Strengthening the national Health Technology Assessment framework for Greece

HTA Guidance Discussion with Pharmaceutical Industry Associations

5 November 2025

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HELLENIC REPUBLIC
Ministry of Health

World Health Organization
European Region

Agenda

15:00-15:20	**Welcome, agenda, and objectives**
15:20-15:40	**Overview of PICO methods and scoping process**
15:40-16:20	**Pilot summary and discussion**
15:45-16:00	**Updates, next steps and close**

Objectives

To apply the new HTA PICO guidance to the Truqap (capivasertib) submission, critically assessing what is relevant to the Greek context, and ensuring the PICO reflects clinical relevance and patient-centered perspectives.

By the end of this session, participants will be able to:

- Apply the new PICO guidance to test the Truqap scoping for completeness and relevance
- Identify which PICO elements align with Greek clinical practice and which require adaptation
    - Confirm relevance of proposed sub-populations in Greek context and feasibility of conducting assessments for them.
    - Select key comparators and outcomes relevant to national patient pathways and patient priorities.

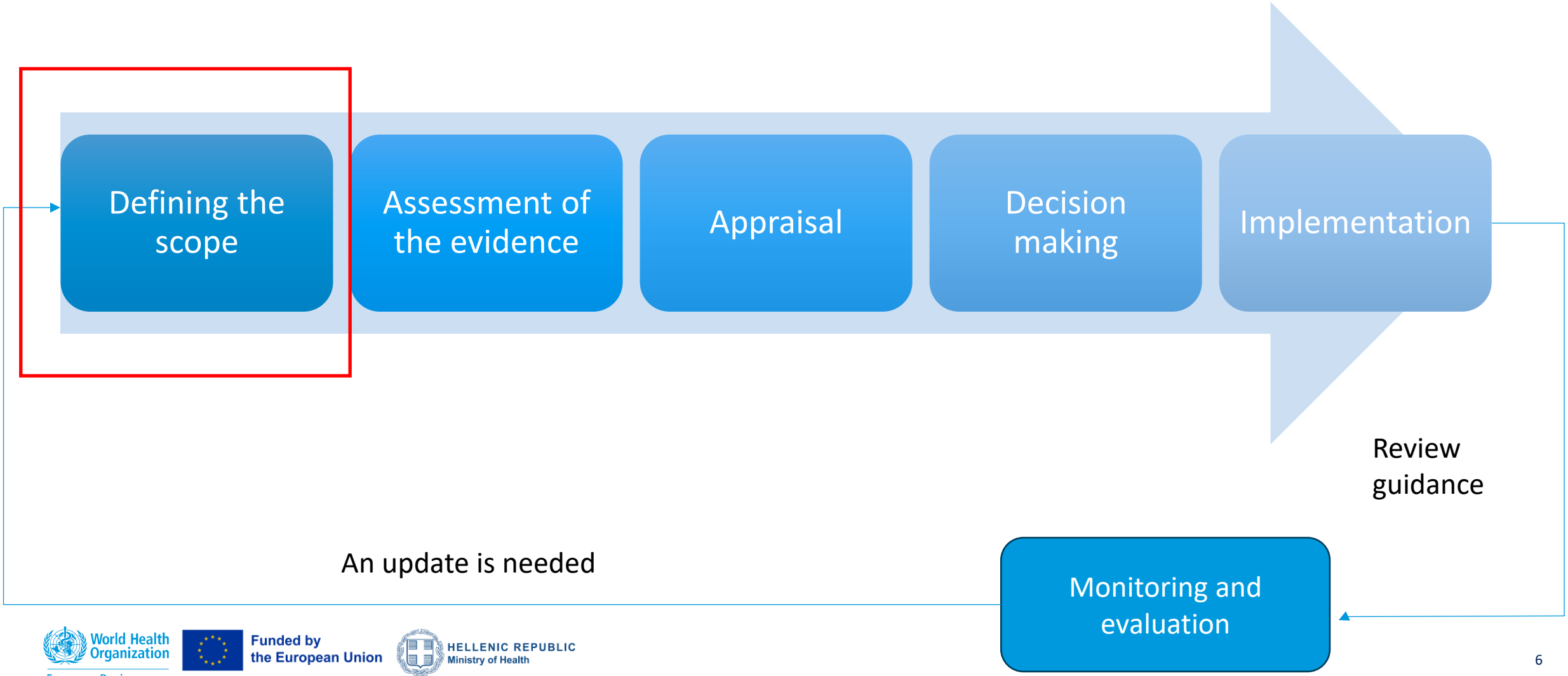
Process overview

1. The initial indication and proposed PICO that is submitted by the HTD will be reviewed by the proposed HTA body *(now the pilot team)*
2. HTA body will select its experts (2-3 each of clinical and patient) from the clinical pool and from registered patient organizations
3. Experts clear the COI requirements and are appointed
4. PICO questionnaire is submitted to experts to consider the parameters as relevant to the Greek context
5. With the input from the clinical and patient experts, the proposed HTA body will submit their final PICO/submit their amendments to the HTD within **4 weeks** of receiving the PICO questionnaire

Submission received by MoH from Astra Zeneca: 17 October
Comments back from selected Committee members, experts: 12 November
Submission due to Astra Zeneca: 17 November

PICO and Scoping Methods Recap

The process of all Health technology assessments (HTAs)



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Components of a HTA scope

- HTA scope is defined using the “PICO”: Population, Intervention, Comparator, Outcomes.
- Structured method for clinical and economic assessment.
- Ensures alignment with EU JCAs while addressing Greek context.

P **population**

I **intervention**

C **comparison**

O **outcomes**

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Population

Define the Patient Population (Greek Setting)

- **Include all relevant patients** for the therapeutic indication:
  - The complete target group
  - Clinically meaningful subgroups with differential response
  - **Describe the likely recipients** of the intervention:
    - Epidemiological characteristics (e.g., average age, gender)
    - Clinical characteristics (e.g., disease severity/stage)
    - Specific to the Greek population
  - **Specify eligibility criteria:**
    - Diagnostic criteria
    - Biomarkers used for patient selection

Equity considerations

- consider whether issues of equity and relevance to specific populations are important to the review
- e.g. sex, age, ethnicity, geographic, economic status, education, etc.

Why?

- different prevalence, progress and impact of disease
- different effects or safety of the intervention
- different outcomes of importance

Intervention

Type of Intervention:

- May be monotherapy or combination therapy
- Can be administered with best supportive care or standard background treatments (pharmacological/non-pharmacological)

Scope of Description:

- Focus only on the intervention under assessment
- Include combination technologies if part of the indication
- Exclude unrelated products

Key Characteristics to Report:

- Regulatory status (e.g., conditional/accelerated approval, orphan designation, ATMP)
- SPC alignment with EMA-approved label
- Expected role in Greek clinical practice
- All relevant details for assessment

- Mechanism of action;
- Pharmacotherapeutic class (ATC codes);
- Mode of administration;
- Dosage (e.g. average daily dosage, loading and maintenance doses; based on weight; duration of therapy);
- Treatment plan, including whether treatment with the pharmaceutical includes combination therapy or any pre-treatments;
- Packaging type, size, durability, strengths and description of any device required, if relevant;
- Handling requirements of the pharmaceutical that may affect usability;
- Monitoring (for example the need for blood samples, biomarker measuring, scans);

Comparator

Definition:

- Comparator = treatment(s) used in Greek clinical practice for the same indication as the assessed medicinal product

Inclusion Criteria:

- Based on routine use in Greece, not relying only on efficacy or clinical trial control arms
- Can include licensed/unlicensed treatments, drug classes, or non-drug interventions

Types of Comparators:

- Pharmacotherapy
- Medical devices, surgery, diagnostics
- Psychotherapy, physiotherapy, radiation, prophylaxis
- Best supportive care, standard of care, watchful waiting

Special Cases:

- If used in both intervention and comparator arms, must be specified
- Dosage and regimen in Greece must be detailed
- Therapeutic sequences (e.g., second-line use) should be highlighted

Multiple Comparator Scenarios:

- One population may require multiple PICOs
- Each comparator = separate PICO unless combined intentionally

Justification:

- There should be justifications for any inclusion/exclusion of comparators
- Local clinical practice and health system context are key for relevance

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Outcomes

Defining Outcomes Measures:

- Outcomes reflect treatment effectiveness and safety
  - *Efficacy outcomes: mortality, morbidity, duration of illness, HRQoL*
  - *Safety outcomes: dropouts, adverse events (total/serious), discontinuations due to adverse events*
- Include healthcare resource use (e.g., hospitalizations)

Sources of outcome data:

- Clinician-reported: clinical exams, biomarkers
- Performance: standardized tasks (e.g., walking tests)
- Patient-reported: symptoms, HRQoL via questionnaires
- Observer-reported: caregiver observations
- Digital: device-collected data (requires validation)

- **Clinical relevance:**
  - Outcomes must reflect Greek context
  - Prioritize critical outcomes (benefit & safety)
  - Surrogate outcomes (e.g., biomarkers) used with justification
  - Composite outcomes: combine related events; analyze components separately

Measurement Instruments & Validity

Outcome measurement instruments quantify outcomes (e.g., HRQoL, response rate)

Must have:

- Validity: measures what it's intended to
- Reliability: consistent and reproducible
- Interpretability: scores are meaningful and clear

Common instruments:

- PROMs – for HRQoL you can have generic (e.g., SF-36, EQ-5D-5L) vs. disease-specific (e.g., EORTC QLQ-C30)
- Ensure cross-cultural adaptation and local validation
- Consider responder definitions to enhance interpretability

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Overview of Pilot Product

Truqap (capivasertib)

Indication for which EMA Committee for Medicinal Products for Human Use (CHMP) provided positive opinion

[Therapeutic indication requested for evaluation]

- TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with:

- Estrogen hormone receptor (ER)-positive
- HER2-negative locally advanced or metastatic breast cancer
- with one or more mutations of PIK3CA/AKT1/PTEN-alterations

following recurrence or progression on or after an endocrine-based regimen.

- *In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.*
- *For men, administration of LHRH agonist according to current clinical practice standards should be considered.*

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Truqap (*capivasertib*)
An overview of Truqap and why it is authorised in the EU

What is Truqap and what is it used for?

Truqap is a cancer medicine used in adults to treat breast cancer that is locally advanced (has spread nearby) or metastatic (has spread to other parts of the body) when the cancer has come back or worsened after hormonal treatment. It is used when the cancer cells have receptors (targets) for certain hormones on their surface (ER-positive) and do not have large quantities of another receptor called HER2 (HER2-negative). The cancer cells must also have been shown to have one or more mutations (changes) in the *PIK3CA*, *AKT1* or *PTEN* genes. Truqap is used in combination with fulvestrant (an anti-oestrogen medicine).

If Truqap is used in women before the menopause or around the time of menopause (pre-menopausal or peri-menopausal), it should also be given in combination with a luteinising hormone-releasing hormone (LHRH) agonist (a medicine that lowers blood levels of the hormones oestrogen and progesterone).

Truqap contains the active substance capivasertib.

How is Truqap used?

Truqap can only be obtained with a prescription and treatment should be started by a doctor experienced in the use of cancer treatments.

Truqap is available as tablets to be taken twice a day, approximately 12 hours apart. The tablets are taken for four consecutive days, followed by three days with no treatment. Fulvestrant is given on days 1, 15 and 29, and once monthly thereafter.

Treatment with Truqap should continue for as long as the patient benefits from it; treatment may be stopped, or the dose reduced, if the patient has unacceptable side effects.

For more information about using Truqap, see the package leaflet or contact your doctor or pharmacist.

How does Truqap work?

The active substance in Truqap, capivasertib, blocks the activity of enzymes known as serine/threonine kinase (AKT) 1, 2 and 3. These enzymes play an important role in the growth and division of cancer

Medicine background

Serine/threonine kinase AKT: novel druggable target in HR+/HER2− breast cancer

Capivasertib is the first available AKT inhibitor for the **second-line treatment of unresectable or metastatic HR+/HER2− breast cancer** that has progressed following endocrine therapy (ET) (with or without a cyclin-dependent kinase CDK4/6 inhibitor)

Mode of Action

There is significant crosstalk between the estrogen receptor and AKT signalling pathways in breast cancer, where AKT activation is associated with endocrine therapy resistance.

Capivasertib plus fulvestrant targets the simultaneous inhibition of the ER and the AKT pathway and therefore aims to help address ET resistance and improve ET sensitivity.

	Overarching	Sub-populations		
Population	Estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer **with one or more PIK3CA/AKT1/PTEN-alterations** following recurrence or progression on or after an endocrine-based regimen **(with or without CDK4/6i)**.	Sub-population **with CDK4/6i**	Sub-population **without CDK4/6i**	Sub-population **with PIK3CA alteration (with or without CDK4/6i).**
Intervention	Oral capivasertib (at a dose of 400 mg twice daily for 4 days, followed by 3 days off) plus **fulvestrant** (500 mg, administered intramuscularly (IM) every 14 days for the first three injections and every 28 days thereafter)			
Comparison*	**Fulvestrant** 500 mg IM on Day 1, 15 and 29 and once monthly thereafter (**Overarching comparison**)	**Overarching** and Everolimus 10 mg + exemestane 25 mg once daily	**Overarching**	Alpelisib 300 mg orally once daily in combination with **Overarching** (in cases where a PIK3CA mutation has been detected)
Outcome	*Comparative measures of effectiveness and safety on subsequent slides*			

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*Chemotherapy has not been considered as a relevant competitor for this analysis

Questions for consideration

Population

Do the subgroups:

- Represent clinically meaningful subgroups with differential response?
- Describe the likely recipients of the intervention (epidemiological and clinical characteristics)?
- Specify eligibility criteria (e.g. diagnostic criteria or biomarkers needed for patient selection)?

Intervention

- Does the intervention description provide all relevant details needed for assessment?

Comparator

- Are the comparators used in routine Greek clinical practice for the same indication as the intervention?
- Are any comparators excluded?

Outcomes

- The classification of the measures that are under evaluation is based on internal expert analysis; due to time limitation consensus has not been obtained from a Delphi panel.
- The content in parentheses indicates whether data for these outcomes are available or not.
- *Outcomes* are quantified on a scale of 1 to 9, according to the GRADE methodology, in order to rank their importance.

Safety outcomes

Evaluation measures	Score*	Classification of importance of the measures*
Any adverse event (AE): Patients with ≥1 AE	6	Important (robust available data)
Grade ≥3 AEs	6	Important (robust available data)
Serious AEs (SAEs)	6	Important (robust available data)
AEs leading to discontinuation	6	Important (robust available data)
Dose interruptions/reductions: Temporary hold / dose change due to AEs	6	Important (robust available data)
Treatment-related deaths: Grade 5 AEs	9	Critical (available data but limited/immature)

Outcomes

Measures of effectiveness

Evaluation measures	Score*	Classification of importance of the measures*
PFS: was defined as the time from the date of randomization until the date of objective disease progression, as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression	8	Critical (robust available data)
OS: the length of time from randomization until the date of death due to any cause	9	Critical (available data but limited/immature)
PFS2: the time from randomization until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause	8	Critical (robust available data)
ORR: the percentage of patients with at least one complete response (CR) or partial response (PR) per RECIST v1.1 criteria, as assessed by the investigator at the local site	6	Important (robust available data)
Duration and onset of response: the time from the date of first documented response until date of documented progression or death in the absence of disease progression	6	Important (robust available data)

Measures of effectiveness continued

Evaluation measures	Score*	Classification of the importance of the measures*
Clinical benefit rate: the percentage of patients who have CR, PR or stable disease (SD) per RECIST v1.1 criteria (without subsequent cancer therapy) maintained ≥ 24 weeks after randomization	6	Important (available data but limited/immature)
Time to response (TTR): Time from randomisation to first CR/PR	6	Important (available data but limited/immature)
HRQoL: Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration	8	Critical (robust available data)
Plasma concentration of capivasertib: plasma concentration of capivasertib pre-dose and post-dose (C1h and C4h)	6	Important (no data available)
Time to definitive deterioration of the ECOG (Eastern Cooperative Oncology Group) performance	6	Important (no data available)
Time to first subsequent chemotherapy or death: time from randomization to the earlier of start date of subsequent chemotherapy after discontinuation of randomized treatment or death due to any cause	2	Low importance (available data)
Healthcare resource use	2	Low importance (no data available)

Questions for consideration

Do the outcome measures reflect the Greek context?

Consider:

- Feasibility for measurement
- Appropriateness of outcome rating/critical score

Next steps

- Review and provide amendments and feedback in writing (to be compiled by HTA Committee and submitted to HTD by 17 Nov)
- Upcoming trainings on clinical and economic assessments: 25 November, 14 January