

Meta-analysis of economic evaluation studies: Data Harmonisation and Methodological issues

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1 **Title: Meta-analysis of economic evaluation studies: Data Harmonisation and**
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3 **Short title:** Meta-analysis of economic evaluation studies

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- 24 • BSB: Conceptualization; Data curation, Formal analysis, Writing - original draft
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39
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1 **Abstract:**

2 **Background:** In the context of ever-growing health expenditure and limited resources,
3 economic evaluations aid in making evidence-informed policy decisions. Cost utility analyses
4 (CUA) are often used in this context, but limitations include pairwise contrasts, missing
5 contrasts, and different sources or quality of data.

6 **Results:** Synthesis of CUA data from multiple studies is therefore desirable to assist policy
7 makers, but there are many challenging methodological issues including: inconsistent reporting
8 of results using different economic parameters, and multiple sources of heterogeneity
9 including: setting, time horizon, perspective, modelling approaches and assumptions, currency,
10 willingness to pay (WTP) threshold, level of country income, and input parameters. In this
11 paper, we provide a step by step description of the methods for data harmonisation and
12 synthesis of aggregated data from CUA studies, as well as a framework for handling
13 heterogeneity; we demonstrate these methods using the example of agents for type 2 diabetes.

14 **Conclusion:** These meta-analytic methods for the synthesis of economic evidence synthesis
15 should be useful for policy makers.

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1 **Background:**

2 In the context of ever-growing health expenditure and limited resources, identifying healthcare
3 services that yield the highest benefit at the lowest cost is a priority. Economic evaluation
4 studies (EES) provide a framework to systematize both clinical and economic outcomes[1]
5 Cost-utility analysis (CUA) is commonly applied to compare clinical and economic outcomes
6 by estimating an incremental cost-effectiveness ratio (ICER). The costs are usually measured
7 in a specific country currency, while the health benefit is usually measured as a quality adjusted
8 life year (QALY), i.e., the product of years lived and health utility score ranging from 0 (death)
9 to 1 (perfect health), or disability adjusted life years (DALY)[2, 3]. The ICER is calculated by
10 $(\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{comparator}})/(\text{QALY}_{\text{intervention}} - \text{QALY}_{\text{comparator}})$, if the ICER is under the
11 willingness to pay (WTP) threshold (measured in monetary cost per QALY gained), the health
12 intervention is considered to be cost-effective.

13 However, many methodological issues in the data synthesis of EESs are more challenging than
14 clinical studies because there are many sources of heterogeneity including: study characteristics
15 (e.g., setting, WTP, country, country income), methodology (time horizon, perspective, data
16 source, model type, input parameters, and assumptions). This is perhaps why most previous
17 systematic reviews of EESs have performed only descriptive analyses and reported only
18 qualitative findings without applying a meta-analysis (MA) to estimate pooled effect measures.
19 Although Crespo et al [4] have described a MA for pooling EES (known as the COMparative
20 Efficiency Research, COMER), it has yet been widely adopted as such MA for clinical
21 outcomes. This might be due to the fact either EESs are too heterogeneous to pool or they chose
22 the lesser known parameter “incremental net benefit” (INB) as the effect measure rather than
23 the more commonly used ICER. However, we believe the choice for pooling INB was justified
24 due to the limitations of the ICER [5]. For instance, a negative ICER may indicate a lower cost
25 compared with higher effectiveness or higher cost along with lower effectiveness of

1 interventions, thus introducing ambiguity in interpretation [4, 6]. In contrast, positive and
2 negative INBs directly indicate cost-effectiveness and non-cost-effectiveness of interventions,
3 respectively, which is the information required by policy makers [7, 8]. Furthermore, the
4 COMER method mainly focused on the statistical methods for pooling, but did not suggest a
5 step-by-step process for data harmonisation and processing to aid the synthesis of economic
6 studies.

7 Hence, in this tutorial paper, we provide step by step of the methods for data harmonisation
8 and synthesis of EESs. Data for cost-effectiveness of diabetic drug controls are used as a
9 demonstration.

10

11 **Methods**

12 Methods are similar to other systematic reviews and MAs [9, 10], and should follow the
13 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]
14 guidelines. This methodological study was a part of previous MAs, in which some additional
15 specific issues apply to EESs are as follows[12-15].

16 **Step 1: Data extraction**

17 All relevant data for comparative EESs (e.g., CUA) should be extracted as follows utilising the
18 PICOS (Population Intervention Comparator Outcome and Study type) framework:

- 19 - General characteristics of EESs including study setting/country, study design (e.g.,
20 CUA with model-based, primary CUA alongside RCT/cohort), study perspective, time
21 horizon, discount rate for cost and utility, type of EESs (e.g., CUA or cost-effectiveness
22 analysis (CEA)), willingness to pay (WTP; country specific or gross domestic products
23 (GDP)-base) or country-level cost-effectiveness threshold[16] where appropriate if
24 WTP was not available, and type of economic models.
- 25 - Characteristics of patients (P) including indication for treatment, sample size, type of

1 patients (e.g., children/adult, general/specific disease, etc.), mean age, percent
2 male/female, mean body mass index (BMI), etc.

- 3 - Type of interventions and comparators (I & C) (with duration of treatment/dosage/day,
4 etc.)
- 5 - Data needed to estimate INB and its variance (O); this includes currency and year,
6 source of cost data (actual data cost collected from patients, central hospital/country
7 costs, etc.) type of cost (e.g., direct/non-direct medical cost, indirect medical cost), and
8 effectiveness outcomes (e.g., life year, QALY, ICER, etc.).

9 Specific data required for pooling include costs or incremental cost (ΔC), and incremental
10 effectiveness (ΔE) along with their standard deviation (SD), standard error (SE), or 95%
11 confidence interval (CI). Some studies may report ICER along with one-way and/or
12 probabilistic sensitivity analysis (PSA). To calculate the INB and its variance, mean and
13 variance of the costs and effectiveness of interventions and comparators along with WTP
14 thresholds are required. In the model-based CUA, studies usually report point estimates of
15 deterministic and/or probabilistic costs and outcomes. We suggest using primarily the measures
16 of central tendency and dispersion measures from PSA results for pooling, as it could be a
17 better representative of real-life situation considering the distribution of all input variables, and
18 conducting sensitivity analyses using point estimates from the deterministic analysis to see
19 robustness of results. The WTP threshold was initiated by the Commission on Macroeconomics
20 and Health in 2002 by the World Health Organization CHOosing Interventions that are Cost-
21 Effective (WHO CHOICE). The WTP threshold in each country usually refers from the
22 standard country guideline based on a fixed value or per capita GDP with returns on
23 investments in health to define whether a health intervention would be (very) cost-effective.
24 [17, 18]. We suggest using the same WTP threshold in monetary units used in the study with
25 further adjustment as per currency conversions as mentioned below.

1 **Step 2: Data harmonisation**

2 *Currency conversions*

3 We need to standardize money units usually reported in different currencies (i.e., US \$, €, £,
4 ¥) and years by converting to purchasing power parity (PPP) adjusted to US\$ for the latest year
5 of analysis. For example, if a study reported cost, ICER, and thresholds in Euros for 2012 and
6 we plan to pool for the current year (e.g., 2020), this currency is firstly converted to 2020 Euros
7 using the historical consumer price index (CPI) of that country. Then, the Euro 2020 value is
8 converted to PPP adjusted US\$ rate using conversion rates from the International Monetary
9 Fund [19]. In addition, GDP-based WTP threshold (K) values also need to be corrected for the
10 current CPI 2020 year and PPP; however, standard/country specific or fixed WTP values only
11 need PPP correction. The variance is calculated as follows:

12
13
$$Var_{PPP_{2020}} = Var_{Euros_{2012}} \times \left(\frac{CPI_{Euros_{2020}}}{CPI_{Euros_{2012}}} \times \frac{1}{PPP_{2020}} \right)^2 \text{----- (1)}$$

14
15 *Estimation of INB and its variance*

16 After currency conversions for cost and K, the INB can be further estimated as follows:

17
18
$$INB = Kx\Delta E - \Delta C \text{----- (2) or}$$

$$INB = \Delta E(K - ICER) \text{----- (3)}$$

19
20 where K is the WTP, and ΔC and ΔE are incremental cost and incremental effectiveness
21 respectively.

22 A positive INB favours treatment, i.e., intervention is cost-effective, whereas a negative INB
23 favours the comparator, i.e., intervention is not cost-effective [4, 7, 8].

1 Variance of INB can be estimated as follows:

$$2 \quad \text{Var}(INB) = K^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2K \sigma_{\Delta E \Delta C} \text{-----(4) or}$$

$$3 \quad \text{Var}(INB) = K^2 \sigma_{\Delta E}^2 + \sigma_{ICER}^2 \text{-----(5)}$$

3

4 Where $\sigma_{\Delta C}^2$, $\sigma_{\Delta E}^2$, $\sigma_{\Delta E \Delta C}$ are variances of ΔC and ΔE and their covariance, and σ_{ICER}^2 is variance
5 of ICER. However, economic studies can report many different parameters; the 5 scenarios
6 below show how to obtain INB and variance starting with different reported data [20].

7

8 **Scenario-1:** The primary EES ideally reports the point estimates and variances for every
9 parameter required for calculation of INB and its variance. The INB can be calculated
10 accordingly to equations (2) to (5)

11 **Scenario-2:** The study reports the means and measures of dispersion (95% CIs) of incremental
12 costs & outcomes, and ICER. The variance of the ICER can be calculated using the following
13 formulas:

$$14 \quad \begin{aligned} 95\%CI \text{ of } \mu_{ICER} &= \hat{\mu}_{ICER} \pm Z_{\alpha/2} \times SE \\ UL_{ICER} &= \hat{\mu}_{ICER} + Z_{\alpha/2} \times SE \\ SE &= \frac{UL_{ICER} - \hat{\mu}_{ICER}}{Z_{\alpha/2}} \text{-----(6)} \end{aligned}$$

14

$$\hat{\sigma}_{ICER}^2 = SE^2$$

$$UL_{ICER} = \text{Upper limit of ICER}$$

$$Z_{\alpha/2} = \text{Standardize normal} = 1.96$$

$$\hat{\mu}_{ICER} = \text{mean ICER}$$

15

16 Once we know the variance of the ICER, the variance of the INB can be estimated using
17 equation (5).

1 **Scenario-3:** The study reports means and 95% CI, SD/SE of costs/outcomes, or $\Delta C/\Delta E$, but
2 does not provide the ICER or its variance. Data for ΔC and ΔE are then used to simulate ΔC
3 and ΔE with 1000 replications using Monte Carlo methods with a gamma and normal
4 distributions for ΔC and ΔE , respectively. The covariance ($\sigma_{\Delta E \Delta C}$) between ΔC and ΔE as well
5 as $\hat{\sigma}_{\Delta C}^2$ & $\hat{\sigma}_{\Delta E}^2$ can be then estimated. If the 95% CI is provided, this is converted to SE using
6 equation (6) above, and used to simulate data. The INB and its variance can be further
7 calculated using equations (2) and (5).

8 **Scenario-4:** The study does not report any dispersion, but does provide the CE plane graphs,
9 a scatter plot of ΔC on Y-axis and ΔE on X-axis, in which individual values of ΔC and ΔE
10 data can be manually extracted from the CE plane using Web-Plot-Digitizer software [21].
11 Then, means of ΔC , ΔE , and their variances and co-variances can be estimated accordingly.
12 Finally, the INB and its variance can be estimated using equations (2) and (5).

13 **Scenario-5:** The study reports neither any dispersion nor the CE-plane graph, but only provides
14 the means (or point estimates) of costs, outcomes, and ICER. In such situations, the measures
15 of dispersions can be borrowed from another similar study if they fulfil the following criteria:

- 16 • They are in the same stratum of country income,
- 17 • Their ICERs are not much different, e.g., $\pm 50\%$ to 75%
- 18 • They are similar in intervention, comparator, time period, country region
- 19 • Similar model type and inputs (i.e., discounting, time horizon).

20 If there is more than one study that meets the criteria, the average of the variances of those
21 studies can be used.

22 **Step 3: Pooling INB**

23 When pooling INBs from many studies, we strongly recommend stratifying by level of country
24 income, model type, time horizon, and perspective in order to reduce heterogeneity. The

1 country income should be classified as low (LIC), lower-middle (LMIC), upper-middle
 2 (UMIC) and high (HIC) as per the World Bank classification⁸. Economic models can include
 3 Markov, decision tree, discrete event simulation, or others. Study perspective should include
 4 societal, third-party payer, and patient perspectives. Time horizon should be lifetime and non-
 5 lifetime (e.g., 5-, 10-years, etc.).

6 The INB can be pooled across studies using a fixed-effect or a random-effect model depending
 7 on the degree of heterogeneity [4, 12, 13, 20].

8

9 A) Fixed-effects model

10
$$INB_p = \frac{\sum_{i=1}^S w_i \cdot INB_i}{\sum_{i=1}^S w_i} \text{-----}(7)$$

11
$$w_i = \frac{1}{Var(INB_i)} \text{-----}(8)$$

12

13 B) Random-effects model

14
$$INB_p = \frac{\sum_{i=1}^S w_i^* \cdot INB_i}{\sum_{i=1}^S w_i^*} \text{-----}(9)$$

15
$$w_i^* = \frac{1}{Var(INB_i) + \tau^2} \text{-----}(10)$$

16
$$\tau^2 = \frac{Q - (S - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \text{-----}(11)$$

17

18 Similar to MA in other areas, heterogeneity needs to be assessed before pooling INB.
 19 Heterogeneity can be visualized by inspection of the forest plot, and quantitated by using the
 20 Cochran-Q test and the I² statistic [4, 12, 13, 20].

21

22
$$Q = \sum_{i=1}^S w_i (INB_i - INB_p)^2 \text{-----}(12)$$

23
$$I^2 = 100\% \times \frac{Q - (S - 1)}{Q} \text{-----}(13)$$

1 If heterogeneity is present, i.e., the $I^2 \geq 25\%$ or p-value of Q test is less than 0.1, the INBs can
2 be pooled using a random-effects model, otherwise a fixed-effect model can be applied [4, 12,
3 13, 20]. Exploring source/s of heterogeneity is strongly recommended. This can be done using
4 a meta-regression to fit each potential source (e.g., time horizon, percent discount rate,
5 threshold values, source of effectiveness measure, etc.) one-by-one. If that potential factor
6 explains some proportion of the heterogeneity, including it in the meta-regression model should
7 reduce the I^2 accordingly. There are no established criteria how much I^2 should be decreased
8 by to consider that factor as a significant source of heterogeneity. In our experience, if the I^2 is
9 reduced by about 50% or more from the baseline model (i.e., the model without any factor),
10 such factor/s may be source/s of heterogeneity. A post-hoc subgroup analysis by that factor
11 should be performed accordingly. In addition, sensitivity analyses excluding a few studies with
12 very different characteristics compared to the rest can be used to see if heterogeneity of INBs
13 can be reduced.

14

15 Similar to general MA, publication bias should be assessed using a funnel plot and Egger's test.
16 A funnel plot graphs INB estimates on the x-axis against their precision on y-axis. If all studies
17 are estimating the same true INB, their INBs should be randomly scattered around the true
18 value and form a funnel shape. Egger's test formally tests if the funnel is symmetrical; if this
19 is significant, it usually indicates that there is heterogeneity or missing studies (publication
20 bias) or both. A contour-enhanced funnel plot is further recommended [22]. This plot will
21 contour area of the funnel into non-significant (P-value >0.05 - <0.1) and significant areas (P-
22 value <0.01 and < 0.05), which will help to differentiate the cause of the asymmetry. For
23 instance, if missing studies fall into the non-significant area, asymmetry might be due to
24 missing studies or publication bias. Conversely, if missing studies are in significant areas,
25 heterogeneity is more likely to be the explanation.

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Example: We used data from a MA of CUA of glucagon-like peptide 1 agonists (GLP1) for treatment of type 2 diabetic (T2D) patients who failed to achieve control with metformin monotherapy [12]. A total of 56 studies with 82 comparisons were eligible for pooling INBs. We included comparisons of GLP-1 and dipeptidyl peptidase-4 inhibitors (DPP4i) (N=10); study characteristics are described in Table 1. All studies were from HICs and used country specific WTP threshold; 9/10 studies used the third-party payer perspective, and 7/10 used a life time horizon.

---Table 1 here---

In terms of preparing the data for pooling, 7, 1, and 2 studies provided data matching scenarios 3, 4, and 5, respectively (Table 1). Data for mean cost, QALY, and their incremental values are described in Table 2. Costs and WTP thresholds from each study were converted to \$US currency using PPP adjusted for the year 2019 using formula (1).

For the 7 studies matching scenario 3 (where mean C and E data along with SDs were reported), the Monte-Carlo method was used to simulate 1000 replicated-data based on gamma and normal distributions for cost and QALY data, respectively. Then, ΔC and ΔE along with variance and co-variance ($\sigma_{\Delta E \Delta C}$) were calculated. The INB and variance was then calculated following formulas (2) and (4).

The study matching scenario 4 provided CE-plane graphs. Data for ΔC and ΔE were directly extracted from the CE plane using Web-Plot-Digitizer [21]. Then, variance and covariance ($\sigma_{\Delta E \Delta C}$) were calculated leading to estimation of the INB and its variance using formulas (2) and (4).

1 For the 2 studies [23, 24] matching scenario 5, the INB variance was adopted from other studies
2 following the steps outlined above. Of the 10 included studies, 2 other studies [25, 26] were
3 also conducted in the USA. For the selection of variance values for the Guillermin et al
4 study[24], the study period, time-horizon, study perspective, ICER values, drug comparison
5 (Sitagliptin) were most similar to Lee et al [26] (Table 1 and Table 2) and hence the INB
6 variance value of the latter was used to estimate the former. The values for Lee et al also
7 matched the second study [23] most closely.

8 --- Table 2 here----

9 INB data along with variances are shown in Table 3. These were then pooled across studies
10 using a fixed-effects (inverse variance) model yielding a pooled INB (95% CI) of US\$ 4012.21
11 (-571.43, 8595.85) with I^2 of 0%, see Figure 1a. In the presence of heterogeneity, as indicated
12 by $I^2 \geq 25\%$ or Cochrane-Q $p < 0.1$, a random-effects model (DerSimonian and Laird model)
13 could be used [27]. The pooled INB value is positive but its 95% CI covers 0, i.e., GLP1
14 agonists might be cost-effective as compared to DPP4 inhibitors but the results did not reach
15 statistical significance.

16 ---Table 3 here---

17 The robustness of the pooled INB as well as heterogeneity can be assessed using various
18 sensitivity and subgroup analyses. Sensitivity analyses omitting the study that used a societal
19 perspective [28] and the study that did not use discounting [25] yielded a pooled INB of US\$
20 4,032.07 (US\$-554.48, US\$8,618.61) and US\$4,068.19 (US\$-650.66, US\$8787.04),
21 respectively.

22
23 The WTP threshold used for these comparisons ranged from US\$ 29,382 to US\$ 58,024 with
24 a median of US \$49,325. Subgroup analyses by median WTP threshold ($<$ vs \geq US \$49,325),
25 time horizon, and source of effectiveness measure were performed (see Table 4), indicating

1 GLP1s were not significantly cost-effective compared with DPP4i in any subgroup. In all these
2 sensitivity and subgroup analyses, the results were similar to that of the overall pooled INB
3 indicating that the results are robust.

4 --- Table 4 here---

5 As in general MA, publication bias was assessed using a funnel plot and Egger's test. There
6 was no evidence of publication bias, seen either by asymmetry on the funnel plot (Figure 1b)
7 or an Egger's test (coefficient=0.32, SE=0.73, p=0.672).

8 **Discussion**

9 We have developed MA methods for EESs focusing on data harmonisation; methodological
10 issues include currency, time, discount, perspective, time horizon, and model used. INB and
11 its variance are estimated based on 5 scenarios. MA is then applied to pool INBs across studies
12 providing a summary estimated CE of treatment relative to control. This evidence should be
13 useful for policy makers in making decisions regarding reimbursement of treatments to
14 population in countries where resources are limited.

15

16 Despite the existence of several guidelines for reporting EESs, studies still vary in how they
17 report the results. This data harmonisation process reported here under the 5 scenarios can help
18 prepare data to calculate and pool INB values. The different monetary units and year can all be
19 converted to a common standard currency.

20

21 We used INB instead of ICER as the economic effect measure because of limitations of the
22 ICER in ambiguity of interpretation for negative ICER as mentioned above [4, 6]. On the
23 other hand, positive INBs indicate cost-effectiveness, while negative INBs shows non-cost-
24 effectiveness. This information will be required by policy makers [7, 8] in making decision
25 from both resource-rich and resource-poor countries.

1 A few challenges should be highlighted when applying a MA in EESs. First, EEs are
2 heterogeneous, which can be caused by model type, population, country income, GDP,
3 perspective, time horizon, and discount rate. We applied the CPI and PPP to harmonise
4 different economic backgrounds as well as the time-lag across the studies [29, 30]. However,
5 it should be noted that using PPP may have some limitations as for the estimation method of
6 price indices, which are calculated from individual prices of only selected commodities rather
7 than all commodities in each country [31]. Considering not only country income, but also
8 model type, time horizon, and perspective in stratified analyses may also reduce heterogeneity,
9 if there are sufficient data for stratifying. Furthermore, sub-group and/or sensitivity analyses
10 should be performed to identify specific types of studies/country income where treatments
11 show cost-effectiveness. Economic factors should be considered for subgroups, including
12 WTP, discount rate, type of EES (e.g., within-trial EES versus model-based EES), quality of
13 EESs, type of health state, and percent herd immunity for vaccine, etc.). Different subgroups
14 of these factors may result in different cost-effectiveness findings within HICs and UMICs.
15 Second, the health EESs are context specific, usually conducted in individual country settings.
16 However, not all countries have EESs that fit their context because conducting well-designed
17 EESs is very resource intensive and requires specialised expertise in economic evaluation.
18 Therefore, there will be an even greater need for some systematic synthesis of evidence where
19 resources are limited. Evidence from a MA will be useful if it is performed with a sensitivity
20 to country contexts (e.g., country income, type of model, life-time, perspective, etc.).

21

22 In conclusion, we have demonstrated a tutorial of MA in EESs by applying the general methods
23 of MA, additional with specific issues for EESs. The step-by-step approach of data
24 harmonization is demonstrated for facilitating the process of MA. Although, evidence of CE is
25 context specific for each country, conducting such specific individual study is challenging as

1 similar to CE studies due to various practical limitations (e.g., trained man-power, time,
2 resources, etc.). Thus, the MA of EESs should be encouraged, evidence synthesis would be of
3 immense values for policy decision making process as well as aid in comparability of such
4 evidences across countries with similar contexts.

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1 **Abbreviations used in the manuscript**

- 2 • **ΔC** – incremental cost
- 3 • **ΔE** – incremental effectiveness
- 4 • **BMI** - body mass index
- 5 • **CE**- cost effectiveness
- 6 • **CE-plane** – cost effectiveness plane
- 7 • **CI** – confidence interval
- 8 • **CPI** – consumer price index
- 9 • **CEA** - cost effectiveness analysis
- 10 • **COMER** - COMparative Efficiency Research
- 11 • **CUA** – cost utility study
- 12 • **DALY** – disability adjusted life year
- 13 • **DPP4i** - dipeptidyl peptidase 4 inhibitors
- 14 • **EES**- economic evaluation studies
- 15 • **GDP** – gross domestic product
- 16 • **GLP1i** - glucagon-like peptide-1
- 17 • **HIC** - high income countries
- 18 • **ICER** – incremental cost effectiveness ratio
- 19 • **INB** – incremental net benefit
- 20 • **LIC** - low income countries
- 21 • **MA**- meta analysis
- 22 • **PPP**- purchasing power parity
- 23 • **PRISMA-P** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 24 protocol
- 25 • **PSA** – probabilistic sensitivity analysis
- 26 • **SD** - standard deviation
- 27 • **SE** – standard error
- 28 • **QALY** – quality adjusted life years
- 29 • **UMIC** - upper middle-income countries
- 30 • **US** – united states
- 31 • **WHO** – world health organisation
- 32 • **WTP** – willingness to pay

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1 **Declarations**

- 2 • **Ethics approval and consent to participate:** Not Applicable
- 3 • **Consent for publication:** Not Applicable
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- 13 • **Authors' contributions:**

- 14 1) Conceived and designed the experiments: BSB, AT
- 15 2) Performed the experiments: BSB, AT
- 16 3) Analyzed and interpreted the data: BSB, UC, AT
- 17 4) Contributed reagents, materials, analysis tools or data: BSB, UC, NC, JA, AT
- 18 5) Wrote the paper: BSB, UC, NC, JA, AT

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1 **References:**

- 2 1. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL: **Methods for the**
3 **Economic Evaluation of Health Care Programmes**, 3 edition edn. Oxford: Oxford University
4 Press; 2005.
- 5 2. Torrance GW: **Measurement of health state utilities for economic appraisal.** *J Health Econ*
6 1986, **5**(1):1-30.
- 7 3. Wisloff T, Hagen G, Hamidi V, Movik E, Klemp M, Olsen JA: **Estimating QALY gains in applied**
8 **studies: a review of cost-utility analyses published in 2010.** *Pharmacoeconomics* 2014,
9 **32**(4):367-375.
- 10 4. Crespo C, Monleon A, Diaz W, Rios M: **Comparative efficiency research (COMER): meta-**
11 **analysis of cost-effectiveness studies.** *BMC Med Res Methodol* 2014, **14**:139.
- 12 5. O'Mahony JF: **The Limitations of Icers In Screening Interventions and The Relative Net**
13 **Benefit Alternative.** *Value Health* 2015, **18**(7):A705.
- 14 6. Hoch JS, Dewa CS: **Advantages of the net benefit regression framework for economic**
15 **evaluations of interventions in the workplace: a case study of the cost-effectiveness of a**
16 **collaborative mental health care program for people receiving short-term disability benefits**
17 **for psychiatric disorders.** *J Occup Environ Med* 2014, **56**(4):441-445.
- 18 7. Willan AR: **Incremental net benefit in the analysis of economic data from clinical trials, with**
19 **application to the CADET-Hp trial.** *Eur J Gastroenterol Hepatol* 2004, **16**(6):543-549.
- 20 8. Willan AR, Lin DY: **Incremental net benefit in randomized clinical trials.** *Stat Med* 2001,
21 **20**(11):1563-1574.
- 22 9. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors): **Cochrane**
23 **Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020);**
24 2020.
- 25 10. Normand SL: **Meta-analysis: formulating, evaluating, combining, and reporting.** *Stat Med*
26 1999, **18**(3):321-359.
- 27 11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA,
28 Group P-P: **Preferred reporting items for systematic review and meta-analysis protocols**
29 **(PRISMA-P) 2015: elaboration and explanation.** *BMJ* 2015, **350**:g7647.
- 30 12. Bagepally BS, Chaikledkaew U, Gurav YK, Anothaisintawee T, Youngkong S, Chaiyakunapruk N,
31 McEvoy M, Attia J, Thakkinstian A: **Glucagon-like peptide 1 agonists for treatment of patients**
32 **with type 2 diabetes who fail metformin monotherapy: systematic review and meta-**
33 **analysis of economic evaluation studies.** *BMJ Open Diabetes Res Care* 2020, **8**(1).
- 34 13. Bagepally BS, Gurav YK, Anothaisintawee T, Youngkong S, Chaikledkaew U, Thakkinstian A:
35 **Cost Utility of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment of Metformin**
36 **Monotherapy Failed Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis.**
37 *Value Health* 2019, **22**(12):1458-1469.
- 38 14. Haider S, Chaikledkaew U, Thavorncharoensap M, Youngkong S, Islam MA, Thakkinstian A:
39 **Systematic Review and Meta-Analysis of Cost-effectiveness of Rotavirus Vaccine in Low-**
40 **Income and Lower-Middle-Income Countries.** *Open Forum Infect Dis* 2019, **6**(4):ofz117.
- 41 15. **Meta-analysis of economic evaluations.** In: *WEEKLY EPIDEMIOLOGICAL RECORD. Volume No*
42 *17,* edn. Edited by (IVIR-AC) IaVIRAC. Meeting of the Immunization and Vaccinerelated
43 Implementation Research Advisory Committee (IVIR-AC), March 2021: World Health
44 Organisation; 2021: 138–140.
- 45 16. Woods B, Revill, P., Sculpher, M., Claxton, C.: **Country-level Cost-Effectiveness Thresholds:**
46 **Initial Estimates and the Need for Further Research.** *CHE Research Paper* 2016:109.
- 47 17. Robinson LA, Hammitt JK, Chang AY, Resch S: **Understanding and improving the one and**
48 **three times GDP per capita cost-effectiveness thresholds.** *Health Policy and Planning* 2016,
49 **32**(1):141-145.

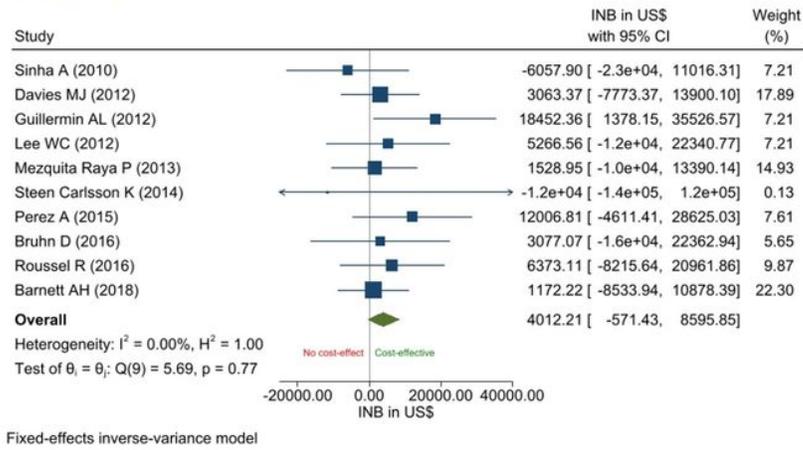
- 1 18. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S: **Thresholds for the cost–effectiveness of**
- 2 **interventions: alternative approaches.** *Bull World Health Organ* 2015, **93**(2):118-124.
- 3 19. **IMF data** [<https://www.imf.org/external/pubs/ft/weo/2018/01/weodata/index.aspx>]
- 4 20. Haider S, Chaikledkaew U, Thavorncharoensap M, Youngkong S, Islam MA, Thakkestian A: **Systematic Review and Meta-Analysis of Cost-effectiveness of Rotavirus Vaccine in Low-**
- 5 **Income and Lower-Middle-Income Countries.** *Open Forum Infectious Diseases* 2019, **6**(4).
- 6 21. **WebPlotDigitizer - Extract data from plots, images, and maps**
- 7 [<https://automeris.io/WebPlotDigitizer/download.html>]
- 8 22. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L: **Contour-enhanced meta-analysis**
- 9 **funnel plots help distinguish publication bias from other causes of asymmetry.** *J Clin*
- 10 *Epidemiol* 2008, **61**(10):991-996.
- 11 23. Sinha A, Rajan M, Hoerger T, Pogach L: **Costs and consequences associated with newer**
- 12 **medications for glycemic control in type 2 diabetes.** *Diabetes Care* 2010, **33**(4):695-700.
- 13 24. Guillermin AL, Lloyd A, Best JH, DeYoung MB, Samyshkin Y, Gaebler JA: **Long-term cost-**
- 14 **consequence analysis of exenatide once weekly vs sitagliptin or pioglitazone for the**
- 15 **treatment of type 2 diabetes patients in the United States.** *J Med Econ* 2012, **15**(4):654-663.
- 16 25. Bruhn D, Martin AA, Tavares R, Hunt B, Pollock RF: **Cost-utility of albiglutide versus insulin**
- 17 **lispro, insulin glargine, and sitagliptin for the treatment of type 2 diabetes in the US.** *J Med*
- 18 *Econ* 2016, **19**(7):672-683.
- 19 26. Lee WC, Samyshkin Y, Langer J, Palmer JL: **Long-term clinical and economic outcomes**
- 20 **associated with liraglutide versus sitagliptin therapy when added to metformin in the**
- 21 **treatment of type 2 diabetes: a CORE Diabetes Model analysis.** *J Med Econ* 2012, **15** Suppl
- 22 **2:28-37.**
- 23 27. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials* 1986, **7**(3):177-188.
- 24 28. Steen Carlsson K, Persson U: **Cost-effectiveness of add-on treatments to metformin in a**
- 25 **Swedish setting: liraglutide vs sulphonylurea or sitagliptin.** *J Med Econ* 2014, **17**(9):658-669.
- 26 29. **Problems and Extensions of PPP** [<http://internationalecon.com/Finance/Fch30/F30-4.php>]
- 27 30. Burdick C, Fisher L: **Social Security cost-of-living adjustments and the Consumer Price Index.**
- 28 *Soc Secur Bull* 2007, **67**(3):73-88.
- 29 31. Pigou AC: **The Foreign Exchanges.** *The Quarterly Journal of Economics* 1922, **37**(1):52–74.
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35 **Figure legends**

36 Figure 1: a) Forrest plot of pooling INBs of GLP1 vs DPP4i; b) Funnel plot of pooling INB of GLP1
 37 vs DPP4i.

Figures

a) Forest Plot



b) Funnel Plot

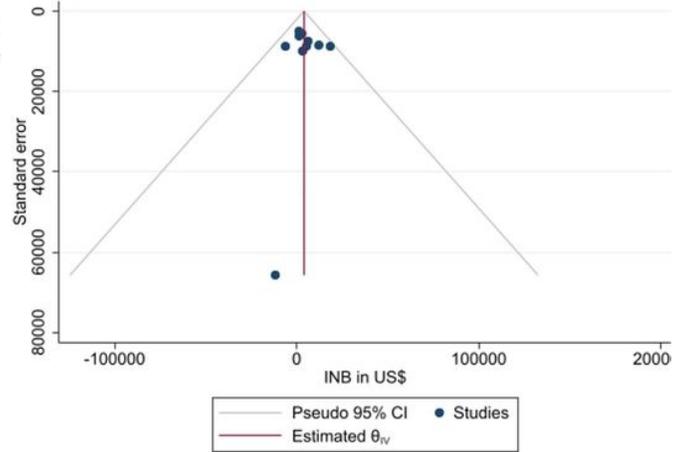


Figure 1

a) Forrest plot of pooling INBs of GLP1 vs DPP4i; b) Funnel plot of pooling INB of GLP1 vs DPP4i.