Joint Clinical Assessments

An Update after the European Parliament's September 2018 Meeting

Are Joint Clinical Assessments (JCAs) just another hurdle or will they help ensure patient access across the EU?

Original EU HTA Directive (January 2018)

On 31 January 2018, the EU Commission outlined the plan for an EU HTA structure, an essential part of which is Joint Clinical Assessments, which include pharmaceuticals, medical devices, and diagnostics where clinical benefits are compared to existing treatments. This covers all EMA approved pharmaceuticals (including line extensions/ new indications) as well as high-risk devices with high impact on patients, public health, and EU health systems.

The Four Areas of Joint HTA Cooperation

Joint Clinical Assessments	Mapping of emerging health technologies
Scientific consultations on the development of new products	Voluntary cooperation on other areas (e.g., surgical procedures)

National assessments include non-clinical assessment (economic, social, and ethical aspects) and national decisions on price and reimbursement. While the regulatory and HTA processes will remain separated as they have different purposes, opportunities exist to create synergies through mutual information sharing and better alignment of the timing between the proposed JCAs and the centralised marketing authorisation.

Main changes to the Directive announced in September 2018

Initial Directive[1]

Member states shall not carry out a clinical assessment or an equivalent assessment process on a health technology included in the List of Assessed Health Technologies.

European Parliament Changes[2]

- According to national needs, Member States should have the right to complement the Joint Clinical Assessments with additional clinical evidence and analyses to account for differences in comparators or the national specific treatment setting. Such complementary clinical assessments should be duly justified and proportionate and should be communicated to the Commission and the Coordination Group.
- After the transitional period, and before the harmonised system for HTA established under this Regulation becomes PPD mandatory, the Commission should submit an impact assessment report on the entire procedure that has been introduced.

U.S. +1 301 654 9729 EUR +44 (0) 208 576 5000 info@evidera.com www.evidera.com

That impact assessment report should evaluate, among other criteria:

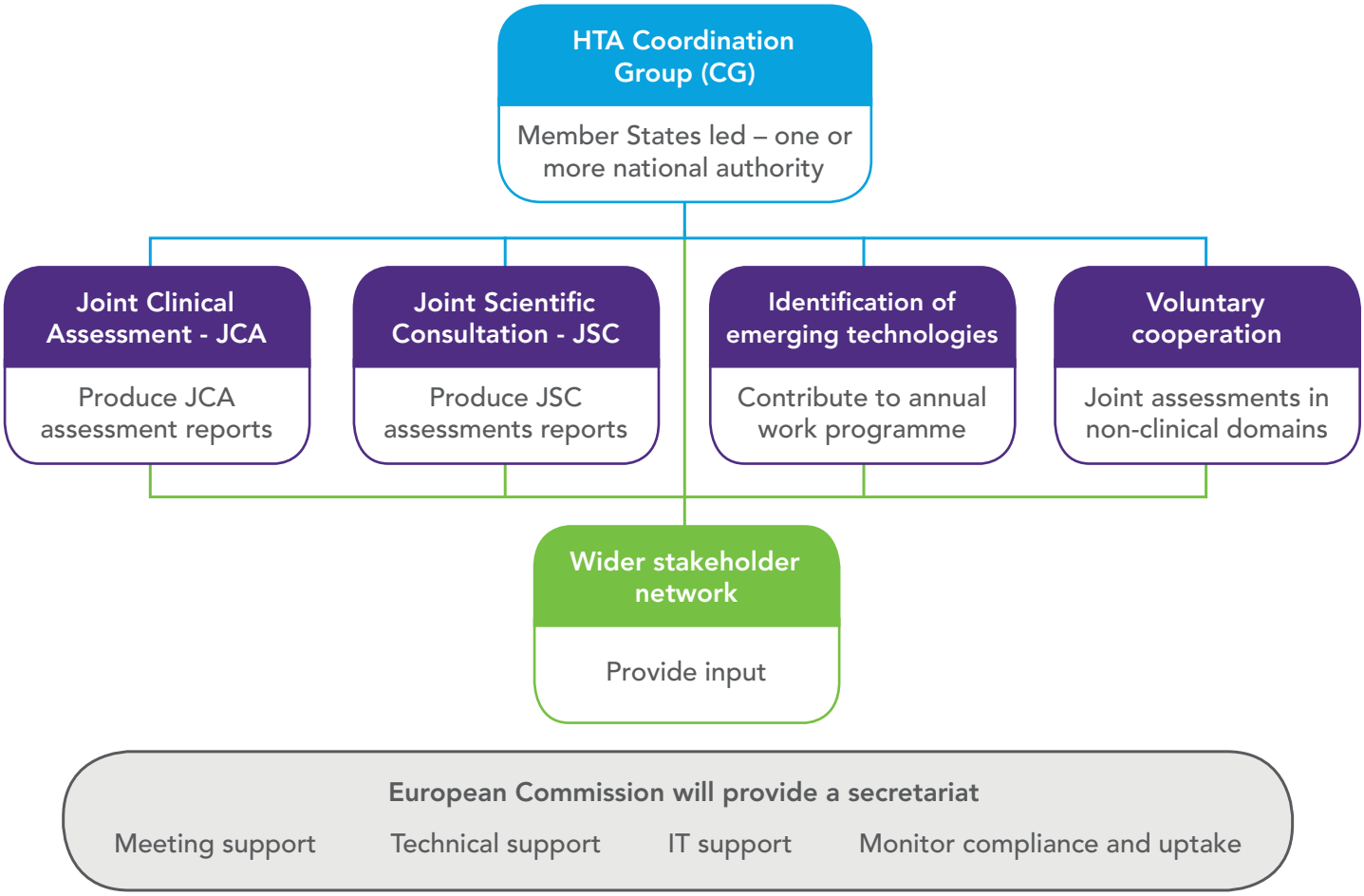
- the progress made in relation to patients' access to new health technologies and the functioning of the internal market
- the impact on the quality of innovation and on the sustainability of health systems
- the appropriateness of the scope of the Joint Clinical Assessments and the functioning of the support framework

Questions

- Will JCAs be in addition to national assessments?
- If both JCAs and national assessments are done, will this delay the access process? Is this a new hurdle to patient access?

Key elements of the new Directive and European Parliament additions

New Structure to Deliver on the Four Areas of Joint Cooperation[1]



HTA Coordination Group (CG)

The CG is led by Member States and may include one or more national authority from national or regional levels.

Roles include:

- **Managing the overall governance** of the joint cooperation
- **Developing overall work programme** including identification of emerging health technologies and setting up the timeframe of JCAs at the time of product's market launch
- **Providing "early dialogues"** with manufacturers, if requested (joint scientific consultation)
- **Conducting updates of JCAs** where: (a) the decision to grant the marketing authorisation of a product was conditional on the fulfilment of additional post-authorisation requirements; (b) the initial JCA report specified the need for an update once additional evidence for further assessment is available. The CG may carry out updates of JCAs where requested by one or more of its members.

Requirements for the Submission Dossier

- For medicinal products, the documentation must at least include:
  - the submission file
  - an indication of the marketing authorisation status
  - if available, the European public assessment report (EPAR), including the Summary of Product Characteristics (SPC); the European Medicines Agency (EMA) shall provide the relevant adopted scientific assessment reports to the CG
  - where applicable, the results of additional studies requested by the CG and available to the health technology developer
  - where applicable and if available to the health technology developer, already available HTA reports on the health technology being assessed
  - information on studies and study registries available to the health technology developer
- Health technology developers shall be obligated to submit all of the requested data
- Assessors may also access public databases and sources of clinical information, such as patient registries, databases, or European Reference Networks, where such access is deemed necessary to complement the information provided by the developer and to perform a more accurate clinical assessment of the health technology. The reproducibility of the assessment implies that such information shall be made public.
- The relationship between evaluators and health technology developers shall be independent and impartial. Developers of health technologies may be consulted but shall not actively participate in the evaluation process.

Rules of Engagement

- The Commission should endorse, by means of implementing acts, the methodology and a common procedural framework for Joint Clinical Assessments and Joint Scientific Consultations
- Where appropriate, and in justified cases, distinct rules should be developed for medicinal products and medical devices
- **Prominence to EUnetHTA methods!** The development of the rules should take into account the results of work already undertaken in the EUnetHTA Joint Actions, including:
  - methodological guidelines and evidence submission templates
  - initiatives on HTAs funded through the Horizon 2020 research programme
  - regional initiatives on HTAs, such as the Beneluxa and Valletta Declaration

- The Commission should establish a system of charges for health technology developers requesting both Joint Scientific Consultations and Joint Clinical Assessments for research on unmet medical needs.
- Since there is currently no commonly **agreed definition of what constitutes high-quality innovation or added therapeutic value**, the EU should adopt definitions of these terms with the agreement of all parties.

Methods

Endpoints

- Assessment of health benefits should primarily consider clinically meaningful endpoints, such as mortality, morbidity, safety, and quality of life
- Surrogate endpoints should only be used if adequately validated
- Both relative and absolute measures should be presented, including uncertainty measures
- Composite endpoints should only be used if a single primary endpoint is not available or if a composite endpoint can be justified to be more suitable (e.g., rare disease/event); components should be limited
  - ⚠ Acceptability of endpoints is expected to be controversial
- HRQL endpoints are considered "important", but guidelines differentiate between their use for clinical versus reimbursement decisions
  - For clinical decisions, the use of disease-specific instruments is recommended, and required confimation that all domains affected by the disease or standard intervention are coverd by the disease-specific HRQL instrument
  - ⚠ Guidelines note that improvement of HRQL is highly subjective and does not necessarily correlate with more objective outcomes (e.g., survival, morbidity); therefore, their role in Joint Clinical Assessments may be limited

Evidence

- Methods should be based on "the best available scientific evidence" stemming primarily from double-blind RCTs, meta-analysis, and systematic reviews
- It is recommended that checklists suitable to assess risk of bias be used in non-randomised studies conducted to evaluate the effects of an intervention
  - ⚠ The role of observational data in the assessment is not clearly defined, but it likely will receive very little weight

Comparators

- The acceptable definition of the relevant comparator: "current routine care in the individual health care system, the most used, or what would be replaced by the introduction of that new health technology"
  - ⚠ Differences in clinical practice and local guidelines means that the actual choice of comparator in different countries will vary – even if the same definitions and selection criteria are used

Indirect Treatment Comparisons (ITC)

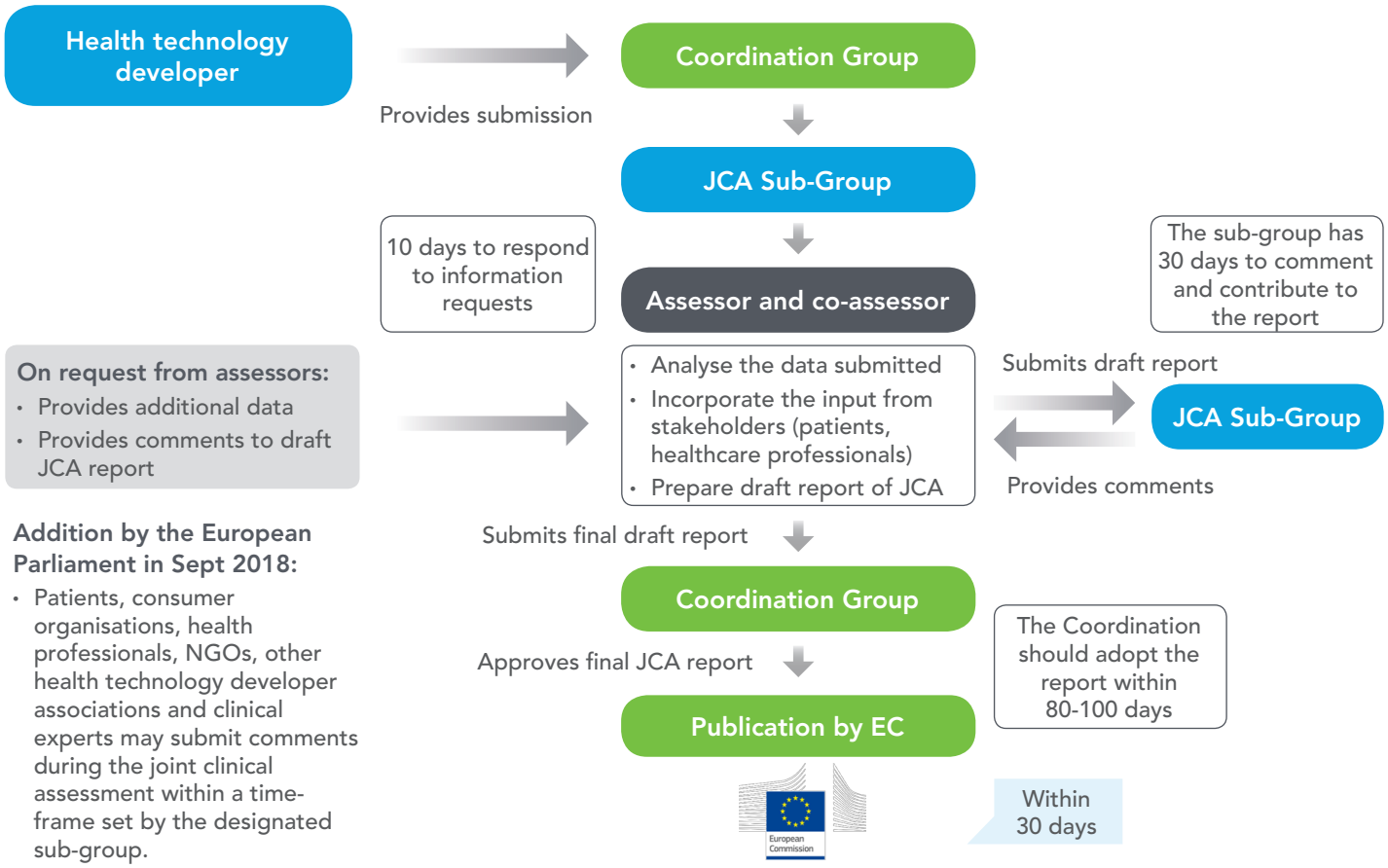
- The role of ITCs incorporating direct evidence are recognized in the EUnetHTA Guidelines
- Bucher's method of adjusted indirect comparison is preferred over Bayesian mixed treatment comparison (MTC)
- Unadjusted indirect comparisons are not recommended
  - ⚠ This is likely a source of debate across countries given the different attitudes towards Bayesian MTCs (e.g., NICE versus IQWiG)

Joint Clinical Assessment Reports[2]

JCA reports should be comprehensive as outlined by the European Parliament. Each report should:

- be accompanied by a summary report, ***which shall contain at least the clinical data compared, the end-points, the comparators, the methodology, the clinical evidence used, and conclusions as regards efficacy, safety, and relative efficacy, the limits of the assessment, diverging views, a summary of the consultations carried out, and the observations made***
- be prepared in accordance with the requirements laid down by the Coordination Group and shall be made public, regardless of the report´s conclusions
- include an ***analysis of the relative effectiveness and safety of the health technology being assessed in terms of the clinical end-points relevant to the clinical entity and patient group chosen for the assessment, including mortality, morbidity and quality of life, and compared to one or more comparator treatments to be determined by the Coordination Group***
- include the degree of certainty on the relative effects based on ***the best available clinical evidence and compared to the best standard therapies. The assessment shall be based on the clinical end-points established in accordance with international standards of evidence-based medicine, in particular with regard to improving the state of health, shortening the duration of the disease, prolonging survival, reducing side effects, or improving the quality of life. Reference shall also be made to subgroup-specific differences.***

Preparation of JCA Reports[3]



Submission Requirements and Suggested Process

- JCAs should aim to identify the added therapeutic value of new or existing health technologies in comparison with other new or existing health technologies by undertaking a comparative assessment based on comparative trials against the current best proven intervention ("standard treatment") or against the current most common treatment where no such standard treatment exists.
- A system of charges should be identified for health technology developers requesting both Joint Scientific Consultations and Joint Clinical Assessments for research on unmet medical needs.
- The sub-group shall appoint, from among its members, an assessor and a co-assessor to conduct the JCA, taking into account the scientific expertise necessary for the assessment.
- With respect to medicinal products, the Coordination Group shall initiate JCAs in accordance with the EMA pre-notification of medicinal products prior to marketing authorisation applications.
- JCAs for medical devices should take into account the highly decentralised market access pathway for medical devices and the availability of appropriate evidence data required to carry out a JCA when establishing a timeframe. In order to allow for the selection of devices for JCAs at an appropriate time, assessments for devices should be allowed to occur following market launch since required evidence may only be available after a device is on the market.
- In vitro diagnostic medical devices for JCAs will be selected by the CG based on cumulative criteria; should be a major innovation with potential significant impact on national health care systems; should have voluntary submission by the health technology developer; and, identification by the stakeholder network will also be considered.

Scientific Advice

Objectives: Clarified and Expanded

- Joint Scientific Consultations should focus on ***clinical aspects for optimal design of scientific studies and research to: improve predictability, align research priorities, and enhance the quality and efficiency of research to obtain the best evidence.***
- Evidence to be submitted for scientific consultation has been outlined, ***including available and up-to-date documentation containing all stages of information processing, and data and studies necessary for the joint scientific consultation, such as available data from all tests performed and all the studies in which the technology was used.***

Specific Pathway for Orphan Drugs

- Joint Scientific Consultations specific to orphan medicinal products have to ensure that any new approach should not result in unnecessary delays for the product's assessment compared to the current situation, and should take into account the pragmatic approach undergone through the EUnetHTA.
- A tailored clinical assessment pathway may be developed for orphan medicinal products due to the limited number of patients enrolled in clinical trials and/or the lack of a comparator.

Transparency

- The designated sub-group shall ensure that stakeholders (including patients, consumers, and clinical experts) are given an opportunity to provide comments during the preparation of the draft joint scientific consultation report and set a timeframe in which they may submit comments.
- Scientific consultation is open to the public to ensure the consultation does not give rise to any conflicts of interest.
- Any declarations of conflicts of interest of consulted stakeholders shall be publicly available.
- Consultations shall be documented, including publicly available declarations of interest from stakeholders, and included in the final joint assessment report.
- Any information made public about the results of Joint Scientific Consultations must be presented in an anonymised format with the redaction of any information of a commercially sensitive nature. ***It should be clarified that the provisions concerning protection of confidential information do not prevent, in any way, public disclosure of Joint Scientific Consultations being evaluated.***
- ***The clinical data employed, the studies, the methodology, and the clinical results used should be made public. The highest possible level of public openness in scientific data and assessments should facilitate progress in biomedical research and ensure the highest possible level of confidence in the system.***

Scientific Advice Report

1. The scientific consultation reports shall be prepared in accordance with the requirements laid down by the Coordination Group and shall be made public, regardless of the report´s conclusions.
2. The Coordination Group shall, no later than 100 days following the start of the preparation of the JCA report, approve the final joint scientific consultation report. Consensus should be achieved whenever possible; if consensus is not reached, a two-thirds majority of Member States is required (the quorum for CG meetings).
3. The subject and the summarised substance of the consultations shall be published on the IT platform.
4. All comments, which shall be public and answered when required, shall be published on the IT platform, following finalisation of the JCA. The published comments shall include stakeholders comments and any differences of opinion expressed by members of the sub-group in the course of the procedure.
5. The joint assessment report should include a summary of the consultations carried out.

What is Known and Unknown about Joint Clinical Assessments as of September 2018

Known

- Joint Clinical Assessments will be implemented, but Member States can carry out clinical assessments where justified and needed
- Price and reimbursement will remain the responsibility of each Member State
- Methods used in these assessments should align with the EUnetHTA Core Model and methods

Unknown

- How will this process delay patient access?
- What is the exact relationship with the EMA?
- What is the benefit of Joint Clinical Assessments if Member States can carry out their own assessments?
- What will be the role of local networks, such as La Valetta, FINOSE, and BENELUXIRA?
- How will EUnetHTA methods be exactly taken into account and would they require updates?
- What will the definition for added therapeutic benefit look like?

1 https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51final_en.pdf
2 http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A8-2018-0289&format=XML&language=EN
3 https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/ev_20180209_co01_en.pdf