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POINT OF VIEW

Implementing the EU HTA Regulation in Italy: a multi-stakeholder perspective from the Mogliano Veneto Working Group

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ABSTRACT

Regulation (EU) 2021/2282 on health technology assessment (HTA), hereafter the HTA Regulation (HTAR), entered into application on January 12, 2025, and has introduced a new framework for Joint Clinical Assessments (JCAs) and Joint Scientific Consultations (JSCs) at the European level. In Italy, this transition raises immediate methodological, organizational and relational questions for the Italian Medicines Agency (AIFA), health technology developers (HTDs), scientific societies, patient associations and civic organizations. This Point of View summarizes the perspective developed by Working Group 3 (WG3) during the 8th Edition of the Mogliano Veneto Seminars (25-26 September 2025), dedicated to the implementation of the HTAR in Italy. WG3 identified methodological heterogeneity in early assessment-scope definition, limited formal interaction between national stakeholders, and the absence of an operational national HTA scientific advice as the main practical issues emerging in the first phase of implementation. Five practical recommendations were developed: reactivation of National HTA Scientific Advice; more structured AIFA-HTD interaction in view of national pricing and reimbursement; better alignment between regulatory and HTA pathways from the start of the European Medicines Agency (EMA) procedure through the Member States (MS) scoping input to the assessment scope; capacity building and support for the participation of Italian scientific societies and patient associations in HTAR-related activities; and systematic use of European capacity-building opportunities. The recommendations do not imply legislative reform. Rather, they point to the need for coordinated implementation, clearer interfaces between European and national levels, and better use of existing institutional and scientific capacities.

Keywords: AIFA, Early dialog, HTAR, Italy, Joint Clinical Assessment, Joint Scientific Consultation, PICO, Pricing and reimbursement

Introduction

Regulation (EU) 2021/2282 on health technology assessment (HTA), hereafter the HTA Regulation (HTAR), entered into application on January 12, 2025 (1). The new framework rests mainly on two procedures. The first is the Joint Clinical Assessment (JCA), a mandatory comparative clinical assessment for medicinal products (MP) and selected medical devices within scope (1,2). The second is the Joint Scientific Consultation (JSC), a voluntary early-dialog mechanism intended to inform evidence generation from a joint regulatory and HTA perspective (1,3). For MP, the first phase of application concerns new active substances for the treatment of cancer and advanced therapy medicinal products, with later stepwise extension to orphan medicinal products and then to the remaining MPs in scope (1,4).

Since the entry into application of the HTAR, the HTA Coordination Group (HTACG) has issued a substantial body of procedural and methodological guidance covering scoping, dossier preparation, study validity, outcomes, reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analysis, and direct and indirect comparisons (5-12). This framework is robust. However,

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its operationalization across Member States (MS) remains a concrete challenge, especially in relation to the scoping phase, the definition of PICOs (Population, Intervention, Comparator, Outcome), and the interface between European clinical assessment and national appraisal.

At the time of the 8th Edition of the Mogliano Veneto Seminars, held on 25-26 September 2025, the first JCA procedures had already started, while the first JCA reports were still pending according to the standard procedural timeline (6,13). In Italy, this raised immediate questions on institutional preparedness, methodological alignment, stakeholder involvement, and the implications of JCA outputs for the subsequent national pricing and reimbursement (P&R) process. Against this backdrop, one of the four Working Groups of the Seminar, WG3, was dedicated to a structured discussion on HTAR implementation in Italy. This Point of View consolidates the analysis and recommendations developed by WG3, with the aim of contributing to the debate on HTAR operationalization.

Working group composition, scope and approach

WG3 was designed as a multi-stakeholder discussion focused on the most actionable dimensions of HTAR implementation in Italy (13). The group concentrated primarily on JCA because of its mandatory character, while also acknowledging the growing relevance of JSC as an early-dialog tool for evidence generation. The impact of HTAR on regional access pathways was deliberately excluded from the perimeter, as this dimension was considered not yet ready for concrete recommendations.

WG3 included 41 members - four coordinators and 37 participants - with the support of one Dephaforum facilitator (13). Based on primary affiliation, HTDs represented the largest component of the group (24/41; 58.5%), followed by academic, HTA and methodological experts (8/41; 19.5%); public institutional and regulatory representatives, including AIFA (3/41; 7.3%); clinicians and scientific society representatives, including the Italian Association of Medical Oncology (AIOM) and the Italian Federation of Internal Medicine Associations (FADOI) (3/41; 7.3%); patient associations and civic organizations, including Cittadinanzattiva and UNIAMO (2/41; 4.9%); and organizational support (1/41; 2.4%). While this composition was consistent with the practical purpose of the exercise—comparing stakeholder perspectives rather than conducting a formal consensus study—it was taken into account when interpreting the outputs (see the Limitation section). The working approach was pragmatic. Inputs were collected during the Seminar through structured thematic discussion and stakeholder experience-sharing, organized around the agreed perimeter of analysis. Inputs were not collected through a formal questionnaire, Delphi process or written survey, and no voting procedure was used to rank or prioritize recommendations. The coordinators structured the discussion, identified recurrent themes and drafted a synthesis of the main issues emerging across stakeholder groups. The Dephaforum facilitator supported the organization and moderation without acting as a scientific adjudicator. Where differences in perspective emerged, they were addressed through clarification and reformulation during plenary discussion. Recommendations were retained when they were recurrent across the discussion, actionable within the existing institutional framework, and coherent with the agreed scope of WG3 (13).

Stakeholder experiences after the entry into application of the HTAR

AIFA

Italy has been actively engaged in HTAR implementation since the preparatory phase. AIFA has contributed to EU-level HTA cooperation over many years, having participated in EUnetHTA Joint Actions 1, 2, and 3, in the EUnetHTA 21 consortium, and in the HTA Committee work supporting the development of the new European framework and its implementing acts. AIFA currently participates in HTACG subgroup activities and has established an internal HTAR Working Group aimed at ensuring technical-scientific coordination and a continuous information flow with the CSE (*Commissione Scientifica ed Economica del farmaco*, Scientific and Economic Commission). (13-15,27,28)

Within the HTACG framework, assessors (ASR) and co-assessors (Co-ASR) are appointed by the designated subgroup based on the expertise required for the procedure (16). At the time of the Mogliano Veneto Seminars, no ongoing JCA involved AIFA as ASR or Co-ASR. Against this background, AIFA's first appointment as ASR in a JSC in September 2025 represented an important step for the Italian agency (13). From this positioning, the agency has also reported relevant methodological heterogeneity across early ASR/Co-ASR pairs, particularly in relation to the definition and number of PICOs (13). This variability appears to be influenced not only by the proposed therapeutic indication and product complexity, but also by different working approaches, levels of experience, organizational cultures, and the interaction dynamics among MSs. During the scoping phase, in accordance with the dedicated scoping and procedural guidance, the Italian PICO requirements are first validated by the AIFA CSE, and then submitted at EU level through the PICO survey and considered in the PICO consolidation process, in which the ASR/Co-ASR prepare a consolidated assessment scope proposal reflecting MSs' needs (5,6,13). The way national scoping requirements are validated and transmitted is therefore central to the future national relevance of the EU assessment.

Health technology developers

HTDs reported an overall positive experience regarding the structured involvement of Italian affiliates by their corporate headquarters in HTAR-related activities. This involvement concerned internal company processes related to EU HTA preparedness, rather than structured interactions with AIFA (13). In the short to medium term, affiliates contribute to the PICO exercise and to JCA submission strategy; in the medium to long term, they also support the alignment of pivotal and supportive studies with emerging EU HTA requirements. This is particularly relevant in light of the JCA dossier

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structure and the increasing importance of comparative evidence generation (7).

The main gap identified by HTDs was the absence of an operational National HTA Scientific Advice (13). Early dialog was considered essential both to strengthen JCA preparedness and to improve coherence with the subsequent national P&R process. WG3 considered National HTA Scientific Advice most valuable before finalization of pivotal confirmatory trial protocols, while later interaction would mainly serve pre-JCA or pre-P&R alignment purposes. HTDs also underlined the importance of understanding how Italian national perspectives enter the scoping process, especially where national comparators and clinical practice may differ from the final European consolidated PICO set (17,18). From their perspective, greater predictability and earlier interaction would facilitate alignment between evidence generation, the European JCA dossier, and the subsequent Italian P&R dossier.

Patient associations and civic organizations

At the time of the Seminar, structured HTA-specific interaction between AIFA and patient or civic organizations was not yet in place (13). Some organizations, particularly those already represented at European level, had started preparatory activities, including training and conflict-of-interest management. This is relevant because stakeholder participation under HTAR is subject to dedicated procedural rules and cannot be reduced to generic consultation (3,19).

WG3 considered the experience of the Stakeholder Network within the National HTA Program for Medical Devices as a useful national reference for future development (20).

Scientific societies

WG3 also discussed the potential contribution of scientific societies, using AIOM as a relevant example (13). AIOM expressed availability to collaborate with AIFA in the event of formal involvement, although no structured interaction was in place at the time of the Seminar. Scientific societies were recognized as a readily available source of clinical and methodological expertise through guideline panels, educational initiatives and thematic working groups.

This role appears particularly relevant in therapeutic areas in which standard of care is evolving, comparators are multiple, and clinical practice patterns differ across settings. In the Italian context, scientific societies contributing to the National Guideline System may provide timely and scientifically qualified input to scoping and to broader HTAR preparedness (21).

Operationalizing stakeholder involvement in Italy

Meaningful participation of scientific societies, patient associations and civic organizations in HTAR-related activities requires a clearer distinction between their potential roles. Scientific societies could contribute primarily by providing disease-specific and methodological input on the clinical pathway, current standards of care, relevant comparators, clinically meaningful subpopulations, outcome relevance and the plausibility of evidence gaps.

Patient associations and civic organizations would be expected to contribute from a different perspective. Their role would not be to define clinical comparators or assess relative effectiveness, but to provide structured input on disease burden, patient-relevant outcomes, treatment acceptability, administration and monitoring burden, quality-of-life implications, and practical barriers to access or use.

The minimum level of preparedness required for both types of stakeholders includes familiarity with the HTAR process, the distinction between European clinical assessment and national appraisal, the logic of scoping, the interpretation of comparative evidence, confidentiality requirements, and conflict-of-interest rules.

In Italy, the main practical barriers are the absence, at the time of the Seminar, of a structured HTAR-specific national interaction pathway with AIFA; uneven familiarity with EU HTA procedures across stakeholder groups; limited methodological capacity outside specialized networks; and the need to ensure eligibility, transparency and conflict-of-interest compliance for participation in European processes. AIFA's institutional configuration also differs from agencies primarily dedicated to HTA, because it combines regulatory, scientific and pricing and reimbursement functions. This partly explains why a dedicated national route for HTAR-focused stakeholder interaction had not yet been formalized.

In practical terms, WG3 considered that participation could be operationalized through a national preparedness pathway coordinated with AIFA's HTAR activities. This could include mapping of eligible scientific and patient expertise, targeted training, standardized templates for rapid input, conflict-of-interest pre-checks, and disease-specific rapid consultation panels activated when national input is needed for scoping or review.

Recommendations of the working group

Drawing on the analysis perimeter and the stakeholder experiences, WG3 identified five practical recommendations to support HTAR implementation in Italy (Table 1) (13).

To strengthen their practical value, the recommendations are presented in terms of four implementation dimensions: governance, institutional ownership, timing of applicability, and feasibility. In this Point of View, "ownership" indicates the most appropriate institutional locus for implementation within the current Italian framework, rather than a formal legal attribution of responsibility.

First, WG3 considered the reactivation of National HTA Scientific Advice as a priority. Governance would naturally sit within AIFA, with coordination between scientific advice functions, HTA-related structures and, where relevant, the CSE. The most appropriate timing would be before finalization of pivotal confirmatory trial protocols, when choices on comparators, endpoints, subpopulations and evidence-generation strategy remain modifiable. Feasibility is supported by AIFA's previous experience with early dialog and by the 2025 reorganization, but would require clear procedures, timelines, templates and resources (17,18,22,23).

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TABLE 1 - WG3 Recommendations for the implementation of the HTAR in Italy

#	Recommendation	Rationale and key actions
1	Reactivation of the National HTA Scientific Advice (early dialog AIFA-HTDs)	Provide national early-dialog input before finalization of pivotal confirmatory trial protocols; clarify Italian comparator relevance, outcome priorities and evidence-generation expectations; enhance visibility within corporate headquarters' decision-making; complement, not duplicate, the European JSC.
2	Structured AIFA-HTD interaction in view of national pricing and reimbursement	Support continuity between the JCA report and the national P&R Dossier; clarify national contextual evidence needs while preserving confidentiality of the MSs' scoping input and avoiding duplication of the European clinical assessment.
3	Alignment between the regulatory and HTA pathways	Coordinate the EMA therapeutic indication wording with the JCA assessment needs to minimize divergence between the two assessment levels.
4	Capacity building and support of Italian Scientific Societies and Patient Associations in the HTACG Stakeholder Network	Strengthen the technical-methodological preparedness; map eligible clinical, patient and civic expertise; support transparency and conflict-of-interest readiness; establish rapid consultation pathways for scoping and review input; exploit the upcoming Italian ESMO presidency as a window of opportunity.
5	Leveraging the EU Capacity Building project	Design specific training activities for AIFA, Scientific Societies, Patient Associations and Civic Organizations to support informed participation in the HTAR.

AIFA, Italian Medicines Agency; ESMO, European Society for Medical Oncology; EMA, European Medicines Agency; HTAR, EU HTA Regulation; HTD, Health Technology Developer; JCA, Joint Clinical Assessment; JSC, Joint Scientific Consultation; HTACG, HTA Coordination Group; MS, Member State; P&R, Pricing and Reimbursement; PICO, Population, Intervention, Comparator, Outcome.

Second, WG3 recommended more structured AIFA-HTD interaction in view of the subsequent national P&R process (13). HTDs emphasized the value of understanding how the Italian system approaches the definition of national scoping requirements and how this may influence later national appraisal. This need is reinforced by the architecture of the Regulation itself. Under Article 13 of Regulation (EU) 2021/2282, when carrying out a national assessment of an MP for which a JCA report has been published, MSs must give due consideration to that report and may not request at national level the clinical information, data and analyzes already submitted by the developer for the joint assessment. National appraisal is therefore expected to build on the European clinical assessment rather than to reproduce it. A more predictable AIFA-HTD interaction could support methodological continuity between European assessment and the Italian P&R dossier, while preserving the confidentiality of MS scoping output (1,2). For clarity, WG3 distinguished this downstream interaction from both the European JSC and National HTA Scientific Advice: whereas these are early-dialog tools supporting evidence generation, AIFA-HTD interaction in view of a national P&R would occur later, closer to national submission, and would support alignment between the JCA report, the Italian P&R dossier and national contextual evidence needs. Its purpose would not be to reopen the JCA or anticipate price negotiation, but to support an efficient and non-duplicative national process.

Third, WG3 recommended better alignment between the regulatory and HTA pathways from the start of the EMA procedure through the EU scoping process, as the proposed therapeutic indication helps shape the subsequent JCA scope (13). Governance would require coordination between HTD regulatory and HTA functions, with AIFA regulatory, HTA and scientific advice interfaces contributing where appropriate. Its feasibility depends mainly on earlier cross-functional planning and timely dialog rather than on new legislation. The objective is not to blur the distinction between regulatory benefit-risk evaluation and HTA comparative assessment, but to reduce avoidable divergence where evidence packages must support both regulatory approval and later HTA use.

Fourth, WG3 recommended targeted capacity building and structured preparedness for Italian scientific societies, patient associations and civic organizations, with the aim of supporting qualified participation in HTAR-related activities (13). This includes methodological training, awareness of transparency and conflict-of-interest requirements, mapping of eligible expertise and national coordination mechanisms able to provide timely input when scoping and review activities require clinical, patient or civic perspective. Although oncology was discussed as an immediate example because of the availability of organized scientific expertise and the upcoming Italian presidency of the European Society for Medical Oncology (ESMO), the recommendation applies more broadly across clinical areas.

Fifth, WG3 recommended a more systematic use of European capacity-building opportunities and stakeholder-oriented information activities (13,24). This recommendation would require shared ownership across AIFA, scientific societies, patient organizations and civic actors. Its timing is immediate and continuous, because capacity should be built before case-specific procedures arise. Feasibility is high if existing EU-level initiatives are translated into targeted national training activities.

Figure 1 represents the multi-stakeholder framework discussed by WG3.

Discussion

The recommendations developed by WG3 suggest that the main Italian challenge in HTAR implementation is practical

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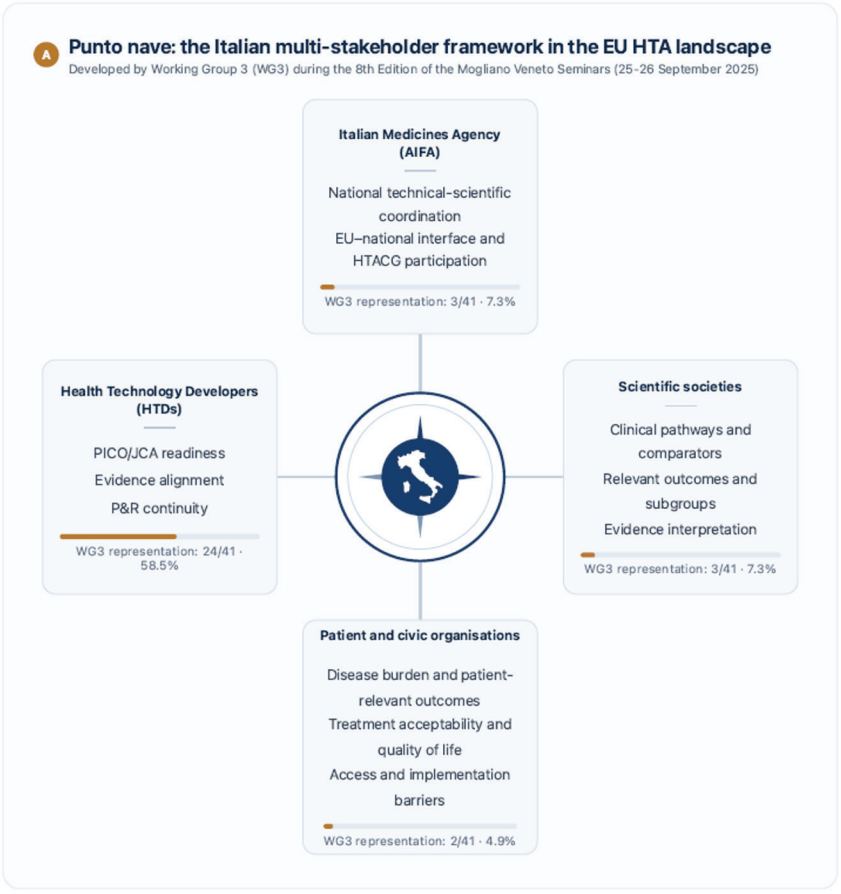




FIGURE 1 - "Punto nave": orienting Italian stakeholders in the EU HTAR.
Figure 1 uses the maritime metaphor of the punto nave to represent the multi-stakeholder framework discussed by WG3. Italy is placed at the center of the EU HTA landscape, with AIFA, scientific societies, patient and civic organizations, and HTDs positioned as the main constituencies involved. Bars show WG3 composition by primary affiliation (n = 41). Academic, HTA and methodological experts (8/41; 19.5%) and organisational support (1/41; 2.4%) are not shown as constituencies. The lower panel summarizes the five WG3 recommendations: National HTA Scientific Advice, structured AIFA-HTD interaction, regulatory-HTA alignment, stakeholder capacity building, and systematic use of EU capacity-building opportunities.
Abbreviations: AIFA, Italian Medicines Agency; EMA, European Medicines Agency; EU,European Union; HTA, Health Technology Assessment; HTACG, HTA Coordination Group; HTAR, Regulation (EU) 2021/2282 on health technology assessment; HTD, health technology developer; JCA, Joint Clinical Assessment; JSC, Joint Scientific Consultation; MS, MemberState; P&R, Pricing and Reimbursement; PICO, Population, Intervention, Comparator, Outcome; WG, Working Group.

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rather than legislative. The national system already includes relevant institutional, scientific and civic resources, but these need to be activated through clearer interfaces, stronger coordination and more structured interaction (13).

A central issue emerging from the first months of implementation is methodological heterogeneity in PICO definition. Part of this variability is inherent to a multi-Member-State process, reflecting differences in standards of care, comparator relevance and national policy questions (5); part also depends on the working methods and experience of ASR/Co-ASR pairs and on the practical dynamics of consolidation. For Italy, this means that methodological convergence cannot be assumed merely because guidance documents exist. It requires training, exchange of practices and stronger national preparedness to formulate timely and robust inputs (5,6,8-12).

Another cross-cutting issue concerns early dialog in the Italian HTA pathway (25,26). WG3 deliberately used the term reactivation of National HTA Scientific Advice rather than creation *de novo*. This wording rests on two complementary elements. AIFA had previously operated National Scientific Advice activities, which were later suspended, as documented in AIFA's 2020 Performance Report (23). In parallel, AIFA had accumulated substantial HTA-related early-dialog experience at European level: between July 2010 and December 31, 2015, 63 parallel scientific advice procedures involving HTA bodies were completed, with AIFA's HTA team participating in 22 of them (22). Reactivation also appears institutionally feasible in light of AIFA's 2025 reorganization, which included an Office for Innovation and Scientific Advice responsible for national and European Scientific Advice procedures (14). The same reorganization also established an AIFA European HTA Procedures Office within the Access to Medicines and HTA Area, specifically involved in HTACG subgroup work, JCA documentation, national activities related to the use of JCA reports, and participation in JSC activities (29).

The rationale for reactivation is both practical and strategic: the absence of an operational national HTA early-dialog pathway creates a gap between European-level methodological requirements and the national appraisal needs, at the time when choices on population, comparators, outcomes and evidence generation need to be addressed earlier and in a more structured way to support both JCA and subsequent national decision-making. In this context, the European JSC is highly valuable, particularly when run in parallel with EMA Scientific Advice (17,18); its capacity is, however, structurally limited. The HTACG Annual Work Program for 2025 planned only 5-7 JSCs for MPs, with a selection process when eligible requests exceed the number of consultations planned (17,24). A complementary National HTA Scientific Advice would therefore not duplicate the European mechanism, but would provide an additional national interface for context-specific issues, particularly Italian comparator relevance, assessment-scope preparedness and downstream P&R expectations.

A third issue concerns stakeholder preparedness. The HTAR framework creates opportunities for patients, clinical experts and stakeholder organizations to provide input during scoping and review activities, but meaningful participation requires more than formal inclusion. The Italian experience of the Stakeholder Network within the National HTA Program for Medical Devices offers a useful reference, although MPs under HTAR require a dedicated model aligned with the JCA timelines and EU procedural constraints (20).

Several limitations should be acknowledged. First, the reflections summarized here derive from an early phase of HTAR implementation, when operational experience was still limited, and the first JCA reports were not yet available (6,13). Second, the analysis focuses on MPs and on JCA/JSC procedures; medical devices, *in vitro* diagnostics and regional access implications require separate assessment. Third, the recommendations emerged from a structured multi-stakeholder discussion and were not generated through a formal consensus methodology (13). Fourth, stakeholder representation within WG3 was uneven: HTDs represented the largest component of the group, which may have increased the granularity of developer-facing issues, while numerically smaller patient and civic organizations and scientific societies may have limited the depth of these perspectives. Accordingly, the recommendations should be interpreted as a technical multi-stakeholder Point of View, not as a quantitatively representative consensus of all Italian HTA stakeholders.

Conclusions

The first months of HTAR application in Italy have already generated a sufficiently concrete experience to identify priorities. WG3 converged on a clear message: the most valuable investment now lies in activating existing constituencies, valorizing available expertise, and structuring spaces for constructive interaction. Italy has the institutional and scientific basis to play a visible role in the European HTA framework; turning this potential into practice is now a matter of coordinated implementation rather than regulatory reform (13).

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