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Selection of indirect treatment comparisons for health technology assessments: a practical guide for health economics and outcomes research scientists and clinicians

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ABSTRACT

Background Health technology assessment (HTA) bodies evaluate the clinical and economic values of health interventions to inform healthcare decision-making. They face the challenge of lacking head-to-head randomised clinical trial data against the standard of care. Indirect treatment comparison (ITC) methods are often used and accepted by HTA bodies worldwide, but there are numerous options with various and inconsistent terminologies. The selection and application of ITC methods are complex from methodological and clinical perspectives.

Objectives This article (1) provides a comprehensive overview of ITC methods by clarifying used terminologies, including fundamental assumptions, frameworks, strengths, limitations, applications and specific considerations; (2) examines recent ITC guidelines with recommendations or preferences from major HTA bodies and (3) guides health economics and outcomes research (HEOR) scientists and clinicians in the strategic selection of ITC methods with case examples.

Methods The authors conducted a rapid review to identify the literature related to ITC methods and ITC-relevant HTA guidelines in various databases between 2009 and April 2024.

Conclusions Comprehensive knowledge of the ITC methods landscape and the evolving ITC-relevant HTA guidelines are essential for ITC methods selection. Effective communication/collaboration between HEOR scientists and clinicians ensures that the selection and justification of ITC methods are robust for HTA submissions.

INTRODUCTION

Health technology assessment (HTA) bodies evaluate health interventions' clinical and economic values to inform healthcare decision-making. They face the challenge of lacking head-to-head randomised clinical trial (RCT) data against the standard of care. To make evidence-based recommendations for adopting innovative technologies, allocating limited resources and developing clinical guidelines, HTA bodies may require comparative evidence against market-relevant alternatives. As the therapeutic landscape in clinical practice is rapidly evolving,[1] to conduct head-to-head clinical trials against the most relevant comparators on the market in a specific country may not be feasible. Furthermore, new interventions are emerging with limited or no comparators available.

HTA bodies have often used and accepted the evidence from indirect treatment comparisons (ITC) worldwide to address these challenges.[2] According to a recent review article, the acceptance rate of ITC findings appears relatively low due to various criticisms of source data, applied methods and clinical uncertainties.[3]

The joint efforts between health economics and outcomes research (HEOR) scientists and clinicians are pivotal in selecting ITC methods in evidence generation. After aligning with the purpose of the ITC, the collaboration should focus on the strategy to identify the source clinical trial data, select ITC methods, design the ITC study and communicate the selected ITC methods to HTA bodies. HEOR scientists contribute by identifying available evidence from various clinical trials, understanding the application of ITC methods, designing ITC and clarifying the ITC selection from a methodological perspective. Meanwhile, clinicians enhance this strategic ITC selection process by deciding the inclusion/exclusion of source data, rationalising the adoption of the ITC method, contributing to the ITC design and communicating the ITC selection from a clinical perspective.

To achieve the goal of collaboration, referring to academic good practices and ITC-relevant HTA guidelines is essential. Some efforts guided researchers in selecting ITC

methods,[4 5] while others educated clinicians to understand ITC methods better.[6 7] Some articles summarised ITC-relevant guidelines from several years ago.[1 8] Still, digesting literature and HTA guidelines is challenging for the reasons below. First, the literature calls the same ITC method differently, addresses the assumptions differently and categorises ITC methods differently.[4 5 9–11] Second, the flow chart or algorithm for selecting ITC methods is often dictated by data availability or from feasibility perspectives but less from scientific and clinical perspectives.[4 5] Last, the articles intending to educate clinicians on ITC focus on network meta-analysis (NMA) without providing a big picture of the ITC landscape.[6 7]

This article aims to (1) provide a comprehensive overview of ITC methods by clarifying used terminologies; (2) examine the recent ITC guidelines with recommendations or preferences from major HTA bodies and (3) guide HEOR scientists and clinicians in the strategic selection of ITC methods with case examples. Understanding these will result in more robust HTA submissions for informed decisions to improve patient outcomes.

METHODS

The authors conducted a rapid review as they noticed the pressing need for clarifying the various and inconsistent terminologies when selecting ITC methods. The searches were run in databases of PubMed, Google Scholar, Cochrane and HTA websites of interest for ITC-relevant review articles, good practices and HTA guidelines published between 2009 and April 2024 in English. The keywords used in the search were various combinations of ITC, NMA, population-adjusted indirect comparison (PAIC), good practice, guideline, review/systematic review and/or HTA.

The lead author conducted the literature screening and data extraction, while all authors (including an HEOR scientist, a clinician and an academician specialised in Health Outcomes and Policy Research) were involved in the in-depth review process. The review first screened abstracts and assessed full-text articles as needed. Then, we tracked down important source articles in the reference list of identified review articles and expanded the search to the literature that could more adequately address our specific questions or concerns to the aims of this rapid review.

Inclusion and exclusion criteria were developed based on the authors' knowledge and experience in this subject. The inclusion criteria were: (1) methodological studies that address the terminological basics, assumptions, framework, strengths and limitations of ITCs; (2) guidelines or good practices relevant to ITCs; and (3) examples relevant for illustration purposes. The exclusion criteria were (1) non-methodological focused or duplicated ITC studies; (2) unrelated or replicated ITC guidelines; and (3) ineffective ITC examples. In summary, the final list of referent articles was selected to align with the aims of this article.

For the websites or publications from HTA or HTA-like bodies, we searched for five European countries (England, France, Germany, Spain and Italy) and two North American countries (the USA and Canada). These countries are our focus as they are the primary pharmaceutical markets that profoundly affect global healthcare decisions. Five European countries and Canada have established formal HTA processes, while the USA sets pivotal health policy standards worldwide despite lacking a formal HTA framework (referred to as HTA-like in this article). Online translational tools were employed for documents from HTA bodies in Spain and Italy. The contents were verified by the multilingual coauthors.

OVERVIEW OF ITC METHODS

Summary of ITC methods

Researchers have developed numerous ITC methods with various and inconsistent terminologies. Due to the evolving development and increasing complexity, ITC methods are categorised differently.[5 11 12] In this article, ITC is a broad term encompassing all types of ITCs, as reported in the literature.[3 12] We present ITC methods in four classes based on the underlying assumptions (constancy of treatment effects vs conditional constancy of treatment effects) and the number of comparisons involved. The categorisation overlap may exist across classes. The four classes refer to the Bucher method (adjusted ITC or standard ITC), NMA, PAIC and Naïve ITC (unadjusted ITC). The classification summary is shown in figure 1, while figure 2 facilitates the understanding of ITC. The fundamental assumptions, frameworks, strengths, limitations and applications are summarised in table 1, while definitions and testing of assumptions are listed in table 2. Additional specific considerations for ITC methods selection are presented according to data requirements and PICO framework (population, intervention, comparator and outcomes) in table 3.

The Bucher method,[13] also called the adjusted ITC or standard ITC,[9 10] assumes the constancy of relative effects (figure 1).[9] It is used in pairwise indirect comparisons with a common comparator (ie, indirect comparison of intervention B and intervention C) with a common comparator (A), figure 2a. It was initially developed for outcomes measured in ORs but has been extended to other outcomes.[12]

NMA methods are developed under the assumption of the constancy of relative effects, the same as for the Bucher method (figure 1, Section Key assumptions). They are used for multiple indirect comparisons by common or connecting comparators. For example, more than one comparator (comparator A and comparator E) could connect the indirect comparison of intervention B and intervention F (figure 2b).[11] The NMA contains three subclasses: (1) Indirect NMA fits for indirect comparisons between intervention B and intervention C; and between intervention B and intervention E (figure 2b).[11] (2) MTC can apply when both direct and indirect comparisons

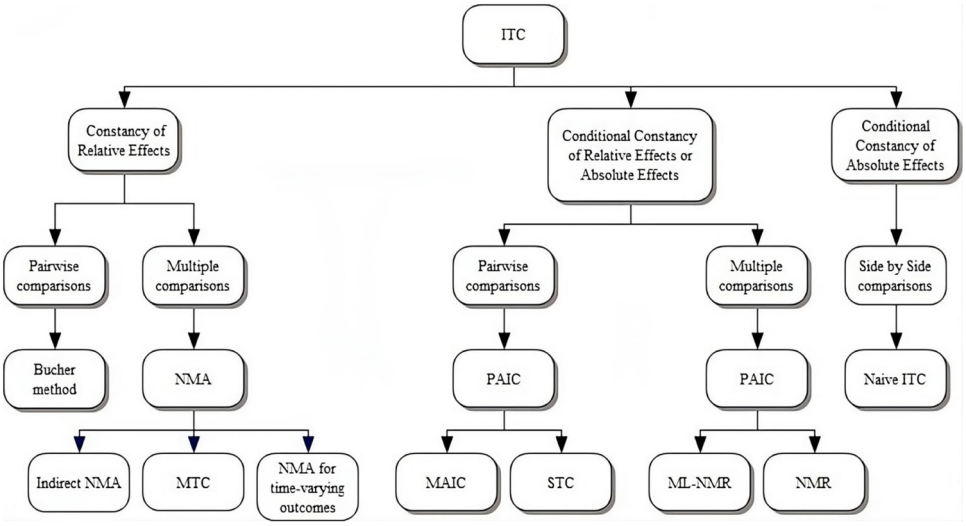

Figure 1 Summary of ITC classification. The Bucher method, NMA and PAIC apply to anchored indirect comparisons. PAIC (MAIC or STC) applies to anchored and unanchored indirect comparisons. PAIC requires at least one IPD from one source data, except NMR. IPD, individual patient-level data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; MTC, mixed treatment comparison; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; STC, simulated treatment comparison.

are available for intervention B and intervention C (figure 2c).[11] An alternative term for MTC is a multitreatment meta-analysis (MTM).[14] The Lumley NMA, often mentioned in publications, is one way of MTC as well.[12 15] (3) NMA for time-varying outcomes is used, as its name suggests, to deal with time-varying outcomes like HRs, such as parametric survival curves, fractional polynomials or beyond.[12 16–18] Although this subclass is specified for analysing time-varying outcomes, other ITC can handle time-varying outcomes as well (table 3).[19 20]

PAIC methods, in contrast, assume the conditional constancy of relative or absolute effects (figure 1, Section Key assumptions, table 3), which are more relaxed than the assumptions of NMA. These methods allow researchers to adjust covariates in analytical models when observing imbalances in covariates of interest. They apply to pairwise or multiple ITC. This class contains four subclasses: matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), network meta-regression (NMR) and multilevel NMR (ML-NMR, the extension of NMR).[5 9 21] MAIC and STC are developed for pairwise comparisons, while NMR and ML-NMR could apply to any network size.[5 22]

Naive ITC, also called unadjusted ITC, refers to a comparison without statistical methods but purely comparing raw data from different clinical trials, randomised or non-randomised. It assumes the constancy of absolute effects (figure 1) and should be avoided as it is subject to the bias of estimates.[12]

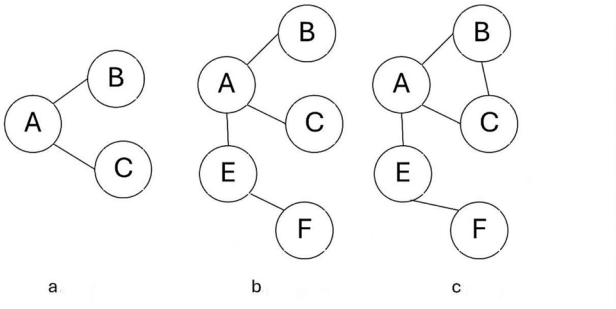

Figure 2 ITC diagrams. A, B, C, E or F indicates a different treatment. ITC, indirect treatment comparison.

Key assumptions

In theory, like other statistical approaches, the underlying assumptions for ITC methods are critical to ensuring the validity of the results. As mentioned in the classification of ITC methods, three assumptions are used to classify ITC methods (figure 1). (1) The constancy of relative effects refers to the constancy of relative treatment effects, that is, all effect modifiers being balanced across trials. (2) The conditional constancy of relative effects refers to the constancy of relative treatment effects across trials when adjusting all imbalanced effect modifiers in the analysis. (3) The conditional constancy of absolute effects refers to the constancy of absolute treatment effects across trials when adjusting all imbalanced effect modifiers and prognostic variables in the analysis (table 1).[4 9 12]

In practice, researchers often examined the three pragmatic assumptions (homogeneity, similarity (also called transitivity) and/or consistency) for practical ITC selection (table 1). The definitions and tests of these assumptions are summarised in table 2. Ultimately, selecting ITC methods does not solely rely on testing but requires methodological and clinical judgement from HEOR scientists and clinicians.[23]

ITC frameworks

ITC methods can be performed using a frequentist or a Bayesian statistical framework. Each framework offers a

Table 1 Overview of ITC methods

ITC methods	Assumptions	Frameworks	Strengths	Limitations	Applications
Bucher Method (adjusted ITC/standard ITC)[9 12 24]	The constancy of relative effects (homogeneity, similarity)	Frequentist	Pairwise comparisons (two intervention comparisons) through a common comparator	Limited to comparisons with a common comparator. Not for closed loops from multiarm trials.	Pairwise indirect comparisons
NMA[2 9 11 12 24 44]	The constancy of relative effects (homogeneity, similarity and/or consistency)	Frequentist or Bayesian	Multiple interventions comparison simultaneously	Complex, with assumptions challenging to verify	Multiple indirect comparisons or ranking. Bayesian framework is preferred when source data are sparse. Multiarm trials could be managed within a frequentist framework.
Indirect NMA[2 11]	Homogeneity, similarity	Frequentist or Bayesian	Multiple interventions Comparison simultaneously	Limited by assumptions	Multiple indirect comparisons with only indirect comparison.
MTC (MTM)[2 11 14 24 45]	Homogeneity, similarity and consistency	Frequentist or Bayesian	Multiple interventions Comparison simultaneously	Limited by assumptions	Multiple indirect comparisons with direct and indirect comparisons, including mutiarm trials.
NMA time-varying outcomes[12 16 17 46 47]	Homogeneity, similarity and/or consistency with relaxing proportional hazard	Frequentist or Bayesian	Assesses the impact of varying doses, tracking changes over time	Complexity in analysing and interpreting curved relationships	This method is beneficial when the treatment effects of varying doses or time-varying endpoints violate the proportional hazard assumption across studies.
PAIC[2 5 9 48]	The constancy of relative or absolute effects	Frequentist or Bayesian	Adjust imbalance across studies.	Limited by IPD availability and quality (optional for NMR). Unable to adjust for differences in treatment administration, cotreatments or treatment switching	Pairwise or multiple indirect comparisons. This applies to studies with considerable heterogeneity in the study population, single-arm studies in rare disease settings or unanchored studies.
MAIC[4 9]	The constancy of relative or absolute effects	Frequentist often	Propensity score weighting IPD to match aggregate data in the comparator population.	Limited to pairwise ITC and adjusted to the population with aggregate data, which may not be the target population for the decision	Pairwise indirect comparisons apply to studies with considerable heterogeneity in the study population, single-arm studies in rare disease settings, or unanchored studies.

Continued

Table 1 Continued

ITC methods	Assumptions	Frameworks	Strengths	Limitations	Applications
SIC[4 9 31]	The constancy of relative or absolute effects	Bayesian often	Predict outcomes in the aggregate data population using the outcome regression model based on IPD.	Limited to pairwise ITC and adjusted to the population with aggregate data, which may not be the target population for the decision	Pairwise ITC. Apply to considerable heterogeneity of the study population, single-arm studies in rare disease settings, and unanchored studies.
NMR[2 4 9 20 49]	Conditional constancy of relative effects with shared effect modifier	Frequentist or Bayesian	Regression techniques to explore the impact of study-level covariates on treatment effects	Not work for multiarm trials	Multiple ITC with a connected network of evidence (anchored) to investigate how distinct factors affect relative treatment effects.
ML-NMR[5 12 21]	Conditional constancy of relative effects with shared effect modifier	Bayesian	Applicable to a network of any size. Estimates can be produced in any target population, given sufficient information on covariate distribution.	This method requires covariate joint distribution in the aggregate studies. It does not apply to time-varying outcomes	Multiple ITCs with any connected network of evidence (anchored), including data (eg, registries) beyond clinical trial to better project the target population of interest
Naïve Indirect Comparison (unadjusted ITC)12	Conditional constancy of absolute effects	Not applicable	Simple side-by-side comparisons without adjustment	Introduces bias	Preliminary evidence comparison. They may be used and accepted by HTA bodies, although they may not be advocated.

HTA, Health Technology Assessment; IPD, individual patient-level data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel NMR; MTC, mixed treatment comparison; MTM, multitreatment meta-analysis; NMA, network meta-analysis; NMR, network meta-regression; PAIC, population-adjusted indirect comparison; SIC, simulated treatment comparison.

distinct way of analysing ITC data and interpreting ITC results.[24 25]

The frequentist framework of ITC methods generates estimates using the likelihood from the observed data with a 95% CI, that is, probability.[24] It is widely used because of its simple execution and straightforward explanation. The interpretation of a 95% CI is: "If we repeat an experiment 100 times and compute the 95% CI for all 100 experiments, then 95% of these CIs would contain the true (unknown) estimates."[25]

The Bayesian framework of ITC methods produces estimates based on the probability distribution of parameters from observed data and prior beliefs/knowledge with a 95% credible interval (CI), that is, conditional probability. This framework benefits ITC methods when modelling complex evidence structures and incorporating varying degrees of uncertainty.[24] The interpretation of a 95% CI is: "There is a 95% probability that the true effect value lies within the interval, given the evidence provided by the observed data."[25]

Other relevant concepts

The current ITC methods use various and inconsistent terminologies, which make their selection/application challenging. This section introduces often-used terminologies through synthesised findings to foster a better understanding of ITC methods.

Aggregate data versus individual patient-level data

Aggregate data refer to the information averaged or estimated across all participants in a study, that is, data at the study level from published RCTs. In contrast, individual patient-level data (IPD) refer to data recorded for each participant in a study, that is, patient-level data in the original form. Researchers often used aggregate data for ITC. IPD is optional for most ITC but is required for the MAIC, STC and ML-NMR under the PAIC class (table 3).[25] When the full IPD is available for each included trial, one can conduct a full IPD NMR, which makes it an observational study. Therefore, sophisticated analytical methods, such

Table 2 Pragmatic assumptions to Inform the selection of ITC methods

Assumption	Definition	How to test	Implication of testing
Homogeneity[11 14 50]	It assumes that the treatment effects are consistent across studies for the same direct comparison (eg, A vs B; A vs C) before the indirect comparison of B vs C. This is common for meta-analysis (figure 2).	Q-test for the existence of heterogeneity and I^2 statistic for quantification of heterogeneity	It highlights variability in treatment effects, informs the choice of fixed-effect or random-effects models, and interprets pooled estimates. I^2 around 25%, 50%, and 75% mean low, medium, and high heterogeneity, respectively.
Similarity (transitivity)[6 14 23 51]	It assumes that the studies within the network are sufficiently similar regarding patient populations, interventions, and outcomes, making it reasonable to compare B vs C (figure 2) indirectly.	It can be evaluated conceptually, that is, it relies on clinical judgement to determine whether study differences affect the adoption of ITC.	It ensures the validity of indirect comparisons by highlighting the need for careful study selection and potentially restricting the network's scope.
Consistency (coherence)[14 20 51 52]	It assumes that direct and indirect estimates of treatment effects agree within the network when a combination of direct and indirect comparisons of B vs C is made (figure 2).	The Z-test (often called the Bucher method) is for single loops. Node-splitting methods (Separating Indirect from Direct Evidence) are for the local network. Incoherence models are for the global network.	When the test does not support this assumption, researchers may consider subgroup analysis, excluding available source studies, NMR, sensitivity analyses or PAIC methods. When there is agreement between direct and indirect estimates, it may not indicate consistency, as the tests are often underpowered.

ITC, indirect treatment comparison; NMR, network meta-regression; PAIC, population-adjusted indirect comparison.

as propensity score weighting or inverse probability of treatment weighting, can apply.[5]

Common comparator versus connecting comparator

Researchers often use common comparators and connecting comparators (or networks) interchangeably. A common comparator refers to comparator A when intervention B and intervention C connect directly to A (figure 2). Connecting comparators refers to comparators of A and E when one intends to compare intervention B to intervention F, in which intervention B is indirectly connected to intervention F through comparators of A and E. In other words, more than one comparator could connect two interventions of interest (figure 2b,c).[11] Having a common comparator or a connecting comparator is presented for each ITC method in table 3.

Anchored versus unanchored ITC

Anchored ITC is the indirect comparison with a common or connecting comparator in each study (figure 2). In contrast, unanchored ITC refers to a disconnected treatment network or single-arm studies.[4 9] Each ITC method is mapped into anchored or unanchored ITC in table 3.[4 5 9]

Effect modifier versus prognostic variables

Covariates are expected to be balanced in RCTs through randomisation to ensure that the relative effect of the intervention is estimated without bias. Effect modifiers and prognostic variables are covariates relevant to ITC methods that allow adjustment in the analysis when using PAIC methods (table 3). Effect modifiers refer to covariates that alter the relative effect of the active intervention compared with a comparator. At the same time, prognostic variables equally affect absolute outcomes on both active intervention and the comparator. Some effect modifiers may overlap with prognostic variables.[21] It is beneficial to have consensus or guidelines for their identification.[26 27] Currently, researchers identify effect modifiers and prognostic variables based on literature review, expert opinion, qualitative observation or quantitative approaches.[27–29]

Adjusted versus unadjusted ITC

For ITC methods, adjustment aims to provide a robust treatment effect estimate for the intervention of interest by ensuring similarity in study design, patient characteristics, treatments and outcome measures. The Bucher method, NMA and PAIC are all forms of adjusted ITC methods, either adjusted carrying over from RCTs for the Bucher method and NMA methods or adjusted in the analysis for the PAIC methods (table 3).[2 5] Naïve indirect comparison, the unadjusted ITC, is less promising but may be accepted by HTA bodies under the circumstances.

Fixed-effect model versus random-effects model

The fixed-effect model and the random-effects model, two often-mentioned statistical models, are choices based on the results of examining the homogeneity assumption (table 2). When the homogeneous assumption is valid, the fixed-effect model fits. However, achieving such homogeneity in practical applications is challenging. Consequently, the random-effects model is often more appropriate and designed to accommodate heterogeneity.[12]

Effective sample size

Researchers should consider reporting effective sample size (ESS) when conducting an ITC and discussing ITC limitations with HTA bodies.[9] An ITC method may be underpowered for detecting true differences when it involves too many comparisons from few studies.[12] Ideally, four times as many similarly sized trials are needed for

Table 3 Specific considerations for ITC methods selection using data requirement and PICO framework

ITC methods	Data requirement (aggregate/IPD)	Populations (adjustments)	Intervention (pairwise vs multiple)	Comparators (anchored vs unanchored)	Outcomes
Bucher method (adjusted ITC/standard ITC)[2 9 12 24]	Aggregate data/IPD	Adjustment per assumptions (eg, randomisation carrying over from randomised studies). It does not adjust for differences in included source trials or other covariates that might directly affect outcomes in the analysis	Pairwise indirect comparison	Anchored with a common comparator	All types, not for time-varying outcomes
NMA[2 9 11 12 24 44]	Aggregate/IPD	Adjustment per assumptions	Multiple indirect comparisons	Anchored (require common or connecting comparators)	All types
Indirect NMA[2 11]	Aggregate data/IPD	Adjustment per assumptions	Multiple indirect comparisons	Anchored	All types but not time-varying outcomes
MTC (or called MTM)[2 11 14 24 45]	Aggregate data/IPD	Adjustment per assumptions	Multiple indirect comparisons	Anchored	All types but not time-varying outcomes
NMA time-varying outcomes[12 16 17 46 47]	Aggregate/IPD	Adjustment per assumptions	Multiple indirect comparisons	Anchored	Time-varying outcomes
PAIC[2 5 9 48]	A mixture of aggregate data and IPD/aggregate data/IPD	Adjustment in analysis	Pairwise/multiple indirect comparisons	Anchored/unanchored (require common or connecting comparators)	All types
MAIC[4 9]	A mixture of aggregate data and IPD	Adjustment in analysis: 1. All effect modifiers, when anchored. 2. All effect modifiers and prognostic variables when unanchored.	Pairwise indirect comparison	Anchored/unanchored with a common comparator for single or fewer comparators	All types for multiple outcomes, including time-varying outcomes
SIC[4 9 31]	A mixture of aggregate data and IPD	Adjustment in analysis: 1. All effect modifiers, when anchored. 2. All effect modifiers and prognostic variables when unanchored.	Pairwise indirect comparison	Anchored/ unanchored for multiple or more comparators	All types for a lesser number of outcomes
NMR[2 4 9 20 49]	Aggregate data/IPD (when full IPD is available, it is an observational study as the gold standard for ITC)	Adjustment in analysis for effect modifiers	Multiple indirect comparisons	Anchored (connecting comparators)	All types, including time-varying outcomes
ML-NMR[5 12 21]	A mixture of aggregate data and IPD	Adjustment in analysis for effect modifiers	Multiple indirect comparisons	Anchored (connecting comparators)	All types, but not for time-varying outcomes
Naïve Indirect Comparison (unadjusted ITC)[12]	Aggregate data	Unadjusted	As needed	Not applicable	As needed

IPD, individual patient-level data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; MTC, mixed treatment comparison; MTM, multitreatment meta-analysis; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison.

an indirect comparison to have the same power as direct RCTs.[30] According to an ITC review paper, a median ESS of 80.0 was reduced by 74.2% of the original sample size.[31]

GLOBAL HTA METHODOLOGICAL GUIDELINES FOR ITCS

The ITC-relevant documents issued by HTA or HTA-like bodies are identified from six out of seven targeted countries.[15] Additionally, we identified indirect treatment guidelines by the European Network for Health Technology Assessment (EunetHTA).[12] No relevant documents are available from the Italian Medicines Agency.[8] These ITC-relevant HTA guidelines are summarised in table 4.

The definition and scope of ITC methods vary but are similar across these ITC-relevant documents. Only National Institute for Health and Care Excellence (NICE), HAS, CADTH and EunetHTA issued ITC-specific documents, while others included ITC methods in their methodological documents. Most guidelines discussed adjusted indirect comparison (or the Bucher method), NMA (or MTC) and unadjusted ITCs.[10 12 15 32–35] The adjusted indirect comparison refers to indirect comparison for interventions of interest that have not been compared directly with each other but indirectly using a common comparator. It is comparable to the Bucher method or

Table 4 Recent global HTA methodological guidelines of ITC methods

Country (HTA)	Document (year of publication/update)	Mentioned method	Recommendations/preferences
England (NICE)[33 39]	NICE Health Technology Evaluations: the Manual with a series of ITC-relevant documents (2012–2022)	NMA (adjusted ITC/MTC)/ PAIC	Ideally, the NMA should contain all interventions, including comparators irrelevant to the decision problem within the scope. If suitable for pairwise head-to-head RCTs, NMA is an additional analysis when there is a lack of direct comparisons. PAIC methods can be considered when effect modifiers between trials are imbalanced (eg, a small number of trials) or single-arm trials. Comparing results from single arms of different randomised studies is not acceptable.
France (HAS)[10]	Indirect Comparisons Methods and Validity (2009)	Adjusted ITC/NMA (Bayesian NMA/mixed linear models/meta-regression)	ITC 'may make it possible to assess the position of a new treatment in relation to existing treatments as soon as it has been licensed…'. NMA is the best way of establishing a complete network with all available treatment sources. Acceptance is on a case-by-case basis. Naïve indirect comparison is inappropriate.
Germany (G-BA/IQWIG)[32]	General Methods—Version 7.0 (2023)	Adjusted ITC: Bucher method/NMA (MTC)	Routine ITC application is not advisable within the framework of benefit assessments due to unsolved methodological problems. Only adjusted indirect comparisons via adequate common comparators, including NMA, are accepted. Using ITC methods requires adequate justification. Single arms from different studies or ITC methods without common comparators are disapproved.
Spain (RedETS)[35]	Standardised Procedure for Clinical Evaluation, Economic Evaluation, and Therapeutic Positioning for the Drafting of Therapeutic Positioning Reports of Medicines in the National Health System (2020)	Adjusted ITC/NMA	Only adjusted ITC or NMA is considered. Adjusted ITC or NMA when meeting specific criteria: high-quality input data and adjusted assumptions are met (homogeneity, transitivity and consistency).
US (ICER)[34]	Methods Guide for Effectiveness and Comparative Effectiveness Reviews, Chapter 12/2020–2023 Value Assessment Framework (2020)	NMA/MAIC	The appropriateness of the chosen method depends on the question and the available evidence.
Canada (CADTH)[15]	Indirect evidence: Indirect Treatment Comparisons in Meta-Analysis (2009)	Bucher method/NMA/ MTC (Lumley NMA/ mixed treatment meta-analysis/muti-parameter synthesis)	The adjusted ITC (the Bucher method) can be used for simple star design and pairwise indirect comparisons when direct comparisons are lacking. NMA or MTC can be used for network patterns presented in the guidelines' summary table.
EunetHTA[12 53]	EUnetHTA21, Individual Practical Guideline Document, D4.3.1: Direct and indirect comparisons. EunetHTA 21: Methods Guideline, D4.3.2 Direct and indirect comparisons (2022)	Bucher method/NMA/PAIC/ unadjusted ITC	Method selection needs transparent justification. Adjusted ITC methods preserve randomisation as the preferred method over naïve ITC (unadjusted ITC). Testing the proportional hazards assumptions for time-to-event data is needed. ITC methods based on aggregated data are not recommended in disconnected networks. PAIC may be considered when assumptions for the usual ITC method are unmet. The target population needs to be described in detail when using PAIC methods.

EunetHTA, European Network for Health Technology Assessment; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MTC, mixed treatment comparison; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; RCTs, randomized clinical trials.

indirect NMA method (eg, remain source randomisation in nature). MTC is discussed separately with one additional consistency assumption compared with the adjusted indirect comparison.[10 33] The PAIC methods are discussed by NICE, ICER and EunetHTA.[12 33 34]

The methodological recommendations or preferences for adopting ITC methods differ but do not conflict. HTA bodies prefer adjusted ITC methods, including the Bucher method and NMA with a common comparator.[1 12 32 33]

Naïve (unadjusted) indirect comparisons are generally not recommended or accepted.[10 12 32 33] Practically, the naïve ITC may have values. NICE and Spain may accept naïve ITC when the adjusted ITC is viewed as inappropriate.[1 3]

SUGGESTIONS FOR THE SELECTION OF ITC METHODS

As detailed in the preceding sections, applying ITC methods in HTA submissions is challenging, and the strategic selection of the appropriate ITC method is multidimensional. This section summarises the main factors to consider when selecting ITC methods based on findings in Section OVERVIEW OF ITC METHODS and Section GLOBAL HTA METHODOLOGICAL GUIDELINES FOR ITCS with case examples in table 5. Subsequently, we offer our suggestions for selecting ITC methods and streamlining the selection process.

In practice, we suggest the Bucher method while adopting NMA methods to assess all practical alternative treatments in the market for anchored studies. When included clinical trials are not balanced, we suggest adjusting the covariates by using PAIC methods. MAIC

Table 5 Factors to consider when selecting ITC methods

Factor	ITC method	Case example	Rationale
Research objectives or HTA expectations	Bucher vs NMA	For renal cell carcinoma: Lenvatinib+everolimus vs cabozantinib with a common comparator everolimus on the outcome of overall survival: 1. Bucher method for G-BA/IQWIG[54] 2. NMA for NICE[55]	IQWIG: The Bucher method works for simple indirect comparison vs appropriate comparator therapy cabozantinib, as suggested by IQWIG. ITC was not conducted for outcomes with a high risk of bias (ie, serious adverse events (AEs), severe AEs, and discontinuation due to AEs). 'Overall survival' was rated low in bias. NICE: NMA for time-varying outcomes is for a broader intervention ranking or landscape (vs axitinib, nivolumab or cabozantinib, respectively) for NICE.
Data availability	NMA with Bayesian Framework	For oncology immunotherapy on safety data using Bayesian[44]	When data are sparse, an NMA with a Bayesian framework is preferred, as it can incorporate prior knowledge and provide more robust estimates.[12]
Population heterogeneity	Anchored trials: NMR	For multiple sclerosis treatment on the outcome of disability progression: Cladribine vs alternative disease-modifying treatments using NMR (in addition to NMA)[56]	NMR was adopted to adjust the baseline risk difference for the outcome of disability progression. However, the NICE Evidence Review Group (ERG) is concerned that the baseline risk difference may not explain the treatment effect from a clinical perspective.
	Anchored trials: ML-NMR	For treating late-onset Pompe disease: Cipaglucosidase alfa (CIPA) plus miglustat vs aval glucosidase alfa (AVAL) using ML-NMR[57]	ML-NMR was used to estimate treatment effects in a mixed population (ERT naïve and ERT experienced) based on randomised trials (single-arm studies were removed). Following technical engagement with NICE, the manufacturer agreed to add AVAL as an additional comparator in its base case, which was not included originally because AVAL was not commercially available in the UK.
	Anchored trials: MAIC	For treating advanced hepatocellular carcinoma: Regorafenib vs cabozantinib using MAIC.[58]	Anchored MAIC could adjust considerable heterogeneity with available IPD.
Comparator considerations	Unanchored trials or single-arm trials: MAIC vs STC	For follicular lymphoma on safety endpoints: Tazemetostat vs PI3-Kinase inhibitors using MAIC.[59]	MAIC works better for multiple outcome comparisons.
	Unanchored trials or single-arm trials: MAIC and STC	For treating advanced cutaneous squamous cell carcinoma on overall survival: Cemiplimab vs best supportive care using multiple ITC methods.[37]	The NICE committee agreed that cemiplimab extended survival compared with best supportive care through consistent results from 3 ITC methods (MAIC, STC and naïve comparison). However, it acknowledged that none of the ITCs provided a reliable estimate.
Outcome consideration	NMA for a time-varying outcome	For treating advanced or unresectable hepatocellular carcinoma on survival: Atezolizumab plus Bevacizumab vs Lenvatinib using NMA.[36]	The manufacturer initially performed a random-effects NMA. NICE ERG advised an NMA for a time-varying outcome (a fractional polynomial random-effects NMA).
Statistical considerations	Homogeneity assumption: Fixed-effect vs random-effects Models	For active ulcerative colitis: Tofacitinib vs other comparators using indirect comparison.[60]	When substantial heterogeneity is detected per NICE ERG, the random-effects model is used instead of the manufacturer's fixed-effect model.
	Consistency assumption: MTC	For treating multiple sclerosis: Alemtuzumab vs other disease-modifying treatments using MTC.[61 62]	NICE ERG suggested including trials before the year 2000 as a base case, although it acknowledged changes in diagnostic criteria. MTC for alemtuzumab considering the consistency assumption equals one, indicating that direct and indirect estimates are the same.[62]
	Naïve treatment comparison	For treating advanced renal cell carcinoma in the prior-cytokine population on survival: Axitinib vs sunitinib.[63]	The NICE review committee agreed that the company's naïve comparison was the best option given the little available evidence, but the results were not robust and were subject to uncertainty.

IPD, individual patient-level data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; STC, simulated treatment comparison.

or STC in PAIC class are options for unanchored studies. Of note, different ITC methods can be involved in one submission for various reasons, such as data availability, different outcomes, sensitivity analysis.[36 37] When using IPD-involved ITC methods, NICE or HAS may require access to IPD to verify the analysis. Therefore, these methods need to be carefully justified if IPD genuinely adds value.[1]

According to the authors' experience in the pharmaceutical industry, when using ITC methods, HEOR scientists and clinicians should effectively collaborate in selecting ITC methods, performing the analysis and presenting the results for successful HTA submissions. For the strategic selection of ITC methods specifically, this practical guide suggests: (1) Conduct a systematic and comprehensive data quality assessment to justify included/excluded studies and outcomes. (2) Review available ITC methods used in the same treatment field to enhance the decision. (3) Provide a clear and transparent description of the ITC method with the assumptions and the limitations. (4) Leverage ITC options with up-to-date ITC-relevant guidelines issued by the HTA body in each country to justify the rationale of ITC selection (table 4). (5) Discuss the implications of the ITC results for the decision ramifications in the HTA submission while acknowledging any potential biases or uncertainties that may affect the validity or generalisability of the findings. (6) Collaborate with key opinion leaders for methodological and clinical opinions to justify ITC selection and design. (7) Engage with the relevant HTA bodies and stakeholders to understand their expectations, preferences for ITC method and evidence needed for HTA evaluation.

DISCUSSION

ITC methods facilitate comparative effectiveness analysis and cost-effectiveness analysis when no head-to-head trials are available.[34] However, the justification for ITC selection was not always compliant with the guidelines.[38] In this article, we elucidated ITC methods by clarifying various terminologies, reviewed updated HTA guidelines and provided a practical guide for HEOR scientists and clinicians to navigate this subject collaboratively for a robust HTA submission.

Challenging in comprehension of ITC options

This article discusses the ITC options and finds it challenging to understand the ITC methods due to different terminology and unclear classifications. For example, the adjusted ITC can refer to the Bucher method for pairwise indirect comparison with a common comparator[9 10 14 33] or refer to both the Bucher method and the indirect NMA with a common comparator.[11] In a recent review article on the acceptance of the ITC methods in oncology by HTA bodies, the Bucher method and adjusted ITC were discussed separately.[3] Based on our analysis of justification in Section Adjusted versus unadjusted ITC, the Bucher method, NMA and PAIC can all be called adjusted ITC methods, either adjustment carried over from RCTs per assumptions for the Bucher method and NMA, or adjustment in PAIC methods (table 3). According to G-BA/IQWIG, EunetHTA and CADTH, the Bucher method is called out by itself.[12 15 32] However, per the Internal Society for Pharmaceutical Outcomes Research (ISPOR), the Bucher method and the indirect NMA are grouped into NMA.[11]

Distinct categorisation of ITCs enhances the in-depth comprehension and communication of selecting ITC methods. Our high level of ITC categorisation is similar to the one adopted by EunetHTA.[12] The Bucher method becomes one class because it is simple and often preferred in practice, which aligns with G-BA/IQWIG, EunetHTA and CADTH guidelines.[12 15 32] We further categorise the NMA class into three subclasses of indirect NMA, MTC and NMA for time-varying outcomes, not the same as EunetHTA guidelines (frequentist framework, Bayesian NMA and NMA for time-to-event data). The rationale is that frequentist or Bayesian refers to a framework that can be applied to different ITC methods (table 1 and Section ITC frameworks). The PAIC class contains MAIC, STC, NMR and ML-NMR, which share the same assumption of the conditional constancy of treatment effects (relative or absolute effects).

Understanding of HTA guidelines

As mentioned in Section GLOBAL HTA METHODOLOGICAL GUIDELINES FOR ITCS, country-specific guidelines vary but do not conflict, as previously reported by Laws *et al*.[8] HTA bodies generally prefer adjusted ITC methods.[1 10 12 15 32–35]

In practice, the acceptance of ITC methods varies in different countries. According to the review article in 2024,[3] discussing oncology products between April 2018 and April 2021, of all dossiers with ITC submitted to NICE, 47% were accepted using various ITC methods. The ITC methods may be used to compare clinical benefit and cost-effectiveness for different treatments. In contrast, in Germany, the Bucher method was the only ITC accepted by G-BA/IQWIG, although the submitted ITC methods included the Bucher method, MAIC and others. The usage of ITC methods was within the framework of benefit assessments. In France, there was no documented acceptance of ITC methods per this review article, although evidence generated by various ITC methods was submitted to HAS. The low acceptance rate might relate to heterogeneity/risk of bias, lack of/unclear data and the statistical methods used. It implies the need to select appropriate ITC methods with high-quality data to reduce bias.

EunetHTA issued updated ITC guidelines in 2022[12] by adding PAIC methods. Meanwhile, this update may mislead audiences when interpreting the terms anchored and unanchored as adjusted and unadjusted ITC.[12] For clarification, our article addresses the terms 'anchor versus unanchored ITC' and 'adjusted versus unadjusted ITC' in Section Other relevant concepts and table 3.

Justification of ITC methods and the importance of literature search

HTA bodies may accept evidence from ITC methods to demonstrate non-inferiority to a comparator when manufacturers adopt appropriate ITC. When superiority is claimed, they are more likely to evaluate ITC evidence carefully.[1]

A rigorous and systematic literature review may enhance the credibility and utilisation of ITC methods in HTA submissions.[3] During this rapid review of ITC methods, two databases were identified: PrismAccess (ITC evidence to HTA bodies)[3] and the ISPOR guideline database (including ones from HTA bodies).[8] These databases support researchers in understanding how ITC methods have been adopted and accepted for specific disease areas and can also be beneficial when one intends to keep up with the updated HTA guidelines.

Strengths and limitations

This article offers a practical guide on selecting suitable ITC methods based on a comprehensive review of ITC options and updated ITC-relevant HTA guidelines. There are other articles on selecting ITC methods, but this article has its strengths. First, this rapid review offers an efficient and timely way to conduct a literature review up to 2024. Second, it clarifies various terminologies and specifies the rationale of the ITC classification. These enhance collaboration between HEOR scientists and clinicians and facilitate communication between manufacturers and HTA bodies. Third, it highlights the evolving ITC-relevant guidelines from major HTA bodies to ensure the ITC selection aligns with HTA guidelines. Lastly, our suggestions are developed from scientific and clinical perspectives rather than methodological and feasible perspectives.

Meanwhile, we acknowledge its limitations. First, it is not a systematic review. This rapid review simplified various aspects of the review process, such as study selection criteria (inclusion/exclusion), detailed search strategy, and quality assurance. Specifically, inclusion/exclusion criteria were developed based on the authors' knowledge and experience in this subject, which may lead to subjectivity bias when interpreting the results. However, this paper provides a comprehensive overview of ITC methods in a timely fashion compared with recent guidelines or review articles.[5 12] Second, it investigates only ITC-relevant HTA guidelines from countries of interest, not all countries globally. The countries selected are the primary pharmaceutical markets that profoundly affect global healthcare decisions. Lastly, we focus on ITC's strategic selection, not its conducting and reporting, which are also important for successful HTA submissions. One can refer to guidelines related to ITC execution and reporting from Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses working group, the GRADE working group, NICE and CADTH.[11 23 39–43]

Future practice on ITC methods

Promoting greater collaboration among HEOR scientists and clinicians is essential to enhancing the impact of ITC methods on HTA decision-making. Future efforts should focus on using consistent ITC terminologies and categorisation when communicating. Moreover, developing consensus or guidelines on identifying effect modifiers and prognostic variables is critical to ensure robust ITC execution. Lastly, it is beneficial to involve more diverse stakeholders, such as academic experts and HTA decision-makers, in improving the use and understanding of ITC methods so that the adopted ITC can be more suitable and acceptable for HTA bodies.

CONCLUSIONS

The appropriate application of ITC methods is pivotal for HTA submissions when there is a lack of evidence from head-to-head clinical trials. Selecting the appropriate ITC methods requires a comprehensive knowledge of the ITC methods landscape and the evolving ITC-relevant HTA guidelines. Effective communication/collaboration between HEOR scientists and clinicians ensures the selection and justification of ITC methods are robust for HTA submissions. Furthermore, this article facilitates clear communication between pharmaceutical companies and policy-makers to ensure appropriate evidence-based decision-making, ultimately contributing to better therapeutic outcomes in patients.

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