**Supplementary File 1:**

**Title**: Adherence to Country-specific Guidelines among Economic Evaluations undertaken in three High-Income and Middle-Income Countries: A Systematic Review

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**Appendix 1: PRISMA Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 5 (not PICOS this is methodological review) |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 7 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 8 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 7 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 7 and Supplementary file 1 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  |  8 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  |  9 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 9 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 8 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 10 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 10 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  |  |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 10 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 11, Figure 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 11-15; Table 1,2)Citation: supplementary file 1 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 15 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 11-15 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | NA (meta-analysis not done) |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | NA (meta-analysis not done) |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | 15,16 |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | Page 17 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | Page 20 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Page 21 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Page 3 |

**Appendix 2: Search strategy**

 **PubMed Search strategy for identifying economic evaluation pertaining to Canada**

1. cost benefit analys\*
2. analys\*, cost benefit
3. cost benefit data
4. data, cost benefit
5. cost-benefit analysis[MeSH Terms]
6. **#1 OR #2 OR #3 OR #4**
7. cost utility analys\*
8. analys\*, cost utility
9. cost-utility analysis[MeSH Terms]
10. **#7 OR #8 OR #9**
11. cost effectiveness
12. effectiveness, cost
13. cost effectiveness analys\*
14. analys\*, cost effectiveness
15. cost-effectiveness analysis[MeSH Terms]
16. **#11 OR #12 OR #13 OR #14 OR #15**
17. cost minimization analys\*
18. analys\*, cost minimization
19. cost-minimization analysis[MeSH Terms]
20. **#17 or #18 OR #19**
21. marginal analys\*
22. analys\* marginal
23. economic evaluation\*
24. evaluation\*, economic
25. economic impact analys\*
26. pharmaco-economic analys\*
27. analys\*, pharmaco-economic
28. pharmaco-economic analysis[MeSH Terms]
29. efficiency analys\*
30. analys\* efficiency
31. incremental cost effectiveness ratio\*
32. incremental costs
33. incremental benefit
34. health economic
35. health economic\*
36. health economics[MeSH Terms]
37. health technology assessment\*
38. technology assessment\*, health
39. assessment\*, health technology
40. biomedical technology assessment\*
41. assessment\*, biomedical technology
42. medical technology assessment\*
43. assessment\*, medical technology
44. **#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43**
45. **#6 OR # 10 OR #16 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #44**
46. canada
47. canadian
48. alberta
49. british Columbia
50. manitoba
51. new brunswick
52. newfoundland NEXT labrador
53. northwest territories
54. nova scotia
55. nunavut
56. ontario
57. prince edward island
58. quebec
59. saskatchewan
60. yukon NEXT territory
61. Canada[MeSH Terms]
62. **#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61**
63. **#45 AND #62**

Filters: Publication date from: 2018/3/1 to 2018/12/31

No language restrictions

We did nott filter out Publication type in PubMed because of avoiding search only in Medline database.

1. **PubMed Search strategy for identifying economic evaluation pertaining to South Africa**
2. cost benefit analys\*
3. analys\*, cost benefit
4. cost benefit data
5. data, cost benefit
6. cost-benefit analysis[MeSH Terms]
7. **#1 OR #2 OR #3 OR #4**
8. cost utility analys\*
9. analys\*, cost utility
10. cost-utility analysis[MeSH Terms]
11. **#7 OR #8 OR #9**
12. cost effectiveness
13. effectiveness, cost
14. cost effectiveness analys\*
15. analys\*, cost effectiveness
16. cost-effectiveness analysis[MeSH Terms]
17. **#11 OR #12 OR #13 OR #14 OR #15**
18. cost minimization analys\*
19. analys\*, cost minimization
20. cost-minimization analysis[MeSH Terms]
21. **#17 or #18 OR #19**
22. marginal analys\*
23. analys\* marginal
24. economic evaluation\*
25. evaluation\*, economic
26. economic impact analys\*
27. pharmaco-economic analys\*
28. analys\*, pharmaco-economic
29. pharmaco-economic analysis[MeSH Terms]
30. efficiency analys\*
31. analys\* efficiency
32. incremental cost effectiveness ratio\*
33. incremental costs
34. incremental benefit
35. health economic
36. health economic\*
37. health economics[MeSH Terms]
38. health technology assessment\*
39. technology assessment\*, health
40. assessment\*, health technology
41. biomedical technology assessment\*
42. assessment\*, biomedical technology
43. medical technology assessment\*
44. assessment\*, medical technology
45. **#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43**
46. **#6 OR # 10 OR #16 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #44**
47. South Africa [MeSH Terms]
48. Republic of South Africa
49. Union of South Africa
50. **#46 OR #47 Or #48**
51. **#45 AND #49**

Filters: Publication from: 2013/12/1 to 2018/12/31

No language restrictions

We did not filter out Publication type in PubMed, because of avoiding search only in Medline database.

1. **PubMed Search strategy for identifying economic evaluation pertaining to Egypt**
2. cost benefit analys\*
3. analys\*, cost benefit
4. cost benefit data
5. data, cost benefit
6. cost-benefit analysis[MeSH Terms]
7. **#1 OR #2 OR #3 OR #4**
8. cost utility analys\*
9. analys\*, cost utility
10. cost-utility analysis[MeSH Terms]
11. **#7 OR #8 OR #9**
12. cost effectiveness
13. effectiveness, cost
14. cost effectiveness analys\*
15. analys\*, cost effectiveness
16. cost-effectiveness analysis[MeSH Terms]
17. **#11 OR #12 OR #13 OR #14 OR #15**
18. cost minimization analys\*
19. analys\*, cost minimization
20. cost-minimization analysis[MeSH Terms]
21. **#17 or #18 OR #19**
22. marginal analys\*
23. analys\* marginal
24. economic evaluation\*
25. evaluation\*, economic
26. economic impact analys\*
27. pharmaco-economic analys\*
28. analys\*, pharmaco-economic
29. pharmaco-economic analysis[MeSH Terms]
30. efficiency analys\*
31. analys\* efficiency
32. incremental cost effectiveness ratio\*
33. incremental costs
34. incremental benefit
35. health economic
36. health economic\*
37. health economics[MeSH Terms]
38. health technology assessment\*
39. technology assessment\*, health
40. assessment\*, health technology
41. biomedical technology assessment\*
42. assessment\*, biomedical technology
43. medical technology assessment\*
44. assessment\*, medical technology
45. **#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43**
46. **#6 OR # 10 OR #16 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #44**
47. Egypt [MeSH Terms]
48. **#45 AND #46**

Filters: Publication from: 2014/8/1 to 2018/12/31

No language restrictions

We did not filter out Publication type in PubMed, because of avoiding search only in Medline database.

**Appendix 3: Methods used to transform HTA guidelines into checklists.**

**Egypt**

The Egyptian guidelines titled ‘Guidelines for reporting Pharmacoeconomic Evaluation’ provide recommendations on 12 key principles listed below:

1. **Disease and Product Background**
2. **Study Design**
3. **Appropriate Pharmacoeconomic Method**
4. **Time Horizon**
5. **Choice of Outcome measure**
6. **Synthesis of Clinical and Economic Evidence**
7. **Costs Determination**
8. **Modelling**
9. **Discounting**
10. **Uncertainty**
11. **Present Study Results**
12. **Equity and Generalizability Issues**

Firstly, all these 12 key areas were listed in the adherence checklists.

Thereafter, recommendations were reviewed under each of these key areas.

1. **Disease and Product Background**

For disease and product background the following recommendations are suggested in the guideline:

“*Economic evaluations should provide information about the epidemiology of the disease and treatment pathways according to most recent treatment guidelines. Data on the product should include pharmacological class, proposed dosing regimen, route of administration and results of clinical studies performed to date* [1].”

With reference to the above text in the adherence checklist we included 6 questions:

Is information provided about:

* 1. The epidemiology of the disease
	2. Treatment pathways according to most recent treatment guidelines.
	3. Product pharmacological class
	4. Dosing regimen,
	5. Route of administration
	6. Results of clinical studies performed to date

Since, the guideline did not elaborate as to what details should be provided, therefore, the response to each of this question was marked as simple Yes- if details are provided and No-if details are not provided.

1. For **Study Design** the guideline recommends

“*The study question should address the needs of the decision makers by clearly establishing the context of the study. It should provide details of the study perspective, the proposed product and its comparator(s), the target population and the impact on specific subgroups where appropriate. Secondary questions that relate to the primary study question should be clearly stated [2].*”

In accordance to the above text the following questions were included in the adherence checklist

* 1. Does the study provide details on Context/Rationale of the study
	2. Are details on Study Perspective provided
	3. Are details provided for the proposed Product/Intervention
	4. Are details provided on Comparator
	5. Are details provided on Target Population
	6. Are details provided on the impact of specific Subgroups

Next, we reviewed if detailed recommendations were provided for each of these points. For example no further details were provided with respect to question 2.1, so the response for this was included as simple yes or no.

For 2.4 additional details were provided as follows:

“*The selection of the comparator has to be justified. Comparators should be policy relevant, therefore widely used and reimbursed health care technology for a given patient group and indication is the preferred option. If no such technologies are reimbursed in tender list at the time when the assessment is conducted, the investigated product can be compared with the most frequently used technologies to treat the same patient groups. If a new product is used as first-line, second-line or third-line, it should be compared with first, second or third-line therapies respectively*”

So for study comparator the following questions two questions were included

2.4.1 Is the selection of comparator justified- Yes/No

2.4.2 Is widely used and reimbursed technology selected as the comparator or most frequently used technology-Yes/No

For 2.5, the guideline text reads as follows

“*The targeted population should include both those who are insured by the Egyptian health system and those who are uninsured. Parameters to define the population include baseline demographic characteristics, disease characteristics, treatment setting, the context of past treatment and any confounders adjusted [1].”*

So for target population the following 3 questions were included

2.5.1 Details provided on demographic characteristics

2.5.2 Details provided on disease characteristics

2.5.3 Details provided on treatment setting, the context of past treatment and confounders adjusted

For 2.6 the guideline provides the following details

“*Specific subgroups should be identified for those whom clinical and cost-effectiveness may be expected to differ from that of the overall population. Stratified analysis used to quantify the differences in cost-effectiveness that may exist in different subgroups is recommended as it may contribute important information to the final advice. The evidence supporting the clinical plausibility of the subgroup effect should be fully documented, including details of statistical analysis*”

With reference to the above text for Subgroup analysis the following questions were added in the adherence checklist

* + 1. Subgroup identified and subgroup analysis undertaken-Yes/No
		2. Subgroup analysis is full documented/Justified: Yes/No
1. **Appropriate Pharmacoeconomic method**

The guideline text reads as follows

“*The choice of method of analysis depends on the research question and must be justified. If the compared health technologies result in equal health gain, cost minimization analysis is the preferred analytical approach.*

*If at least one of the compared health technologies is better than the other, and the clinical benefit can be aggregated and interpreted as naturalistic clinical outcomes, cost-effectiveness analysis (CEA) is the preferred method. Cost-effectiveness analysis, where an intermediate marker is chosen, must have a validated, well established link with an important hard-end point (e.g. patient survival, heart attack, bone fracture) [5]. As the measure of primary clinical outcome may differ in different therapeutic areas, cost-effectiveness analysis cannot be used to compare or rank the cost-effectiveness of a broad set of products.*

*If quality of life of patients is an important clinical outcome in the treatment course of patients, cost-utility analysis (CUA) is the preferred analytical approach. In CUA the health gain is expressed in a combined single measure of life years and health related quality of life (HRQoL), e.g., in quality adjusted life years (QALYs) [6]. Ignoring quality of life differences among products would provide less than complete data to decision makers to address the healthcare dilemma of where to allocate resources [7]. Adherence to reference case approach for estimating QALYs for inclusion in economic evaluations would facilitate comparability [8].”*

The guidelines suggests that different types of economic evaluation CMA or CEA or CUA can be and the choice should be justified. Accordingly the following question was included in the adherence checklist

* 1. Choice of pharmacoeconomic method justified-Yes/No
1. **Time horizon**

For time horizon the guideline recommends

“*In choosing the time horizon, it should be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period to reflect the course of the disease and the effects of the interventions. The same time horizon should be applied to both costs and outcomes [5]. A decision to use a shorter timeframe should be justified*”

To capture this point we included the following question in the adherence checklist

* 1. Is time horizon of analysis justified such that it ensures that the chosen outcome and resource consumption are observable in this period- Yes/No
1. **Choice of Outcome measure**

“*HRQoL is an appropriate outcome indicator for the evaluation of health status. HRQoL can be measured by using generic questionnaires, disease-specific questionnaires, or preference-based measures. If HRQoL is to be included in the study design, this variable must be measured by validated instruments. The direct use of EQ-5D, SF-6D or similar generic measures is recommended, because they are easy to use and interpret and are based on preferences of the general public. If the use of disease specific HRQoL instruments increases the sensitivity of measurement, mapping of disease specific HRQoL results with EQ-5D or similar generic measures can be useful to translate the findings into QALYs.”*

The above text from the guideline was translated into two questions which were included in the checklist

* 1. HRQol is taken as the Outcome measure
	2. Methodology- HRQoL is measure using generic/disease specific or preference based measures using tools such as EQ5D, SF-6D etc
1. **Synthesis of Clinical and Economic Evidence**

“*Estimation of health gain must be based on scientific literature review and /or results of primary data collection, the best available evidence should be considered. Meta-analysis based on large randomized controlled trials is the highest hierarchy of evidence with the heterogeneity of data accounted for. If compared drug therapies differ in adherence or persistence of patients, then these factors should be incorporated in calculating the relative effectiveness. In case of orphan drugs where randomized controlled clinical studies have not been conducted, the results of uncontrolled clinical studies can be accepted, including studies with small sample size. All product safety data need to be included whether from clinical studies or from national and foreign pharmacovigilance centers and patient registries with attention given to those that differ substantively among the products being compared [11].*”

* 1. It is reported that Evidence is based on meta-analysis/RCT/primary data collection-Yes/No
1. **Costs**

*Official sources of unit cost data for products (e.g. tender lists) are preferable. In the absence of a published tender list price, the price submitted by a manufacturer for a product may be used. The quality, validity, relevance and generalizability of local data should be clearly described. Both estimated consumption of resources and their unit prices must reflect real-world settings in Egypt as relative and absolute price levels differ among countries [12].*

*Resource use and costs should be identified, measured in their natural units and values [13]. The primary perspective for these studies is the overall health care services. Therefore, the resources that should be considered are direct medical costs which include drugs, medical devices, medical services including procedures, laboratory or diagnostic tests, hospital services and emergency department visits, and primary care visits. Other direct non-medical and indirect costs paid by patients, including lost productivity costs, might be included only in the sensitivity analysis. If indirect costs are included in the analysis, the rationality of the costs and how they are estimated should be explained. Current and future costs arising as a consequence of a product, and occurring during the specified timeframe of the study, should also be included. Mean values should be used. Different costs or costs of the same resources that are used in different quantities should be included in the analysis [14].*

*Out of the two general approaches to determine costs, micro-costing and macro-costing, macro-costing is preferred [15]. The source of cost data must be reported in details. Data should be the most recently available, with the cost year specified. Retrospective input costs should be inflated to the most recent calendar year using the Consumer Price Index for health [16]. The drug cost used should reflect the formulation and pack size that gives the lowest cost. For drugs available in the outpatient pharmacies, the full public price should be used for calculating costs. For hospital products the wholesale price should be used for cost-calculations. Future costs should be calculated at constant current costs, therefore results are not subject to uncertainty in future inflation rates.*

Accordingly the following questions were added

* 1. Data source
	2. Reference period costs
	3. Unit price mentioned
	4. Direct medical costs
	5. Direct non medical (SA optional)
	6. Indirect costs (SA optional)
	7. Indirect costs rationality
	8. Indirect costs methods
1. **Modelling**

The following lines elaborate the recommendation on modelling

*The results of economic modeling studies presented should take into account the following requirements: a) the model should be described in detail and should correspond to real practice of patient management, b) the model should be as simple as possible, and easily understood, c) to facilitate assessment of the outputs of a model, full documentation of the structure, data elements and validation of the model should be addressed in a clear manner, with justification provided for the options chosen and presented through diagrams (e.g. decision trees, Markov models) [18].*

Based on the above text the following 4 questions were included in the adherence checklist

8.1 Model described in detail and corresponds to real practice?

8.2 Model structure documented (decision tree/Markov diagrams)

8.3 Data elements are reported

8.4 Validation of the model is done in a clear manner?

1. **Discounting**

“Discounting should be made according to the time horizon. Any costs or outcomes occurring beyond one year should be discounted using standard methods [15]. For comparability of results across evaluations, it is important that a common discount rate is used. As constant prices and outcomes are used in the economic evaluation, there is no need to take into account inflation in the discount rate. A real discount rate of 3.5 % per year should be used for both costs and health gains. The discount rate should be varied from 2% to 6% in the sensitivity analysis.”

* 1. Are costs beyond one year discounted
	2. Are outcomes beyond one year discounted
	3. Is a common discount rate of 3.5% used for both costs and outcomes
	4. Is discount rate varied from 2%-6% in sensitivity analysis
1. **Uncertainty**

“*We propose, given the difficulty in interpreting the PSA, that DSA should be required, whilst PSA remains optional. To avoid potential bias and uncertainty that arise from the modeling process, assumptions about the model structure should be clearly stated and justified and their impact on cost effectiveness explored though a series of plausible scenario analyses so that whether the study results will be changed can be observed. All choices and the ranges of the parameters, and the method used in sensitivity analysis should be clearly explained”*

* 1. Is DSA done? Yes/No
	2. Are assumptions (all choices and ranges of parameters and methods of sensitivity analysis) clearly stated? Yes/No
1. **Present Study Results**

“*Total costs and health outcomes must be reported separately and the aggregated result be explained. All parameters used in the estimation of clinical and cost-effectiveness should be itemized in tabular form with data sources transparently. Negative results should be reported. Incremental cost-effectiveness ratio (ICER) has to be calculated, unless one of the compared health technologies dominates the other one. In addition, the potential impact of the introduction of the new treatment on the society also needs to be assessed [20]. Where more than two products are being compared, the results should be presented in the order of increasing costs and the ICER calculated by comparing each product with the one above it, excluding those products that are dominated. Equity issues, affordability, resource constraints should be considered in judging the cost effectiveness of a product for reimbursement [16].*

*Tornado diagrams are useful tools to display DSA. If PSA are performed, the probability that the intervention is cost-effective at a range of threshold values should be reported and the data should be displayed graphically to facilitate the uncertainty interpretation [5]”*

The above excerpts from the guideline were translated into following questions

* 1. Total costs reported separately
	2. Total health outcomes separately
	3. Aggregate results explained
	4. Parameters presented in in tabular form with data sources/references
	5. ICERs calculated
	6. Equity discussed
	7. Affordability, resource constraints discussed

There is no recommendation to use tornado diagrams- it just states these are useful tools to display DSA, however it is not mentioned whether use of tornado diagrams is mandatory or recommended. Hence, no adherence question was included related to this.

Next, the recommendations regarding PSA are optional i.e. if performed therefore no adherence question was included for this part as well.

1. **Equity and Generalizability Issues**

“*Analysts must consider two specific areas of concern regarding generalizability of clinical and economic data in the assessment of technologies. The first area of concern is the extent to which the clinical efficacy data is representative of the likely effectiveness and similarly, the extent to which economic data is representative of the costs and resource utilization [4]. The second area of concern is the generalizability of the economic and clinical data across different patient ages and genders as well as regional differences in healthcare practice within Egypt. These areas of concern should be identified and discussed and the likely impact on the results and conclusions of the report should be highlighted [21].”*

Pertaining to the above recommendation, the following two questions were included in the adherence checklist

* 1. Generalizability of clinical efficacy data representative of effectiveness discussed?
	2. Generalizability of economic data across different patient ages and genders as well as regional differences in healthcare practice within Egypt are discussed?

**Appendix 4: Summary of key features of the three National Guidelines**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Canada | South Africa | Egypt |
| GENERAL FEATURES |
| Title | Guidelines for the Economic Evaluation of Health Technologies: Canada | Guidelines for Pharmacoeconomic submissions | Guidelines for reporting pharmacoeconomic evaluations in Egypt |
| Year of the publication | 2017 | 2012 | 2013 |
| Guidelines’ document length | 76 pages | 61 pagesPart A: Process of submission (9 pages)Part B: Content of submission (52 pages) | 14 pages |
| Version | 4th  | 1st  | 1st  |
| Previous versions | 1994, 1997, 2006 | NA | NA |
| Organization  | Canadian Agency for Drugs ad Technologies in Health (CADTH) |  National Department of Health | Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Minister of Health and population |
| Guideline development process | • Guideline topics from the 3rd edition were reviewed to determine areas where methodological advancements had occurred. • Health economic methods literature was reviewed and health economic experts were consulted. • Gaps within the topic areas were identified and research was commissioned  | •Were developed as a Regulation to the Medicines and Related Substance Act (Act 101/1965)  | • Review of existing guidelines •Quasi delphi approach for Focus group discussion including experts from academics and industry  |
| Objective  | Inform decision makers regarding the cost effectiveness of health technologies including drugs. Provide best practices for conducting economic evaluations of health care interventions in Canada. Useful for providing standardized ad reliable information to the target audience. Providing a template for final reports. | To create a standard for conducting pharmacoeconomic evaluation of new and existing medicines; and the criteria for medicines which require submissions; To create a forum which provides independent and objective review of the value of medicines | To provide a scientific guidance to conduct ad report a pharmacoeconomic study |
| Target Audience | Canadian decision and policy makers | Pharmaceutical companies, researchers ad decision makers | Public a Pharmaceutical companies, researchers ad decision makers d Private payers, healthcare industries ad clinicians |
| Whether mandatory  | No | No Though regulations allow for a mandatory request for a particular medicine to be made | No |
| Key Principles Included | 1. Decision Problem 2. Types of Evaluations 3. Target Population 4. Comparators 5. Perspective 6. Time Horizon 7. Discounting. 8. Modelling 9. Effectiveness 10. Measurement and Valuation of Health11. Resource Use and Costs 12. Analysis 13. Uncertainty 14. Equity 15. Reporting | 1. Executive Summary
2. Description of Disease/Clinical Condition
3. Details of Medicine
	1. Pharmacological Class and Action
	2. Clinical Indication(s)
	3. Treatment Details
	4. Co-administered Therapies
	5. Choice of Comparator Treatment
	6. Expert Opinion
4. Clinical Outcomes (Effectiveness)
	1. Description of Search Strategies for Relevant Data
	2. List of all Comparative Trials
	3. Selection of Comparative Trials used in the Submission
	4. Exclusion of Clinical Trials
	5. Evaluation of Clinical Trials for Inclusion in the Submission
5. Perspective
6. Time Horizon
7. Type of Pharmacoeconomic Analysis
8. Modelled Evaluations
	1. Application for Use of a Model
	2. Modelling Options
	3. Population Used in the Modelled Evaluation
	4. Presenting Clinical Inputs
	5. Resource Use and Costing Inputs
	6. Discounting
	7. Dealing with Uncertainty and Sensitivity Analyses
	8. Presenting the Results of the Evaluation
 | 1. Disease and Product Background
2. Study Design
3. Appropriate Pharmacoeconomic Method
4. Time Horizon
5. Choice of Outcome Measure
6. Synthesis of Clinical and Economic Evidence
7. Costs Determination
8. Modeling
9. Discounting
10. Uncertainty
11. Present Study Results
12. Equity and Generalizability Issues
 |
| RECOMMENDATIONS ON PRINCIPLES OF ECONOMIC EVALUATION |
| Decision Problem/ Background | should be clearly stated, a comprehensive specification of the interventions to be compared, the setting(s) in which they are to be compared, the perspective of the evaluation, which costs and outcomes are to be considered, the time horizon, and the target population for the evaluation should be provided.  | Demographics of patients suffering from this condition including targetpopulation for treatment; Epidemiological data; Burden of Disease; Current treatments; Challenges of current treatments; and any existing Clinical Guidelines for the condition | Provide information about the epidemiology of the disease and treatment pathways according to most recent treatment guidelines. Data on the product should include pharmacological class, proposed dosing regimen, route of administration and results of clinical studies performed to date |
| Type of Economic Evaluation | Cost utility analysis, any departure should be clearly justified  | Selection of the type of analysis should be clearly stated with justification of use of that particular analysis | The choice of method of analysis depends on the research question and must be justified |
| Comparator | Compare all relevant interventions, including current care  | Standard of care for local practice such as those described in the Prescribed Minimum Benefits (PMB) and Essential Drugs List (EDL). | widely used and reimbursed health care technology for a given patient group and indication is the preferred option |
| Perspective | Publicly funded health care payer.  | Third-party payer (i.e. a funder) | Perspective should be relevant to the research question and adapted to benefits gained by the health care system. |
| Measure of costs | Researchers should systematically identify, measure, value, and report all relevant resources based on the perspective of the publicly funded health care payer.  | Systematically identify, measure, and value resources that are relevant to the study perspective. Provide a clear tale identifying: type of resources, unit of measurement, unit cost, source/ reference. In general, indirect costs should not be included in the submission. | Direct medical costs which include drugs, medical devices, medical services including procedures, laboratory or diagnostic tests, hospital services and emergency department visits, and primary care visits. Other direct non-medical and indirect costs paid by patients, including lost productivity costs, might be included only in the sensitivity analysis |
| Measure of health outcome | QALY should be used, health preferences obtained from an indirect method of measurement that is based on a generic classification system (e.g., EuroQol 5-Dimensions questionnaire [EQ-5D], Health Utilities Index [HUI], Short Form 6-Dimensions [SF-6D]). Researchers must justify where an indirect method is not used  | Life years gained, deaths prevented or QALYs, Where a quality of life instrument is used, details should be provided on the instrument. Currently, there is no golden standard for quality of life instruments | Health related quality of life (HRQoL) is an appropriate outcome indicator HRQoL can be measured by using generic questionnaires, disease-specific questionnaires, or preference-based measures |
| Time Horizon  | Should be long enough to capture all relevant differences in the future costs and outcomes associated with the interventions being compared  | Based on the natural course of the condition and the likely impact that the treatment will have on it.Sufficient to capture all relevant clinical outcomes and future costs. | It should be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period to reflect the course of the disease and the effects of the interventions. |
| Discounting | 1.5% for costs and outcomes, Non-reference case analyses, 0% and 3% per year.  | 5% for costs and; Sensitivity analysis using 0% to 10% | 3.5% for costs and outcomes ,Sensitivity analysis 2% to 6% |
| Uncertainty Analysis  | Probabilistic sensitivity analysis  | One-way sensitivity analyses on all variables, two-way sensitivity analyses on sensitive variables, For complex models probabilistic sensitivity analysis. | Deterministic sensitivity analysis is required, Probabilistic sensitivity analysis is optional |
| Presenting Study Results | Should be reported in a transparent and detailed manner with enough information to enable the reader or user (e.g., decision-maker) to critically assess the evaluation. Use a well-structured reporting format  | Firstly in disaggregated form, then in aggregated form. Present Incremental Cost-effectiveness Ratios (ICERs) | Total costs and health outcomes must be reported separately and the aggregated result be explainedAll parameters to be presented in tabular formICERs to be reportedTornado diagrams are useful |
| Equity  | All outcomes should be weighted equally, regardless of the characteristics of people receiving, or affected by, the intervention in question  | NA | An attempt should be made to include equity considerations in the study report. |

Note: For Canada Recommendations for Reference case analysis are summarized;

NA: Not Applicable; QALY: Quality Adjusted Life Years