \$3,265 | 86.7% | \$2,831 |
| Vomiting | \$895 | 61.6% | \$551 |
| Total | | | \$4,332 |

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

APPLICATION OF RESULTS TO MODEL (OPTION 2)

Cost of AE per Person = Cost Per Episode × Incidence of AE (Grade 3/4)

Assumption: AEs observed in claims analysis are similar to Grade 3/4 in severity

| | Cost per Episode | Incidence of Grade 3/4 AE | Cost of AE per person |
|-------------|------------------|---------------------------|-----------------------|
| Anemia | \$4,353 | 5.1% | \$222 |
| Fatigue* | \$167* | 5.1% | \$9 |
| Pneumonitis | \$9,941 | 5.9% | \$587 |
| Diarrhea | \$3,265 | 2.7% | \$88 |
| Vomiting | \$895 | 4.7% | \$42 |
| Total | | | \$947 |

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

APPLICATION OF RESULTS TO MODEL (OPTION 3)

$$\text{Cost of AE per Person} = \left[\begin{array}{l} (\text{Cost Per Episode Inpatient} \otimes \% \text{ Treated Inpatient}) \oplus \\ (\text{Cost Per Episode Outpatient} \otimes \% \text{ Treated Outpatient}) \end{array} \right] \otimes \text{Incidence of AE (Grade 3/4)}$$

Assumptions:

1. AEs observed in claims analysis are similar to Grade 3/4 in severity
2. Percent treated inpatient vs. outpatient is based on expert opinion

| | Cost per Episode (Inpatient) | % Treated Inpatient | Cost per Episode (Outpatient) | % Treated Outpatient | Incidence of grade 3/4 AE | Cost of AE per person (weighted) |
|-------------|------------------------------|---------------------|-------------------------------|----------------------|---------------------------|----------------------------------|
| Anemia | \$ 20,260 | 10% | \$4,353 | 90% | 5.10% | \$303 |
| Fatigue* | 0 | 0% | \$167* | 100% | 5.10% | \$9 |
| Pneumonitis | \$ 21,929 | 80% | \$ 9,941 | 20% | 2.70% | \$527 |
| Diarrhea | \$ 16,510 | 10% | \$ 3,265 | 90% | 5.90% | \$271 |
| Vomiting | \$ 16,899 | 5% | \$ 895 | 95% | 4.70% | \$80 |
| Total | | | | | | \$1,189 |

*For AEs with no data, existing guidelines-based approach was used

RECOMMENDATION

- Option 2

$$\text{Cost of AE per Person} = \text{Cost Per Episode} \times \text{Incidence of AE (Grade 3/4)}$$

- Rationale:

- AEs which are observed in claims are those which require resource utilization; hence may most closely align to Grade 3 or 4 severity based on CTCAE

| | |
|---------|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death |

APPLICATION OF RESULTS TO MODEL (OPTION 2)

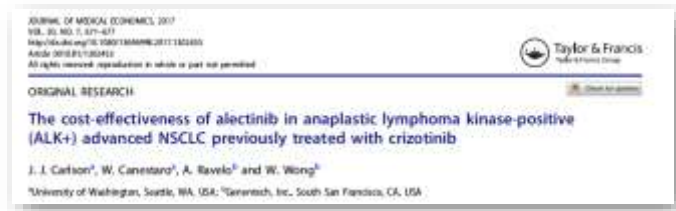
Cost of AE per Person = Cost Per Episode × Incidence of AE (Grade 3/4)

5% incidence cut-off for inclusion

| | Cost per Episode | Incidence of grade 3/4 AE | Cost of AE per person |
|-------------|------------------|---------------------------|-----------------------|
| Anemia | \$4,353 | 5.1% | \$222 |
| Fatigue* | \$167* | 5.1% | \$9 |
| Pneumonitis | \$ 9,941 | 5.9% | \$587 |
| Diarrhea | \$ 3,265 | 2.7% | \$0 |
| Vomiting | \$895 | 4.7% | \$0 |
| Total | | | \$817 |

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

IMPACT OF SELECTION OF AES



| Inclusion Criteria | Cost/QALY |
|--|-----------|
| >\$1000 or >5% Incidence (Grade 3 or 4) | \$31,180 |
| All Grade 3 or 4 regardless of cost or incidence | \$31,189 |

Depending on model, may be appropriate to simplify AE assumptions given potential limited impact



FUTURE RESEARCH AND CHALLENGES

- More robust estimates of self-limiting AEs
- Require updating estimates to account for
 - Changing management of AEs over time
 - Emergence of new AEs (e.g., immunotherapy-related AEs)



CONCLUSION

- Robust estimates of AEs are important given CARSE standard guidelines
- Guidelines-based and claims-based approaches may provide different estimates
- Recommend combination of both approaches