Preliminary ITC Assessments Informing Evidence Generation Planning for JCA

Stage of roadmap	1 PICO Framework	2 Treatment Effect (TEMs) Modifiers and Prognostic Factors (PFs)	3 Working ITC Assessments	4 Pivotal Trial Design	5 Supplementary Evidence
Key objectives of early evidence synthesis	• To identify the likely PICOs required at the point of JCA via landscaping, and consolidate and prioritise these PICOs through simulation to obtain a pragmatic, shortened list of comparators and subpopulations that need to be addressed or mitigated • To provide initial insights on how the pivotal trial may address PICOs and whether comparators would be connected or unconnected in networks with the pivotal trial	• To conduct targeted searches to develop a working summary of identified (and prioritised) TEMs and PFs to inform evidence generation • To elicit expert clinical validation for the working summary of TEMs and PFs in order to establish the direction and size of treatment effect modification • To inform expectations for ITCs across PICOs and to optimise pivotal trial design elements to facilitate making similarity assumption in ITCs	• To compile available study data for comparators • Using available comparator trial data, update considerations from **stage 1** regarding network architecture for ITCs connecting a planned pivotal trial for the manufacturer's product to comparators • To assess the comparability of patient populations and reported outcomes in potential networks, with focus on identified TEMs from **stage 2** • To identify if data gaps exist and optimise the pivotal study design for ITCs (**stage 4**), and determine if supplemental evidence generation activities are required (**stage 5**)	• To ensure that the design of the pivotal trial is informed by requirements of future ITCs as outlined in recommendations from the ITC assessment conducted in **stage 3** • To ensure that evidence generation from the pivotal trial (and any supplementary evidence generation activities outlined in **stage 5**) cover required evidence to address all PICOs	• To explore if supplementary (non-trial) evidence can and should be used for PICOs that cannot be addressed with head-to-head trials or ITCs • To determine the type of supplementary evidence that may be required, for example external control arms constructed from real-world evidence • To commence assessment of required non-trial data generation activities to navigate potentially long timelines associated with database access
	• The objectives above can be addressed comprehensively or pragmatically, depending on, for example, whether focus is placed on a smaller number of priority PICOs, or the level of availability of evidence for pivotal comparator trials. The assessments outlined below represent a wide range of considerations manufacturers should be aware of, even if it is not practical or possible to assess these in full				

Key assessments to conduct	• Landscaping should be conducted to identify launched comparators across key priority markets and track emerging comparators in ongoing or upcoming pivotal trials, through review of:
	  • The scopes of prior HTA appraisals in the disease area
	  • EU-wide and national treatment guidelines
	  • Competitor intelligence and horizon scanning reports
	  • Targeted searches of trial databases (e.g. ClinicalTrials.gov)
	• Early PICO simulations should be conducted with input from local affiliates and/or clinicians to help prioritise the most relevant PICOs that need to be addressed by indirect evidence generation methods
	  • As a pragmatic approach, manufacturers could consider conducting the PICO simulation using input from a narrow pool of countries ahead of the pivotal trial, to predict the likely PICOs that need to be addressed through evidence generation
	  • Repeating the simulation at a later stage (e.g. at pivotal trial readout, ahead of JCA) could be a validatory exercise, ensuring that all key PICOs have been accounted for, and allowing development of mitigation strategies for any additional PICOs identified that cannot be addressed through evidence generation
	  • If needed, manufacturers can consider prioritising Member States for inclusion in the simulation exercise, based on:
	  – Transparency of HTA reports
	  – Availability of national treatment guidelines (manufacturers could assume member states without available national guidelines would be more likely to defer to EU-wide guidelines, which could be used as a proxy source for local PICOs)
		• A targeted literature search should be conducted to develop a working summary of identified (and prioritised) TEMs for validation to inform evidence generation
		• A TLR protocol should be developed and tailored to the crowdedness of the disease area; for comprehensive approaches in crowded disease areas, the following elements should be considered:
		  • The PICO eligibility criteria in the TLR protocol to identify TEMs and PFs should consider the following:
		  – Population: planned target population
		  – Intervention/Comparator: for PFs, no interventions need to be specified; for TEMs, all relevant comparators in PICOs for which ITCs may be required should be included
		  – Outcomes: for PFs, a range of demographic, behavioural, disease-specific and co-morbid factors; for TEMs, any variable that modifies how a treatment works
		  • The study types included can cover:
		  – HTA submissions including presentation of an ITC
		  – SLRs, MAs (for PFs) and ITCs
		  • The search parameters, particularly for a crowded disease area, should prioritise recent evidence (e.g. previous 2 years)
		  • An evidence prioritisation strategy should focus on literature which provides information on:
		  – Subgroup results from trials
		  – Stratification factors of comparator pivotal trials
		  – Other trial design elements of comparator pivotal trials
			• Based on the PICO simulation exercise from **stage 1**, available pivotal study information for comparators (launched or preparing for an upcoming launch) or should be identified:
			  • For identified comparator studies in **stage 1**, data from the clinical trial record, study protocol, or available publications should be extracted, with this data forming the basis of further assessments at this stage
			  • Since pivotal trial data are not available for the manufacturer's product under investigation, assessments may assume an expected pivotal study design (to directly incorporate in assessments of connectivity as below)
			• Extracted key data elements from comparator trials initial networks from **stage 1** should be used to further assess connectivity of comparators. This should conclude with reporting of more formal working ITC networks and how they address the list of consolidated PICOs as follows:
			  • The definitions of included interventions from pivotal studies of comparators in initial networks should be assessed and compared, including dosing regimens, dose escalation schedules, and methods of administration, which can confirm the appropriateness of these comparators as connecting nodes
			  • The need for multiple ITCs to satisfy PICOs from **stage 1** should be assessed, including whether bias may arise from the inclusion or exclusion of comparators in each
			  • Disconnected networks which may require additional evidence generation from supplementary sources such as real-world evidence should be noted for further assessment in **stage 5**
			  • If previously published ITCs or treatment appraisals for approved comparators have been identified, the type of comparisons (anchored versus unanchored) that have been conducted should be reviewed to provide reference for proposed networks
				• Based on the working ITC assessments in **stage 3**, a portfolio of recommendations for the design of the pivotal trial should be obtained as follows:
				  • While regulatory requirements for the choice of control arm in some Member States may take precedent in the choice of comparator arm, working ITC assessments may reveal a choice of comparator arm that is best suited to optimise connectivity of networks, which can be recommended for the pivotal trial
				  • Evaluations of the dosing regimens conducted in **stage 3** should inform decisions regarding features of the doses of interventions used in the pivotal trial, to limit differences in dosing regimens across comparator studies in working ITCs
				  • Concomitant medications permitted in the pivotal trial would ideally be specified to allow for harmonisation with comparator studies in working ITCs, and further assessments should consider:
				  – Whether the number and/or type of concomitant therapies received by the planned study population were identified as TEMs in **stage 2** and any differences identified between other trials in the anticipated network in **stage 3**
				  – Including number and/or type of concomitant therapies as stratification factors at randomisation to allow subgroup analyses to be conducted to explore the impact of restricting to a certain number or type of concomitant therapies
					• Based on the working ITC assessments in **stage 3** alongside recommendations for pivotal trial protocol in **stage 4**, the working ITC networks which may require supplementary evidence due to non-connectivity and data gaps should be further assessed as follows:
					  • If networks are disconnected, and unanchored comparisons of trial data are precluded (for example by sample size or severe limitations in comparability of patient populations), the extent to which an external control arm constructed from real-world data may address data gaps or limitations should be assessed:
					  – If required, database landscaping could occur at this stage (i.e. in parallel with pivotal trial protocol development) to identify suitable sources of comparator evidence to fill comparator data gaps, which may follow a target trial emulation framework, and assessments of timelines associated with database access can accommodate longer timeframes
					  – The key variables required for collection and population adjustment in analyses will likely be the TEMs and PFs established earlier in the roadmap, and should closely inform the suitability of real-world databases in terms of data availability
					  • 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 should be collected in parallel with the conduct of the pivotal trial
					  • For more complex methods which may be required for some working ITC networks, 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)

Key assessments to conduct	– Presence of a dedicated local affiliate and/or ex-payer and/or clinician expert network to support with validating the findings from desk research – Launch sequencing (manufacturers should prioritise including Member States where it is commercially planned for the product to launch soon after EMA marketing authorisation and the availability of the JCA report. By the time the product launches in later-launch markets, additional evidence [e.g. RWD from early-launch markets] might be available and the JCA report might therefore have a more limited impact on access decision-making) • During the consolidation process, PICOs can be prioritised based on: • The number of countries requesting them • Whether they were considered essential or optional in the countries that requested them • The relevance of identified PICOs based on current treatment patterns • The available comparator literature should be identified to characterise the available evidence base for these prioritised PICOs, which will feed directly into **stage 3** – Manufacturers can be as comprehensive or pragmatic as resources allows. For instance, when characterising the evidence base, an SLR to identify all relevant evidence is not necessarily required, given that manufacturers are not conducting an ITC at this stage, but optimising pivotal trial design for a future ITC and informing additional evidence planning	• Data should be extracted into a prespecified extraction grid designed to highlight the TEM effect, for example, by comparator, outcome, and the way in which the relative effect is modified • Clinical experts should ratify the summary of identified TEMs and fill gaps in understanding of action of TEMs and the expected magnitude and direction of their impact in ITCs • For a candidate list of characteristics expected to be TEMs or PFs, ideally arising from a TLR, the following key questions should be posed to clinical experts (who should be reminded of the definition of TEMs and PFs in the context of ITCs): – *Are any of the listed characteristics not expected to be TEMs and PFs?* – *Are any of the listed characteristics only expected to have a treatment modifying or prognostic effect on certain outcomes (e.g. only on safety or only on efficacy)?* – *[For each outcome expected to be required for analysis in ITCs e.g. OS/PFs/TTD] In which direction is there expected to be a treatment modifying or prognostic effect?* – *Which of the listed characteristics are expected to be the most important TEMs and PVs? Which are the least important?* – *Are there any important characteristics which may be a TEM or PFs which have not been listed?*	• For the working ITC networks, available patient baseline and outcome data from comparator trials should be extracted and summarised to permit a working side-by-side comparison for the following aspects of patient populations across studies in networks: • Key eligibility criteria including comorbidities, prior therapies or disease severity, to determine the population in which treatment effects would likely be estimated in ITCs, and an assessment of its relevance to the decision problem outlined in **stage 1** • Populations investigated in reported subgroup analyses, including consideration of whether stratification factors for randomisation ensure subgroup analyses remain randomised in RCTs (this will also have informed TEM identification in **stage 2**) • Baseline characteristics, with particular focus on those identified as TEMs and PFs from **stage 2**, with an initial assessment of whether population adjustment is likely to be required based on any identified imbalances • The definition of outcomes including assessor type and assessment criteria, including any data gaps across studies which may preclude ITCs for those outcomes • A brief initial investigation of the proportional hazards assumption to indicate whether complex approaches for ITC of survival data may be required, with reference to precedent from previous ITCs if available, or whether disease specific phenomena such as delayed effect of treatment is expected (which should be clinically validated) • Based on connectivity and comparability assessments conducted above, working ITC networks across PICOs should be equipped with reporting on: • Whether the expected ITC is anchored or unanchored, and the initial proposed method of ITC • The expected robustness of the ITC, pending inclusion of pivotal trial data, to generate reliable comparative evidence • Expected limitations that can be addressed by possible optimisations to pivotal trial design for ITCs (**stage 4**) or the need for supplementary evidence (**stage 5**)	• Study eligibility criteria could be specified to closely align with comparator trials in working ITCs to avoid imbalances in patient characteristics identified as TEMs in **stage 2** • Patient baseline data collected should cover all characteristics identified as TEMs and PFs from **stage 2** • Stratification factors at randomisation should be specified to include key TEMs in **stage 2** and to maintain randomisation in subgroups defined by the stratification factors, assessed in **stage 3** • Pivotal trial endpoints should be defined to maximise harmony between the pivotal trial and comparator trials, with alignment as far as possible on time of assessment (including specifying multiple times of assessment if required), estimands, assessor type and assessment criteria • Based on the selection of recommendations that are incorporated for pivotal trial design, updates to working ITCs should include: • Inclusion of the pivotal trial in working ITC networks based on the finalised pivotal trial protocol • A re-assessment of connectivity and similarity of populations in working ITCs • A re-assessment of any disconnected networks which may require supplementary evidence from real-world data, and assessment of these networks in **stage 5**	• Updates to the working ITC assessment should be reported, evaluating increases in robustness arising from the use of supplementary evidence such as through an ECA
Output	• List of consolidated and prioritised PICOs • Preliminary networks of evidence for PICOs where ITCs may be required due to lack of H2H evidence	• TLR protocol and data extraction file • Detailed summary of identified TEMs with clinical input	• Early evidence synthesis assessment document which reports the type of ITCs which may be required across PICOs, and which can be updated as additional evidence becomes available	• Clear portfolio of recommendations for amendments to pivotal trial protocol to optimise ITCs • Update of the working ITC assessment, incorporating any changes to pivotal trial design	• 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 • Update of the working ITC assessment, incorporating any supplementary evidence

Abbreviations: ECA: external control arm; **EMA:** European Medicines Agency; **EU:** European Union; **H2H:** head-to-head; **HTA:** health technology assessment; **ITC:** indirect treatment comparison; **JCA:** joint clinical assessment; **MA:** meta-analysis; **OS:** overall survival; **PF:** prognostic factor; **PICO:** population, intervention, comparator, outcome; **PFS:** progression-free survival; **PF:** prognostic factor; **RCT:** Randomised Controlled Trial; **RWD:** Real-World Data; **SLR:** Systematic Literature Review; **TEM:** Treatment Effect Modifier; **TLR:** Targeted Literature Review; **TTD:** Time to Discontinuation.

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