EFSPI EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Indirect treatment comparisons - choosing the right tool for the job

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Norwegian Medical Products Agency

Scientific Advice Working Party member
Methodology Working Party member
Member HTACG JSC and MPG subgroups

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of:

- Norwegian Medical Products Agency (NOMA)
- The European Medicines Agency (EMA) or its scientific committees
- The HTAR Coordination Group (HTACG)

The ‘HTA position’ can be found here

Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

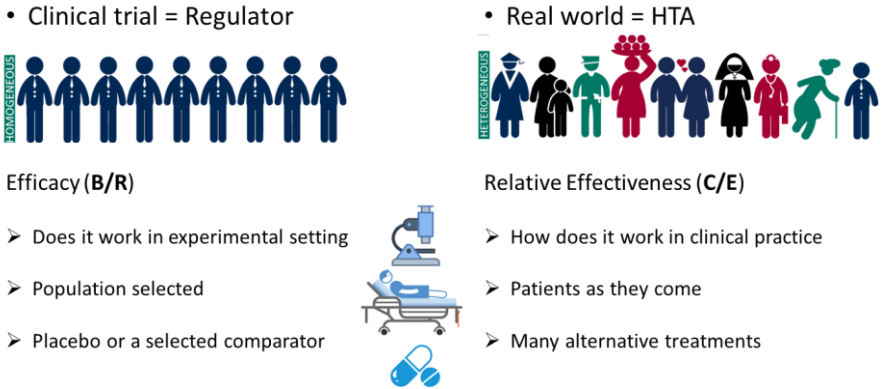
Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

Previous versions can be found here: https://www.eunethta.eu/jointhtawork/

D4.3.1 and D4.3.2 -> they form the basis for these revised versions, commissioned by the HTACG

Why do we need ITC's in the first place?

'To assess the relative efficacy or effectiveness of a new intervention compared to one or more existing interventions (the comparators; e.g., the current standard treatment) in the presence of multiple sources of evidence, appropriate methods for evidence synthesis should be used.'



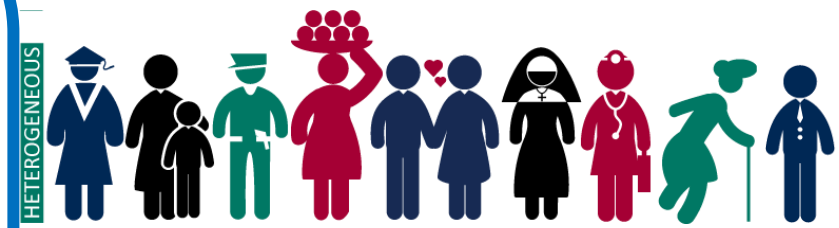
The experiment, intervention and causality

- Clinical trial = Estimand

Efficacy (**B/R**)

- Does it work in experimental setting
- Population selected
- Placebo or a selected comparator

- Real world = PICO



Relative Effectiveness (**C/E**)

- How does it work in clinical practice
- Patients as they come
- Many alternative treatments

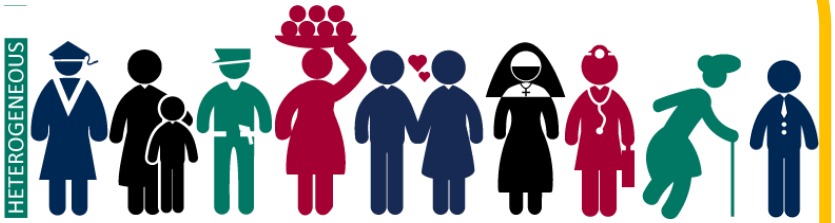
The translation, relative effectiveness, context

- Clinical trial = Estimand

Efficacy (**B/R**)

- ➢ Does it work in experimental setting
- ➢ Population selected
- ➢ Placebo or a selected comparator

- Real world = PICO



Relative Effectiveness (**C/E**)

- ➢ How does it work in clinical practice
- ➢ Patients as they come
- ➢ Many alternative treatments

The what? …..The PICO

The Estimand versus the PICO

- Estimand
  - Describes the intention of the experiment
  - Regulators assess the shown benefits, risks, then choose the appropriate wording in the indicating that describes the clinical setting in which the experiment was performed and to what extend it might be extrapolated/contextualised (setting, population, sub-groups etc / ICH E9)

The Estimand versus the PICO

- PICO
  - Describes the reality in which the drug will be used *
  - HTA's assess the match/mismatch between the evidence the experiment provides and the reality (setting, population, sub-groups and sub-populations, etc)
  - Sub-populations can be post-baseline event driven (Responder/Non-responder) groups, non-randomised with impact on treatment/reimbursement decisions.
  - Or they can be defined based on clinical practice (national) and might also be non-randomised (because not part of the protocol)

* we come back to this (policy PICO versus data driven PICO), types of HE decision frameworks and perspective

The Estimand versus the PICO

- Estimand -> clearer in language (one Estimand with one set of properties, and yes ☺ the ICE)

- PICO more ambiguous (and potentially HTAb's/decision makers are not aware of the fact that switching the perspective has some fundamental implication?)
  - Population
  - Intervention
  - Comparator(s)
  - Outcomes(s)

What drives the PICO

“We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients.”

Which perspective are we talking about?

Societal perspective

- Medical costs borne by third-party payers and paid out-of-pocket by patients
- Time costs of patients in seeking and receiving care
- Time costs of informal (unpaid) caregivers
- Transportation costs
- Effects on future productivity and consumption
- Other costs and effects outside the health care sector

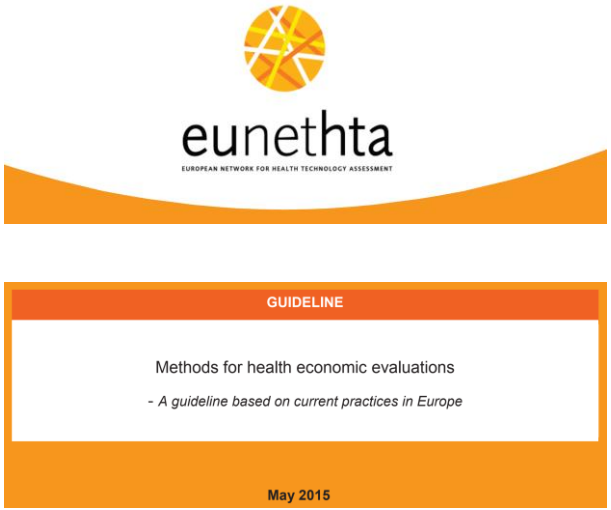
Health sector perspective

- Include all costs and benefits impacting a system of providers, payers and patients.
- Do not consider impact outside of the health system (e.g. long-term value to patients)
- Based on Direct Medical Costs reimbursed by a third party
- Can include out-of-pocket costs to the patient
- Can include current and future costs as a result of a pathway of care

Patient perspective

- Fees for consultation
- Bed day charges at the health facility
- Expenses on medicines, diagnostic tests,
- Travelling expenses to the health facility for the patient and accompanied persons for treatment,
- Amount spent on meal / food taken while waiting for treatment
- Time loss of the patient and the accompanied persons for seeking treatment
- Informal caregiving
- Pain and suffering

Landscape of perspectives in 2015 -> 2025?

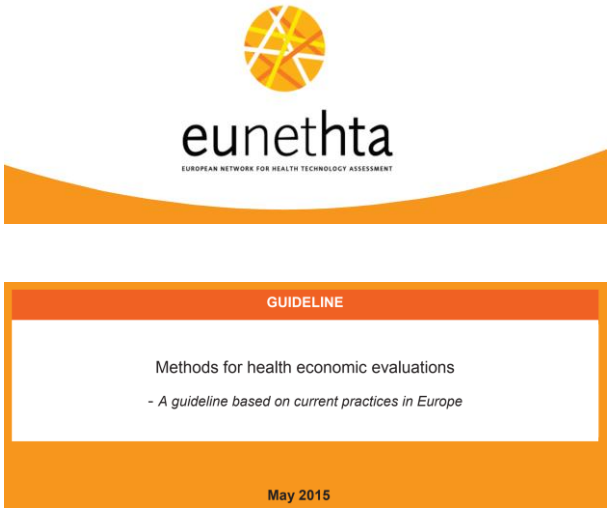


https://www.eunethta.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

Country	Preferred type of analysis
Austria	No preferred type
Belgium	CUA, CEA or CMA.
Croatia	CUA or CEA
Czech Republic	CUA
Denmark	Not explicitly stated. CEA and CUA seem to be accepted.
England	CUA (Technology Appraisals and NICE Diagnostics Assessment Programme) CCA (NICE Medical Technologies Evaluation Programme Methods Guide)
Estonia and Latvia	CEA or CMA
Finland	CUA, CEA, CMA or CBA
France	CUA and CEA
Germany	CEA (several endpoints= several efficiency frontiers)
Hungary	CUA, CEA or CMA,
Ireland	CUA or CEA
Italy	CUA or CEA
The Netherlands	CUA, CEA or CMA
Norway	CUA, CEA or CMA.
Poland	CUA (preferred according to the regulation), CEA or CMA and a CCA. CBA is possible only as an additional analysis (according to the guidelines).
Portugal	CUA, CEA, CMA or CBA (CUA is preferred)
Russia	CEA or CMA (Ministry of health) CMA, CEA, CUA or CBA (ISPOR Russian HTA Chapter)
Scotland	CUA or CMA
Slovakia	CUA, CEA or CMA
Slovenia	CUA, CEA or CMA and Cost Analysis.
Spain	CUA, CEA, CMA or CBA. CUA is preferred. (Spanish recommendations, Osteba) CUA, CEA or CMA (AETSA) CUA or CMA (CEA only if a CUA cannot be conducted) (CatSalut)
Sweden	CUA, CEA, CMA or CBA
Switzerland	CEA

CBA: Cost-benefit analysis, CCA: Cost-consequence analysis, CEA: Cost-effectiveness analysis, CUA: Cost-utility analysis, CMA: Cost-minimization analysis.

Landscape of perspectives in 2015 -> 2025?



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CBA: Cost-benefit analysis, CCA: Cost-consequence analysis, CEA: Cost-effectiveness analysis, CUA: Cost-utility analysis, CMA: Cost-minimization analysis.

The Philosophy / Methodology

Type	Unit of effect	Strength	Limitations
Cost–benefit analysis (CBA)	All effects measured in €	The net benefit (NB) is easy to interpret. When a new treatments extra benefits are worth more than the extra costs then NB > 0	• It is difficult to measure the value of all health outcomes (positive or negative) in € • Ethical aspects come into the discussion (Prioritisation, discrimination, the Pareto principle)
Cost-utility analysis (CUA)	Two effects (quality and length of life); reflected as quality-adjusted life years (QALY's)	Patient relevant outcomes involving both quality and length of life can be incorporated into the analysis. In theory the QALY measure is 'universal', allowing evaluation of very different decision problems with each other.	• QALY outcomes can be biased by method, indication and population • Society might value a QALY for different patient groups differently (and who should we ask, patients or healthy people form the street?)
Cost-effectiveness (CEA)	Effect measured in 'natural units'	There is one outcome and it is measured in it's 'natural unit'.	• Only one outcome is considered for the effect conclusion (no context)
Cost-minimization (CMA)	No effects measured	Only cost data are needed	• Few treatments have truly identical outcomes • Still some evidence is needed to confirm the assumption of 'equality'

The population-average perspective

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The ambiguous perpspective

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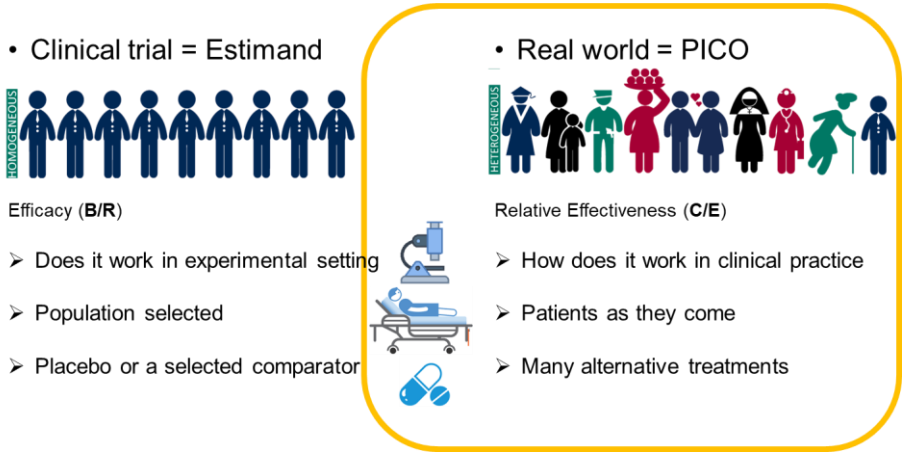
Why do we need ITC's in the first place?

'Randomised controlled trials (RCTs), provided they are well designed and have low risk of bias, are the gold standard for informing estimates of treatment effectiveness and should be used for evidence synthesis when possible.'

But, in particularly in crowded, rapidly evolving treatment landscapes, RCT's can't reflect all potential treatment options.

- Indirect treatment comparisons are needed for contextualisation



What do we mean with ITC?

Start with what the HTA's consider the definition of ITC:

'….., we use the term indirect comparison as the broadest term to refer to any evidence synthesis incorporating indirect evidence, which therefore includes NMA, population-adjusted methods such as matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC), and comparisons made in disconnected evidence networks.'

Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

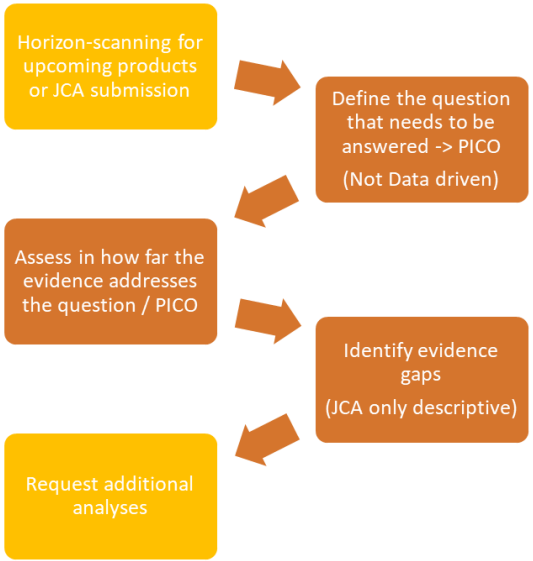
Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

There are two PICO philosophies

“We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients.”

The policy PICO

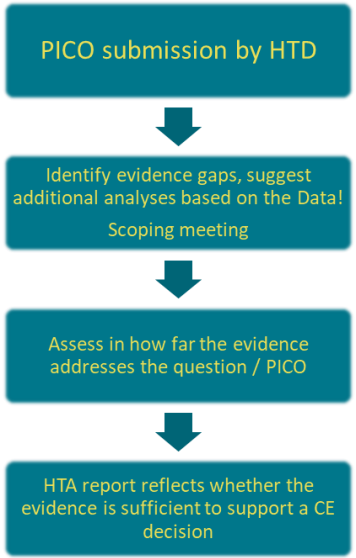
By principle, the scope of the assessment of an intervention should not be data driven, that is, the research questions should not be deduced from the available studies. Rather, an appropriate translation of national policy questions into research questions is performed during the planning stage of the assessment. This means that a particular research question (the PICO) is prespecified for a given assessment.



https://www.eunethta.eu/wp-content/uploads/2022/09/EUnetHTA-21-D4.2-practical-guideline-on-scoping-process-v1.0.pdf

The data driven PICO

Health Technology Developer (HTD) submits a dossier to HTAb's with a request to assess the evidence in the context of what the HTD has identified as the supported PICO.



The data driven PICO

The HTAb assesses:

- Whether the submitted evidence has sufficient internal validity
- Whether the evidence allows assessment of relative effectiveness
- Whether the submitted evidence supports the HTDs PICO
- Whether the submitted PICO has relevance to national PICO(s)

The data driven PICO

The HTAb assesses:

- Whether the submitted evidence has sufficient internal validity
- Whether the evidence allows assessment of relative effectiveness
- Whether the submitted evidence supports the HTDs PICO
- Whether the submitted PICO has relevance to national PICO(s)

- PICO
  - Describes the reality in which the drug will be used *
  - CUA will use modelling to predict the impact the introduction will have on a counterfactual future

How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

- **Indication:** Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy.

How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases and no known visceral metastasis who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Radium-223*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

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How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive

PICO 2 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and one previous line of taxane based chemotherapy and who are suitable for cabazitaxel
I	PLUVICTO
C	Cabazitaxel*
O	*See outcomes table*

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PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive

PICO 2 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive

PICO 3 (subpopulation)

P	Adult patients with BRCA 1/2-mutated progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Olaparib*
O	*See outcomes table*

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How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive

PICO 2 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive

PICO 3 (subpopulation)

P	Adult patients with BRCA 1/2-mutated progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been

PICO 4 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are not suitable for chemotherapy or have been treated with docetaxel as 1st line and cabazitaxel as 2nd line or patients who have taken all available treatments to their own clinical condition (patient may be eligible for best supportive care or PLUVICTO)
I	PLUVICTO
C	Best supportive care
O	*See outcomes table*

How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 5 (full population)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Physician choice for control arm, with at least: Cabazitaxel*, or Abiraterone* + prednisolone, or Enzalutamide*, or Apalutamide*, or Olaparib*, or Radium -223*, or BSC
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 5 (full population)

PICO 6 (full population)

P	Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy
I	PLUVICTO
C	Individualized treatment, taking into account previous therapies, with selection of - abiraterone +prednisone /prednisolone* - enzalutamide* - cabazitaxel*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standard in the treatment of prostate cancer relapse or metastatic disease as it aims to reduce levels of circulating androgens, which induce prostate cancer growth and survival. The association of ADT with other agents is often indicated in the context of castration-sensitive metastatic prostate cancer.

How PICOs look like (Pluvicto (lutetium (177Lu) vipivotide tetraxetan)

PICO 1 (subpopulation)

P	Adult patients with progressive prostate-specific membrane antige

PICO 2 (subpopulation)

P	Adult patients with progressive prostate-specific membrane a

PICO 3 (subpopulation)

P	Adult patients with BRCA 1/2-mutated progressive pros (PSMA)-positive metastatic castration-resistant prostate c
I	
C	
O	

PICO 4 (subpopulation)

P	Adult patients with progressive prostate-specific
I	
C	
O	

PICO 5 (full population)

P	Adult patients with progressive prostate-specific metastatic castration-resistant prostate cancer (mCRP pathway
I	PLUVICT
C	Physicia Cabazita Abirater Enzaluta Apaluta Olaparit Radium BSC
O	*See outc*

* Androgen depr aims to reduce le other agents is of

PICO 6 (full population)

P	Adult patients with progressive metastatic castration-resistant pros pathway inhibition and taxane base
I	PLUVICTO
C	Individualized treatment, taking into - abiraterone +prednisone /predniso - enzalutamide* - cabazitaxel*
O	*See outcomes table*

* Androgen deprivation therapy (ADT) is the standa aims to reduce levels of circulating androgens, which other agents is often indicated in the context of cas

Outcomes table

Overall survival
Radiological tumor assessment, including overall response rate and duration of response
Progression free survival (radiological, clinical or PSA) by investigator and blinded independent committee review
Symptomatic skeletal event, including time to first skeletal event
Prostate specific antigen levels
Pain measured by a patient-reported outcome measure such as a numeric rating scale or a visual analogue scale
Fatigue
Health-related quality of life, measured preferably by generic and disease specific questionnaires, ie EORTC QLQ C30 plus, if possible, EORTC PR25 or FACT-P, FACT-G
Health status measured preferably by EQ-5D-5L
Any other patient centred outcome measured by patient-reported outcomes measures
Adverse events (total)
Serious adverse events
Severe adverse events (Grade ≥ 3)
Discontinuation and interruption due to adverse events
Adverse events of special interest (AESI)
Suspected unexpected serious adverse reaction (SUSAR)

The good news, ITC's are acceptable

The bad news, ITC's are acceptable per PICO

'Evidence networks for indirect comparisons determine which methods are potentially applicable and should be constructed systematically from the PICO question(s) to avoid bias. The resulting networks may differ depending on whether multiple comparators in the same population are considered separately (potentially resulting in different networks for each comparator) or simultaneously (resulting in a single network for all comparators)'

Most likely the expectation is that JCA submission should therefore generally include both

- an evidence synthesis in the 'population-level' network, including all comparators defined by the PICOs that form a connected network with the intervention, and
- evidence synthesis in each individual 'comparator-level' network, if these differ from the population-level network

The bad news, ITC's are acceptable 'per HTAB'

Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems

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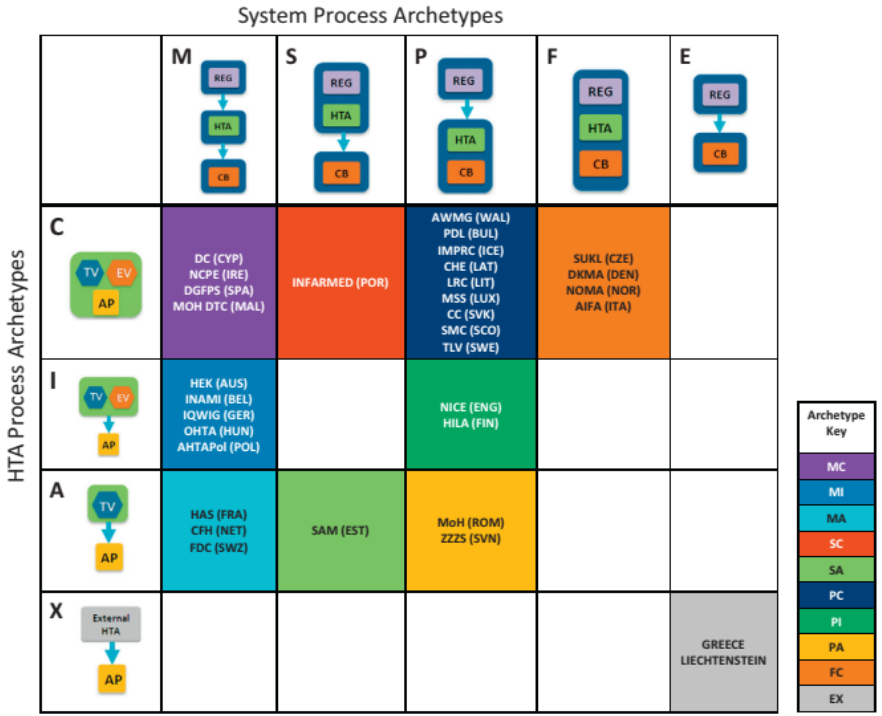
[c] Eli Lilly and Company, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK



The bad news, ITC's are acceptable 'per HTAB'

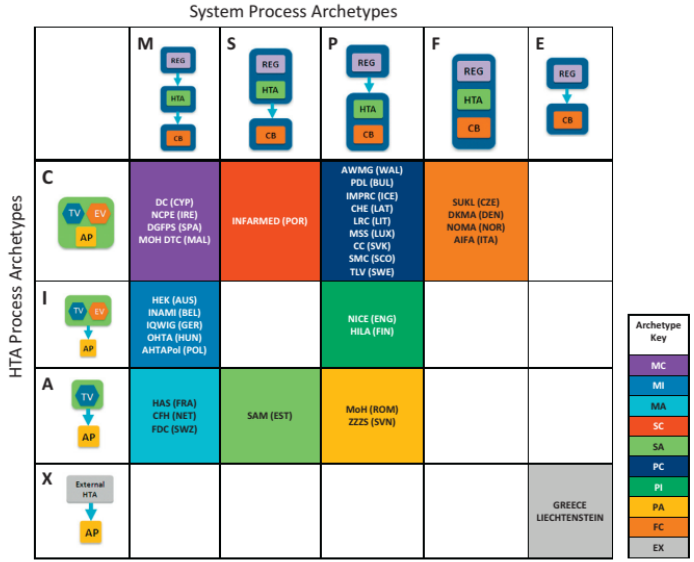
M: the regulatory, HTA and coverage body functions are performed by separate agencies.
S: the regulatory and HTA functions are performed by a single agency and the coverage body functions are independent.
P: the HTA and coverage body functions are performed by a single agency with the regulatory function performed independently.
F: the regulatory, HTA and coverage body functions are all performed within a single agency.
E: no HTA is performed within the national regulatory to reimbursement system.

C: the therapeutic value is assessed prior to independent appraisal.

I: the therapeutic value assessment is conducted within the same agency as Economic evaluation, but the appraisal is performed independently, usually by health professionals rather than civil servants.

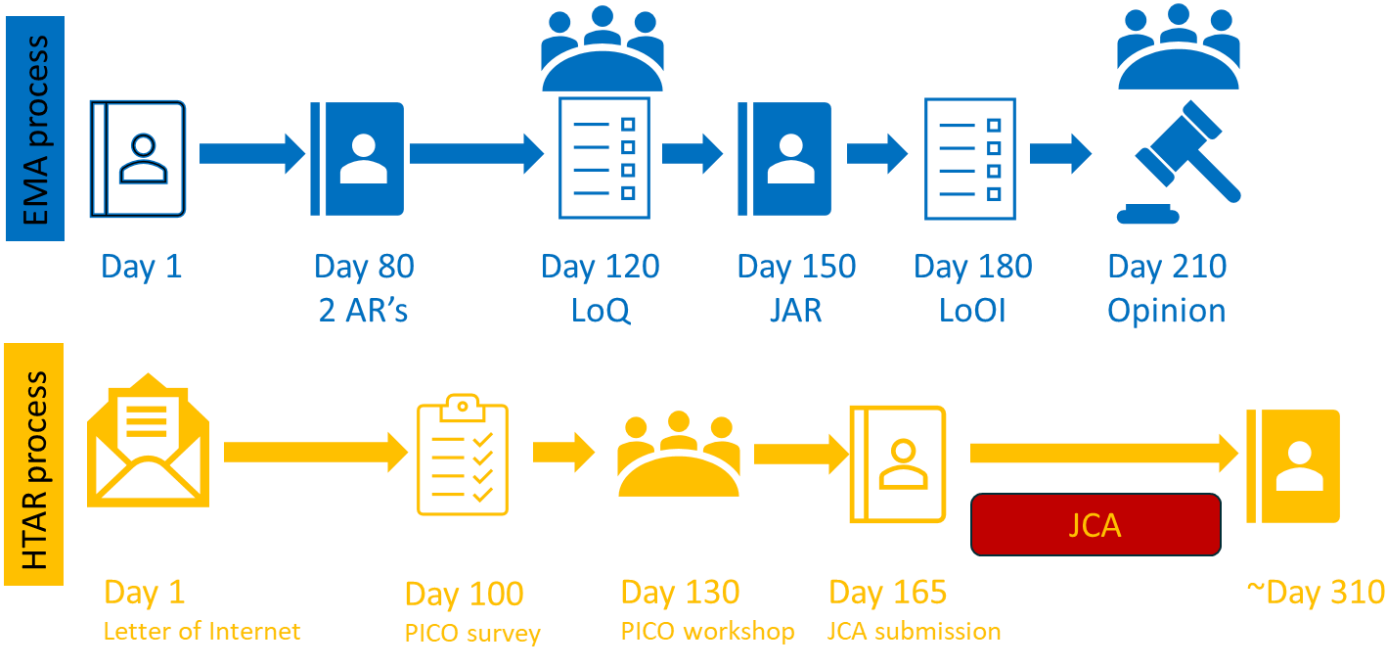
A: the therapeutic value assessment, economic evaluation and appraisal are performed within the same agency.

X: the appraisal is conducted using information from an external HTA report or by considering the coverage decisions of reference countries.

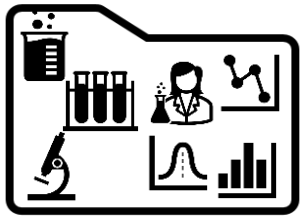


Why is it bad news?

Time is of the essence



Time is of the essence



EMA process

Day 1

Day 80
2 AR's

Day 120
LoQ

Day 150
JAR

Day 180
LoOI

Day 210
Opinion

HTAR process

Day 1
Letter of Internet

Day 100
PICO survey

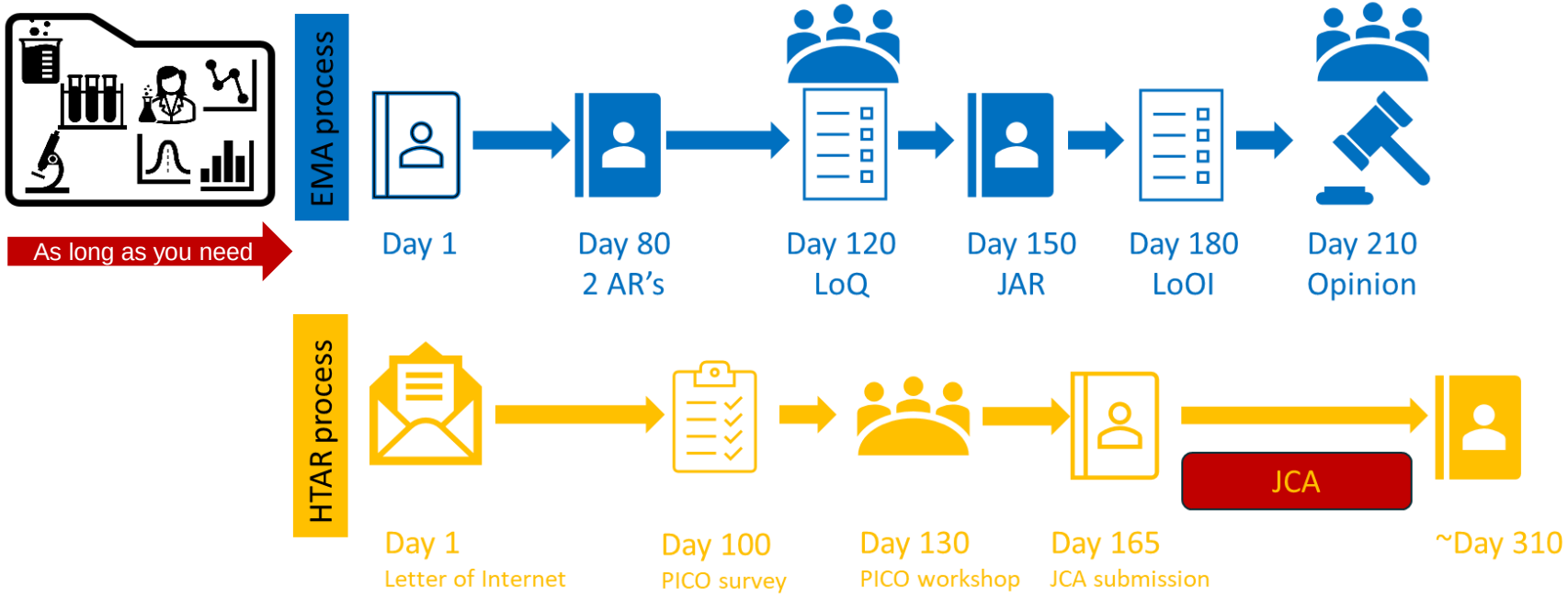
Day 130
PICO workshop

Day 165
JCA submission

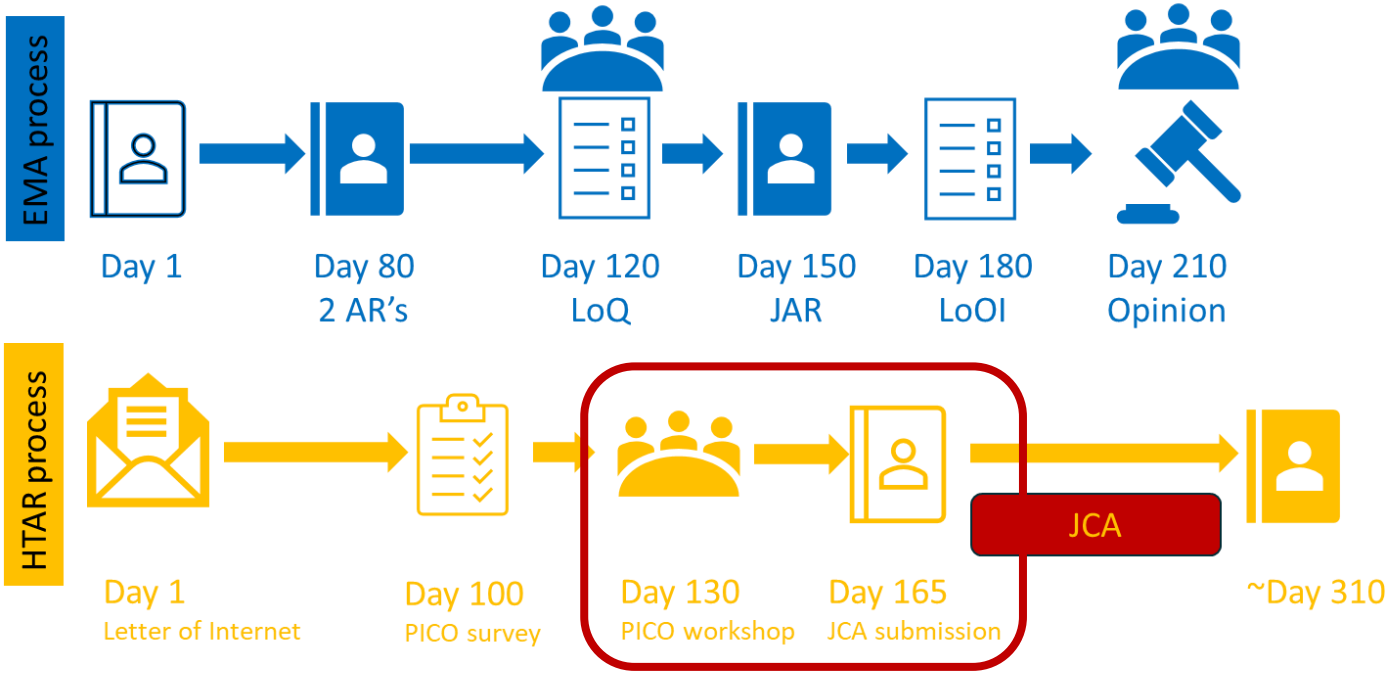
JCA

~Day 310

Relative effectiveness, the elephant....



Relative effectiveness, the elephant....



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