# "The importance of safety issues in economic evaluation"

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# "THE REMEDY MUST NOT BE WORSE THAN THE DISEASE"

EFFICACY/EFFECTIVENESS

↓

"average" concept

SAFETY

↓

individual matter

In Germany alone, 10,000 **babies were** born affected by **Thalidomide**. **Many were** too damaged to survive for long.

# FACTORS CONTRIBUTING TO THE COST OF ADVERSE EVENTS (AE)

- There are several factors contributing to the costs for adverse events to be included in a budget impact analysis. Not only is it important to estimate the rates at which these events occur, but it is important to determine when these events are likely to occur (i.e., only upon initiation of treatment, as long as the patient takes the treatment, or only after several years on the treatment), severity of the events, and the extent to which these events may lead to discontinuation of the drug.

# The importance of adverse drug events in health economics and in economic evaluation

- The drug adverse events as % of the public hospital spending: In Australian hospitals amounted to AUD 1.2 billion, or 4% of the public hospital spending. In Germany this figure is a 2% (OECD ,2017).
- Oncology: Metastatic melanoma: monthly AE costs between 4.0% and 37% of overall health care costs for different systemic therapies.

Copley-Merriman, C., Stevinson, K., Liu, F. X., Wang, J., Mauskopf, J., Zimovetz, E. A., & Chmielowski, B. (2018). Direct costs associated with adverse events of systemic therapies for advanced melanoma: Systematic literature review. *Medicine*, *97*(31). Australia, France, Germany, Italy,UK

OECD (2017), the economics of patient safety

# Assigning healthcare costs to the adverse events

- In order to assign health-care costs to the adverse events, side effect rates are needed by level of severity, since severity of the side effect will likely determine the intensity and cost of treatment. At the very least, serious adverse events might be separated from nonserious adverse events.

# Adverse events included in economic evaluations: The case of budget impact analysis

A budget impact analysis (BIA) is an economic assessment that estimates the financial consequences of adopting a new intervention. There is no consensus as to which AEs to include but the majority of economic evaluations focusing on grade 3+ or severe AEs. Cut off: an incidence between 1% and 5%

| | |
|---|---|
| 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-case ADL |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death |

ADL: Activities of daily living

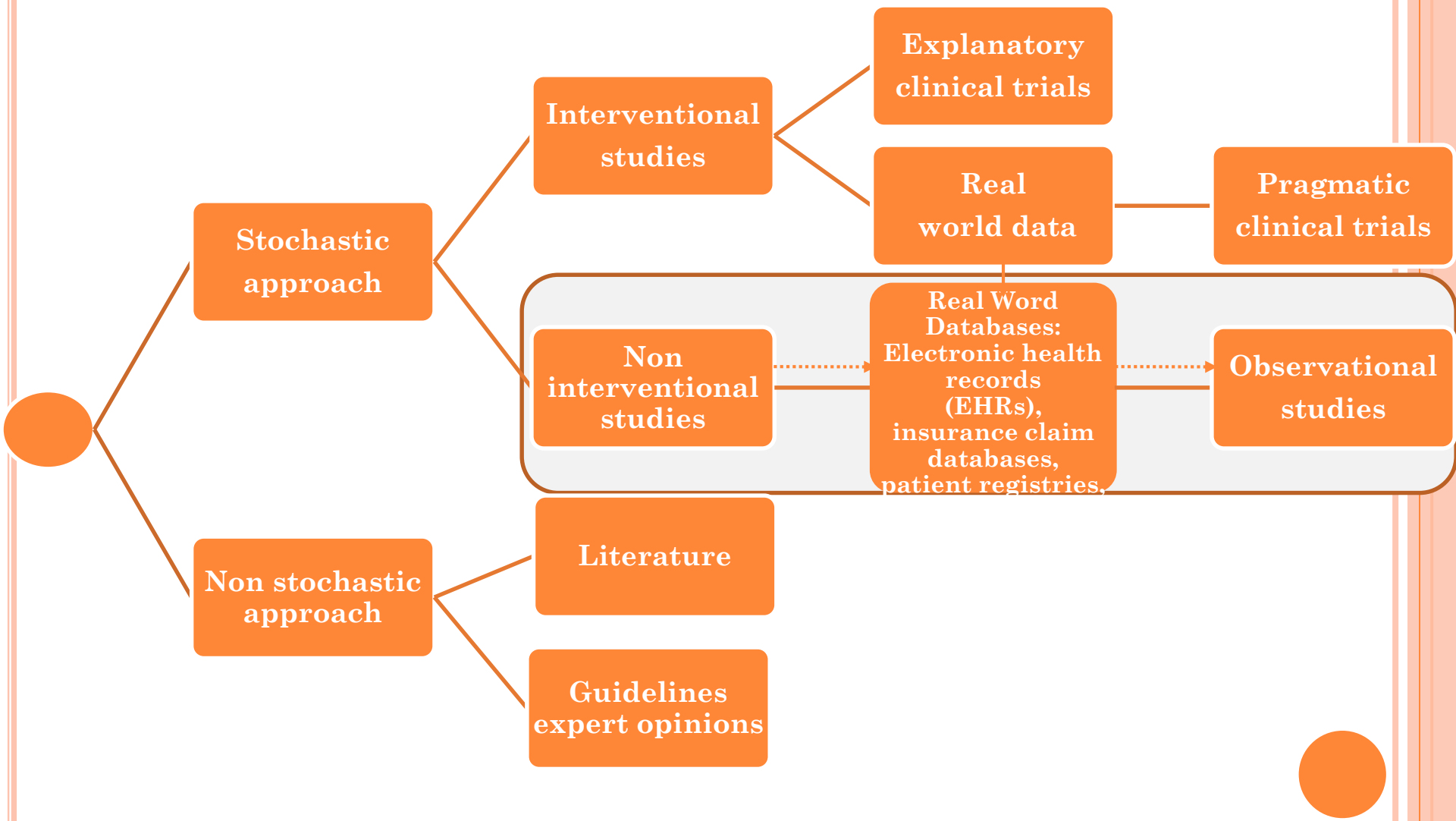
# MEASURING THE COST OF ADVERSE EVENTS

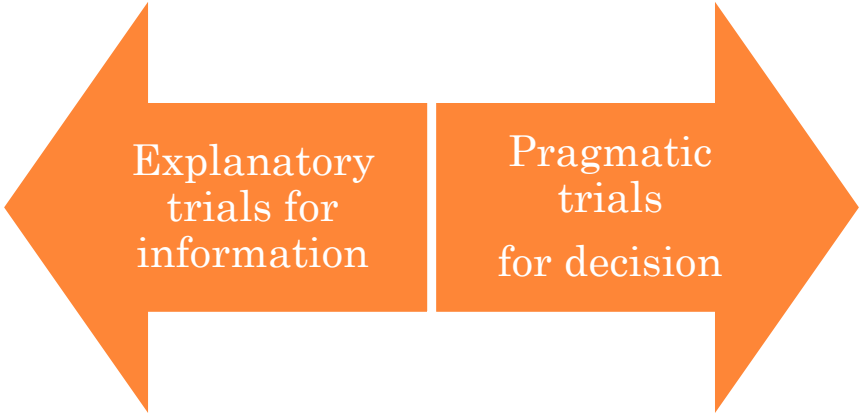
- **Monitoring:** Additional resource use may include blood tests and other laboratory tests to ensure that known adverse events are not occurring.
- Monitoring for adverse events is more intensive the first year on therapy.
- Adverse events are likely to be more frequent and more severe the first year on treatment because the body adapts to the medicine and/ or because those with severe adverse events switch to another drug.
- ***Other costs***: physician visits, emergency department [ED] visits, medications, hospitalizations or other services or procedures

# Measuring the cost of adverse events: 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
- While incidence of AEs is commonly derived from clinical trials costs of AEs can be derived from a number of different sources/approaches

# SOURCES FOR RESOURCE USE DATA





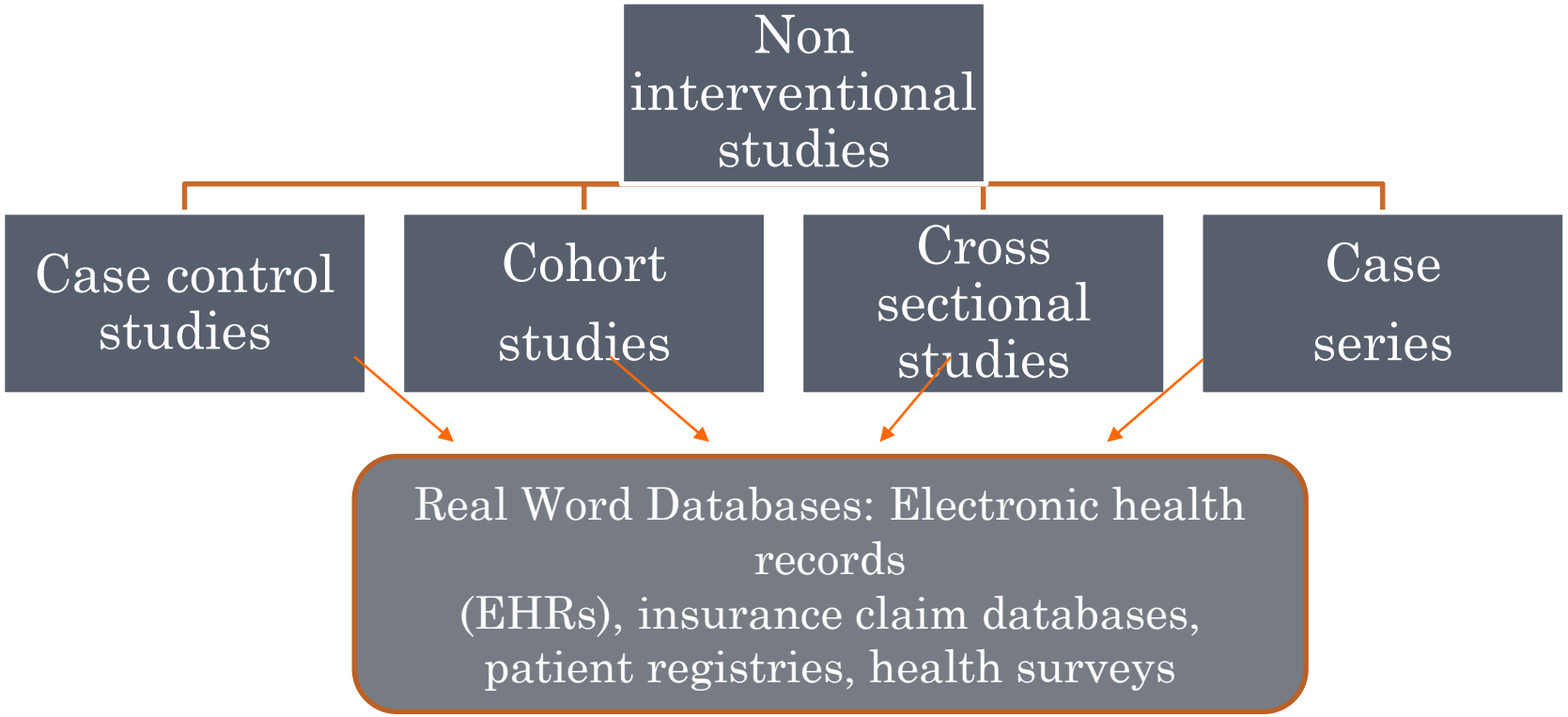

Internal validity vs external validity

THE DOMAINS OF PRECIS-2 tool

| Domain | Description |
|---|---|
| *Eligibility* | to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? |
| *Recruitment* | how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients? |
| *Setting* | how different is the setting of the trial to the usual care setting? |
| *Organisation (intervention)* | how different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care? |
| *Flexibility (delivery)* | how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care? |
| *Flexibility (adherence)* | how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care? |
| *Follow-up* | how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care? |
| *Primary outcome* | to what extent is the trial's primary outcome relevant to participants? |
| *Primary analysis* | to what extent are all data included in the analysis of the primary outcome? |

# Different designs different results ?

- Protocol driven tests or procedures may induce detection of extra cases of adverse events , treated more aggressively. The follow up duration in the case of explanatory attitudes is shorter than in pragmatic attitudes
- A challenge for pragmatic clinical trials is to establish a process supporting the timely collection and reporting of safety data with sufficient detail while minimizing the number of follow-up visits beyond the visits that are part of usual care.
- Adherence and persistence to all drugs used for treatment are likely to be lower in a real-world setting,




- \+ Costs may not be limited to AE management (e.g., include treatment delay/disruption)
- \+ Large sample size from real world setting (more generalizable)
- − Limited to AEs requiring health resource utilization
- − Lack of information on the severity of an AE
- − Costs related to AEs cannot be perfectly distinguished from disease-related costs

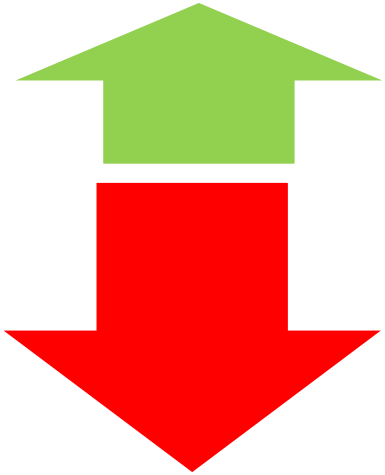
# NON STOCHASTIC APPROACHES

1. Guidelines

➕ Strong clinical validity and it is less time/ resource consuming

➖ The potential to miss costs and the inability to account for variation in care across practices or AE management

## 2. Literature



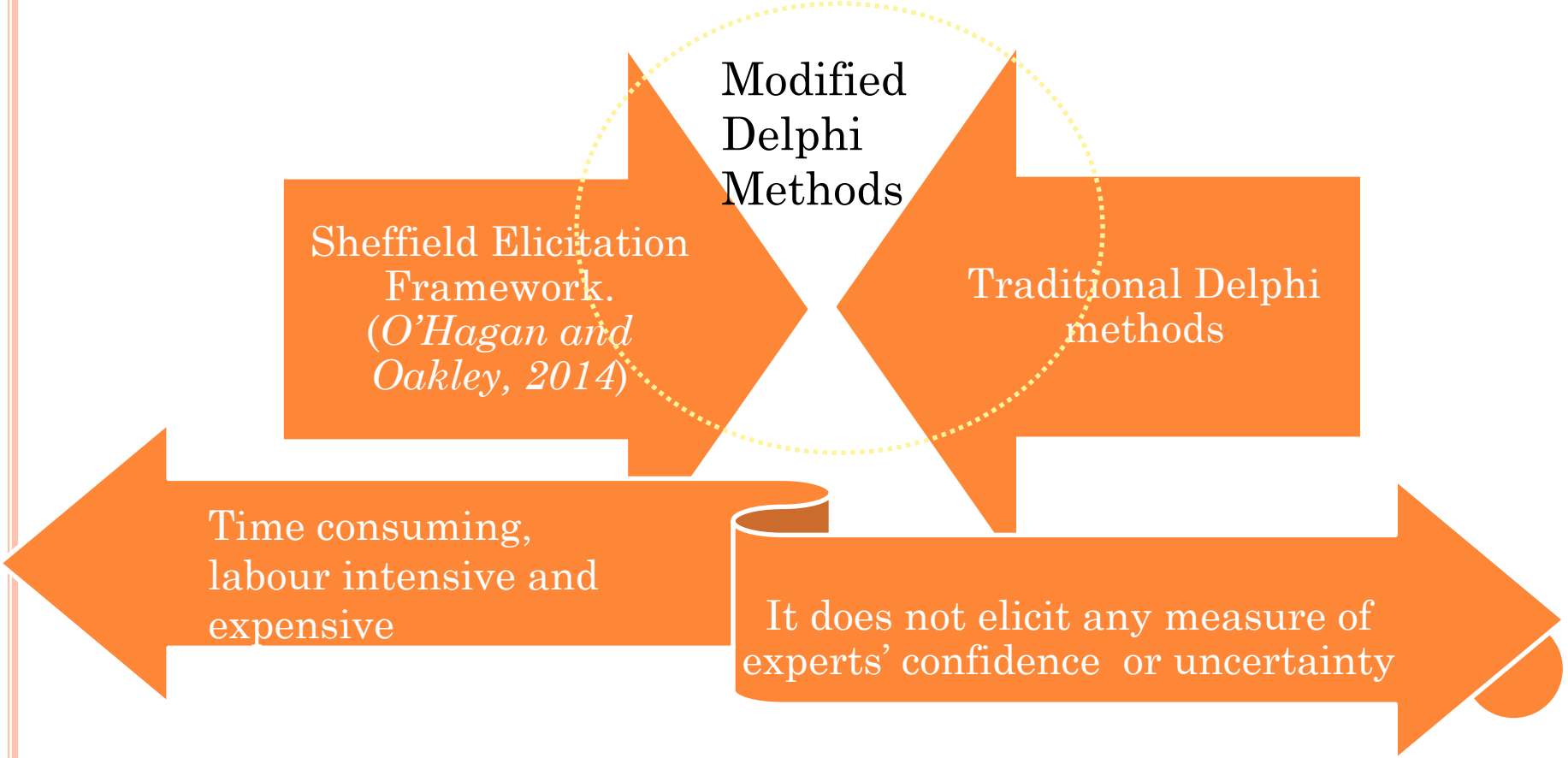
Peer-reviewed evidence

1.Generalizability issues. Additionally, a single study may not have all adverse events required for a model,

2. Resource use and costs are sensitive to variability across settings, both *within a* country and *between* countries,in features of the local context, such as local prices or aspects of service organization and delivery).

# NON STOCHASTIC APPROACHES

## 3. CLINICAL EXPERT OPINION



# PROS AND CONS OF EXPERTS ELICITATION METHODS

- ↗ Clinical validation for new drugs not yet on the market,
- ↗ Expert opinion might be the best source.

- ↘ Time and resources consuming if the number of quantities of interest is very large
- ↘ Not reflective of variation in care across practices

# EXAMPLES FROM ONCOLOGY

Guideline-based and claims-based approaches may provide different estimates of AE costs

| Study AE | Management Assumption | Claims Analysis Cost (Incremental Cost per Episode) | Guidelines Based Cost of AE | Difference |
|---|---|---|---|---|
| Anemia | One outpatient visit ($146) +CBC test ($0) + 50% of the patients treated with 40,000 units of epoetin weekly for 8 weeks (20*$30/2000 units*8 weeks=$4800) | $4353 | $2577 | $1776 |

Wong et al , **Estimating the Costs of Adverse Events in Economic Models: Is There a "Right" Approach?** Value & Outcomes Spotlight May/June 2019

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|---|---|---|---|---|
| Thrombocytopenia | 2 units of platelet transfusion ($6427) + ER visit ($176) required 25% of time | $6325 | $6472 | $147 |
| Neutropenia | 4 administrations of pegfilgrastim by subcutaneous injection (4*[$4,685+$25]) +10% of patients have: ER visit ($176), primary physician consultation each day ($138 + $73 + $73), specialist | $5321 | $19,933 | $14,612 |

# DATA SOURCES PREFERRED FOR BUDGET IMPACT ANALYSIS

| RESSOURCE USE | National Agencies |
|---|---|
| RCTs, meta-analysis (synthesising data from several sources), clinical practice guidelines, local administration and accounting data, and expert opinion. | **Health Information and Quality Authority , Ireland** |
| Real World Data, clinical trials , experts opinion | **Patented Medicine Prices Review Board (PMPRB), Canada** |
| RTC's, Observational studies , experts opinion, meta-analyses | **Pharmaceutical Benefits Advisory Committee (PBAC),** |

# DATA SOURCES PREFERRED FOR BUDGET IMPACT ANALYSIS

| RESSOURCE USE | National Agencies |
|---|---|
| RTC's, "Protocols-driven costs" must be excluded | **Belgian Health Care Knowledge Centre (KCE),** |
| Medico-administrative databases, pragmatic clinical studies, market studies, patient registries, litterature review or ad hoc studies.<br>The use of resource use data collected in the context of a clinical trial must be justified and generally supplemented because such data rarely covers the full range of resource use associated with a health intervention. | **Haute Autorité de Santé (HAS)** |

# CONCLUSIONS

- Estimates of adverse event (AE) costs are an important input into economic evaluations and their inclusion has been outlined
- No accordance exists between researchers about the methodology used to measure and include the economic impact of adverse events in economic evaluations

# CONCLUSIONS

- Different  study approaches may provide different estimates of AE costs and which can potentially have a large impact on estimates, depending on the circumstances.
- Given the strengths and limitations of stochastic and non stochastic methods, applying a combination of both approaches may be optimal in some cases.

# THANK YOU FOR YOUR ATTENTION!!!