An Early Start: Preliminary ITC Assessments Informing Evidence Generation Planning for JCA

Karlsson A,[1] Kochar N,[1] Gurney J,[1] Porteous A[1]

[1]Costello Medical, London, UK

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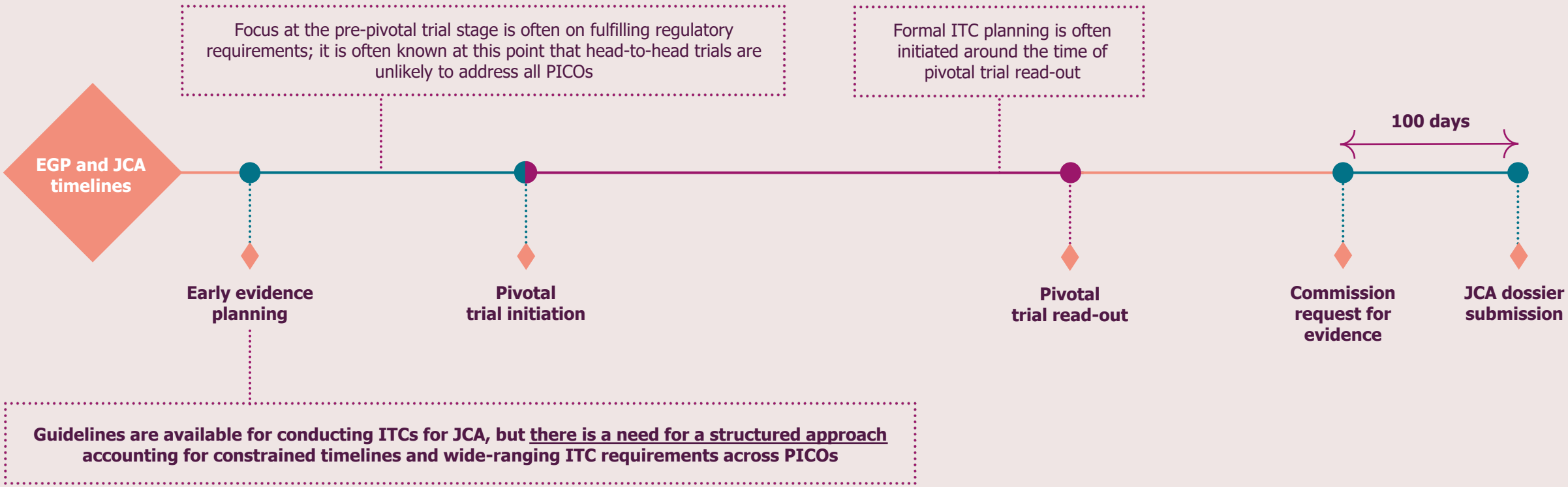
PRESENTED BY

ANDREI KARLSSON

costello medical

Background

- Initial JCA PICO simulations and HTA Coordination Group exercises have revealed the potentially large numbers of PICOs that may need to be addressed[1]
- ITCs are likely to be central to JCA evidence packages for submitting manufacturers

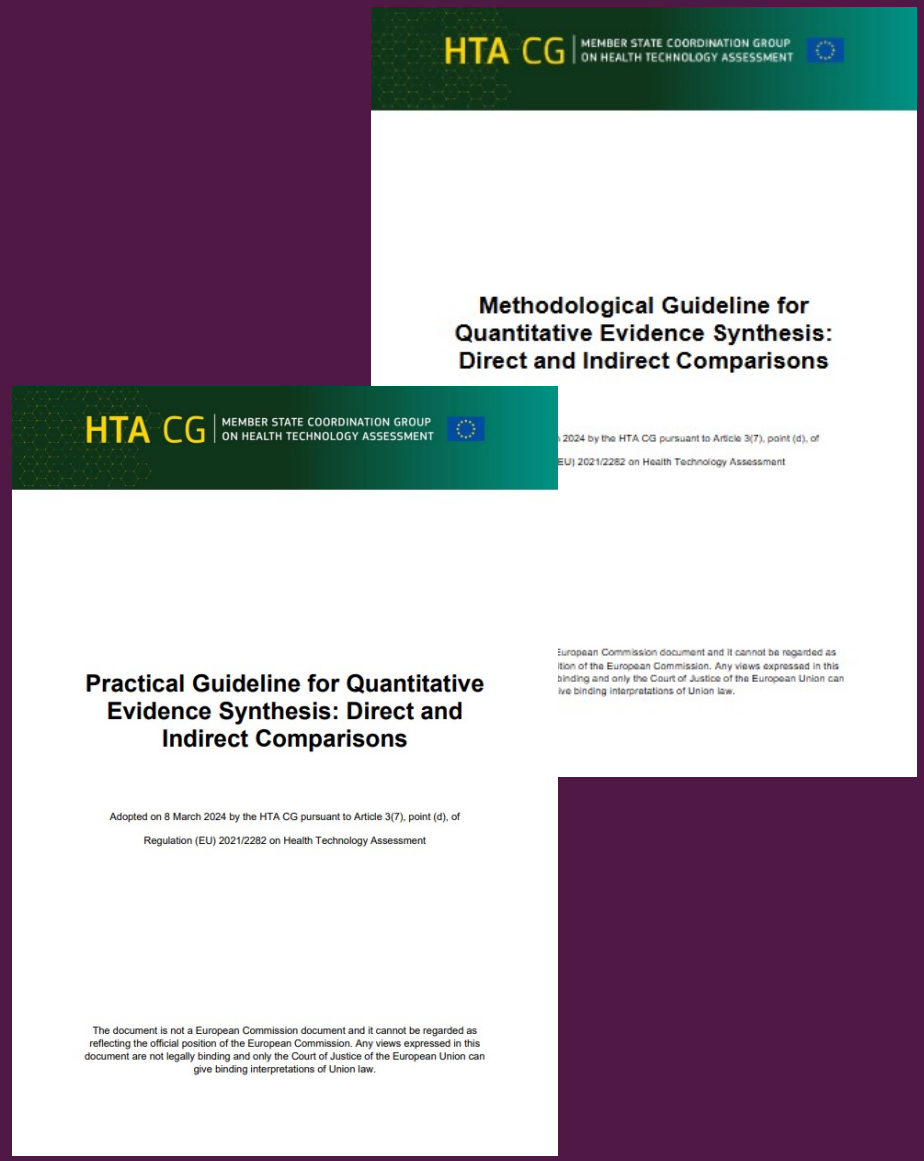


Abbreviations: EGP: evidence generation plan; **HTA:** health technology assessment; **ITC: i**ndirect treatment comparison; **JCA:** joint clinical assessment.

References: [1]Public Health – European Commission. PICO exercises. 2025. Available at: https://health.ec.europa.eu/publications/pico-exercises_en. Last accessed: November 2025.

Methods

1. Reviewed HTA CG published methodological and practical guidelines, including compiling and assessing reporting requirements for ITCs
2. Evaluated where assessments could be conducted at the pre-phase III stage of a product to plan JCA-ready ITCs
3. Defined domains of a structured roadmap and key assessments with application to scenarios
4. Designed the roadmap to be comprehensive and practically implementable while capturing the unique value of the intervention



Abbreviations: HTA CG: Member State Coordination Group on Health Technology Assessment; **ITC:** indirect treatment comparison; **JCA:** joint clinical assessment.

References: [1]Member State Coordination Group on Health Technology Assessment. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Available here. Last accessed: November 2025; [2]Member State Coordination Group on Health Technology Assessment. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Available here. Last accessed: November 2025.

Roadmap Overview

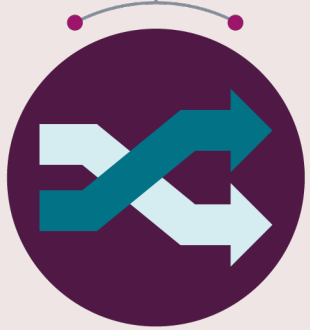
The stages and key outputs of the roadmap are shown below

1. PICO Framework

Comparator landscape and consolidated PICOs

2. Treatment Effect Modifiers and Prognostic Factors

Targeted literature search and clinical input



3. Working ITC Assessments

Early evidence synthesis report for JCA

4. Pivotal Trial Design

Optimisation of design elements for ITCs

5. Supplementary Evidence

Additional data to supplement evidence base for ITCs

Abbreviations: ITC: indirect treatment comparison; **JCA:** joint clinical assessment.

Roadmap Overview

1. PICO Framework

Comparator landscape and consolidated PICOs

1. PICO Framework

Identification of the likely PICOs via landscaping and PICO simulation, and determination of whether comparators are connected or unconnected

Key Assessments

The roadmap outlines:

- Landscaping to identify **launched comparators** across key priority markets and **track emerging comparators**
- **Early PICO simulations** with **input from local affiliates and/or clinicians**
- **Identifying available comparator data** to characterise the available evidence base for these PICOs

Example Application: *RET*+ NSCLC

- Through the conduct of assessments at this stage of the roadmap, manufacturers launching a new product in 1L mNSCLC could identify insights such as:
  - A new treatment for patients with ***RET*+ NSCLC** (regardless of treatment line) would likely need to demonstrate effectiveness vs the first-in-class RET inhibitor selpercatinib. If a H2H trial vs selpercatinib is not feasible:
    - **Untreated patients:** A H2H trial of selpercatinib vs chemotherapy is available and could potentially be connected to the new treatment using a chemotherapy anchor.[1] Manufacturers would need to consider aligning the type, posology and RoA of the chemotherapy selected in the pivotal trial to that in the trial of selpercatinib vs chemotherapy
    - **Previously treated patients:** Selpercatinib trial data are only available from a single-arm study, and hence unanchored methods may need to be explored[2]

Value

- Early assessment of the comparator landscape informs:
  - Consideration of a comparator arm for the pivotal trial to optimise network connectivity
  - Whether anchored or unanchored approaches will be needed in ITCs versus comparators expected to be relevant at JCA (both approved and emerging)

Output

- List of consolidated PICOs
- Preliminary networks for each subpopulation

Stage 2:
Treatment effect modifiers and prognostic factors

Abbreviations: 1L: first-line; **H2H:** head-to-head; **ITC:** indirect treatment comparison; **JCA:** joint clinical assessment; **mNSCLC:** metastatic non-small cell lung cancer; **NSCLC:** non-small cell lung cancer; ***RET*+:** *RET*-positive; **RoA:** route of administration.

References: [1]Zhou C, Solomon B, Loong HH, et al.: First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. N Engl J Med. 2023, 389:1839-50; [2]Drilon A, Oxnard GR, Tan DS, et al.: Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020, 383:813-24.

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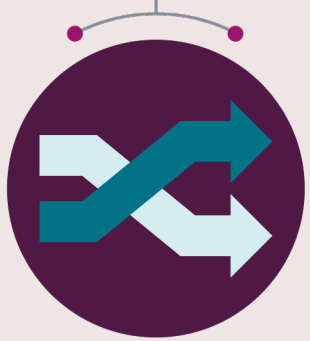

2. Treatment Effect Modifiers and Prognostic Factors

Identification of potential treatment effect modifiers and prognostic factors via literature searches and clinical expert input

Key Assessments

- JCA guidelines point to requirement of comprehensive assessment of all potential TEMs and PFs as the key assessment of the crucial similarity assumption of ITCs

The roadmap outlines:

- Suggested parameters of a **targeted literature search** that can be conducted to develop a **working summary of identified (and prioritised) TEMs for validation**
- Key questions to pose to **clinical experts** in order to establish the direction and size of treatment effect modification

Example Application: NSCLC without AGAs and *RET*+ NSCLC

- The specific method used to identify TEMs varies with factors such as treatment landscape crowdedness. For example, in mNSCLC:
  - **NSCLC without AGAs:** Several RCTs have been conducted in EGFRm mNSCLC, and trial data and published ITCs report on TEMs; these may provide subgroup analyses by TEMs and how these have previously influenced trial design[1]
  - ***RET*+ NSCLC:** For rarer types of disease (e.g. *RET*+ NSCLC) where trial data are sparse, there may be a greater reliance on clinician validation
  - Reviewing clinician input and assessor critique of the generalisability or the trial population and ITC methodology in prior NSCLC appraisals may also elucidate what local clinicians/assessors consider to be key PFs/TEMs

Value

- A comprehensive knowledge of TEMs at an early stage:
  - Sets expectations for ITCs across PICOs with time for updates
  - Allows for pivotal trial to be designed to facilitate the similarity assumption in ITCs

Output

- TLR protocol and data extraction file
- Detailed summary of identified TEMs with clinical input

Stage 3:
Working ITC assessments

Abbreviations: AGA: actionable genomic alteration; **EGFRm:** EGFR-mutant; **ITC:** indirect treatment comparison; **JCA:** joint clinical assessment; **NSCLC:** non-small cell lung cancer; **PF:** prognostic factors; **RCT:** randomised controlled trial; **RET+:** RET-positive; **RoA:** route of administration; **TEM:** treatment effect modifier; **TLR:** targeted literature review.

References: [1]Samuelsen C. Griebsch I. Network meta-analyses for EGFR mutation-positive non-small-cell lung cancer: systematic review and overview of methods and shortcomings. Journal of Comparative Effectiveness Research 2020; 9(17).

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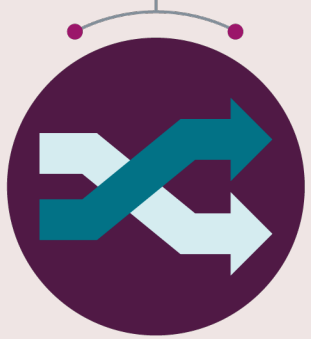
Targeted literature search and clinical input



3. Working ITC Assessments

Early evidence synthesis report for JCA

Abbreviations: ITC: indirect treatment comparison; **JCA:** joint clinical assessment.

3. Working ITC Assessments

Preliminary comparisons of trial design, patient populations and reported outcomes, based on available data, to inform the validity of similarity and homogeneity assumptions in future ITCs

Key Assessments

- Working ITC assessments should cover initial networks arising from the PICO framework assessment (**stage 1**) and draw upon knowledge of TEMs (**stage 2**)
- Based on identified comparators from **stage 1**, the exchangeability of studies should be assessed for inclusion in a future ITC:
  - Available patient baseline data and outcome data should be extracted, summarised and compared for identified comparator pivotal studies
  - Depending on pivotal trial timelines, the manufacturers' pivotal trial may be a placeholder or may be incorporated using expected trial design from KDEs or a draft protocol
- Further assessment of connectivity for preliminary networks in **stage 1** should result in working networks, both anchored and unanchored, for ITCs required for priority PICOs
- Early assessments of connectivity and identification of data gaps can also inform:
  - Optimisation of phase III trial design (outlined in **stage 4** of the roadmap) to enable robust ITCs
  - Supplemental evidence generation activities from RWE (outlined in **stage 5** if required)

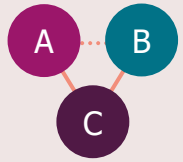
Output

- Living early evidence synthesis assessment document which covers PICOs required by JCA MSs, and subject to updates

Stage 4: Study Design

Stage 5: Supplementary Evidence

Anchored ITC:



Unanchored ITC:

Example Application: RET+ NSCLC

- **Untreated patients in *RET*+ NSCLC:** For the potential ITC between the new treatment and selpercatinib, anchored through chemotherapy:[1]
  - Chemotherapy arms and stratification factors at randomisation should be carefully assessed (e.g. permitted regimens, dosing details) to justify the anchoring strategy
  - Assessment of heterogeneity in baseline characteristics should focus initially on key treatment effect modifiers (e.g. ECOG PS, presence of brain metastases)
  - Absence of comparator efficacy data in a particular subgroup which may be included in JCA PICOs (e.g. in patients with KEAP1 or KRAS) might necessitate evidence generation potentially using RWE
- **Previously treated patients in *RET*+ NSCLC:** Since selpercatinib trial data are only available from a single-arm study:[2]
  - Formal comparisons of baseline characteristics will need to extend to prognostic factors (e.g. age, sex)
  - Initial assessments of the robustness of the unanchored comparison can be formed

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; **ITC:** indirect treatment comparison; **JCA:** joint clinical assessment; **KDE:** key design element**; KEAP1:** Kelch-like ECH-associated protein 1; **KRAS:** Kirsten rat sarcoma viral oncogene homolog; **MS: m**ember state; **NSCLC:** non-small cell lung cancer; **RET+:** RET-positive; **RWE:** real-world evidence; **TEM:** treatment effect modifier.

References: [1]Zhou C, Solomon B, Loong HH, et al.: First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. N Engl J Med. 2023, 389:1839-50; [2]Drilon A, Oxnard GR, Tan DS, et al.: Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020, 383:813-24.

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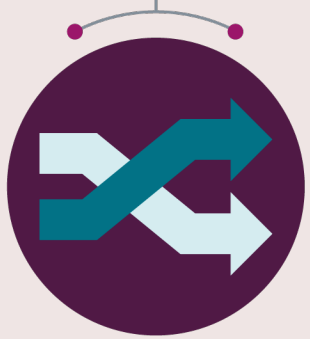

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4. Study Design

Recommendations for pivotal trial key design elements to facilitate consistent comparisons across PICOs concerning comparator arm selection, eligibility criteria, concomitant medications, stratification factors for randomisation, outcome variables and timepoints

Key Assessments

- Based on findings of working ITC assessment conducted during or before pivotal trial planning, the roadmap outlines elements of trial design that can be optimized for future ITCs, including:
  - Specifying control/comparator arms that permit connections in anchored ITCs
  - Aligning eligibility criteria to those of key comparator trials e.g. permitting a key supportive therapy if that is used in clinical practice
  - Including data collection for all patient baseline characteristics identified as potential TEMs or PFs
  - Modifying the proposed stratification factors at randomisation to align with comparator trials to preserve randomization in subgroup ITCs
  - Outcome definition harmonisation to ensure comparability with comparator trials

Output

- Clear portfolio of recommendations for tailoring of upcoming pivotal trial design for ITCs
- Update of the working ITC assessment, incorporating any changes to pivotal trial design

Stage 5: Supplementary Evidence

Example Application: 1L NSCLC

- When developing a pivotal trial in 1L mNSCLC, stratification factors at randomisation should include key TEMs (e.g. ECOG PS, presence of brain metastases) and key subgroups for which ITCs may be required
- Consideration of emerging comparators will be important in the 1L mNSCLC setting, where various trials of novel therapies are ongoing
  - Differing eligibility criteria/outcome definitions may affect **trial population comparability** and **data harmony**, for example:
    - New trials may use updated versions of tumour staging criteria
    - Definitions of PFS may vary compared with those used in existing trials
  - If it is anticipated that these novel therapies will represent SoC at the point of JCA, the manufacturer could consider aligning the eligibility criteria and outcome definitions of the pivotal trial to those of these ongoing trials

Abbreviations: 1L: first-line; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **ITC: i**ndirect treatment comparison; **mNSCLC:** metastatic non-small cell lung cancer; **PFS:** progression-free survival; **SoC:** standard of care; **TEM:** treatment effect modifier.

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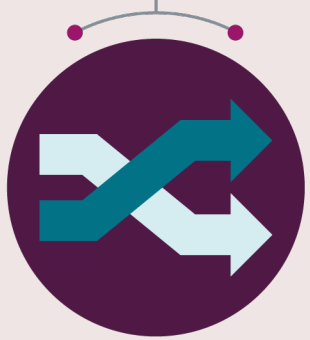

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5. Supplementary Evidence

Recommendations for supplementary evidence generation as needed, including real-world evidence-based external comparators

Key Assessments

- Following formal comparisons in **stage 3**, PICOs that cannot be adequately addressed with ITCs versus comparator trial data should be identified and the need for further supplementary evidence considered
- The type of supplementary evidence that is required should be identified; the roadmap outlines assessments required for typical scenarios:
  - If an ITC versus an external control arm (ECA) constructed using RWE is required, **database landscaping c**ould occur at an early stage, with reference to the (draft) pivotal trial protocol in **stage 4**
  - If the primary outcome of the pivotal trial is a **surrogate outcome**, strong evidence for the relationship between the surrogate and outcome assessed in ITCs may be developed in parallel with the conduct of the pivotal trial
  - For more complex scenarios such as incorporating Bayesian hierarchical models to ITCs of basket trials, expert elicitation can be sought at an early stage (e.g. to test exchangeability assumption)[1]

Example Application: RET+ NSCLC

- **Previously treated patients in *RET*+ NSCLC:** Selpercatinib trial data are only available from a single-arm study, and unanchored methods are required[2]
- If it was concluded that the unanchored method would not be sufficiently robust for JCA/HTA purposes, the manufacturer could design an **ECA using RWD** (e.g. from registries and databases)
- Understanding the need for an ECA early would allow the manufacturer to **collect RWD and select variables for adjustment**, well ahead of the point of JCA

Value

- Assessments for requirement of further data generation activities at an early stage allow:
  - Determination of whether these are central to the ITC strategy using the pivotal trial
  - Easier navigation of longer timelines associated with database access if required

Output

- Summary of appropriateness of non-trial evidence for PICOs not adequately addressed by ITCs of trial data
- If required, preliminary data source assessments for real-world evidence generation

Completion of roadmap… requiring regular updates towards JCA

Abbreviations: ECA: external control arm; **ECOG PS**: Eastern Cooperative Oncology Group performance status; **HTA**: health technology assessment; **ITC**: indirect treatment comparison; **JCA**: joint clinical assessment; **mNSCLC**: metastatic non-small cell lung cancer; **PFS**: progression-free survival; **RWD**: real-world data; **RWE**: real-world evidence; **SoC**: standard of care; **TEM**: treatment effect modifier.

References: [1]Mackay E, Springford A, Nagamuthu C, et al. MSR73 Bayesian Hierarchical Models for Indirect Treatment Comparisons of Histology-Independent Therapies for Survival Outcomes. Value in Health. 2023; 26(6). [2]Drilon A, Oxnard GR, Tan DS, et al.: Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020, 383:813-24.

Conclusions

Our roadmap offers a structured approach for manufacturers to develop a stronger data package for JCA, with ITCs that are carefully planned, methodologically sound and suitable across PICOs

Manufacturers can and should take a proactive approach to conduct ITC assessments during pivotal trial design

Assessments do not need to be highly comprehensive or resource intensive to complete – valuable insights can be gained from pragmatic approaches to addressing the roadmap assessments

Updates to outputs developed at each stage will be required up to the point of JCA!

Abbreviations: ITC: indirect treatment comparison; **JCA:** joint clinical assessment.

Scan the QR code to access the full roadmap!

The authors thank Becky Chesworth and Courtney Gray, Costello Medical for the graphic design assistance in the preparation of this presentation.

For more information about our services, please don't hesitate to get in touch.

Andrei Karlsson
Senior Statistician, Evidence Development
andrei.Karlsson@costellomedical.com