Join at
slido.com
#3465 520

PSI 2026 – Workshop

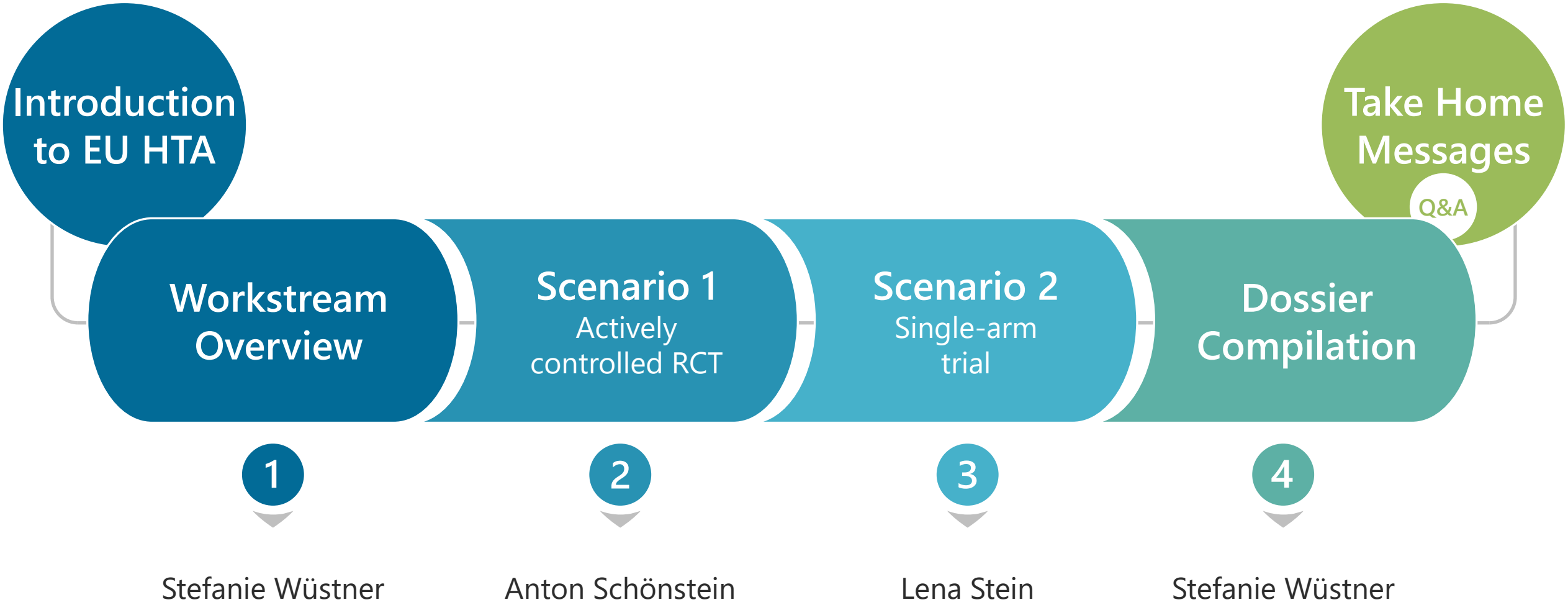
Navigating EU HTA

From Pivotal Trial to Evidence Networks based on First Experiences

Lena Stein & Stefanie Wüstner (*AMS* Advanced Medical Services)
Anton Schönstein & Amelie Elsäßer (Boehringer Ingelheim)

15.06.2026

AGENDA FOR THIS WORKSHOP



DISCLAIMER

Conflict of Interest Statement

Stefanie Wüstner and Lena Stein are employees of AMS Advanced Medical Services, a full service CRO providing services in the field of clinical development and market access.

The views expressed in this workshop are our own and do not necessarily reflect those of our employer.

Where Do You Stand on EU HTA today?

Live Poll

Observer

I am mainly following developments and building awareness

Preparer

I am actively preparing (e.g., processes, evidence, strategy)

Active Contributor

I am already directly involved in EU HTA / JCA activities

EVIDENCE GENERATION DOES NOT END

With Approval

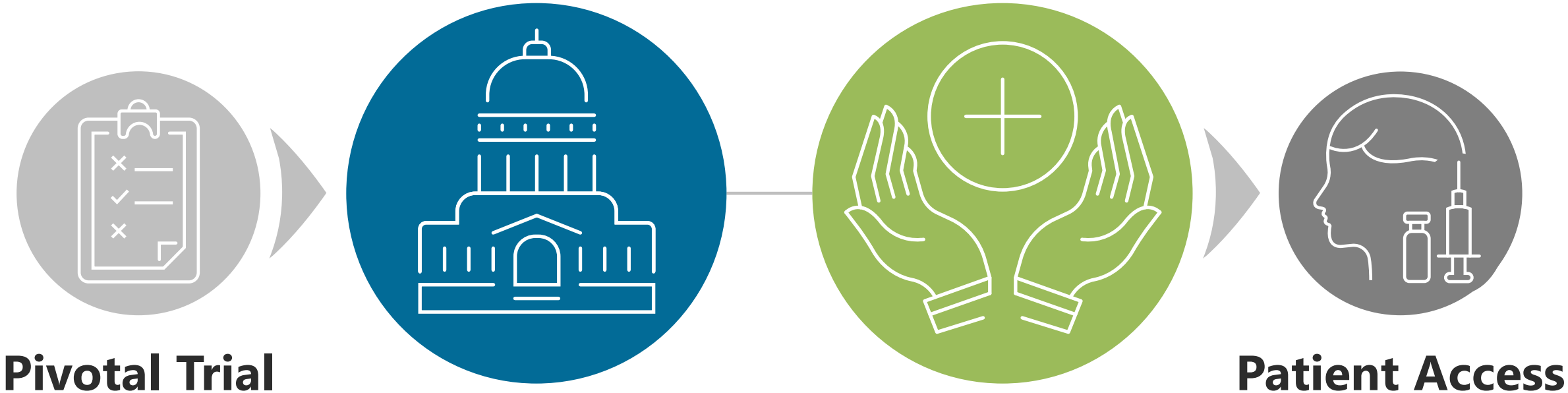
Pivotal Trial

EU Marketing Authorisation

Patient Access

DIFFERENT QUESTIONS

Require Different Evidence



DIFFERENT QUESTIONS

Require Different Evidence

EU Marketing Authorisation

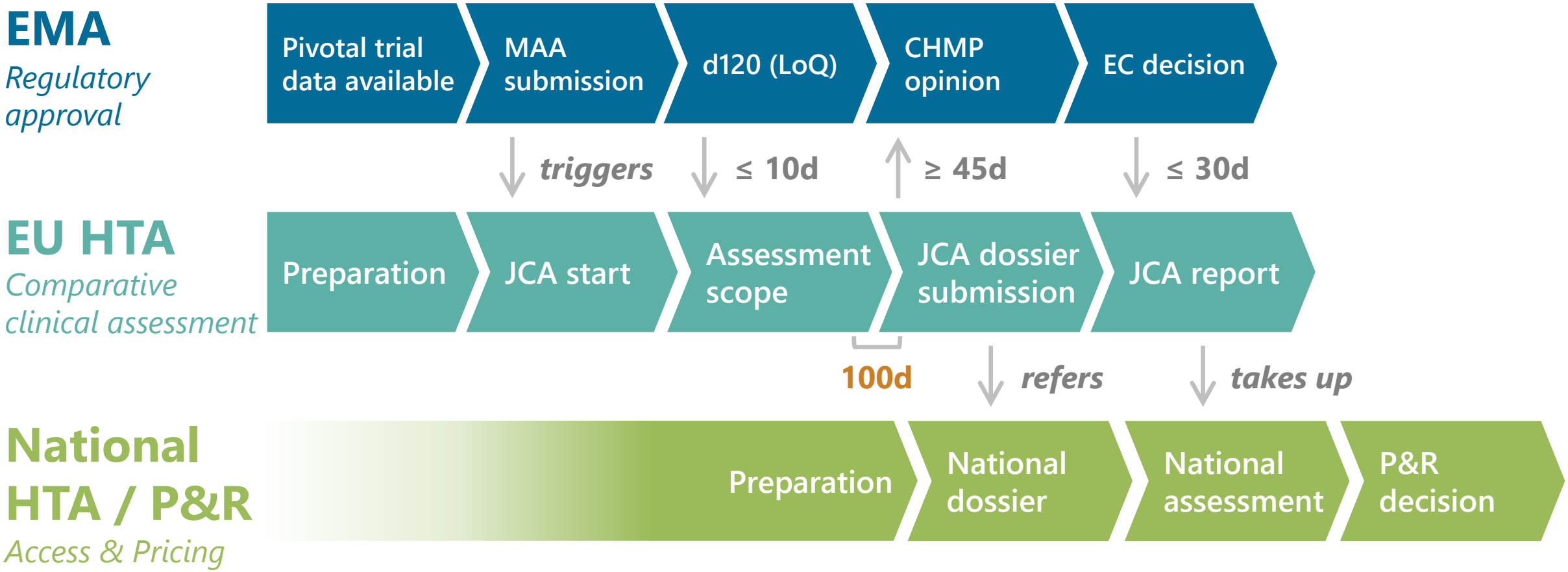
EU HTA

National HTA

P&R

JCA TIMELINE IS SHORT

So Preparation Starts Early



JCA IS NO LONGER THEORETICAL

Early Implementation

Where Are We Now?

16 JCA procedures for medicinal products
(13 started in 2025, 3 in 2026)

11 oncology, 3 ATMP, 2 unknown)

1 procedure discontinued (Zumrad/sasanlimab)

1 endorsed JCA report (Ojemda/tovorafenib)

What To Expect in 2026?

Expected procedures
~35 oncology JCAs
~15 ATMP JCAs
~5 medical device JCAs

Preparation window:
Ideally 1-2 years in advance

Think HTA early when planning pivotal trials and evidence generation

PSI 2026 – Workshop

1 Workstream Overview

Stefanie Wüstner (*AMS* Advanced Medical Services)

15.06.2026

SCOPE OF EVIDENCE GENERATION

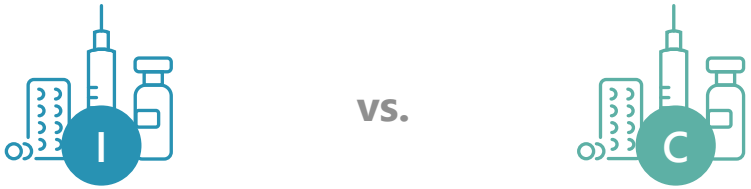
for EU HTA

HTA requires comparative evidence

✓ Policy questions of MS

✗ Questions not based on available evidence

Population **I**ntervention **C**omparator **O**utcome



Pivotal trial(s) only cover **subset of PICOs** or sometimes not even one

JCA EVIDENCE PACKAGE

Based on Pivotal Trial and Further Evidence

Pivotal study results and CSR outputs

Additional HTA analyses e.g. further subgroups, safety, or sensitivity analyses

(Network) meta analyses

Indirect treatment comparisons e.g. Bucher, PAICs

Non-randomised comparisons e.g. external controls

EU HTA EVIDENCE WORKSTREAM

Early HTA advice

Assess feasibility & generate analyses

PICO anticipation

Documentation

Further requests

Information retrieval

Post-submission

JCA dossier compilation

Dossier-ready tables and narratives

JCA SAP

Gap analysis

Defensible argumentation strategy

Identify relevant evidence

Strategic preparation

Updated and extended analyses

Complementary analyses

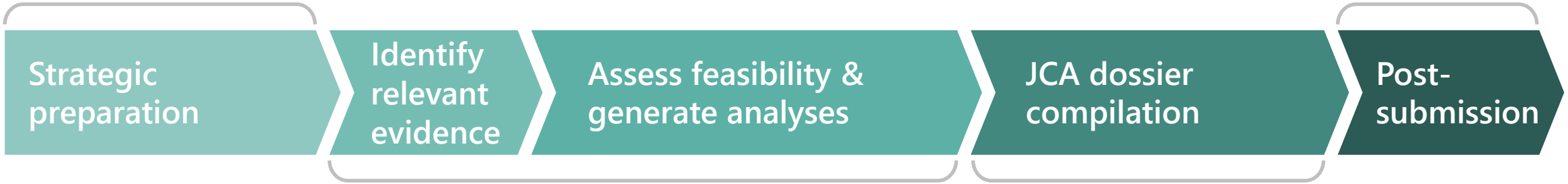
ITC feasibility

Evidence synthesis

EU HTA EVIDENCE WORKSTREAM

- Early HTA advice
- PICO anticipation

- Further requests



- Information retrieval
- Gap analysis
- JCA SAP
- ITC feasibility
- Complementary analyses
- Evidence synthesis

- Updated and extended analyses
- Dossier-ready tables and narratives
- Defensible argumentation strategy
- Documentation

THE ASSESSMENT SCOPE

Is a Set of PICOs

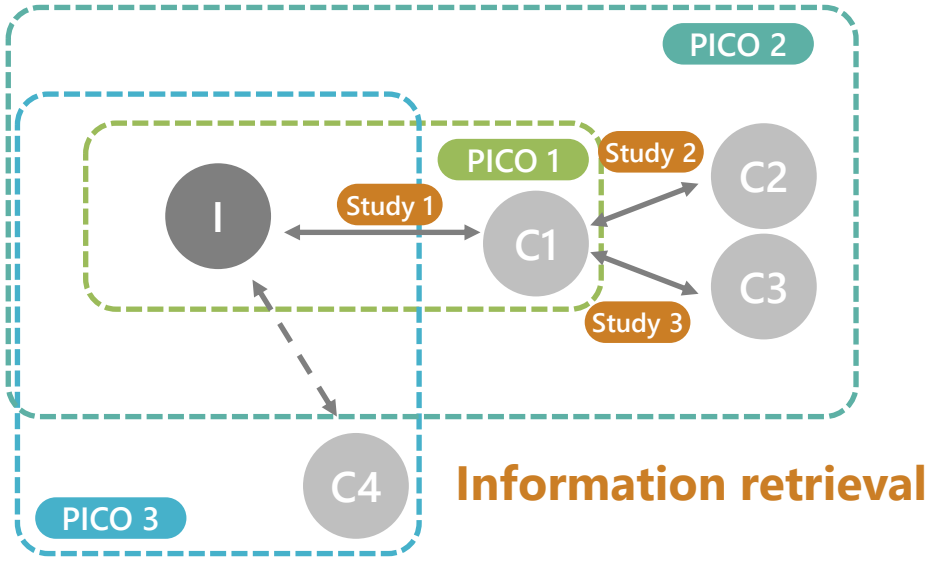
	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	…
I	Intervention	Intervention	Intervention	…
C	Trial comparator	Individualised therapy	Other standard of care	…
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			

If predicted PICOs were considered at pivotal trial planning phase, results could become more relevant for HTA

THE ASSESSMENT SCOPE

Is a Set of PICOs

	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	...
I	Intervention	Intervention	Intervention	...
C	Trial comparator	Individualised therapy	Other standard of care	...
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			



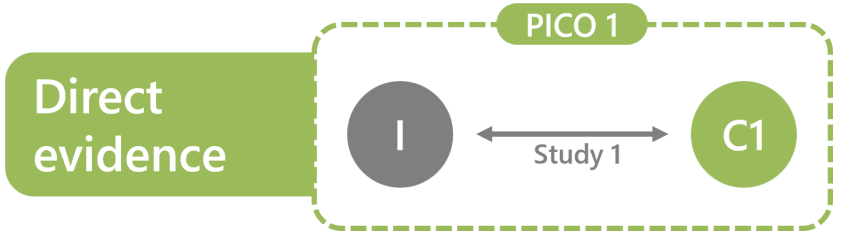
Information retrieval

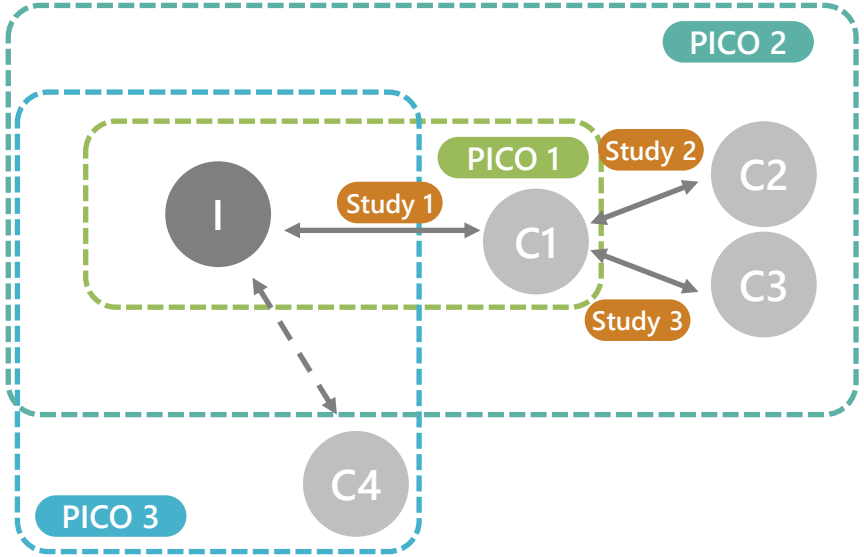
Direct evidence

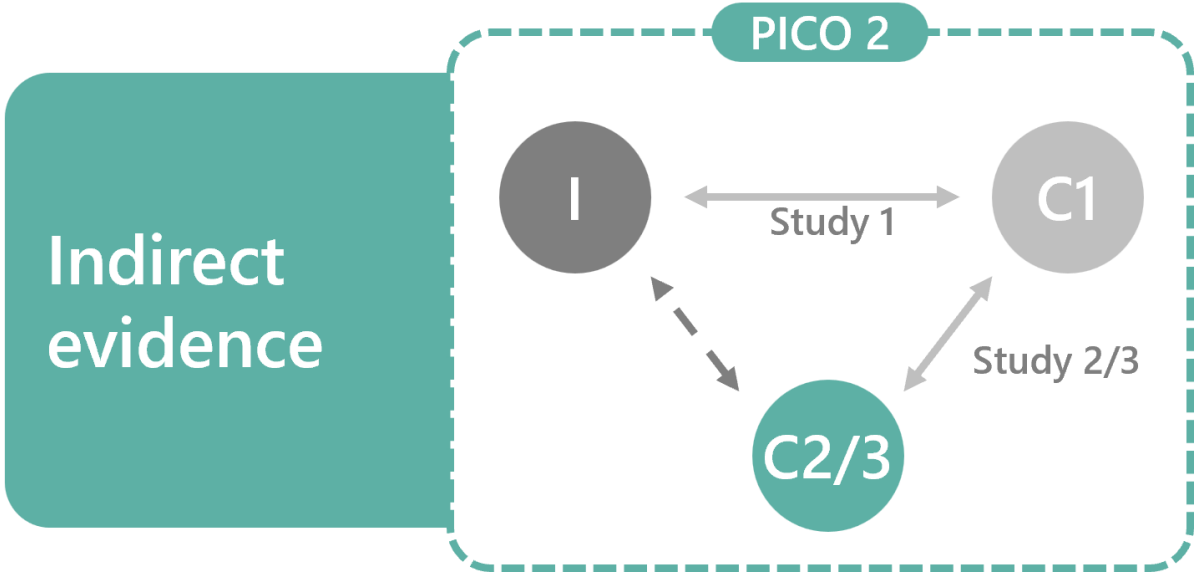
THE ASSESSMENT SCOPE

Is a Set of PICOs

	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	...
I	Intervention	Intervention	Intervention	...
C	Trial comparator	Individualised therapy	Other standard of care	...
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			



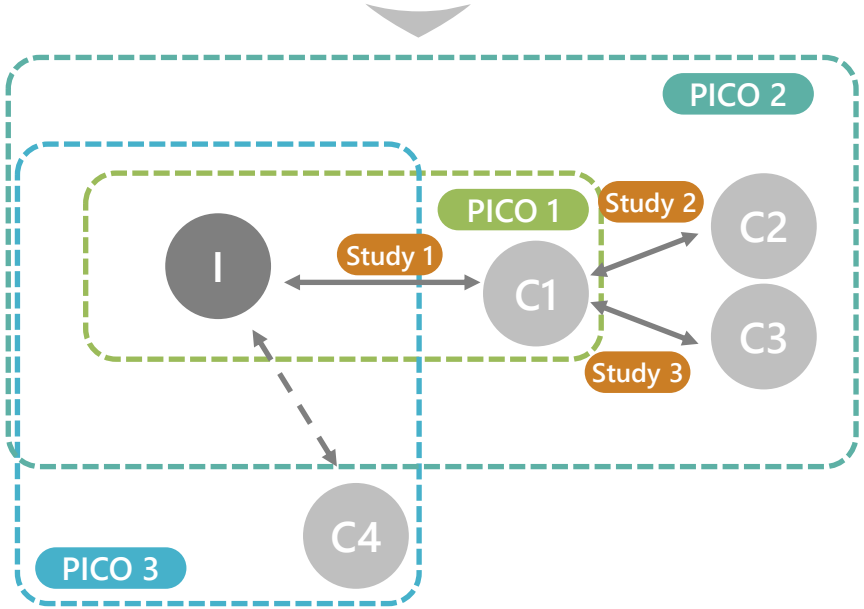


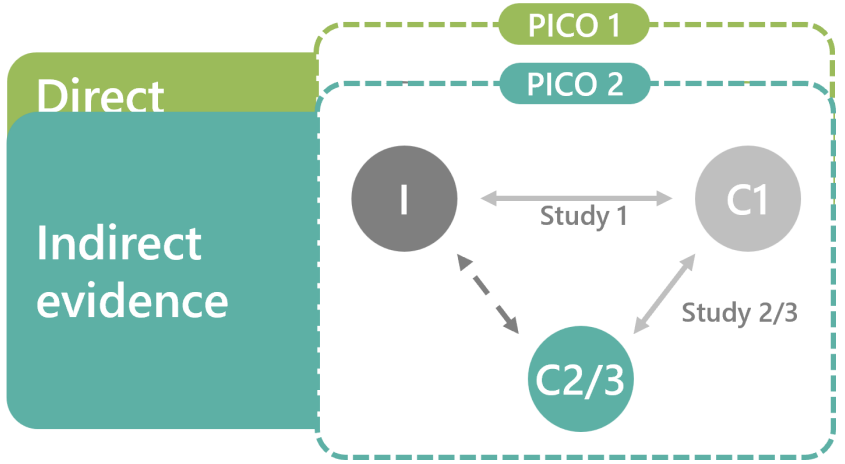


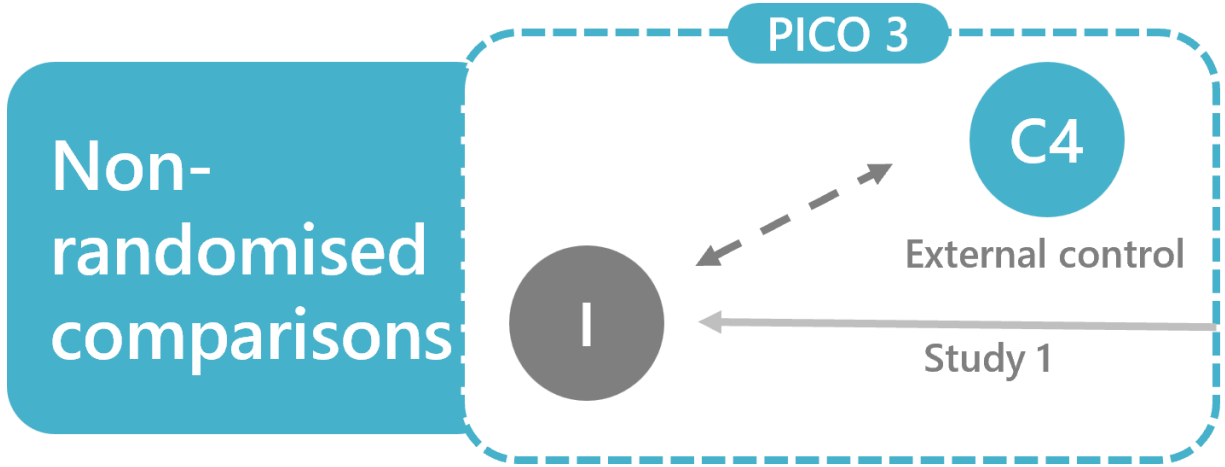
THE ASSESSMENT SCOPE

Is a Set of PICOs

	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	...
I	Intervention	Intervention	Intervention	...
C	Trial comparator	Individualised therapy	Other standard of care	...
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			



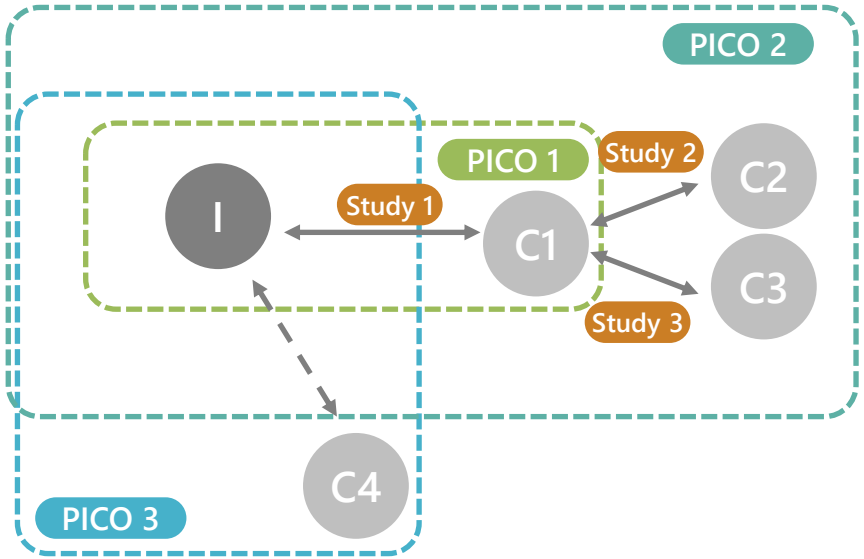


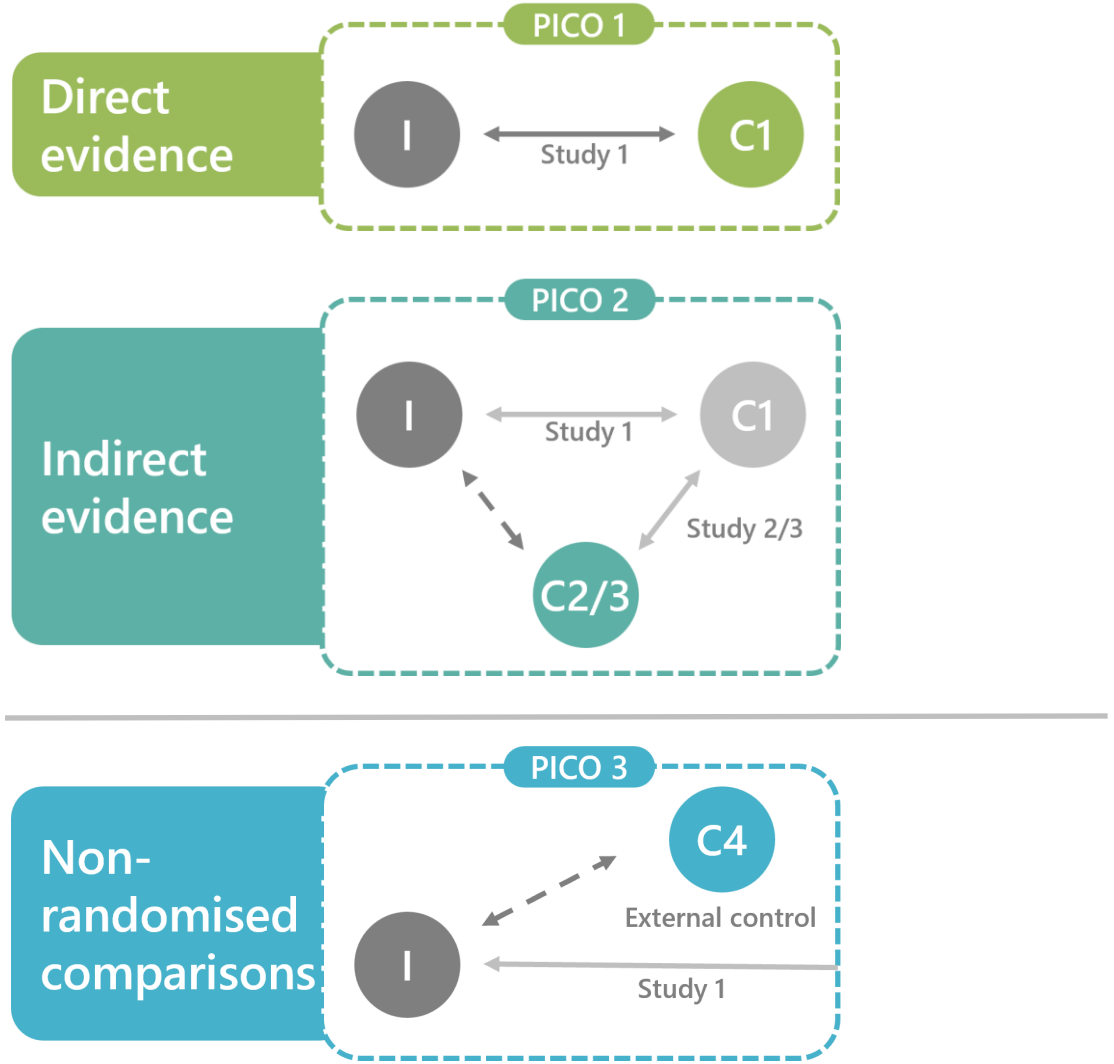


THE ASSESSMENT SCOPE

Is a Set of PICOs

	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	...
I	Intervention	Intervention	Intervention	...
C	Trial comparator	Individualised therapy	Other standard of care	...
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			

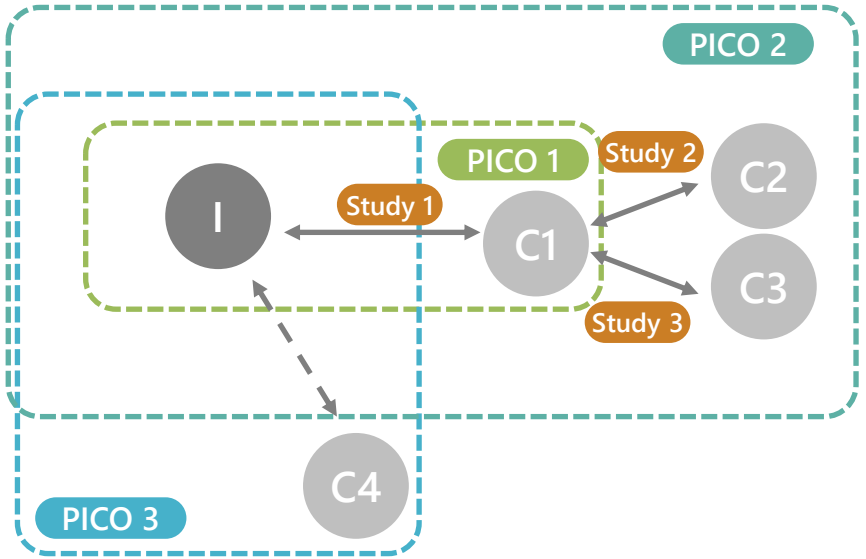


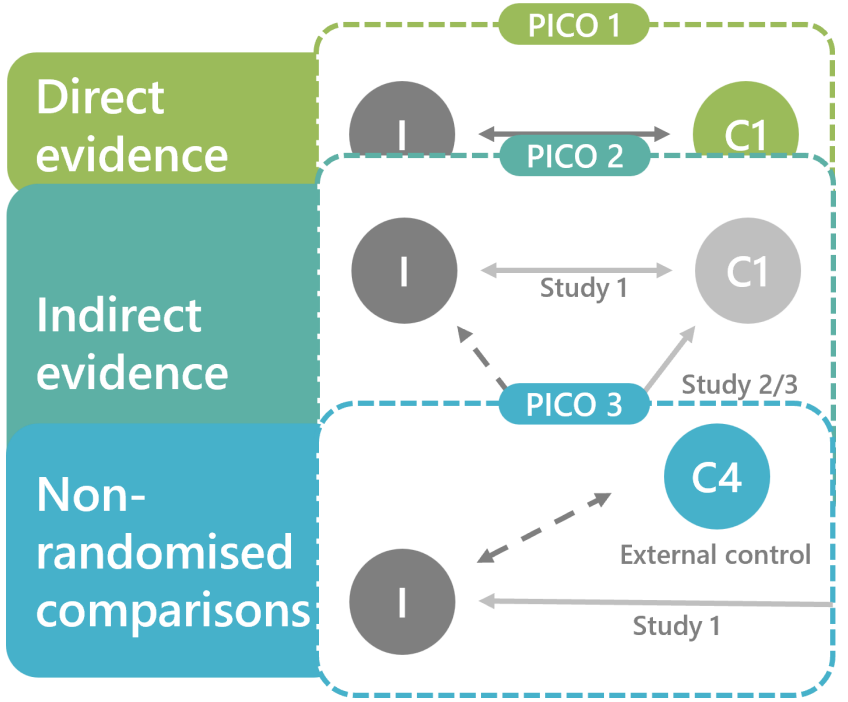


THE ASSESSMENT SCOPE

Is a Set of PICOs

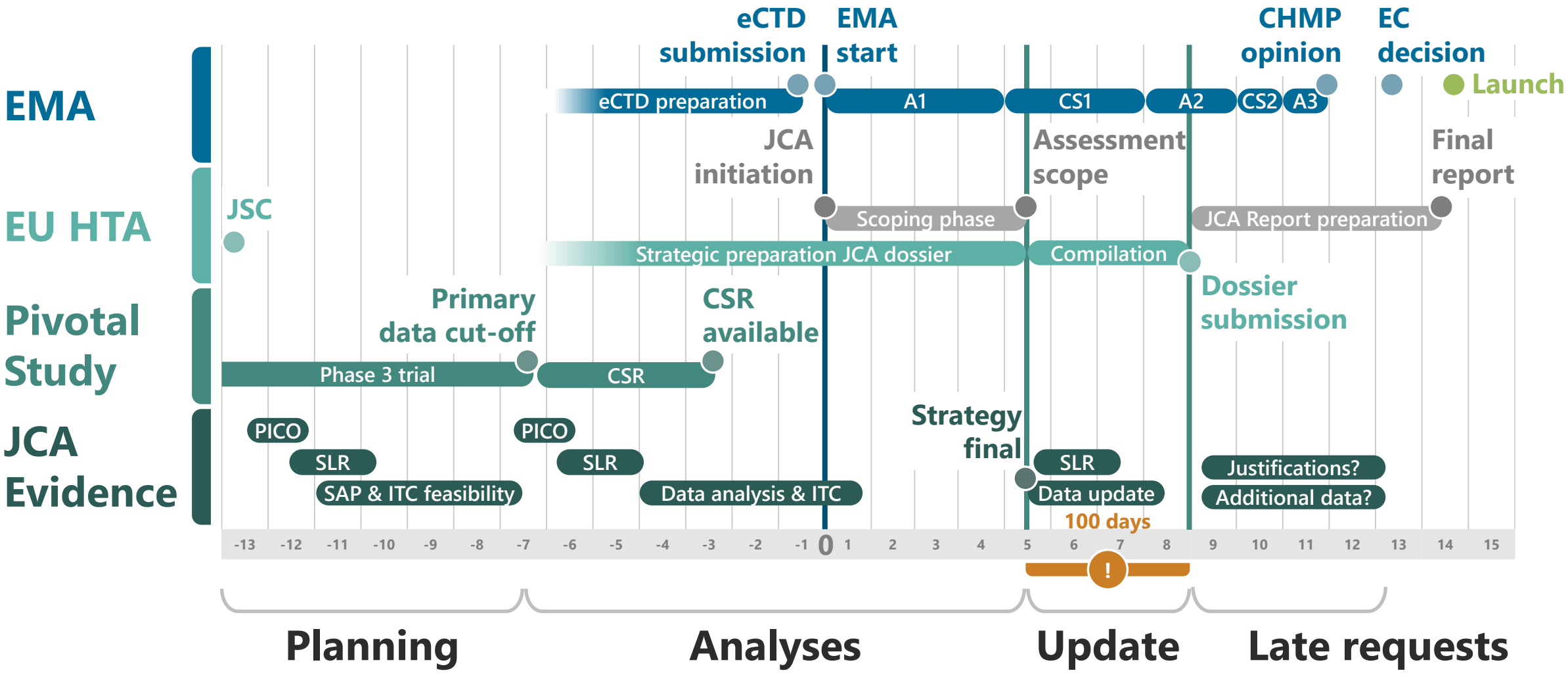
	PICO 1	PICO 2	PICO 3	PICO X
P	Full population	Full population	Subpopulation	...
I	Intervention	Intervention	Intervention	...
C	Trial comparator	Individualised therapy	Other standard of care	...
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety including subgroups			





- **Gap analysis of pivotal trial ▸ JCA SAP**
- **ITC feasibility assessment**
- **Identify external control arm**

PROACTIVELY PREPARING HTA EVIDENCE



Prepare well before the assessment scope arrives

Boehringer Ingelheim

Workshop: Joint Clinical Assessment including a randomized pivotal trial

Anton Schönstein & Amelie Elsäßer

Life forward

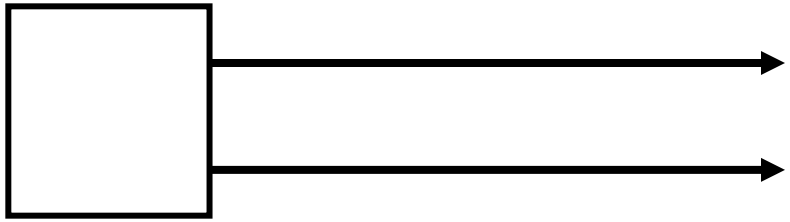
Conflict of Interest:

Anton Schönstein & Amelie Elsäßer are employees of Boehringer Ingelheim Pharma GmbH & Co. KG.

All opinions expressed are those of the presenters.

Boehringer Ingelheim

Workshop Scenario:



- Assume an oncological compound with a pivotal trial that is an RCT
- Primary endpoint is
  → Progression Free Survival (PFS)
- Key secondary endpoints
  →Health-related Quality of Life
  → Overall Survival

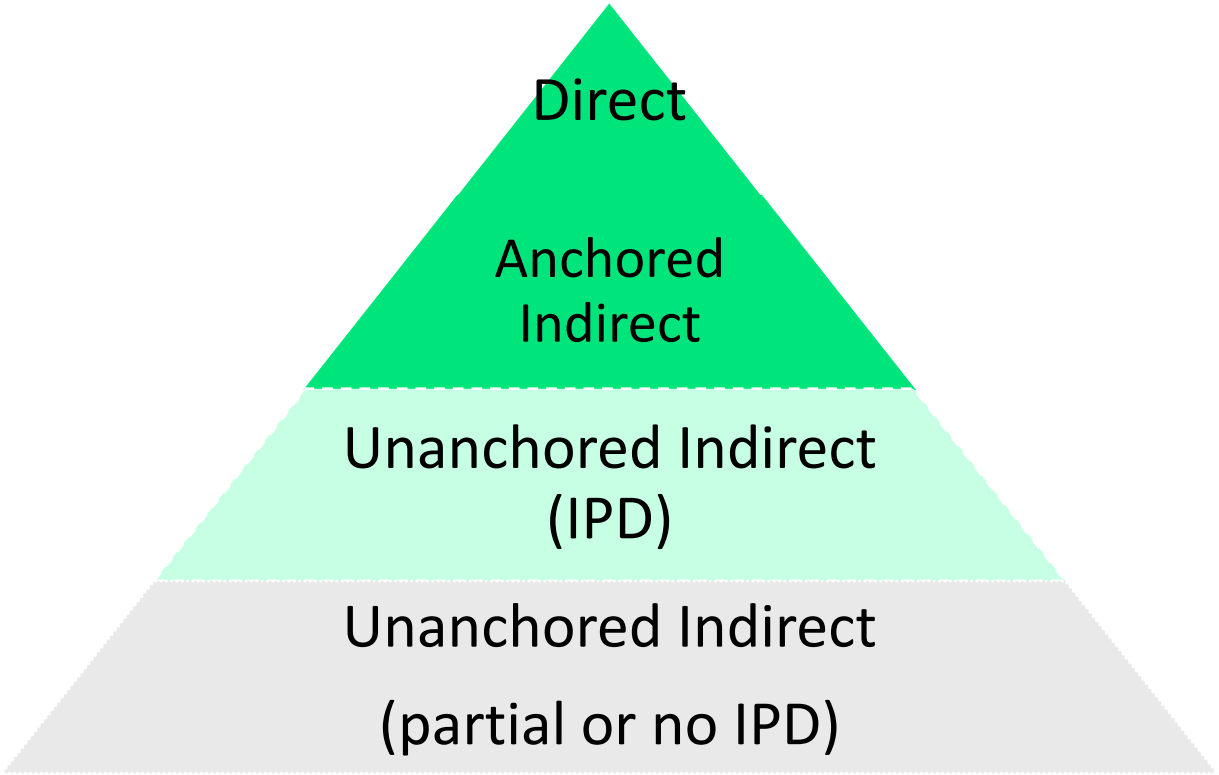
Boehringer Ingelheim

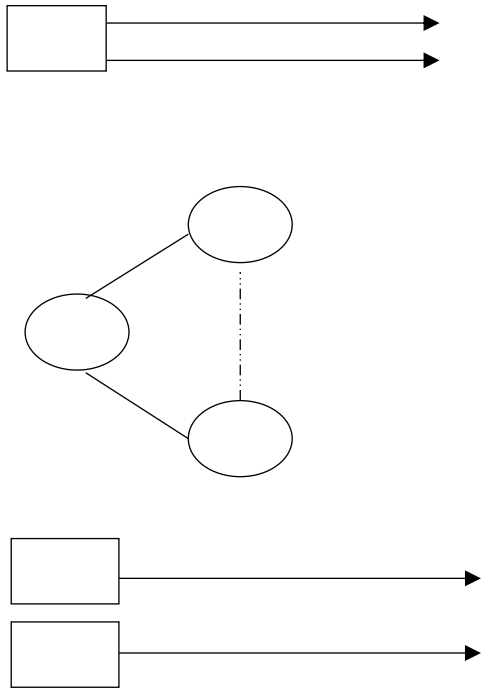
PICO prediction: what would we expect in such a case?

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Trial Population	Trial Pop. + Biomarker	Trial Pop.	Trial Pop. + Biomarker	Trial Pop.	Trial Pop. + Biomarker
I	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor	Competitor	Older SOC	Older SOC
O	Overall Survival, Progression Free Survival, HRQOL (disease specific), HRQOL (general), Safety					

Boehringer Ingelheim

Hierarchy of Evidence in the Guidelines:



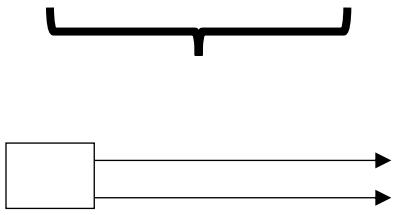


Source: See, e.g., **Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons**
https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en.pdf

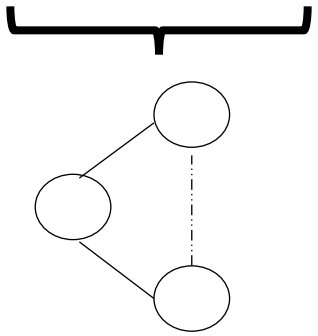
Boehringer Ingelheim

How different PICO types can be addressed:

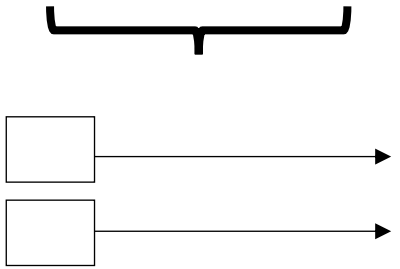
	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Trial pop.	Trial pop. + Biomarker positive	Trial Pop.	Trial Pop. + Biomarker positive	Trial Population	Trial Population + Biomarker positive
I	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor 1	Competitor 1	Older SOC	Older SOC



Supplementary RCT analysis or meta-analysis of RCTs



RCT with a common Comparator



External control arms from RWE etc. or Single Arms

Three topics for a trial PICO (RCT):

1. Safety and the HTA perspective

2. Patient-reported Outcomes (PROs)

3. Surrogate Endpoints

Regulatory vs HTA body perspective on Safety

- Regulatory Agencies: *Is this medicine's benefit–risk balance acceptable for authorisation and continued use?*

→ „Isolating" Safety Signals, Estimand „While on treatment", descriptive reporting, exposure adjustment

- HTA bodies*: Is this medicine worth paying for, compared with alternatives?*

→ Conservative estimates focused on causality, treatment policy estimand, comparative safety (Effect sizes with p-values)

Boehringer Ingelheim

Example Safety: What goes into the dossier?

Main part

- **Descriptive** reporting (= absolute numbers & percentages) of:
  - AE
  - SAE
  - Severe AE
  - Death related to AE
  - Treatment discontinuation due to AE
  - Treatment interruption due to AE

Appendix

- **Relative safety** (= effect measures with 95%-CI & p-values)
- AEs according to SOC / PT
  - AEs of any severity → ≥5% in any treatment group
  - SAE and severe AE → include regardless their incidence

in case of relevant differences in observation periods between treatment groups: appropriate analysis methods (e.g., survival analysis, including Kaplan-Meier curves) should be conducted for all outcomes (including adverse events (AEs)) for which this would be applicable.

AE= Adverse Event, SAE = Serious Adverese Event, 95%-CI = 95% Confidence Interval, SOC = System Organ Class, PT = Preferred Term

Boehringer Ingelheim

Key Message:

Safety analyses for HTA need to be considered at the design stage of the trial

Example PROs:

- Likely some adjustments necessary to follow the treatment policy approach more strictly
- Early preparation for pre-specification required
- Responder analysis follows meaningful change thresholds as opposed to 15% rule

Requirements for JCA reporting

- The characteristics of the scale on which outcomes are measured (continuous, discrete or qualitative; boundaries; unit of measurement, if any; labels for the categories; direction of interpretation).
- The responder definition, if proposed, and as provided by the HTD (rationale and methods for estimation, perspective, rule for classifying patients, information on pre-specification of responder definition).
- References, as provided by the HTD, to allow full access to the bibliography justifying the responder definitions used.
- The measure of an outcome that was pre-specified as part of the primary analysis for each outcome measure (e.g., on a continuous or categorical scale).
- Along with results expressed according to a responder definition (summary measure, effect measure), also report results expressed using the original quantitative scale.
- Results expressed via a graphical representation such as a cumulative distribution function are highly encouraged.

European Commission HTA CG. (2024). *Guidance on outcomes for joint clinical assessments*. https://health.ec.europa.eu/publications/guidance-outcomes-joint-clinical-assessments_en

Boehringer Ingelheim

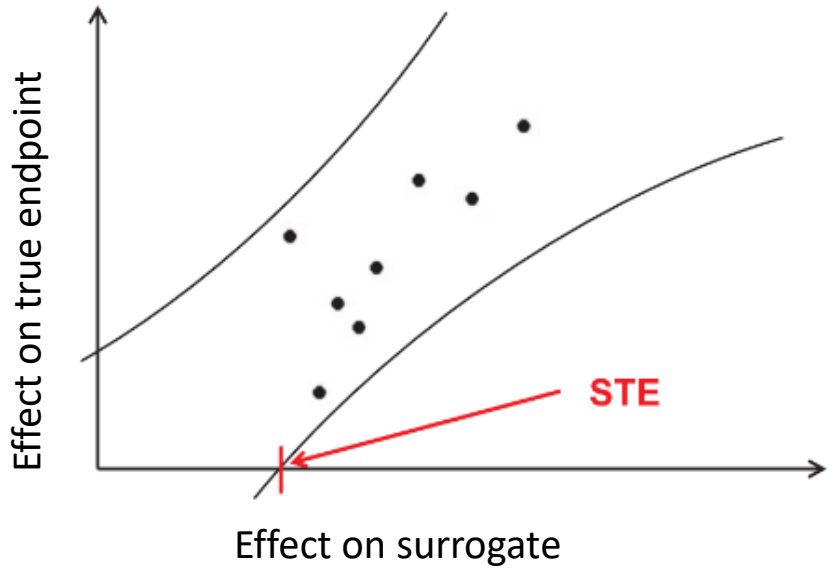
Key Message:

Meaningful Change Thresholds useful for interpreting PRO results

Surrogate Outcomes:

- Both regulators and HTA bodies identified Surrogates as a controversial topic
- EU HTA Guidance grades Evidence for surrogacy on three levels (biological level, patient-level, trial level)
- Meta-analytical methods across multiple RCTs (→ German HTA procedure)

Surrogate Threshold Effect:



- **The surrogate threshold effect (STE) is the minimum treatment effect on a surrogate that is reliably predictive of a treatment effect on the real clinical outcome.**

Source: Translated and adpated from C. Schürmann (2012).

Boehringer Ingelheim

Originalarbeit

Surrogatvalidierung durch Korrelation und Surrogate Threshold Effect – Ergebnisse von Simulationsstudien

Validation of surrogates by correlation and surrogate threshold effect – Results of simulation studies

Johanna Gillhaus - Pfizer Deutschland GmbH, Berlin, Deutschland
Ralf Goertz - AMS Advanced Medical Services GmbH, Mannheim, Deutschland
Ulli Jeratsch - AMS Advanced Medical Services GmbH, München, Deutschland
Friedhelm Leverkus - Pfizer Deutschland GmbH, Berlin, Deutschland

GMS Med Inform Biom Epidemiol 2017;13(1):Doc01

doi: 10.3205/mibe000168, urn:nbn:de:0183-mibe0001683

Methoden: In Simulationsstudien wird nun untersucht, welche Bedingungen für eine erfolgreiche Surrogatvalidierung mit korrelationsbasierten Verfahren erfüllt sein müssen. Variierende Parameter sind die Effektschätzer des Surrogats und des patientenrelevanten Endpunkts, die Korrelation zwischen den Effektschätzern, die Patientenanzahl sowie die Anzahl der Studien. Es wird analysiert, in welchen Szenarien der Nachweis einer hohen Korrelation gelingt und falls nicht, welche Voraussetzungen vorliegen müssen, dass anhand des Surrogats unter Einbeziehen des STE-Konzepts noch Schlüsse auf den patientenrelevanten Endpunkt gezogen werden können. Die Herausforderungen der vom IQWiG präferierten Methodik zur Surrogatvalidierung in der Praxis werden analysiert.

Ergebnisse: Die Simulation der Surrogatvalidierung über das korrelationsbasierte Verfahren sowie die analytische Herleitung der Power zeigen, dass diese bei moderater Studienanzahl und starker zugrundeliegender wahrer Korrelation dennoch sehr gering ist. Die Power liegt für n=5 Studien und Korrelation ρ=0,9 unter 6%. Es wäre eine sehr hohe Korrelation von ρ=0,95 in mindestens n=25 Studien erforderlich, um eine Power von 80% zu erhalten. Dieses Szenario ist in der Realität allerdings als unplausibel anzusehen. In der Simulation zur Anwendung des STE-Konzepts lag die Power nur bei etwa ein Fünftel der betrachteten Szenarien über 80%. Dabei handelte es sich jedoch um Szenarien, in denen die Parameterkonstellationen aus hoher Studien- und Patientenanzahl und großem Effekt des OS eher unrealistisch sind. Der Parameter der Korrelation ρ zwischen den Effektschätzern der Studien wirkt sich ebenso wie verschiedene Effekte des PFS kaum auf die Power des STE-Verfahrens aus.

Schlussfolgerung: Die durchgeführten Simulationen zeigen, dass die im Rapid Report beschriebene Methodik, wonach die untere Grenze des Konfidenzintervalls ausschlaggebend für eine hohe Korrelation bei der Surrogatvalidierung sein soll, eine in der Praxis kaum zu überwindende Hürde darstellt. Bei gering bis moderat angenommener Studienanzahl - wie es für eine Validierung von Surrogatendpunkten im Rahmen der frühen Nutzenbewertung realistisch erscheint - ist die Power selbst bei hoher, wahrer Korrelation äußerst gering. Problematisch erscheint weiterhin die Empfehlung, die Aussagekraft der Studien in die Analyse mit einzubeziehen, auch wenn dies prinzipiell gerechtfertigt erscheint. Bei Betrachtung der Definition des Korrelationskoeffizienten und dessen Dichtefunktion wird zudem klar, dass die empirische Korrelation unter Annahme einer festen wahren Korrelation gar nicht von der Varianz der Einzelschätzer, sondern nur von der Anzahl der Wertepaare abhängt. Die Patientenanzahl hat somit keine Auswirkung auf das Konfidenzintervall der Korrelation. Dies gilt ebenso, wenn Modelle mit Gewichtung der Studien verwendet werden. Die Anwendung des STE-Konzeptes gemäß der im Rapid Report beschriebenen Methodik erscheint ebenfalls schwierig. Ein Vergleich des STE mit dem Punktschätzer des Surrogatendpunkts wäre eine Alternative, die in realistischen Szenarien geringe α-Fehler zeigte.

Schlüsselwörter: Surrogatvalidierung, Korrelation, Surrogate Threshold Effect, progressionsfreies Überleben, Nutzenbewertung

STE not a simple "Plan B", but rather very strict criterion that is only viable under very optimistic assumptions

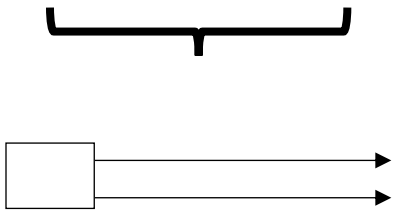
Boehringer Ingelheim

Key Message:

Do not rely solely on surrogate outcomes

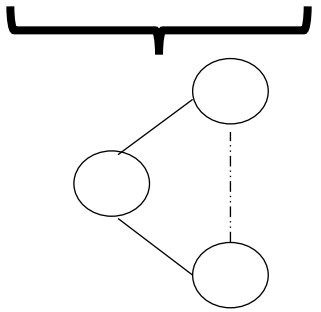
How different PICO types can be addressed:

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Trial pop.	Trial pop. + Biomarker positive	Trial Pop.	Trial Pop. + Biomarker positive	Trial Population	Trial Population + Biomarker positive
I	Intervention	Intervention	Interventon	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor 1	Competitor 1	Older SOC	Older SOC



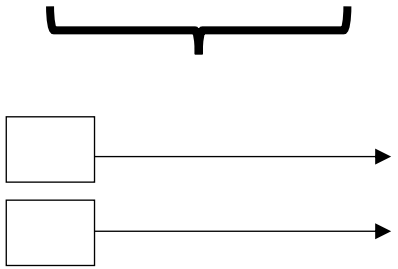
Direct comparison:

Supplementary RCT analysis or meta-analysis of RCTs



Anchored Indirect Comparison:

RCT with a common Comparator



Unanchored Indirect Comparions, external control arms from RWE etc.

Anchored Indirect Comparisons:

Commonly used when a common comparator exists:

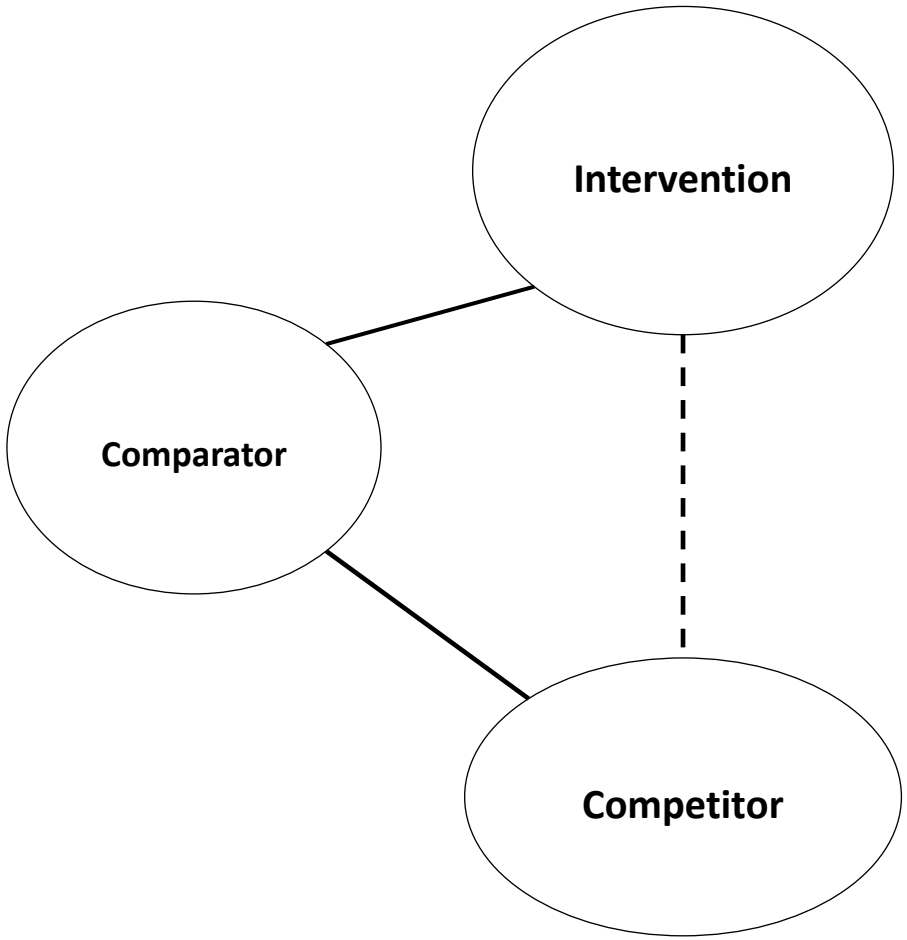
- Bucher Method (simplest case of a Network)
- Network Meta-Analysis
- Anchored Population-adjusted methods

„Populations are similar enough“ (**Transitivity**)

„Populations can be made comparable with correct adjustment“ (**No unmeasured confounding**)

Boehringer Ingelheim

Anchored indirect comparisons:



(a) Similar interventions in different trials
The interventions of the network do not differ systematically across the corresponding trials. Namely, in a triangle network with interventions A, B, and C, intervention A would be similar in AB and AC trials. The same holds for intervention B which appears in BC and AB trials, and intervention C in AC and BC trials
(b) Missing-at-random treatments
Missing interventions in each trial of the network are missing for reasons unrelated to their benefit-harm profile. Namely, interventions A, B, and C are randomly missing in BC, AC, and AB trials
(c) Exchangeable missing and observed relative treatment effects
Underlying treatment effects of any observed and unobserved comparison do not differ beyond what is expected by the between-trial heterogeneity alone. For instance, the AB trials provide evidence for comparison AB only. Under the random-effects model, had these trials included intervention C, the underlying treatment effect of AC and BC comparisons could have been estimated, assuming that these missing treatment effects are exchangeable with the corresponding underlying treatment effects estimated directly in AC and BC trials, respectively
(d) Jointly randomisable participants
If all network interventions could be investigated in one trial, the participants would be eligible to be randomised to any intervention. Namely, the participants share a similar demographic and clinical profile that makes them suitable for any network intervention for their underlying condition
(e) Similar treatment comparisons concerning important effect modifiers
Different observed treatment comparisons comprise clusters of several trials. These clusters are considered to be similar regarding the distribution of important effect modifiers. Hence, if AB and AC trials are similar in terms of the distribution of important effect modifiers, the indirect estimate for BC using these two sets of trials will be valid

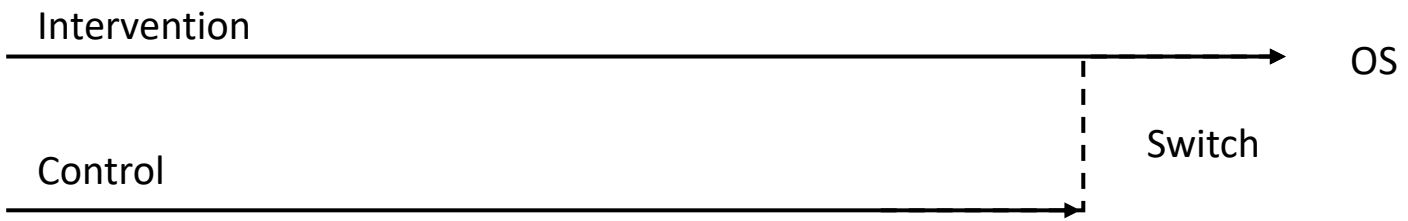
Spineli et al. (2024): Low awareness of the transitivity assumption in complex networks of interventions (...)

Boehringer Ingelheim

Transitivity and treatment switches:

- What looks like the same comparator might not be the same **across the entire observation period**
- In oncology often after progression

→ Analyze endpoints within the comparable periods



Practical Challenges:

- Comparison of Inclusion/ exclusion criteria

- Statistically: How to check if populations are too different?
  - Published summaries of baseline data can be compared to blinded data (pooled arms)
  - Use of standardized effect sizes with established thresholds from causal inference methods
  - Often conservative! Decision rules should be clear

Key Message:

Devil is in the detail: Transitivity assumption

Population Adjusted Methods:

- E.g., Anchored MAIC
- Selecting variables in adjustment lays out the understanding of the disease/indication
- Relevant for a multitude of methods (anchored maics, unanchored maics, external controls etc.)

→Strategy needs to be well supported by the literature and requires consistency across PICOs!

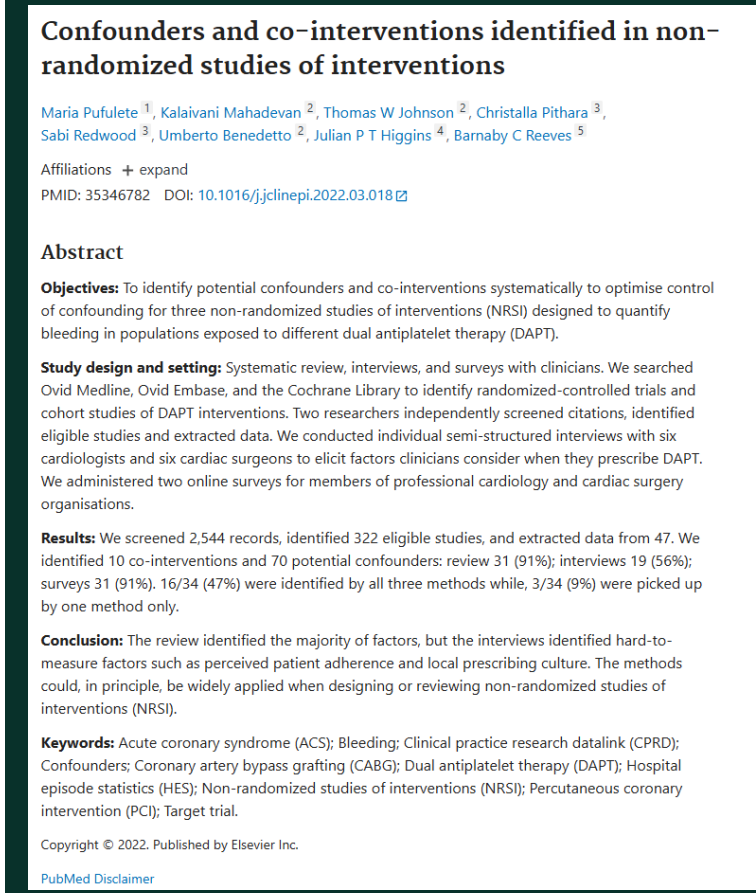
What to adjust for?

Positioning in the German HTA procedure:

- Systematic Review
- Clinician Interviews

In practice:

- Identified numbers can be **very high**
- In combination with low patient counts in oncological studies questionable validity



Confounders and co-interventions identified in non-randomized studies of interventions

Maria Pufulete [1], Kalaivani Mahadevan [2], Thomas W Johnson [2], Christalla Pithara [3], Sabi Redwood [3], Umberto Benedetto [2], Julian P T Higgins [4], Barnaby C Reeves [5]

Affiliations + expand

PMID: 35346782 DOI: 10.1016/j.jclinepi.2022.03.018

Abstract

Objectives: To identify potential confounders and co-interventions systematically to optimise control of confounding for three non-randomized studies of interventions (NRSI) designed to quantify bleeding in populations exposed to different dual antiplatelet therapy (DAPT).

Study design and setting: Systematic review, interviews, and surveys with clinicians. We searched Ovid Medline, Ovid Embase, and the Cochrane Library to identify randomized-controlled trials and cohort studies of DAPT interventions. Two researchers independently screened citations, identified eligible studies and extracted data. We conducted individual semi-structured interviews with six cardiologists and six cardiac surgeons to elicit factors clinicians consider when they prescribe DAPT. We administered two online surveys for members of professional cardiology and cardiac surgery organisations.

Results: We screened 2,544 records, identified 322 eligible studies, and extracted data from 47. We identified 10 co-interventions and 70 potential confounders: review 31 (91%); interviews 19 (56%); surveys 31 (91%). 16/34 (47%) were identified by all three methods while, 3/34 (9%) were picked up by one method only.

Conclusion: The review identified the majority of factors, but the interviews identified hard-to-measure factors such as perceived patient adherence and local prescribing culture. The methods could, in principle, be widely applied when designing or reviewing non-randomized studies of interventions (NRSI).

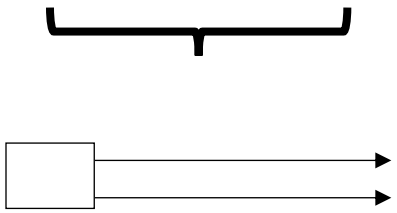
Keywords: Acute coronary syndrome (ACS); Bleeding; Clinical practice research datalink (CPRD); Confounders; Coronary artery bypass grafting (CABG); Dual antiplatelet therapy (DAPT); Hospital episode statistics (HES); Non-randomized studies of interventions (NRSI); Percutaneous coronary intervention (PCI); Target trial.

https://doi.org/10.1016/j.jclinepi.2022.03.018

Boehringer Ingelheim

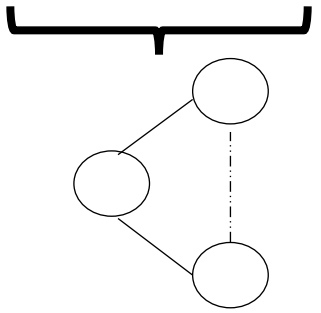
How different PICO types can be addressed:

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Trial pop.	Trial pop. + Biomarker positive	Trial Pop.	Trial Pop. + Biomarker positive	Trial Population	Trial Population + Biomarker positive
I	Intervention	Intervention	Interventon	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor 1	Competitor 1	Older SOC	Older SOC



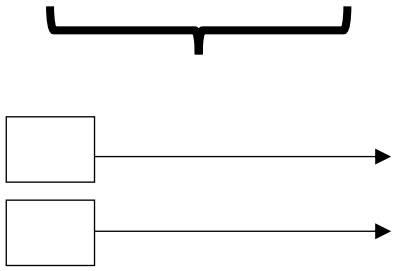
Direct comparison:

Supplementary RCT analysis or Meta analysis of RCTs



Anchored Indirect Comparison:

RCT with a common Comparator



Unanchored Indirect Comparions, external control arms from RWE etc.

References:

European Commission HTA CG. (2024). *Guidance on outcomes for joint clinical assessments*. https://health.ec.europa.eu/publications/guidance-outcomes-joint-clinical-assessments_en

European Commission HTA CG. (2024). *Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons.* https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en.pdf

Gillhaus J, Goertz R, Jeratsch U, Leverkus F. Surrogatvalidierung durch Korrelation und Surrogate Threshold Effect – Ergebnisse von Simulationsstudien. GMS Med Inform Biom Epidemiol. 2017;13(1):Doc01

Pufulete et al. (2022) Confounders and co-interventions identified in non-randomized studies of interventions. *Journal of Clinical Epidemiology,* 2022; 148, 115-12

Spineli, L. M., Kalyvas, C., Yepes-Nuñez, J. J., García-Sierra, A. M., Rivera-Pinzón, D. C., Seide, S. E., & Papadimitropoulou, K. (2024). Low awareness of the transitivity assumption in complex networks of interventions: a systematic survey from 721 network meta-analyses. *BMC medicine*, *22*(1), 112. https://doi.org/10.1186/s12916-024-03322-1

Schürmann, C. (2012). Darum führen Surrogatendpunkte zu erhöhter Unsicherheit. IQWiG im Dialog, https://www.iqwig.de/veranstaltungen/2012-06-22_christoph_schuermann_unsicherheit_bei_surrogaten.pdf?rev=187823

Boehringer Ingelheim

PSI 2026 – Workshop

Scenario 2

3 Single-Arm Trial

Lena Stein (*AMS* Advanced Medical Services)

15.06.2026

SINGLE-ARM TRIALS (SAT)

In Approval & HTA

"SAT" in HTA context

Studies with multiple arms may be treated like an SAT in HTA if there is no control (e.g., dose-finding)

Pivotal Study for Approval is a SAT

EMA: ~20%

~35 orphan (1999 – 2014)

18 oncology medicinal products (2012 – 2021)

~70% ATMP

SATs in HTA

Current number of JCAs: 16 (15 ongoing)

~38% of these with an SAT in HTA context

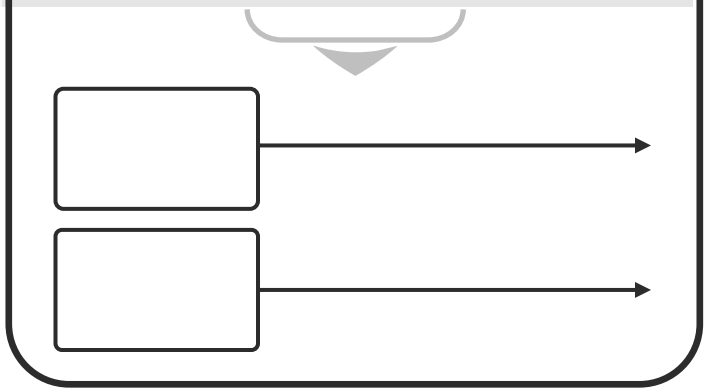
~25% with an actual SAT as pivotal study

THE NEED FOR COMPARATIVE EVIDENCE

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Full population	Trial population + biomarker ⊕	Full population	Trial population + biomarker ⊕	Full population	Trial population + biomarker ⊕
I	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor 1	Competitor 1	Older standard of care	Older standard of care
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety *including subgroups*					

THE NEED FOR COMPARATIVE EVIDENCE

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Full population	Trial population + biomarker	Full population	Trial population + biomarker	Full population	Trial population + biomarker
I	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention
C	Trial comparator	Trial comparator	Competitor 1	Competitor 1	Older standard of care	Older standard of care
O	List of HTA-relevant endpoints on mortality, morbidity, PRO and safety *including subgroups*					



CHOOSING THE APPROPRIATE ITC METHODS

Non-Randomised Comparisons

Own SAT

Individual Patient Data

External Control

Aggregated Patient Data

Methods: unanchored population-adjusted methods

Reliance on conditional constancy of absolute effects, highly problematic

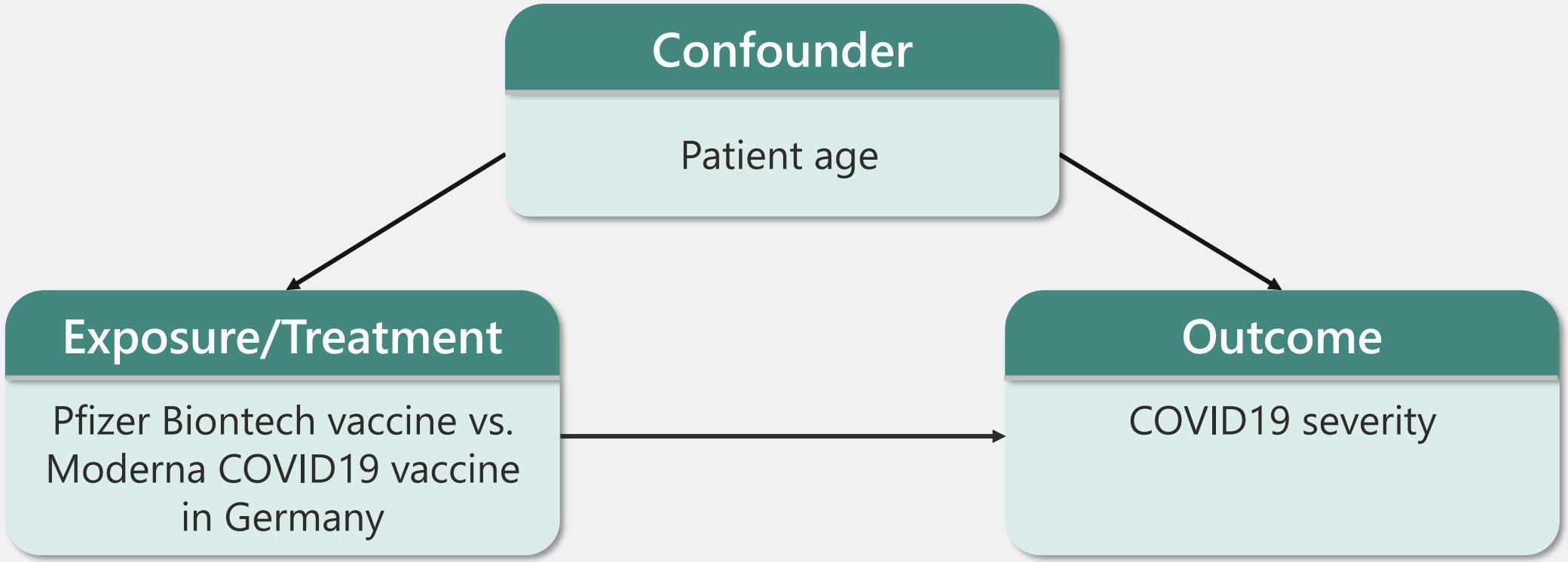
Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

REPORTING REQUIREMENTS IN JCA

In Case of Having Non-Randomised Data

Justification for confounder selection



REPORTING REQUIREMENTS IN JCA

In Case of Having Non-Randomised Data

- Justification for confounder selection
- Justification of model choice
- Assessment of model assumptions
- Bias assessment using ROBINS-I
- Additional presentation of unadjusted comparison
- Testing against shifted null hypothesis or sensitivity analyses to assess residual confounding
- Comparison of analysis population to target population

CHOOSING THE APPROPRIATE ITC METHODS

Non-Randomised Comparisons

Own SAT

Individual Patient Data

External Control

Aggregated Patient Data

Methods: unanchored population-adjusted methods

Reliance on conditional constancy of absolute effects, highly problematic

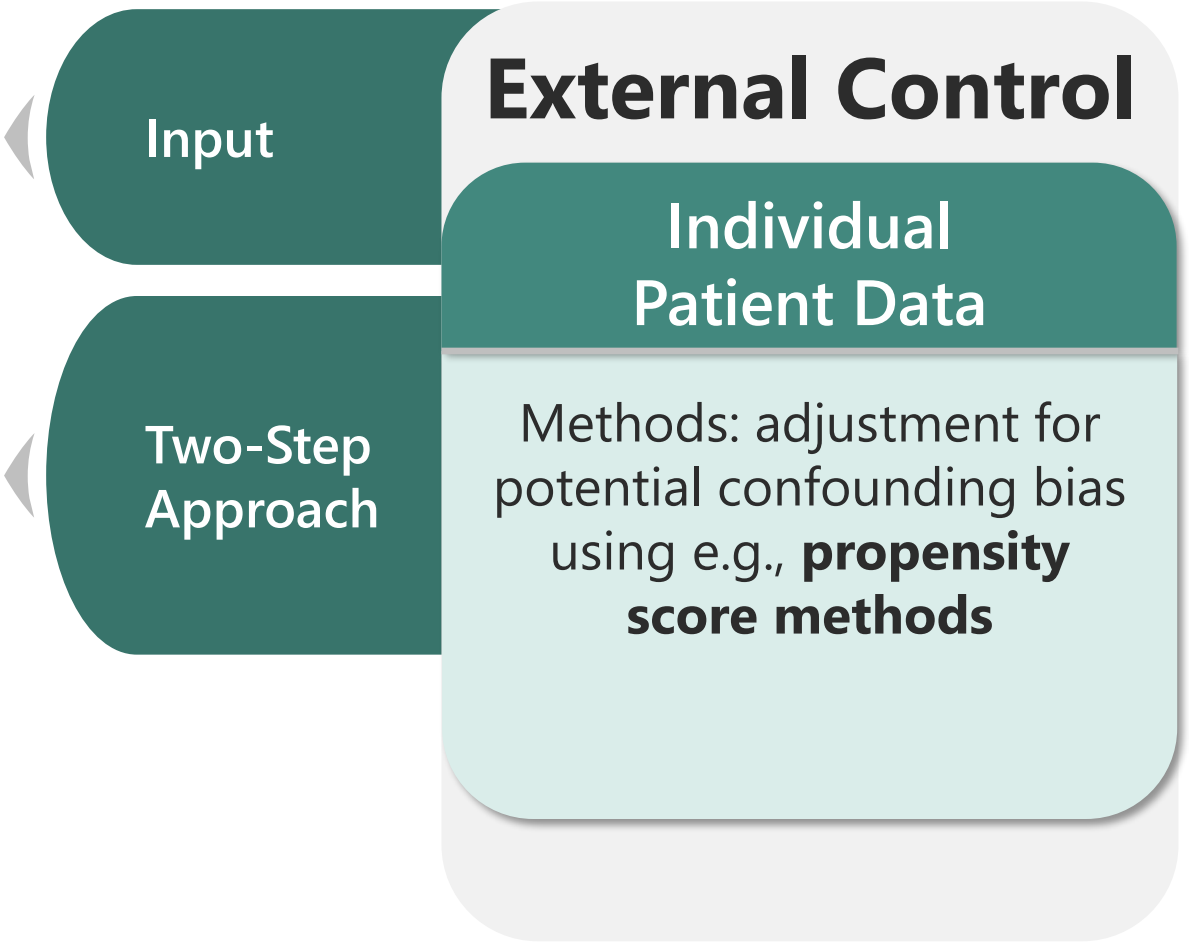
Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

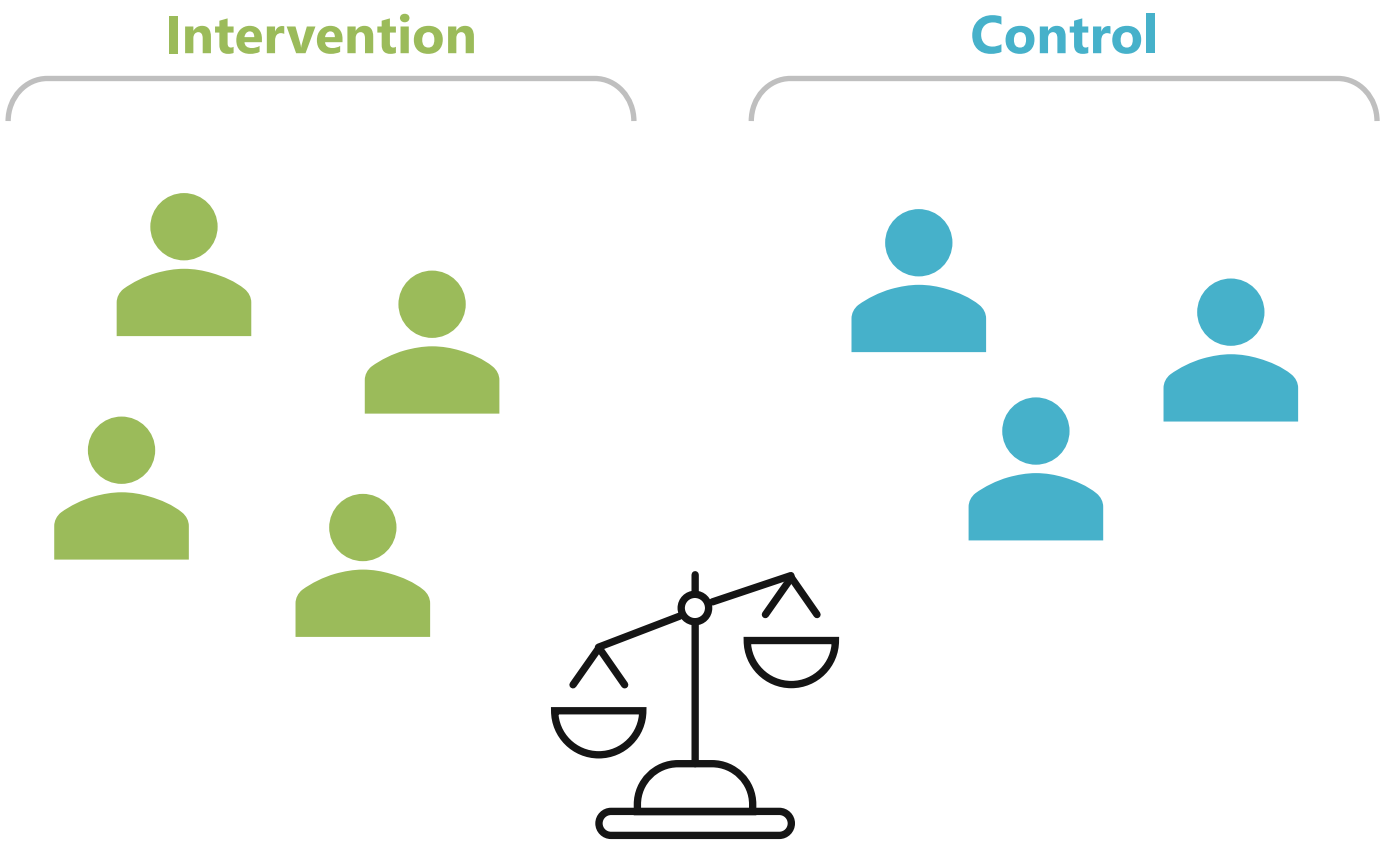
PROPENSITY SCORE METHODS

Individual Patient Data (IPD) on both sides
(intervention and control)

1. **Estimate propensity scores (PS) based on treatment assignment and baseline characteristics, then match or weigh using PS.**
2. **Use weighted/matched populations for effect estimation**



PROPENSITY SCORE METHODS



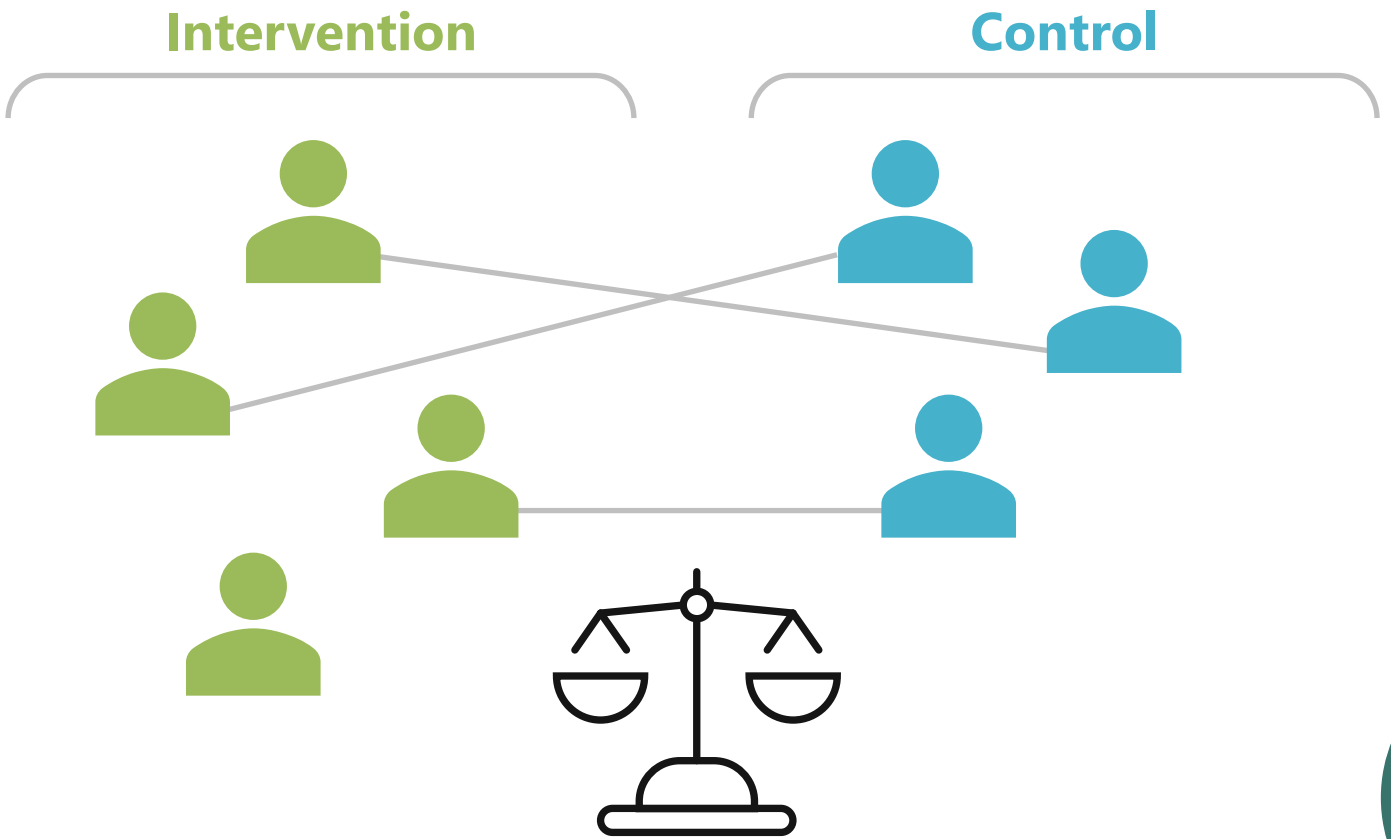
Confounders not balanced between groups

External Control

Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

PROPENSITY SCORE METHODS



Confounders balanced in matched population

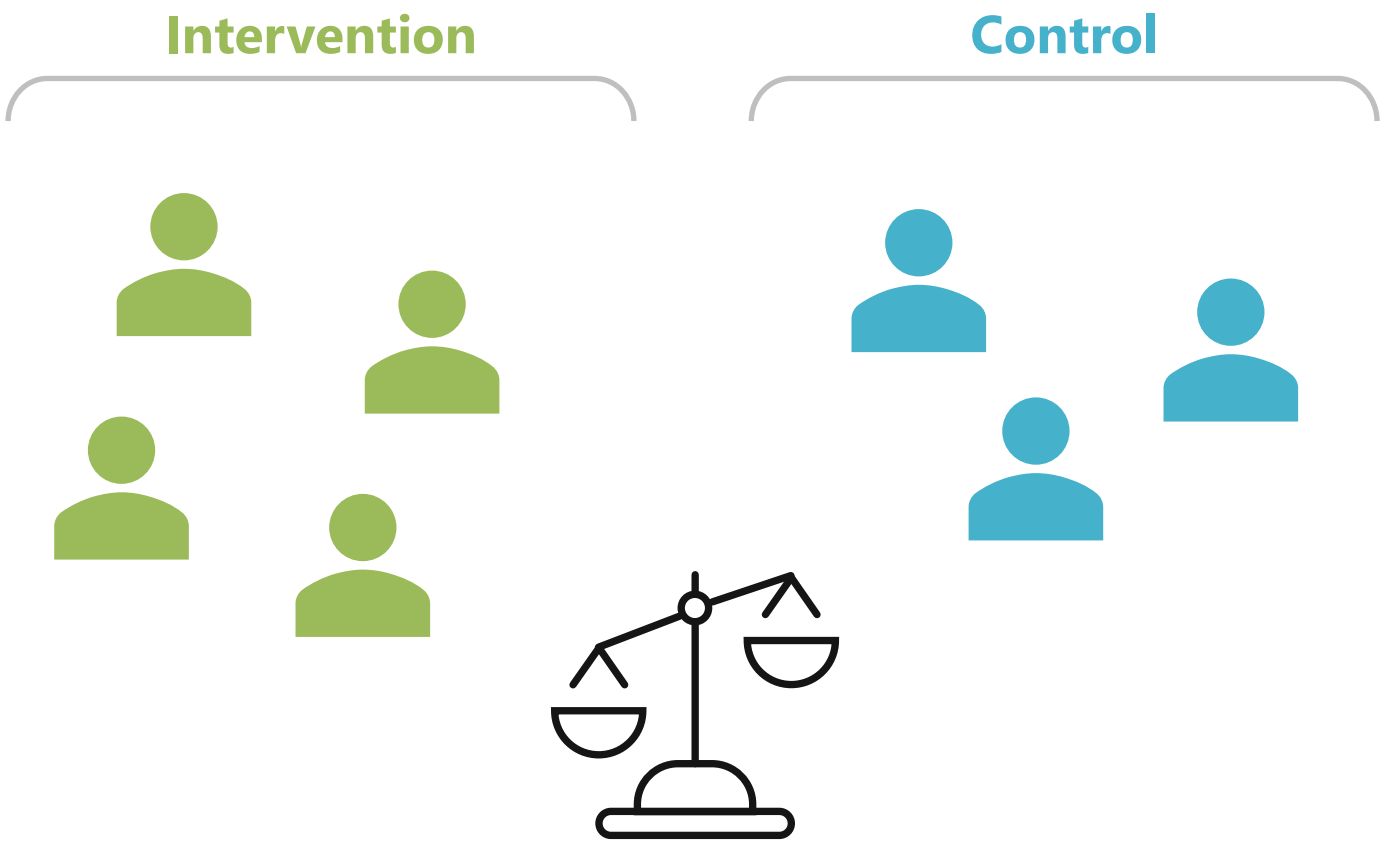
External Control

Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

Matching

PROPENSITY SCORE METHODS

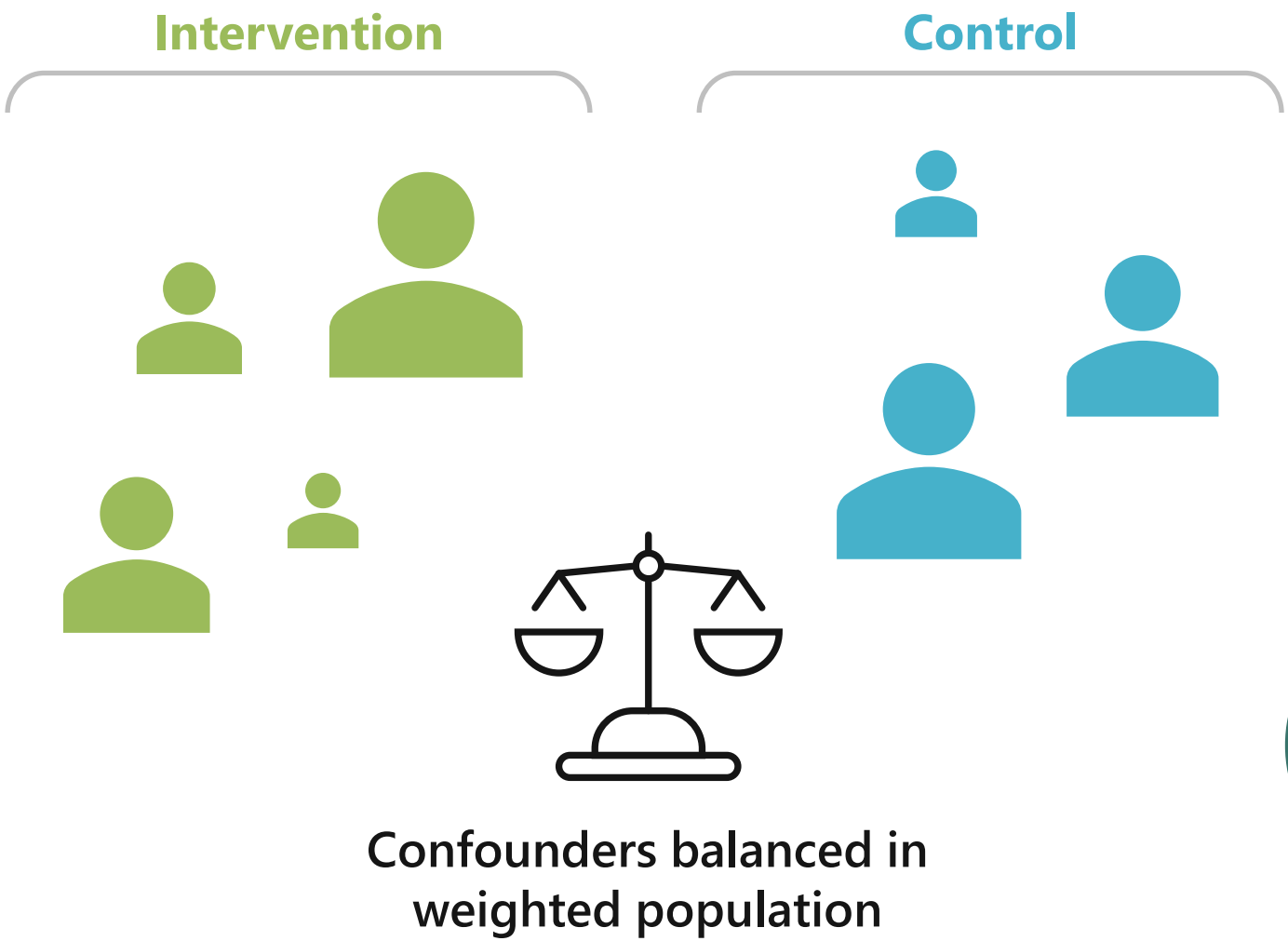


External Control

Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

PROPENSITY SCORE METHODS



External Control

Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

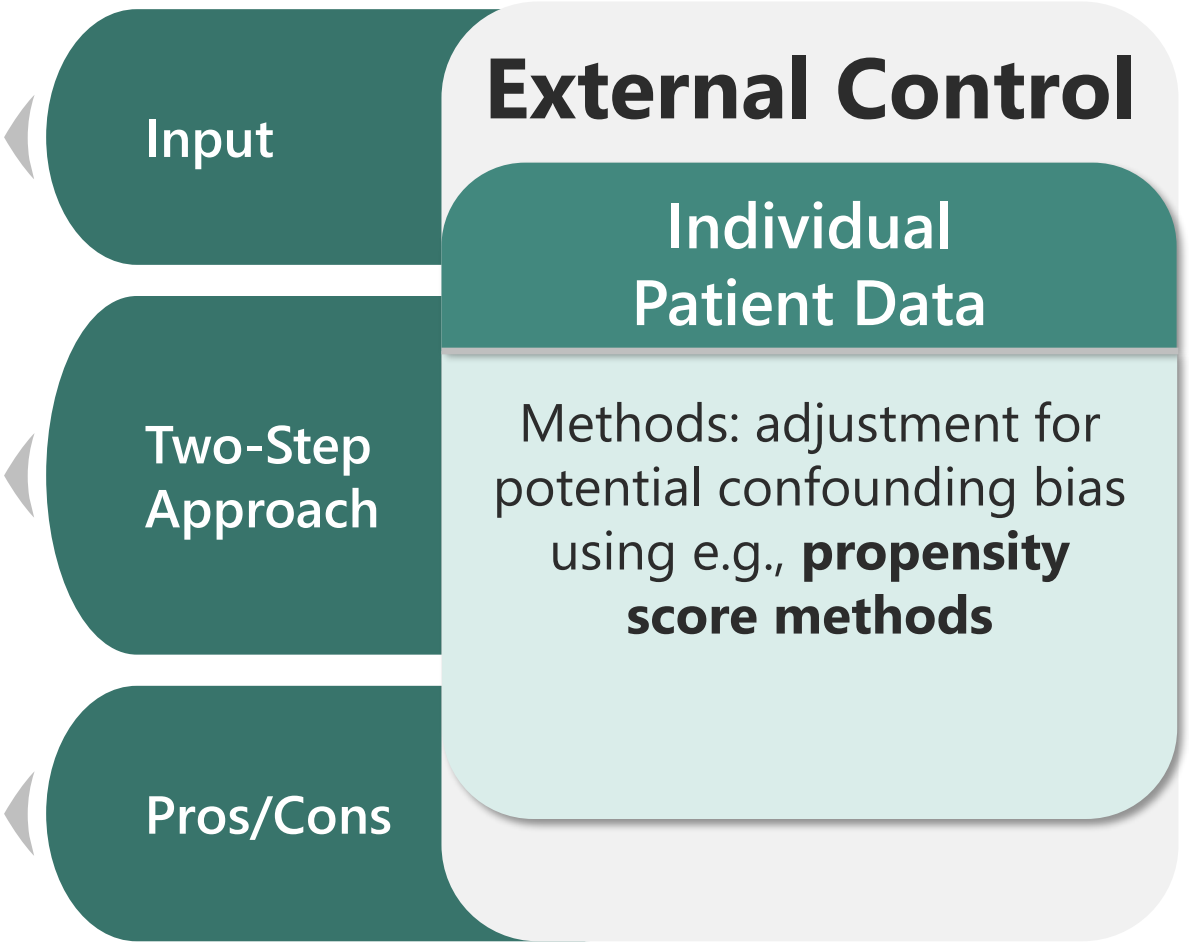
Weighting

PROPENSITY SCORE METHODS

Individual Patient Data (IPD) on both sides
(intervention and control)

1. **Estimate propensity scores (PS) based on treatment assignment and baseline characteristics, then match or weigh using PS.**
2. **Use weighted/matched populations for effect estimation**

Recommended in EU HTA and on national level; but the need of IPD on both sides



CHOOSING THE APPROPRIATE ITC METHODS

Non-Randomised Comparisons

Own SAT

Individual Patient Data

External Control

Aggregated Patient Data

Methods: unanchored population-adjusted methods

Reliance on conditional constancy of absolute effects, highly problematic

Individual Patient Data

Methods: adjustment for potential confounding bias using e.g., **propensity score methods**

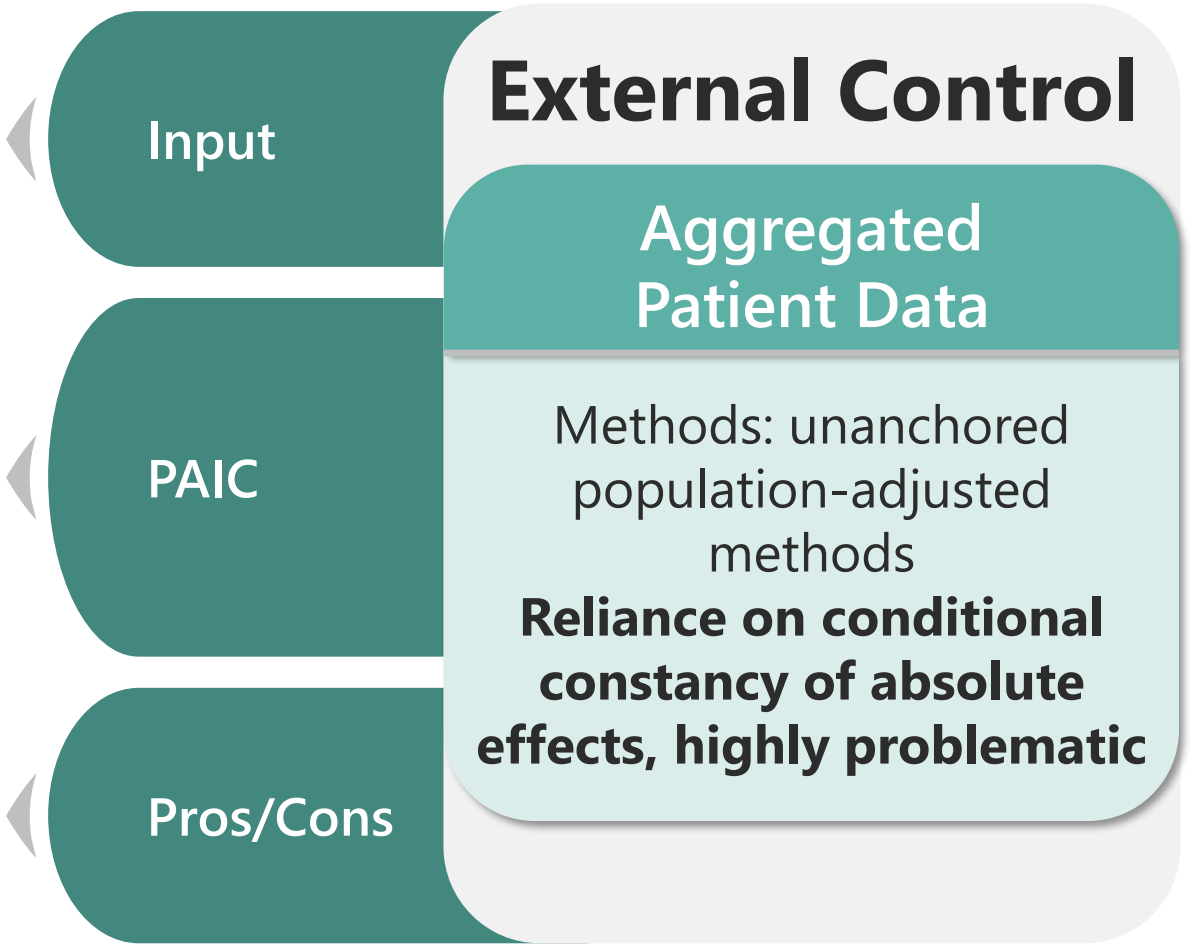
POPULATION ADJUSTED METHODS

Individual Patient Data (IPD) for own SAT

Aggregated Patient Data (AggD) for external control

1. Simulated Treatment Comparison (STC)
2. Matching-Adjusted Indirect Comparison (MAIC)

AggD more readily available;
Not recommended in EU-HTA



POPULATION ADJUSTED METHODS

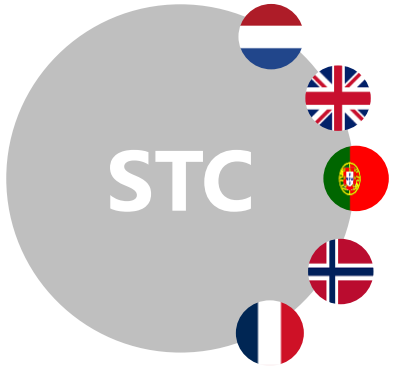
External Control

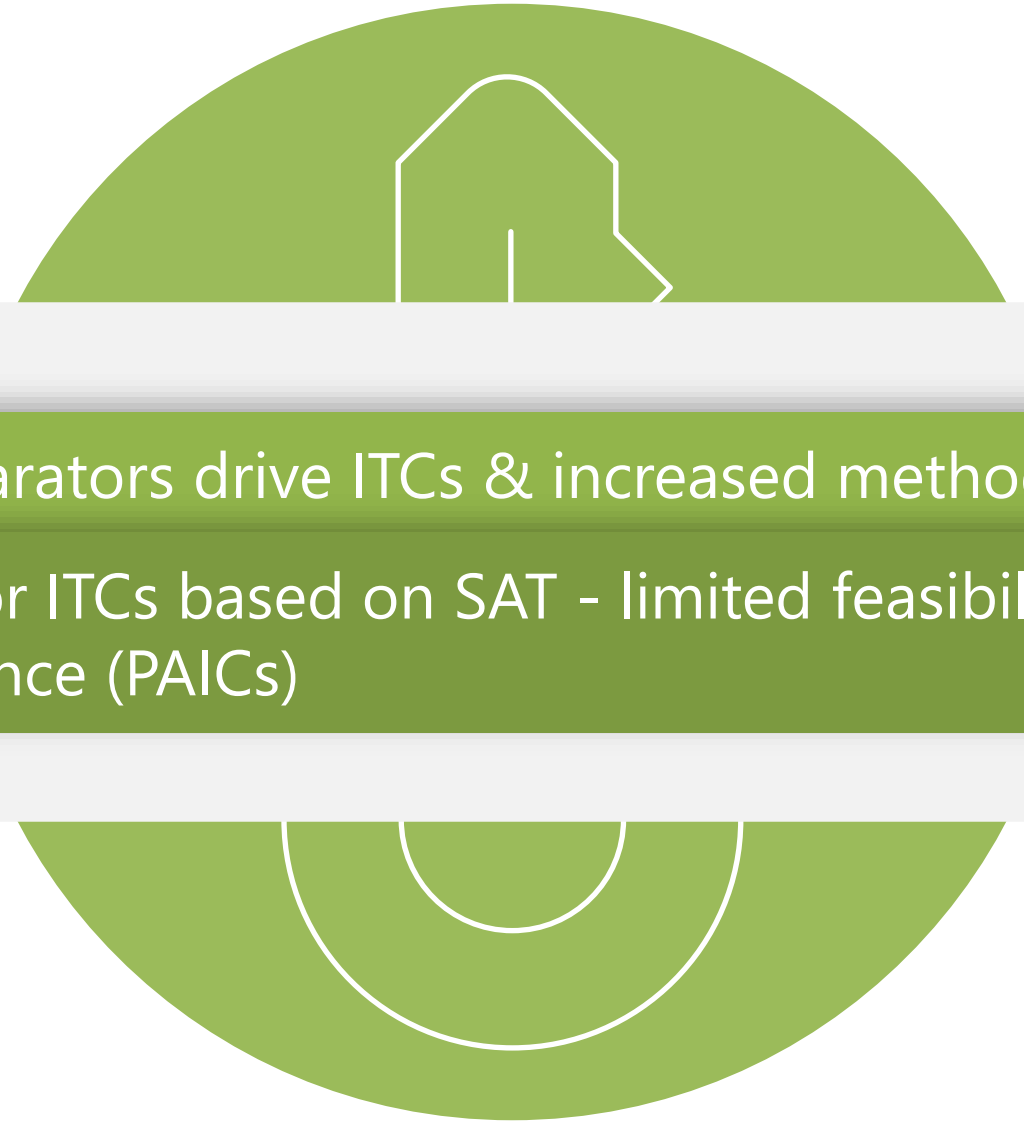
Aggregated Patient Data

Methods: unanchored population-adjusted methods

Reliance on conditional constancy of absolute effects, highly problematic

So much effort… for nothing?!





- Multiple comparators drive ITCs & increased methodological complexity
- High hurdles for ITCs based on SAT - limited feasibility (PS-Methods) or lack of acceptance (PAICs)

FROM THEORY TO PRACTICE

Ojemda® (Tovorafenib) – Ipsen S.A.

FIREFLY-1

Screening	**Arm 1** BRAF-altered pediatric low-grade glioma	Long-term extension
	Arm 2 RAF-altered pediatric low-grade glioma extension	Long-term extension
	Arm 3 RAF fusion advanced solid tumors	Long-term extension

Primary Endpoint: Overall Response (RANO-HGG)

Indication (CHMP)

"Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies."

- **Orphan**
- **Oncology**

3 Scenario 2 Single-Arm Trial

OJEMDA® (TOVORAFENIB) – IPSEN S.A.

PICOs by Assessment Scope and The Need of External Data for Comparison

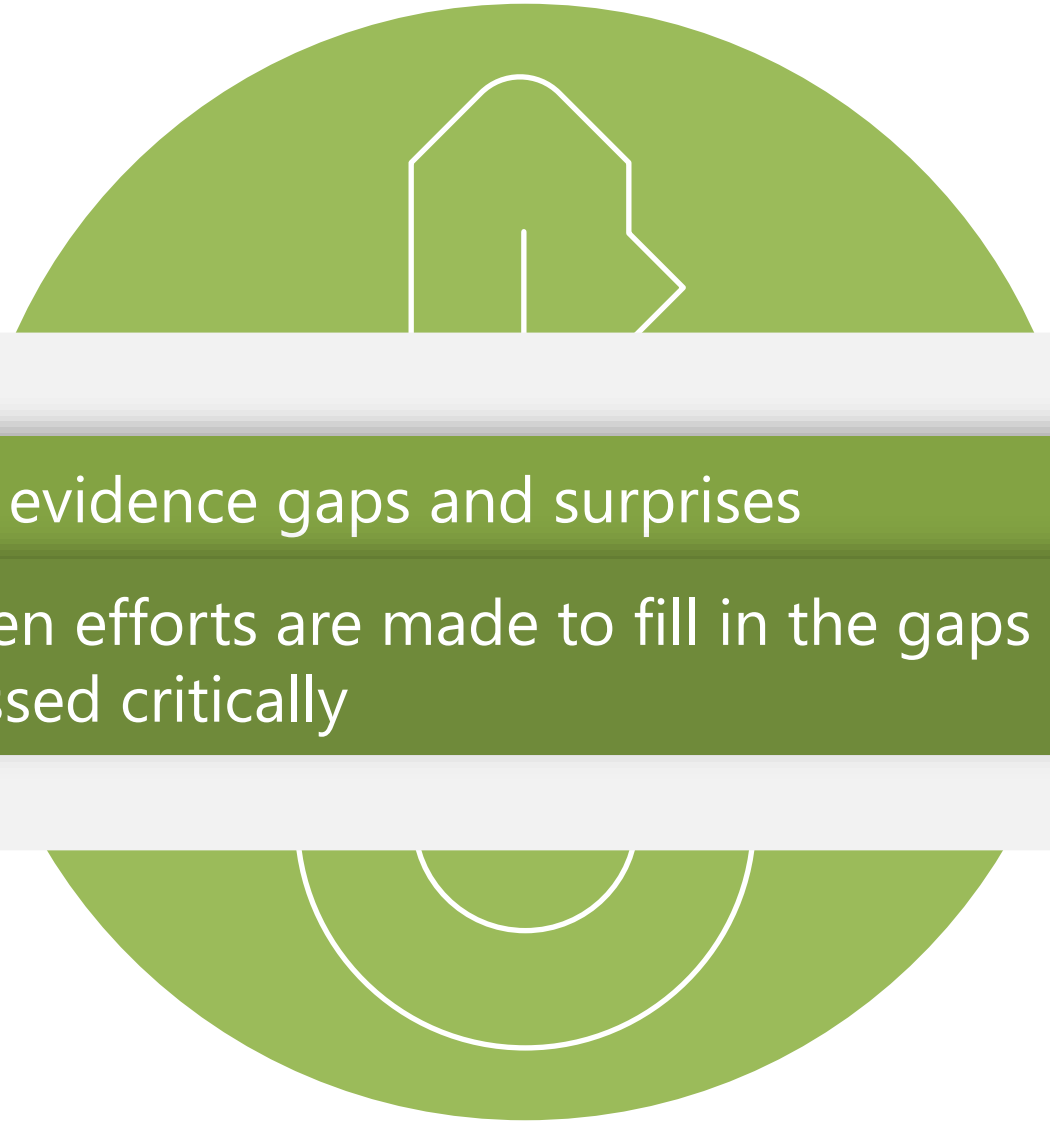
	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6	PICO 7	PICO 8
P	Patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have received one or more prior systemic therapies **(full claimed indication)**				BRAF V600E mutation in patients >1 year **(subpopulation)**		BRAF fusion, rearrangement, or V600 (non-E) mutation **(subpopulation)**	
I	**Tovorafenib**							
C	Individualised treatment (A)	Individualised treatment (B)	Combination of carboplatin and vincristine	Vinblastine	Combination of dabrafenib and trametinib	Individualised treatment	Trametinib	Individualised treatment
O	Safety outcomes according to the guidance on outcomes for JCA OS PFS Objective response, a composite outcome including complete response and partial response Health-related quality of life (HrQoL), generic & disease-specific Symptoms of the disease Composite outcome comprising of complete response, partial response, or stable disease lasting a minimum of (i) 6 and (ii) 12 months General and cognitive fatigue **Descriptive**: Duration of response; Time-to-response; Best overall response **Subgroups**: Prior lines of therapy; Age							

3 Scenario 2 Single-Arm Trial

OJEMDA® (TOVORAFENIB) – IPSEN S.A.

PICOs by Assessment Scope and The Need of External Data for Comparison

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6	PICO 7	PICO 8
P	Patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have received one or more prior systemic therapies **(full claimed indication)**				BRAF V600E mutation in patients >1 year **(subpopulation)**		BRAF fusion, rearrangement, or V600 (non-E) mutation **(subpopulation)**	
I	**Tovorafenib**							
C	Individualised treatment (A)	Individualised treatment (B)	Combination of carboplatin and vincristine	Vinblastine	Combination of dabrafenib and trametinib	Individualised treatment	Trametinib	Individualised treatment
JCA Evidence – Dossier	Only pivotal SAT used				Unanchored PAIC		Unanchored PAIC	
JCA Evidence – Report	Not relevant				Major uncertainties		Not relevant	



- Plan ahead for evidence gaps and surprises
- SAT – Even when efforts are made to fill in the gaps in the evidence, these are assessed critically

PSI 2026 – Workshop

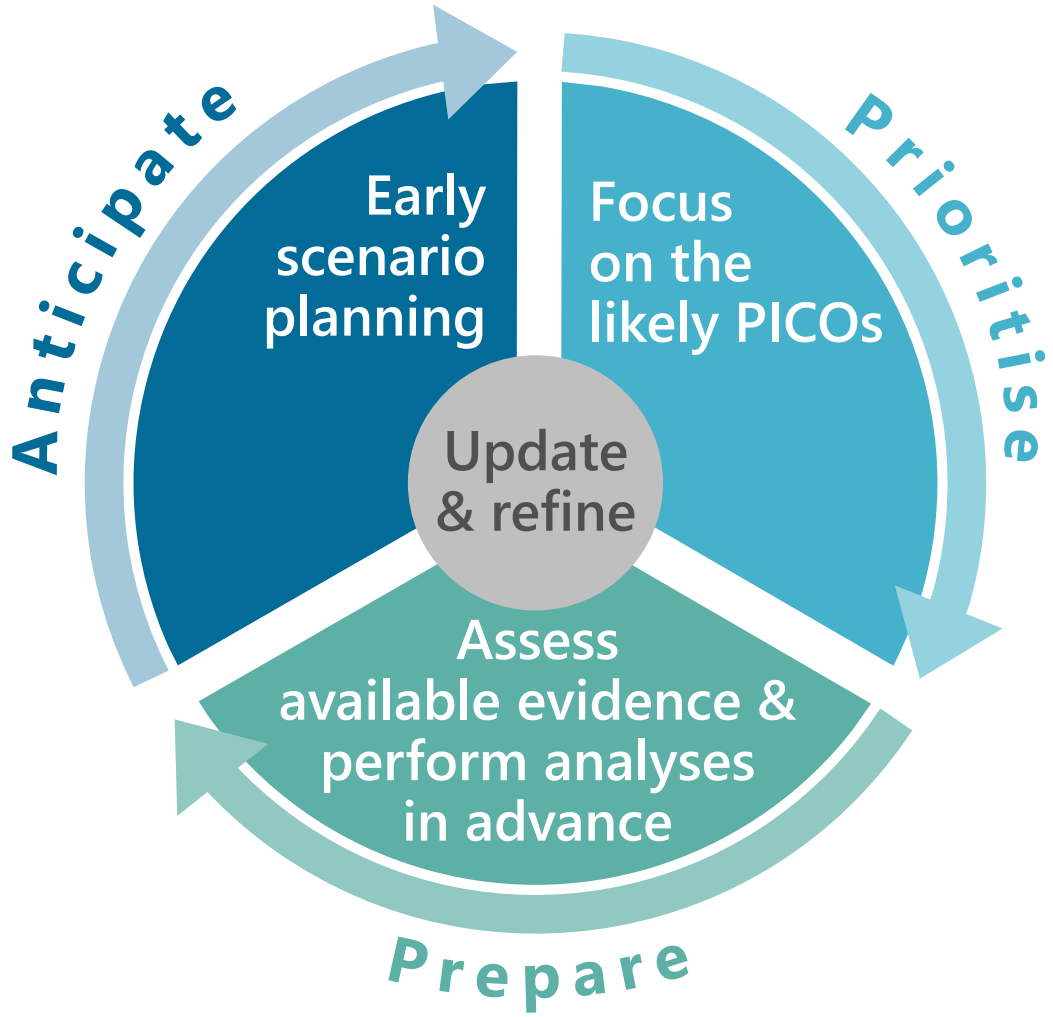
4 Dossier Compilation

Stefanie Wüstner (*AMS Advanced Medical Services*)

15.06.2026

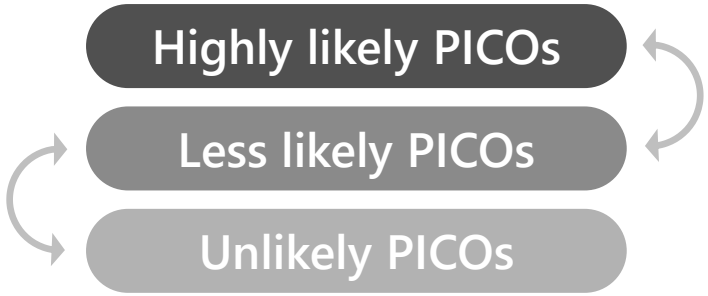
ASSESSMENT SCOPE AS A MOVING TARGET

Preparation Must Balance Uncertainty, Complexity, And Readiness



Pre Assessment Scope

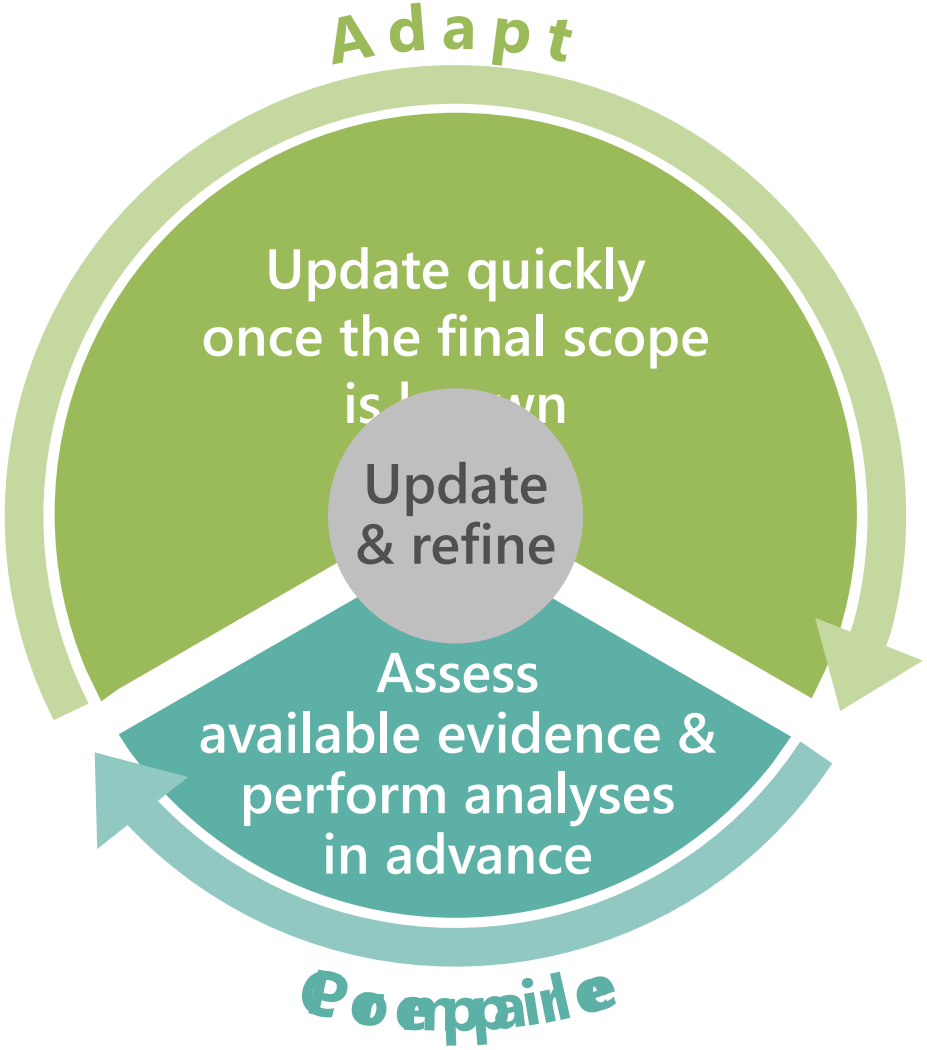
Several factors impact predicted scope



- Indication updated
- New treatment guideline
- Standard of care updated

ASSESSMENT SCOPE AS A MOVING TARGET

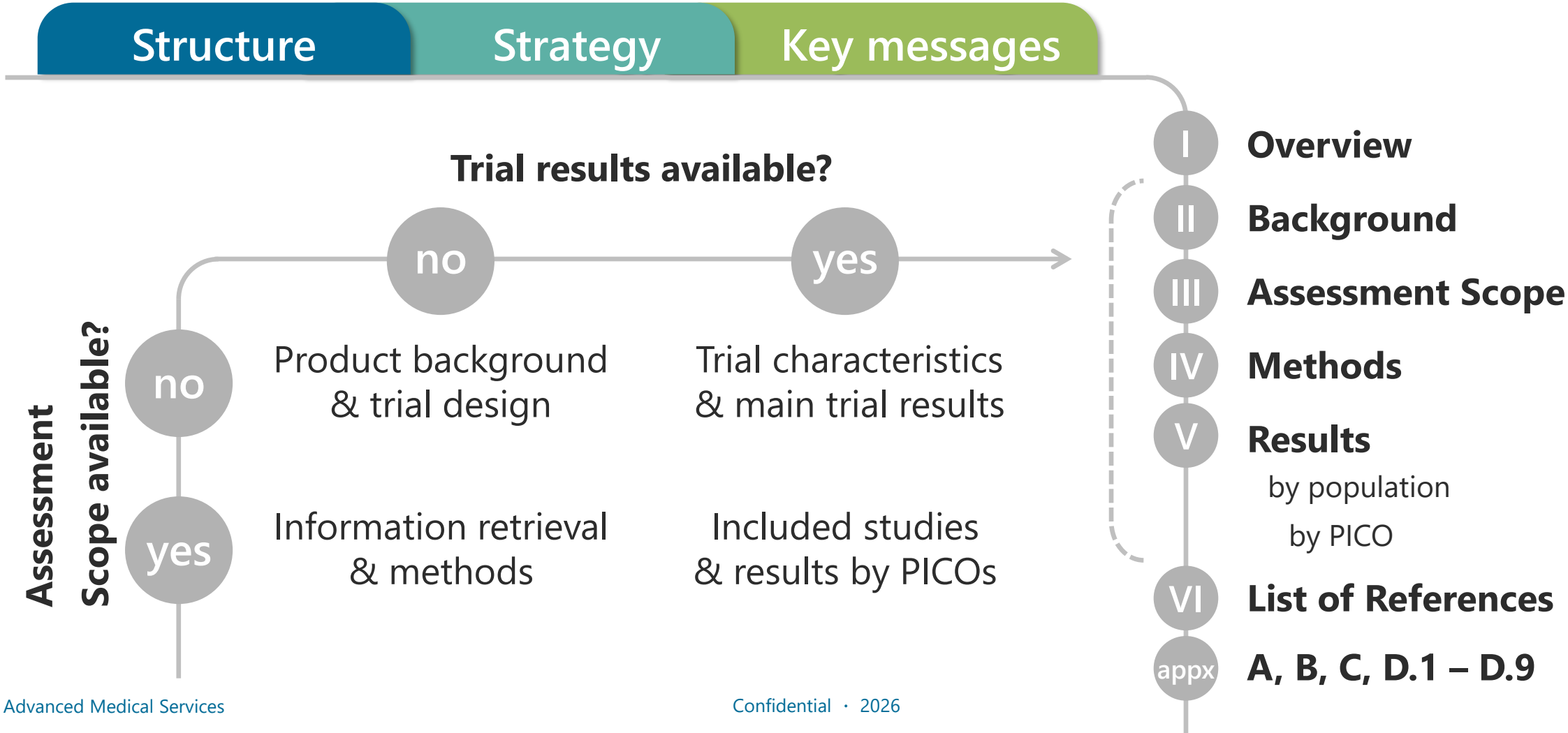
Preparation Must Balance Uncertainty, Complexity, And Readiness



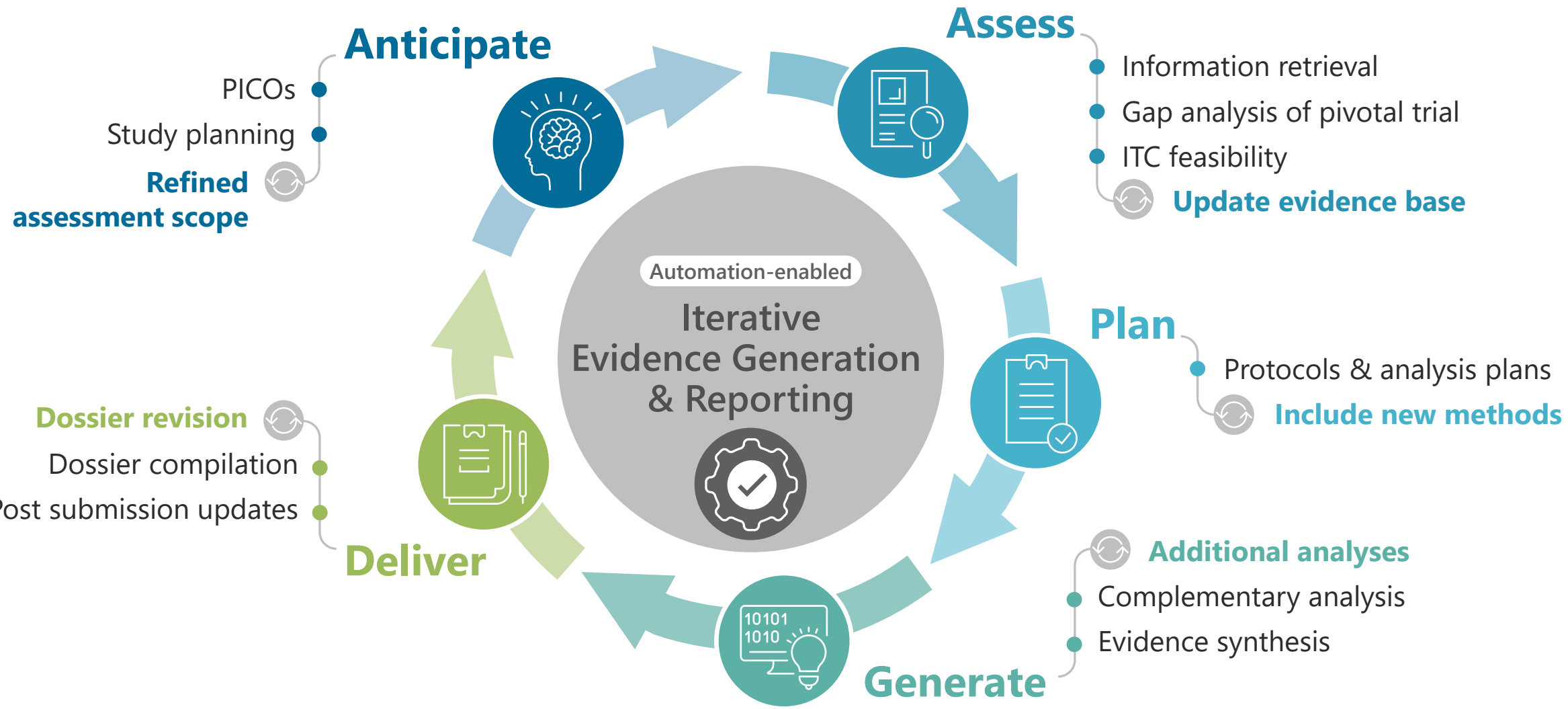
Post Assessment Scope

Adapt & compile JCA dossier in accordance with final assessment scope

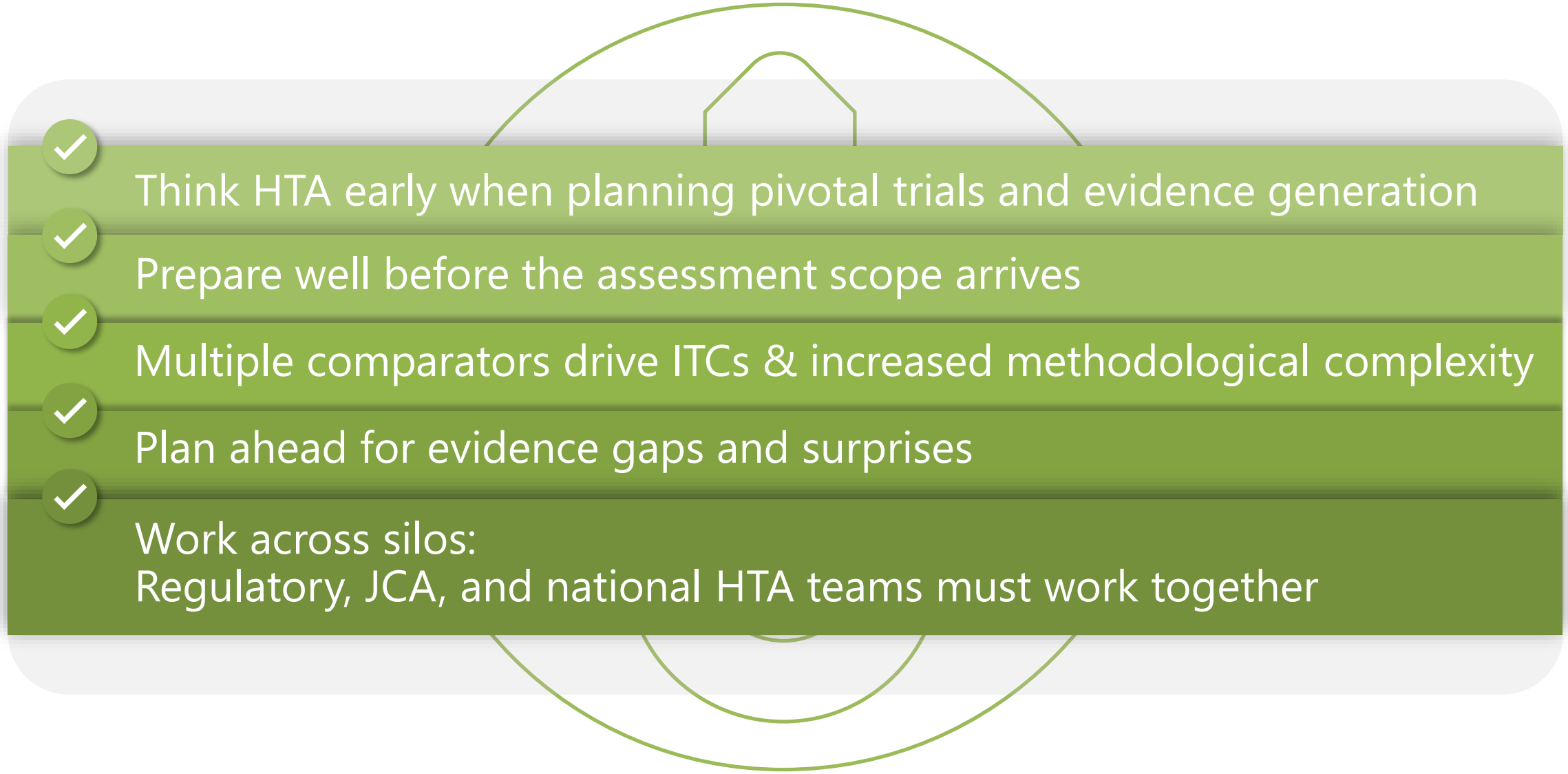
MODULAR JCA COMPILATION



JCA PREPARATION RUNS IN CYCLES



Work across silos:
Regulatory, JCA, and national HTA teams must work together


Think HTA early when planning pivotal trials and evidence generation
Prepare well before the assessment scope arrives
Multiple comparators drive ITCs & increased methodological complexity
Plan ahead for evidence gaps and surprises
Work across silos:
Regulatory, JCA, and national HTA teams must work together

Where Do You See the Biggest Need for Action in Your Organisation?

Live Poll

In one or two words

Join at slido.com

Code #3465 520

REFERENCES

Evidence Supporting EMA Drug Approvals (2020–2023): A Cross-Sectional Study of Trial Design and Outcomes; Maximilian Siebert, Laura Caquelin, Florian Naudet, Joseph S. Ross, Reshma Ramachandran; medRxiv 2026.02.04.26345500; doi: https://doi.org/10.64898/2026.02.04.26345500

Evidence supporting regulatory-decision making on orphan medicinal products authorisation in Europe: methodological uncertainties; Caridad Pontes, Juan Manuel Fontanet, Roser Vives, Aranzazu Sancho, Mònica Gómez-Valent, José Ríos, Rosa Morros, Jorge Martinalbo, Martin Posch, Armin Koch, Kit Roes, Katrien Oude Rengerink, Josep Torrent-Farnell, Ferran Torres; PMID: 30442155 PMCID: PMC6238348 DOI: 10.1186/s13023-018-0926-z

Single-arm trials supporting the approval of anticancer medicinal products in the European Union: contextualization of trial results and observed clinical benefit; Mulder J, Teerenstra S, van Hennik PB, Pasmooij AMG, Stoyanova-Beninska V, Voest EE, de Boer A. ESMO Open. 2023 Apr;8(2):101209. doi: 10.1016/j.esmoop.2023.101209. Epub 2023 Apr 11. PMID: 37054504; PMCID: PMC10163162

Addressing clinical uncertainties in ATMP reimbursement: a review of methodological guidelines and European practic; Delemarre L, Huys I, Van Dyck W and Simoens S (2026) Front. Pharmacol. 17:1749386. doi: 10.3389/fphar.2026.1749386

European Commission HTA CG. (2024). **Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons**. https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en

European Commission HTA CG. (2024). **Guidance on filling in the joint clinical assessment (JCA) dossier template – Medicinal products**. https://health.ec.europa.eu/publications/guidance-filling-joint-clinical-assessment-jca-dossier-template-medicinal-products_en

European Commission HTA CG. (2025). **Implementation of the Regulation on health technology assessment** https://health.ec.europa.eu/health-technology-assessment/implementation-regulation-health-technology-assessment_en

European Commission HTA CG (2025) **Annual Work Programme 2026.** https://health.ec.europa.eu/publications/2026-work-programme-member-state-coordination-group-hta-htacg_en