



EVERSANA™

**Developing and Implementing an Indirect
Treatment Comparison Program to Support
Global HTA and Reimbursement Submissions**

ISPOR 2020 Workshop

Wednesday, May 20, 2020; 10:00 AM - 11:00 AM EST



Workshop Introduction

- Thank you everyone for joining the workshop on ***“Developing and Implementing an Indirect Treatment Comparison Program to Support Global HTA and Reimbursement Submissions”***
- We will answer audience **questions** at the end of the workshop.

Today's Presenters



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CAMERON**

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at EVERSANA*



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PETERSON**

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Market Access –
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NAIR**

*Manager, Janssen Health
Economics Design &
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*Compound Market Access
Leader for Dermatology &
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Europe, Middle East &
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Conflicts of Interest

- Chris Cameron is an employee and shareholder for EVERSANA. EVERSANA provides commercialization services to life science industry.
- Steve Peterson, Sandhya Nair, and Agata Schubert are employees of Janssen, the Pharmaceutical Companies of Johnson & Johnson.
- Steve Peterson and Agata Schubert are shareholders of Johnson & Johnson.



1. Introduction to Indirect Treatment Comparisons (ITCs)
2. Guidance on Selecting the Most Appropriate ITC Methods for a Global ITC Program
3. Developing a global ITC Program, including early feasibility assessment with timelines
4. Building a Global ITC Program – Guidance from a Global HEOR Lead
5. Global ITC Program – A European Perspective
6. Application of a Global ITC Program – Interactive Case Studies

Agenda

Developing and Implementing an Indirect Treatment Comparison Program to Support Global HTA and Reimbursement Submissions

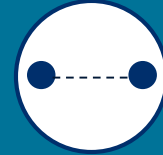
Introduction to Indirect Treatment Comparisons (ITCs)

“

Indirect treatment comparison refers to a comparison of different healthcare interventions using data from separate studies, in contrast to a direct comparison within randomized controlled trials. Indirect comparison is often used because of a lack of, or insufficient, evidence from head-to-head comparative trials.

Types of indirect treatment comparisons

Summary Level Data Only



Naïve Indirect Comparison



Anchored Indirect Comparison

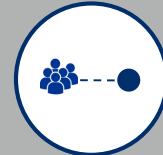


Network Meta-Analysis (NMA)

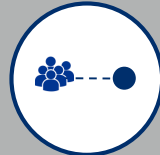


NMA Involving Meta-Regression

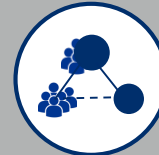
Mix of IPD and Summary Level Data



Unanchored MAIC



Unanchored STC



Anchored MAIC



Anchored STC



NMA Leveraging IPD

IPD Only



Propensity Score Reweighting and Matching



Multivariable Regression Using IPD

NMA:	Network meta-analysis
IPD:	Individual patient data
MAIC:	Matching-adjusted indirect comparison
STC:	Simulated treatment comparison

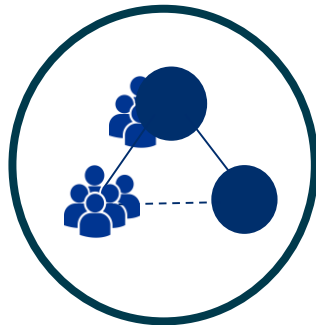
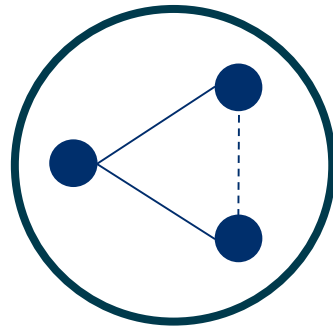
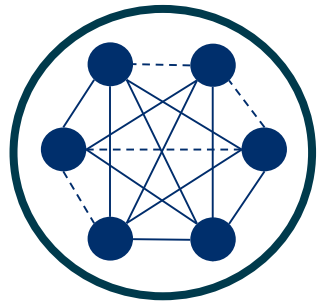


Guidance on Selecting the Most Appropriate ITC Methods for a Global ITC Program

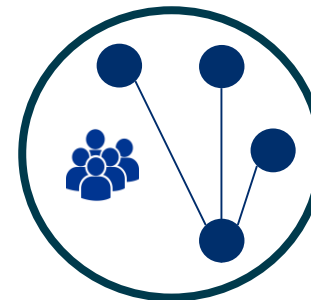
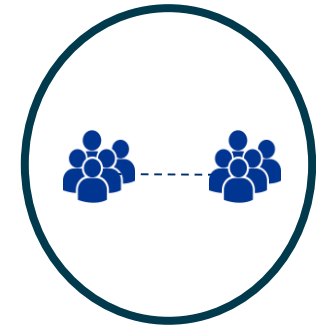
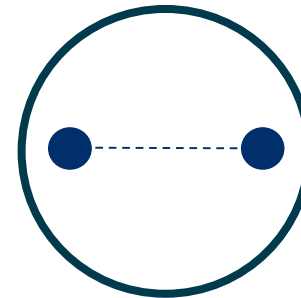
Connected Versus Disconnected Networks

Subhead can go here

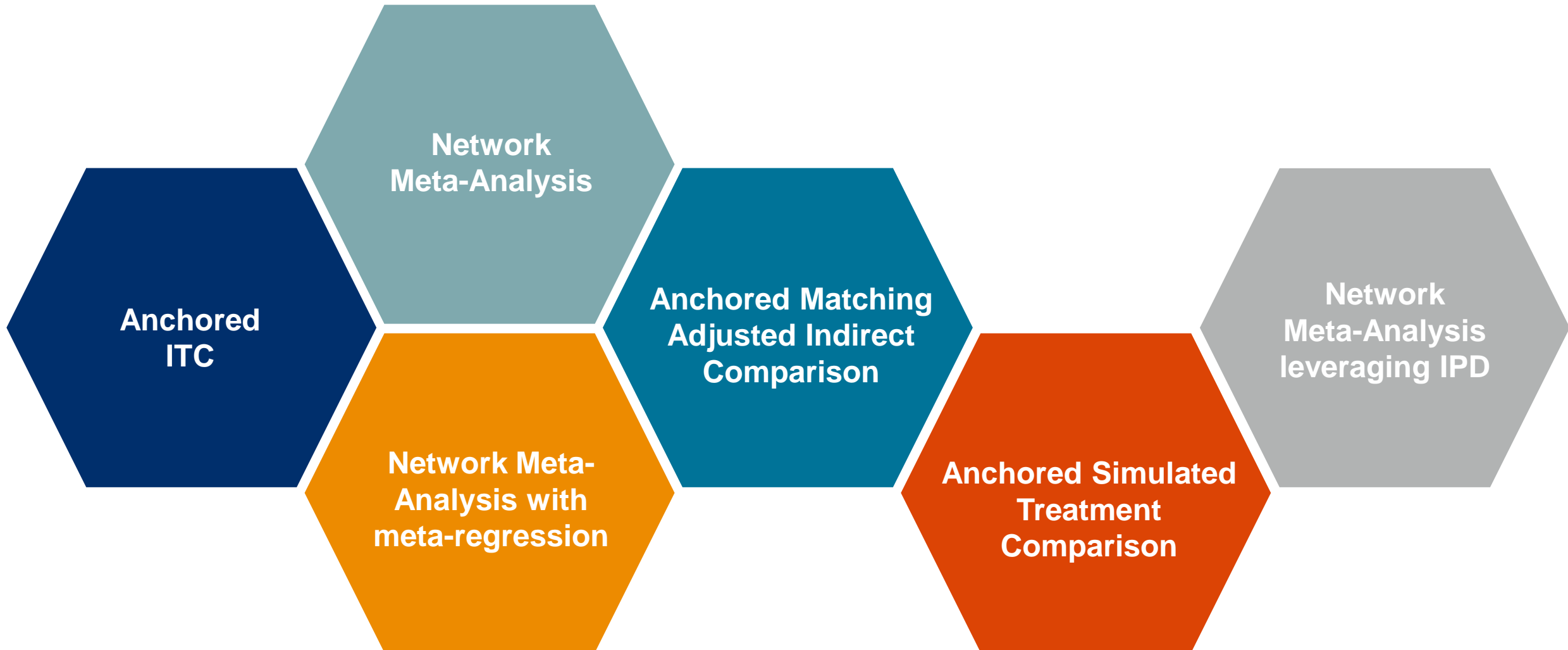
CONNECTED NETWORKS







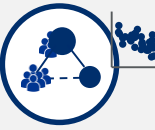

DISCONNECTED NETWORKS



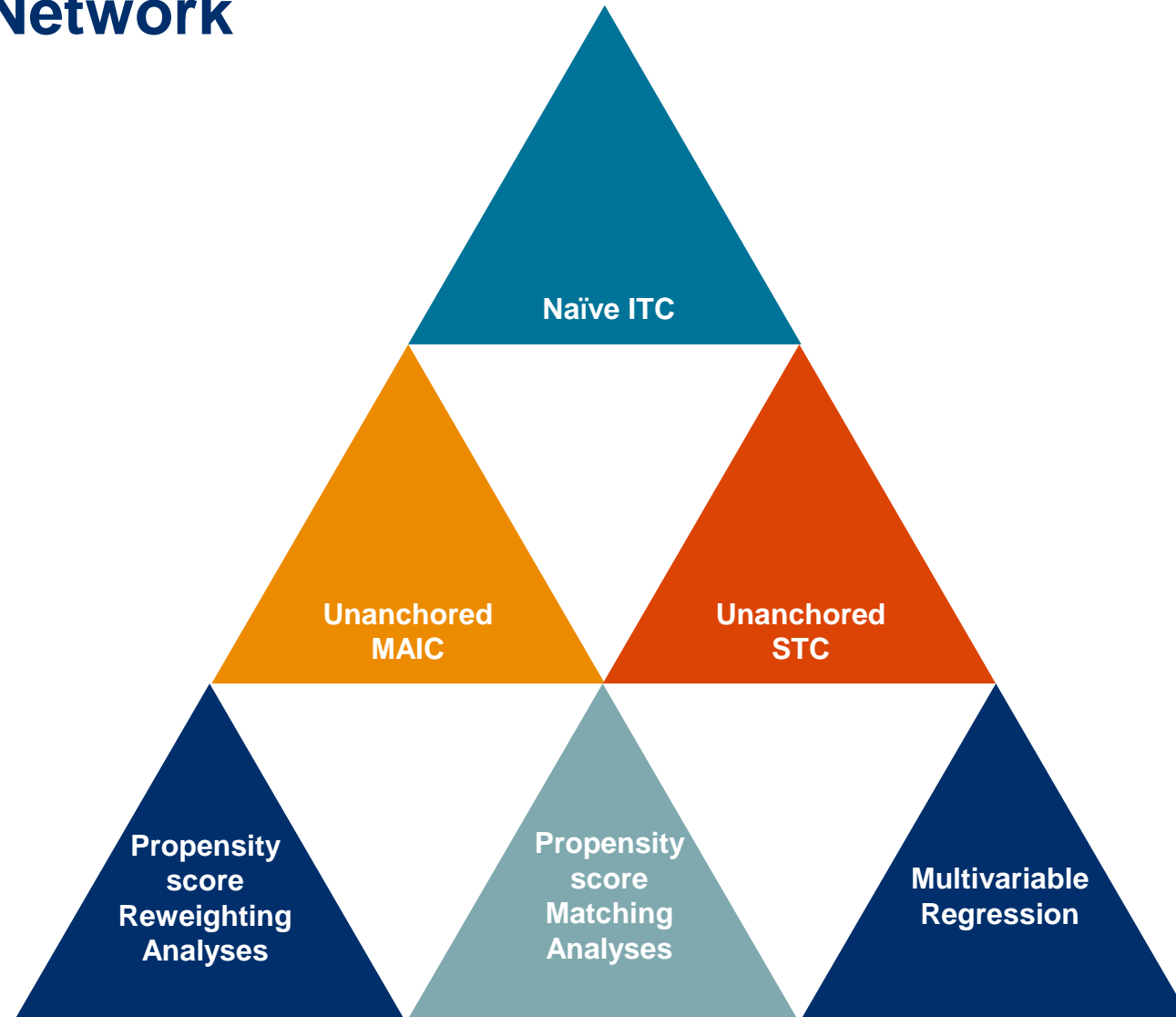
Most Common ITC Options when Comparative Data Can Connect with Network







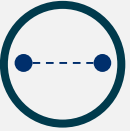




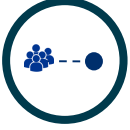




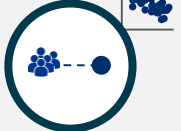




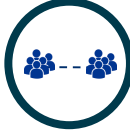




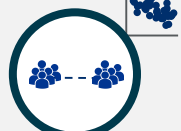
Choice of ITC when Comparative Data Can Connect with Network

Moderate to high Heterogeneity?	≥ 2 comparators?	Access to IPD?	Connections with ≥ 5 studies?		
✗	✗	✗	✗	Anchored (Bucher) ITC	
✗	✓	✗	✗	Network Meta-Analysis	
✓	✓	✗	✓	Network Meta-Analysis with Regression	
✓	✗	✓	✗	Anchored MAIC	
✓	✗	✓	✗	Anchored STC	
✓	✓	✓	✗	Network Meta-Analysis leveraging IPD	

Most Common ITC Options when Lack of Comparative Data or Disconnected Network



Choice of ITC when Lack of Comparative Data or Disconnected Network

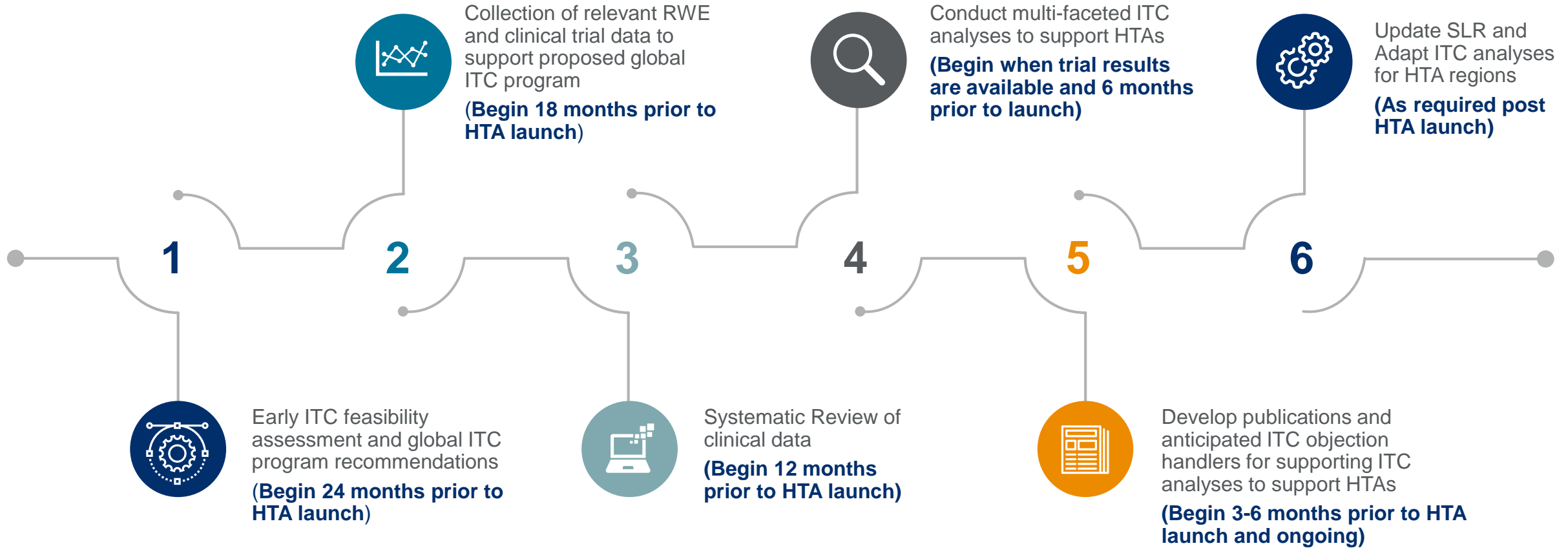
Moderate to high Heterogeneity?	≥ 2 comparators?	Access to IPD?	Connections with ≥ 5 studies?		
				Naïve ITC	
				Unanchored MAIC	
				Unanchored STC	
				Propensity Score Matching/Reweighting	
				Multivariable regression	



Developing a Global ITC Program, Including Early Feasibility Assessment and Timelines

Steps in Developing a Global ITC Program for HTA submissions

Timelines to implement Global ITC Program for New Product



Results from Early Feasibility Assessment for Sample Global ITC Program in 2020 with Comparative Data and Connected Network

EARLY ITC FEASIBILITY ASSESSMENT

- Key studies for indication were compared for similarities and differences across: study design, inclusion/exclusion criteria, baseline patient characteristics, outcome definitions, and placebo response
- Evidence Networks Developed and availability of data for comparators assessed

RECOMMENDATION #1

Develop a multi-faceted indirect treatment comparison program to support many HTA regions

RECOMMENDATION #2

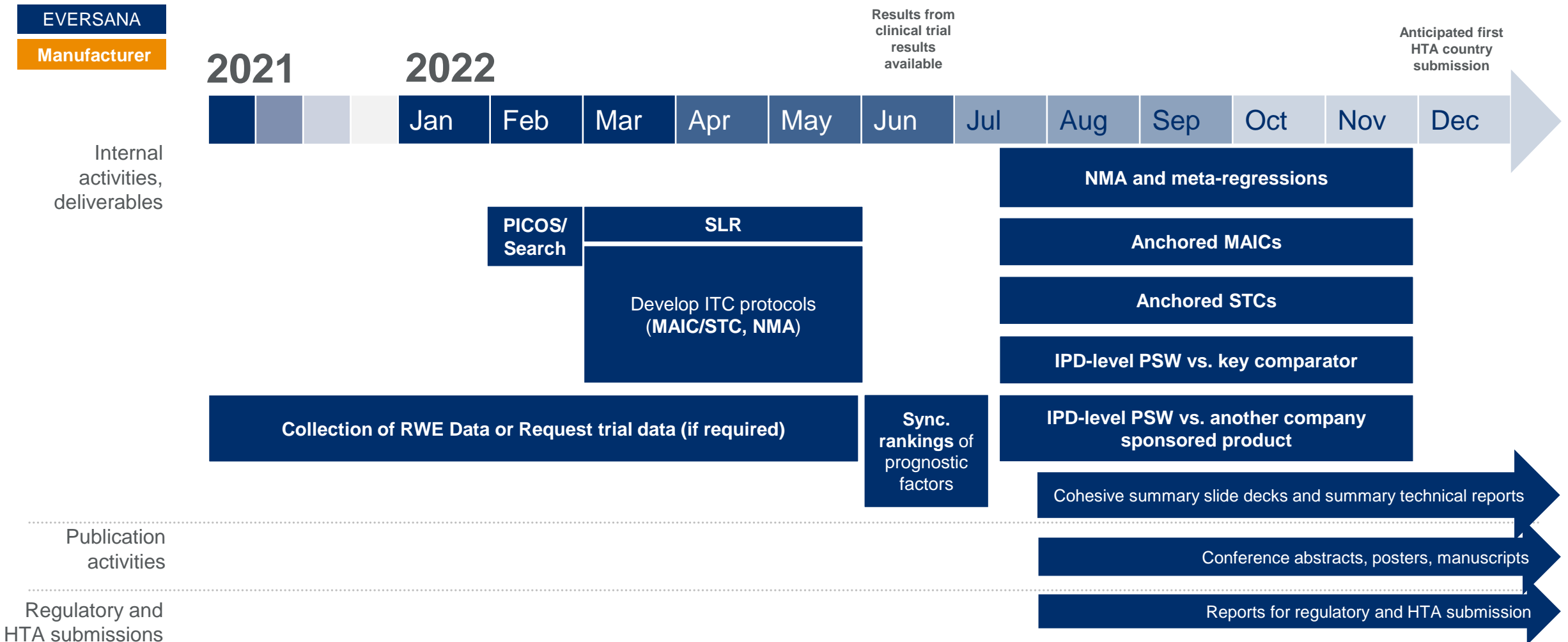
Systematically collect and summarize applicable data to be prepared for launch; initiate SLR at least 12-months prior to launch

RECOMMENDATION #3

Develop publication program and data communication plan for ITCs

Abbreviations: IPD = individual patient data; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; STC = simulated treatment comparison.

Timelines and Activities for sample Global ITC Program



Abbreviations: HTA = health technology assessment; IPD = individual patient data; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison, PSW = propensity score weighting; RWE = real-world evidence; SLR = systematic literature review; STC = simulated treatment comparison.



Building a Global ITC Program – Guidance from a Global HEOR Lead

Global ITC Program: Grounding Principles, Team Requirements

Governing Principles: Best Care of Patients, Best Information for all Stakeholders

CORE PRINCIPLE

TEAM REQUIREMENTS

Most Robust Applicable Methods Chosen: *A Priori*

Methods approaches chosen according to HTA requirements, and data availability

Transparent and Documented Process

Internal medical alignment and protocol establishment, and external protocol declaration.

Adherence to Vetted / Accepted Practices

From SLR, to model designation, to production of results: Adherence to accepted, rigorous methods.

Balance and Conservatism in Interpretation

Careful articulation of defensible conclusions; Fair accounting of limitations of study where applicable.

Thorough Peer-Reviewed Reporting

Presentation of results in rigorous peer-reviewed congresses.

Global ITC Program Checklist for New Products

1

Begin early ITC Feasibility Assessment and global ITC Program at least two years before HTA launch

2

Find the right partner with ITC expertise and global HTA experience

3

Ensure medical team within company involved in co-production of Global ITC Program

4

Engage regional affiliates early in development of Global ITC Program

5

Develop various ITC analyses to support global HTA requirements

6

Develop technical ITC reports and explanatory materials before HTA launch and update as required

7

Develop ITC publication and communication program to support Global ITC Program

8

Ensure partner is available to adapt regional ITCs and respond to HTAs in timely manner

Global ITC Program in Action – Guselkumab for Psoriasis**

Signorovitch et al.
"The importance of adjustment for reference arm response identified in this study, using methods consistent with recommendations made by the NICE DSU, suggests that network meta-analyses of biologics in psoriasis that do not include this adjustment do not provide reliable comparative evidence."

Methods Publication

Sbidian et al.
 Conducted an NMA and did not adjust for baseline risk.

Cochrane Review

Cameron et al.
 Conducted an NMA which adjusted for baseline risk and properly considered multiple Betas for each PASI outcome.

Janssen NMA

Cameron et al.
 Registered the guselkumab NMA in the PROSPERO database

PROSPERO Registration



NICE TSD 3

Dias et al.
"[...] clearly suggests a relation between efficacy and baseline risk that needs to be incorporated into CEA models. Secondly, [...] if not controlled for, introduce severe heterogeneity in pairwise meta-analysis and potential inconsistency in network synthesis."

ICER Review: Original

Original:
 Conducted an NMA and did not adjust for baseline risk.

ICER Review: 2018 Update

2018 Update:
 Conducted an NMA and adjusted for baseline risk but assumed one Beta for all PASI outcomes.

NICE brodalumab and guselkumab recommendations

"The committee agreed that there was variation in the placebo response rates, and that adjusting for these differences could reduce unexplained variation between studies and improve the precision of the PASI response rate estimates. The committee preferred the adjusted model for decision-making."

Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis

Journal of Comparative Effectiveness Research

Chris Cameron^{1,2}, Brian Hutton^{2,3}, Cheryl Druchok¹, Sean McElligott⁴, Sandhya Nair⁵, Agata Schubert⁶, Aaron Situ¹, Abhishek Varu¹ & Reggie Villacorta⁴
¹Cornerstone Research Group, Inc., Burlington, Ontario, Canada
²Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada
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Original Research



Guselkumab for the Treatment of Moderate-to-Severe Plaque Psoriasis During Induction Phase: A Systematic Review and Network Meta-Analysis

C. Cameron, PhD¹, C. Druchok, PhD¹, B. Hutton, PhD^{2,3}, S. McElligott, MSc⁴, S. Nair, PhD⁵, A. Schubert, MSc⁶, A. Situ, MSc¹, A. Varu, MSc¹, and R. Villacorta, PhD⁴



**All visuals and information below in public domain: ISPOR 2018 Cameron et al. Importance of properly adjusting for heterogeneity among network meta-analyses considering outcomes with multiple pre-defined levels: An illustrative example in psoriasis

Acceptance of ITCs in North America and Asia



United States

Preference for NMA;
less acceptance of
other ITC techniques
but will accept if
methods if rationale
clearly described



Canada

Preference for NMA
but accept all forms of
ITC methods if
rationale clearly
described



Australia

Pairwise ITCs such
as Bucher ITCs,
MAICs and STCs
accepted



Japan

Acceptance of
NMAs; often include
adaptations to Asian
populations



Acceptance of ITCs by HTA Bodies – A European Perspective

Acceptance of ITCs by HTA bodies



United Kingdom

Preference for NMA
but accept all forms of
ITC methods if
rationale clearly
described



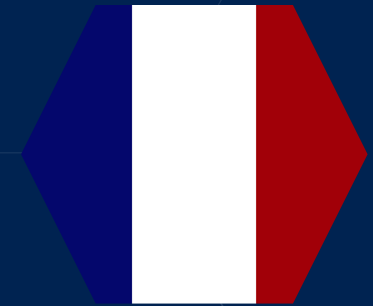
EUnetHTA

Preference for NMA
but accept all forms of
ITC methods if
rationale clearly
described



Germany

Strong preference for
RCT; Acceptance of
ITCs have been
limited



France

Preference for NMA;
less acceptance of
other ITC techniques
but will accept if
methods if rationale
clearly described

Available ITC Guidelines in Europe

NICE National Institute for Health and Care Excellence



Process and methods guides

Guide to the methods of technology appraisal 2013

<http://publications.nice.org.uk/pmg9>

Published: 04 April 2013

NICE DSU TECHNICAL SUPPORT DOCUMENT 1: INTRODUCTION TO EVIDENCE SYNTHESIS FOR DECISION MAKING

REPORT BY THE DECISION SUPPORT UNIT

April 2011
(last updated April 2012)

Sofia Dias¹, Nicky J Welton¹, Alex J Sutton², AE Ades¹

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Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Tel (+44) (0)114 222 0734

NICE DSU TECHNICAL SUPPORT DOCUMENT 18: METHODS FOR POPULATION-ADJUSTED INDIRECT COMPARISONS IN SUBMISSIONS TO NICE

REPORT BY THE DECISION SUPPORT UNIT

December 2016

David M. Phillippo,¹ A. E. Ades,¹ Sofia Dias,¹
Stephen Palmer,² Keith R. Abrams,³ Nicky J. Welton¹

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HAS
HAUTE AUTORITÉ DE SANTÉ



A METHODOLOGICAL GUIDE

Choices in Methods for Economic Evaluation

October 2012

Department of Economics and Public Health Assessment


Available ITC Guidelines in Europe




Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Guidelines for the Economic Evaluation of Health Technologies in Ireland

2019



EUnetHTA JA2 HTA Core Model® for Rapid REA WP5




eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT


Joint Action on HTA 2012-2015

HTA Core Model for Rapid Relative Effectiveness
Date: November 2015

Was developed by Work Package WP5
WP 5 Lead Partner: Dutch National Health Care Institute
WP Co-Lead Partner: Ludwig Boltzmann Institute for HTA





Zorginstituut Nederland



Ludwig Boltzmann Institut
Health Technology Assessment

Disclaimer: EUnetHTA Joint Action 2 is supported by a grant from the European Commission. The sole responsibility for the content of this document lies with the authors and neither the European Commission nor EUnetHTA are responsible for any use that may be made of the information



Guidelines for pharmacoeconomic evaluations in Belgium
KCE reports 78C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2008

Increasing Acceptance of ITCs by Major HTA Bodies in Europe and around the World

“The use of MAIC in the absence of direct comparisons between treatments has been increasing across different therapeutic areas, and so has its acceptability by HTA bodies”¹

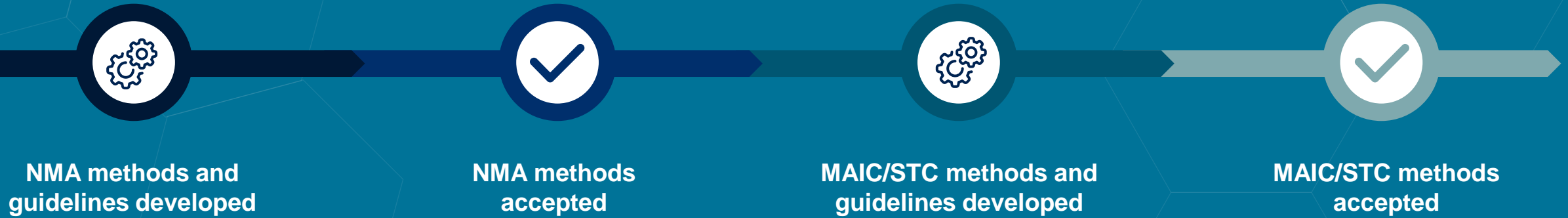
“An increased trend was found in the use of MAIC in published literature as well as NICE TA submissions. This methodology was also well received by NICE TAs. Overall, MAICs can provide comparative evidence to enable informed policy decisions.”²

“ITC is generally accepted as a technique that allows demonstration of noninferiority to a comparator provided the chosen methodology and underlying assumptions are clear and justified.”³

“Network meta-analyses and indirect comparisons are acknowledged methodologies by HTA agencies worldwide including the NICE, CADTH, HAS, and PBAC, as well as... Austria, Brazil, Colombia, Cuba, and Ireland..”⁴

¹Thom et al. 2016; ²Ndirangu et al. 2016; ³Skali and Spoors. 2018; ⁴Baston et al. 2016.
Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = French Haute Autorité de la Santé; HTA = health technology assessment; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee (in Australia); STA = single technology appraisal; STC = simulated treatment comparison TA = technology appraisal

Adoption of ITCs by HTA bodies





Application of a Global ITC Program – Interactive Case Studies

The manufacturer of the mid-size biotech company should:

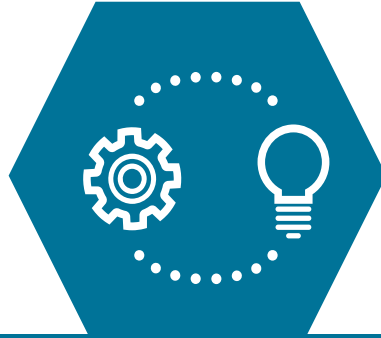
- A. Initiate global ITC program for each drug in pipeline years in advance of HTA launch
- B. Conduct multiple ITC analyses to meet various global HTA requirements
- C. Engage regional affiliates within their company when developing the global ITC program for each product
- D. Engage cross-functional teams within their company when developing global ITC program
- E. All of the above

Case Study (1): *Pipeline of candidate novel drugs for market access in mid-size biotech company*



A **mid-size biotech** company has **two novel drugs** in development across various therapeutic areas. The manufacturer has **limited HTA experience** and has not previously submitted ITCs, but plans to launch for market access for both drugs in **2022**.

Case Study (2): Novel Drug for Treatment of Atrial Fibrillation



A **new drug** is under development for **atrial fibrillation**. The manufacturer requires estimates of comparative efficacy versus **five key comparator drugs** in atrial fibrillation to support HTA submissions and market access. All drugs have been compared with **standard adjusted dose vitamin K antagonists**. Key comparators have also been approved largely based on **one large multi-national trial**, but they anticipate that there will be **cross-trial differences** between their drug and comparator drugs.

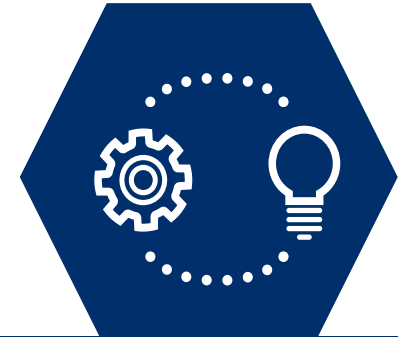
The Global ITC Program for a novel drug for atrial fibrillation with RCT data could consider:

- A. Network Meta-Analysis
- B. MAICs versus key comparator(s)
- C. Anchored ITCs versus key comparator(s)
- D. STCs versus key comparator(s)
- E. All of the above

Case Study (3): *Novel Drug for Treatment in Oncology*

The Global ITC Program for a novel drug for oncology with single arm data could consider:

- A. Unanchored MAIC versus key comparator(s)
- B. Unanchored STC versus key comparator(s)
- C. Propensity score reweighting/matching versus RWD standard of care
- D. Multivariable regression versus RWD standard of care
- E. All of the above



A **new drug** is under development for **oncology**. The manufacturer requires estimates of comparative efficacy versus **two key comparator drugs** in oncology to support HTA submissions and market access. The novel drug was approved based on a **single arm trial**. Key comparators have also been approved based on **single arm trials**, and manufacturer anticipates that there will be **cross-trial differences** between their drug and comparator drugs.

THANK YOU

QUESTIONS?