



eunethta

**EUnetHTA JA2
WP7 DELIVERABLE**

**Consolidated Procedure
For Early Dialogues
(Drug and Non-Drug)**



The EUnetHTA JA 2 (2012-2015) has received funding from the European Union, in the framework of the Health Programme



Joint Action on HTA 2012-2015

Consolidated Procedure for Early Dialogues

(Drug and Non-Drug)

December 2015

Was developed by Work Package 7 – Methodology development and evidence generation: Guidelines and pilots production

WP 7 Lead Partner: HAS



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Procedure for EUnetHTA Early Dialogue Pilots

Final Version – November 2015

This consolidated procedure on early dialogues is a deliverable of
EUnetHTA Joint Action 2 Work Package 7 Subgroup 1

EUnetHTA JA2 Partnership for the Early Dialogue (ED) Activity

Coordinator (Lead Partner), Associated and Collaborating Partners, and Stakeholders

ED coordinator (Lead Partner)¹:

Country	Organisation (including department)
France	French National Authority for Health, HAS (International Affairs Unit)

Associated Partners (organisations nominated by Ministry of Health to participate in JA2):

Country	Organisation	Type of ED
France	French National Authority for Health, HAS	Drug and non-drug
Austria	Association of Austrian Social Insurance Institutions, HVB	Drug
Belgium	Belgian Health Care Knowledge Center, KCE	Drug and non-drug
Germany	Institute for Quality and Efficiency in Health Care, IQWiG	Drug and non-drug
Hungary	National Institute for Quality- and Organizational Development in Healthcare and Medicines, GYEMSZI	Drug
Italy	Agenzia Nazionale per i Servizi Sanitari Regionali, AGENAS	Non-drug
Italy	Italian Medicines Agency, AIFA	Drug
Italy	Regional Agency for Health and Social Care, ASSR	Drug and non-drug

¹ The HAS coordinating team, working within the International Affairs Unit, was distinct from the HAS technical and scientific staff that provided advice in the early dialogue pilots. Only the technical and scientific departments at HAS could act on its behalf, as a participating HTA body. The coordinating team included a senior scientific coordinator who oversaw the procedure and chaired the meetings, a senior scientific officer, a project manager and an administrative assistant.

Netherlands	National Health Care Institute, ZIN	Drugs
Spain	Instituto de Salud Carlos III, ISCIII	Non-drug
United Kingdom	National Institute for Health and Care Excellence, NICE	Drug and non-drug

Collaborating Partners:

Country	Organisation	Type of ED
Belgium	Rijksinstituut voor Ziekten Invaliditeitsverzekering, RIZIV-INAMI	Drug
Germany	Gemeinsamer Bundesausschuss, G-BA	Drug and non-drug
Spain	Galician Agency for HTA Assessment, AVALIA-t	Drug and non-drug
Spain	The Andalusian Agency for Health Technology Assessment, AETSA	Drug
Sweden	Dental and Pharmaceutical Benefits Agency, TLV	Drug

Involvement of other institutions and stakeholders:

Country	Stakeholder	Type of ED
Belgium	European Commission, DG Sante representatives (observer only)	Drug
United Kingdom	European Medicine Agency, EMA representative (observer only)	Drug
Canada	Canadian Agency For Drugs and Technologies in Health, CADTH representative (observer only)	Drug
France	External Expert	Drug
France	European Organisation for Rare Diseases, EURORDIS, Patient organisation	Drug
France	Patient	Non-drug
Poland	Patient	Drug
Netherlands	Patient	Non-drug

Early dialogue (ED) pilots within EUnetHTA JA2 are part of the deliverables of work package 7, dedicated to methodology development and evidence generation and particularly improvement of the quality and adequacy of data produced for REAs.

The first draft procedure was drawn up by HAS during EUnetHTA JA1 and included basic information needed to conduct two preparatory early dialogue pilots for drugs. These 2 ED took place in the summer of 2012 (June and July) with the participation of health technology developers and a number of HTA agencies. Based on the preliminary work undertaken within EUnetHTA JA1 WP5, the draft procedure was amended following the collection of feedback from participating agencies. During EUnetHTA JA2, eleven ED pilots were conducted (9 on drugs and 2 on medical devices) between December 2012 and September 2015 with the participation of developers, HTA agencies and a single EMA representative as observer.

As part of EUnetHTA JA2 WP7 SG1 deliverables, a survey on early dialogue drug pilots was completed during the 4th quarter of 2013. Survey participants included 11 HTA agencies, 1 EMA representative and 8 developers, all having participated in at least one of the drug early dialogues. In accordance with the workplan, the results of the survey were presented and discussed with HTA agencies during the course of a WP7 face to face meeting (2nd FTF in January 2014). The procedure for EUnetHTA early dialogues was further amended on the basis of the survey responses and feedback received during and following the face to face meeting.

Additional amendments were made and validated during the 3rd WP7 F2F in November 2014 following completion of the SEED project (Shaping European Early Dialogues) and the last 2 EUnetHTA ED pilots conducted in medical devices (April and September 2015).

1. Scope of European multi-HTA Early Dialogues

The goal of this EUnetHTA activity is to pilot a mechanism for HTA body assessors in Europe and **companies developing health technologies**, seeking marketing and reimbursement access in European markets, to exchange their views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics) and non-drug technologies (i.e., medical devices, diagnostics and procedures). The overarching goal is to improve the quality and adequacy of initial evidence generation in order to facilitate the HTA process and support coverage decisions.

Taking into account the national and regional reimbursement differences that exist in Europe, a multi-HTA early dialogue with European HTA bodies allows input from HTA bodies on the clinical development programme of a new technology). The premise being that this drug or non-drug technology is expected to result in added health benefits, for patients affected by a given health condition, when compared to existing methods (standard of care). Technology co-developments, such as drug-diagnostic combinations, may also be considered for early dialogues; however products carrying no innovative component are out of scope (e.g. generics and biosimilar products).

Furthermore, an early dialogue is prospective in nature and focuses on development strategies and not on data pre-assessment. Therefore the advice cannot be provided for on-going pivotal trials. An ED can only be requested during the initial clinical development phase for a given technology. For drugs, it should ideally be requested during the phase II to discuss the content of the planned Phase III (i.e. planned confirmatory

trials) and economic rationale. The scope of early dialogues may be broadened in the future (EUnetHTA JA3) to include consideration on post launch studies.

The company is free to choose areas of interest with regards to the development plan for further discussion during the early dialogue face to face meeting. However, early dialogues are restricted to one indication; but one or more lines of treatment may be discussed within a same indication. Company questions should be related to HTA objectives and pertain mainly to relative effectiveness, economic aspects and other areas relevant for technology reimbursement by a national/regional health care system.

Representatives of HTA bodies give advice on the basis of the planned studies and scientific knowledge provided in the documentation file submitted by the developer. Company requests to modify the file (see briefing book templates in Annex 1 for pharmaceuticals and Annex 2 for devices) and/or questions once the procedure has commenced are generally not accepted. However, modifications that may have a major impact on the drug development and meeting discussion (trial design, intended indication, safety issues, etc.) should be brought to the coordinator's attention as soon as possible.

The HTA agencies reserve the right to not respond to any last minutes changes in the health technology development.

Confidential and non-binding, the advice does not predetermine the outcome of the assessment that may be later performed by the individual HTA agencies.

2. Structure/content of the request for an early dialogue pilot:

▪ Letter of intent

The company sends a letter of intent by email to the coordinating institution (e.g. HAS for JA2) at least 4 months prior to the anticipated procedure start date. The letter of intent does not require additional documentation attached. If accepted for an early dialogue, the company is requested to submit an application file at least 3 months before the face-to-face meeting with HTA bodies.

The letter of intent should include:

- Applicant and contact details
- Name of technology (company code or INN, and proposed trade name)
- Description of the technology and mechanism of action
- Type of technology or product (chemical, biotechnological, advance therapy, therapeutic scientific or technical innovation, diagnostic)
- Intended indication and line of treatment that will be discussed during the early dialogue
- Therapeutic field (and ATC code if applicable)
- Development status
- Rationale for seeking advice
- main topics/questions to be discussed with regards to the planned studies
- proposed time-frame for the procedure start date and face-to-face meeting

Upon reception of the Letter of Intent by the coordinating institution, the company receives an e-mail of acknowledgement. Following analysis of the information included in the Letter of Intent by the coordinator

and discussion amongst participating HTA agencies², the company is then informed on either the acceptance or refusal of its request for an early dialogue. In case of acceptance, procedural calendar including the date of the face to face meeting with the company, are decided.

▪ **Application file including company's questions and position statement**

Once the selection of the technology for an early dialogue has been confirmed, the company submits the application file as part of the start of the procedure.

The application file (also called Briefing Book) should contain the following information (approximately 50 pages)

- Table of contents
- Lists of figures, tables, abbreviations
- I. Summary: background information on the disease/target population including relevant information (epidemiology, natural history of the disease, treatments and evolution under treatment), the technology, the development plan, the regulatory status and rationale for seeking advice
- II. Company's questions and position statements: questions should pertain to relative effectiveness and economic aspects for the technology under development. Questions should be clearly and concisely worded. Each question should be followed by a position statement and include a comprehensive explanation of the chosen approach. Key information on the topic should be sufficiently discussed so that the company position can function **as a 'stand-alone' argument**. In general, it is recommended to allocate **1 to 3 pages for each company position**. Cross-references and annexes should be included when additional detail is needed to support the argument.
- III. Background documentation: this section should provide a comprehensive scientific overview of the product development program (clinical data obtained to date, rationale and proposal for the confirmatory clinical trial), including relevant systematic information in sufficient detail, together with a critical discussion.
- IV. List of key references i.e. study protocols (final, draft or outline/synopsis), study reports (final/draft/synopsis), previous scientific advice received (if applicable), relevant therapeutic guidelines and literature references.

3. Procedure for the early dialogue pilots

The company sends an official letter of intent by email to the coordinating institution (e.g. HAS for JA2) at least **4 months** prior to the anticipated procedure start date. The letter of intent does not require additional documentation attached.

If accepted for an early dialogue, the company is requested to submit an application file 3 months before the face-to-face meeting with HTA bodies to the secretariat of the coordination institution, which communicates it to the HTA participating bodies.

After checking the content of the application file for completeness, the HTA bodies send their list of points that would require further clarification to the coordination institution for compilation and validation. The final list of points for clarification is sent for their consideration to the company at D-75 which will allow them to revise their dossier. The revised dossier should be submitted to the coordinator at D_60 prior to the face-to-face meeting as 1 electronic copy (start of procedure). In addition, a single paper copy of the briefing document (without annexes) may be requested by the coordinator.

² by e-mail, e-meeting, or during a face to face meeting

The cover letter, briefing book including company question/ position statements and table of contents should be submitted in MS Word format. Annexes and references may be submitted as either MS Word or searchable PDF documents (scanned PDFs that are non-searchable, non-annotated are not acceptable). Prompt delivery of the final package as requested will enable HTA organizations to review the information in a timely manner.

Procedure description	
DAYS (calendar days)	ACTIONS concern : <ul style="list-style-type: none"> »» ED applicant (company) »» ED coordinator »» HTA body representatives
D -90: START	Draft briefing book: <ul style="list-style-type: none"> »» Company submits the draft briefing book, annexes and references to the Coordinator^{3,4} »» ED Coordinator communicates the draft briefing book, annexes and references to participating HTA bodies »» HTA bodies check the document for completeness and clarity of information
D -75	Written points for clarification: <ul style="list-style-type: none"> »» HTA bodies send written points for clarification to the ED coordinator »» ED coordinator compiles HTA body written responses in a single document, the consolidated list of points for clarification »» ED coordinator sends the consolidated list to the company with administrative and specific instructions
D -60	Final briefing book: <ul style="list-style-type: none"> »» Company sends to the ED coordinator the final briefing book with responses to the list(s) of clarification points integrated in track mode »» ED coordinator forwards the final briefing book to participating HTA bodies

³ It is recommended that the coordinating institution assign a unique email address for all incoming/outgoing electronic exchanges related to the early dialogue activity.

⁴ The use of a secure link system (for authorized personnel only) is necessary to ensure proper transmission of large files and the confidentiality of sensitive documents. An IT platform for uploading/downloading documents will greatly optimize work flow for all parties involved (e.g. Eudralink at the EMA).

Procedure description	
D -30	<p>Key issues raised by HTA bodies:</p> <p>HTA bodies identify a list of issues that deserve particular attention from the company, with the overall objective of helping the company to prepare for the face to face meeting and possibly reconsider its development plan, if and where needed.</p> <ul style="list-style-type: none"> ▶▶ HTA bodies send key issues, raised by the proposed development, to the ED coordinator ▶▶ ED coordinator organises and leads an e-meeting with participating HTA bodies to discuss the list of key issues. ▶▶ Following the e-meeting, the ED coordinator consolidates the list of key issues for the company, indicating which require a written response and which are to be discussed the day of the face to face meeting. ▶▶ ED coordinator sends the consolidated list to the company with appropriate instructions
D -15	<p>Company response to key issues:</p> <ul style="list-style-type: none"> ▶▶ Company sends to the ED coordinator their responses to the key issues in writing.
D -10	<p>HTA draft written answers:</p> <ul style="list-style-type: none"> ▶▶ Each HTA participant drafts written answers to company questions and then submits them to the ED coordinator⁵. ▶▶ ED coordinator compiles draft answers for all HTA participants in a single document⁶ ▶▶ ED coordinator sends compiled draft document to all participating HTA bodies in preparation of the Face to Face meeting.

⁵ HTA bodies should use the template provided to them by the Agency Secretariat for this purpose.

⁶ Due to potential errors involved in copying voluminous text from one document to another, it is recommended to put into place a quality control system involving two staff members of assistant-level. One person may be responsible for compiling all responses; the second, for double checking the final consolidated document by scanning relevant copied sections (beginning and ending text for each section copied). This should apply also to HTA final written answers (D +10).

Procedure description	
D 0: Early Dialogue Meeting	<p>Face to Face Meeting:</p> <p>The early dialogue meeting is a 1-day meeting dedicated to 1 early dialogue procedure. It is organised and hosted by the ED coordinator (e.g. HAS for JA2). The meeting is generally organised as follows:</p> <ul style="list-style-type: none"> ▶▶ Morning session: Preliminary discussion among HTA bodies only <p>Two-hour session to exchange to identify common views (general opinion) and differences in HTA bodies' positions and further discuss them in order to reach convergence when possible</p> <ul style="list-style-type: none"> ▶▶ Afternoon session: face-to-face meeting of HTA bodies with the company <p>Three hour meeting, co-chaired by the ED scientific coordinator and a vice-chair, designated amongst the HTA agencies. The company addresses each question, including key issues that were identified by the HTA organisations (if applicable). For each question, a general opinion expressed by the chair/vice-chair of the meeting. Official HTA body representatives, knowledgeable on the HTA process and requirements in their home country, are then invited by the meeting Chair to provide an their expert opinion.</p> <ul style="list-style-type: none"> ▶▶ Final discussion on lessons learned (HTA bodies only)
D +7	<p>Company meeting minutes:</p> <ul style="list-style-type: none"> ▶▶ Company provides detailed minutes of the meeting and submits these to the ED coordinator. ▶▶ Meeting minutes are forwarded by the ED coordinator to participating HTA bodies for informational purposes. They may serve in finalizing the HTA written answers.
D +10	<p>HTA final written answers:</p> <ul style="list-style-type: none"> ▶▶ Each HTA participant finalises their draft written answers to company questions, integrating: main issues from the closed discussion among HTA bodies, the company's response to key issues and the discussion at the face to face meeting. ▶▶ Final HTA written answers are submitted to the ED coordinator, who compiles the final document integrating a statement based on all HTA responses. ▶▶ ED coordinator sends the final document to both the participating HTA bodies and company as a final deliverable.

The advice provided by HTA body representatives is non binding and therefore does not commit the respective agencies, in anyway, with regards to the application and/or outcome of a future assessment for the product under development.

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ANNEX 1

Briefing book template for pharmaceuticals

Briefing book template for pharmaceuticals to support a multi-HTA Early Dialogue

November 2015

This template is to be used by companies willing to submit an overview of relevant information necessary to support an early dialogue discussion.

The document must be submitted in Word format. It will summarize key information about the product, its previous and proposed development, and its intended use. The recommended length of the briefing book is approximately 50 pages, not including annexes. All pages should be numbered.

Questions to be addressed during the face-to-face meeting should be listed in Section 2. Each question should be followed by company's justification of its position.

Any essential self-standing documents such as study protocols, reports etc. should be placed in the annex (section 4 of this template) or should be submitted as separate documents in a Word or PDF format. Referenced articles should be submitted in full text versions.

The cover page of the document should contain the name of the product (or its chemical name or both, if available), intended indication, name of the company, date and version of the document. The following pages should be dedicated to Table of contents, Table of figures and tables, List of annexes and List of abbreviations.

The briefing book should respect the structure indicated and should address each listed domain. Guidance and explanation are provided below for each section. Absence of required data should be always justified.



The EUnetHTA JA 2 has received funding from the European Union, in the framework of the Health Programme.

1. Summary

1.1. Background information on the disease

1.1.1. Overview of the disease

Relevant epidemiological data, information on natural history of the disease and evolution on treatment should be discussed.

1.1.2. Treatment options

The company should list all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) together with their labelling status in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development, this information should be included.

1.2. Background information on the product

1.2.1. Indication

The company is asked to specify clearly the intended indication (1st line, 2nd line, 3rd line of treatment; add-on or monotherapy) of the product in development, as well as the aim of treatment (preventive, curative, palliative, symptomatic, disease modifying...). The position of the product in the treatment algorithm should be proposed. The target population of the product should be described as precisely as possible.

1.2.2. Form, route of administration, dose, dosage

Route of administration and the pharmaceutical form of the product should be described. Dose, frequency of administration and the duration of use should be discussed based on the available evidence at the stage of development.

If the administration of the product is associated with the use of a diagnostic test, a medical device or with a medical procedure, this information should be stated and adequate information given on the associated test or device.

1.2.3. Characteristics of the product

Chemical/biological product; orphan product; advanced-therapy medicinal product.

1.2.4. Mechanism of action

Pharmaco-therapeutic group should be indicated. ATC code should be given if applicable.

The mechanism of action should be described as well as key information on pharmacodynamics and pharmacokinetics.

1.3. Status of the clinical development programme

This section should contain a summary of clinical development of the product and give a clear idea of the stage of development of the product. Evidence obtained in the field of

the required indication should be mentioned. Existence of trials supporting the use of the product in other indications should be mentioned for completeness.

Non-clinical development programme will be summarised if adequate (on the case by case basis)

1.3.1. Clinical development up to date

Data on efficacy and safety coming from phase I (if relevant), phase II and phase III clinical trials that are completed or ongoing should be presented. For each trial the design, doses and duration of treatment, comparator, number of subjects and description of studied population, results of the trial (or preliminary results of ongoing trials if available) and all other important information should be given. Data and results may be summarized in tables. Detailed information should be available in study reports in annexes. Cross-links to annexes are recommended.

1.3.2. Planned trials

This section should provide a comprehensive overview of all planned trials with the product in the intended indication. For the trial that is to be the subject of the early dialogue, a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), comparators, endpoints (primary, secondary etc.), flowchart, follow up, methods of analysis etc. All relevant systematic information should be given at a sufficient level of detail, together with justification for the choice made and a critical discussion of key issues.

1.4. Economic aspects

If the company desires to discuss economic assessment as a part of the early dialogue, then all relevant information about the planned economic analysis should be provided.

The company should state the scope of the planned economic analysis, clearly defining the research questions.

The company should describe the main aspects of the economic analysis, in particular the type of analysis, the perspective, the time horizon, the population and the comparator(s).

An outline of the structure of the model could be provided if available. Relevant published papers could be provided as annexes to the briefing book. Expected data sources and planned sensitivity analyses should be described. Trial endpoints used to derive the model health outcome should be stated where relevant. Tools used to measure resource utilization should be described.

1.5. Regulatory status of the product

Information should be given on the marketing authorisation status of the product in other indications in EU and North America. In case the product is on the market, its reimbursement status should be given. The company should indicate whether a scientific advice has been received from other national or European institutions and provide minutes or if it is planned at any further stage. Eventually, estimated timelines for market entry may be given if this information is available.

1.6. Rationale for seeking advice

The scope of the questions and the rationale for the advice request should be elaborated.

1.7. Discussion on added benefit

The company should provide arguments supporting the added benefit of the product in the target population in comparison with the standard of care and with a pharmacologically similar product aimed to be replaced (if adequate).

2. Questions and company's positions

The company should list all questions that will be discussed during the face-to-face meeting. Any subject pertaining to relative effectiveness, economic assessment or other aspects of the development can be addressed. Both clinical and economic areas can be covered or just one of them according to the preferences of the company. The wording of questions should be clear and concise. Open questions are not acceptable. Given the timeframe, a high number of questions (i.e. more than 10) is not feasible to be discussed during the meeting. Questions should be ordered by area of expertise.

Each question should be followed by a separate explanation of the company's position including a comprehensive justification of the chosen approach. Each position description should not be longer than 3 pages. Cross-references to the relevant parts of the briefing document or to annexes can be included if additional detail is needed to support the argument.

All scales and scores that will be used for endpoint measurement should be presented and their validity should be commented.

2.1. Clinical questions

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- »» population
- »» comparator
- »» trial design and duration
- »» endpoints to support reimbursement
- »» statistical issues (stratification, subgroups etc.)

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trial.

2.2. Economic questions (if applicable)

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- » population
- » choice of comparator
- » choice of economic model
- » data used to populate the model
- » time horizon and extrapolation hypothesis
- » perspective (societal, healthcare related etc.)
- » utility values
- » resource utilisation data

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trial.

3. References

This section should contain a list of all documents referenced in the text.

4. Annexes

Any of the following documents can be attached to the briefing book, if applicable:

- » Referenced articles in full text versions in English
- » Trial protocols, summaries and reports
- » Relevant clinical practice guidelines
- » Previous scientific advice received

5. Contact point

Any question or comment concerning this document or any other point related to the Early Dialogues conducted in the frame of the EUnetHTA project should be sent to:

earlydialogues@has-sante.fr

The letter of intent, and any request for additional information should be sent to the early dialogue coordinating unit at HAS:
earlydialogues@has-sante.fr

ANNEX 2

Briefing book template for medical devices

Briefing book template for medical devices to support a multi-HTA Early Dialogue

November 2015

This template is to be used by companies willing to submit an overview of relevant information necessary to support an early dialogue discussion.

The document must be submitted in Word format. It will summarize key information about the product, its previous and proposed development, and its intended use. The recommended length of the briefing book is approximately 50 pages, not including annexes. All pages should be numbered.

Questions to be addressed during the face-to-face meeting should be listed in Section 2. Each question should be followed by company's justification of its position.

Any essential self-standing documents such as study protocols, reports etc. should be placed in the annex (section 4 of this template) or should be submitted as separate documents in a Word or PDF format. Referenced articles should be submitted in full text versions.

The cover page of the document should contain the name of the product (or its chemical name or both, if available), intended indication, name of the company, date and version of the document. The following pages should be dedicated to Table of contents, Table of figures and tables, List of annexes and List of abbreviations.

The briefing book should respect the structure indicated and should address each listed domain. Guidance and explanation are provided below for each section. Absence of required data should be always justified.



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6. Summary

6.1. Background information on the disease

6.1.1. Overview of the disease

Relevant epidemiological data, information on natural history of the disease and evolution on treatment should be discussed.

6.1.2. Treatment options

The company should list all technologies (drugs, devices, procedures) that present relevant alternatives for the diagnosis and/or treatment of the disease/condition (stage, line of treatment) relative to the intended use of the medical device, together with the status of these technologies in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development, this information should be included.

6.2. Background information on the medical device

6.2.1. Intended use

The company is asked to specify clearly the intended use of the medical device in development, as well as the aim of use (preventive, diagnostic, curative, palliative, symptomatic, disability/handicap compensation...). The position of the medical device in the treatment algorithm should be proposed and described in a wider context. The target population of the medical device should be described as precisely as possible.

6.2.2. Description of the medical device

Technical characteristics of the medical device should be given at a sufficient level of detail. A plan, drawing or photo can be included to provide insight into the characteristics or use of the medical device.

If the use of the device is associated with the use of other accessories and services (ex. software) this information should be provided and the description should be given. Technical limits (shelf-life, warranty period, etc.) of the device should be provided and discussed.

6.2.3. Mode of action

Description of the mode of action in respect of the condition or disability should be given.

6.2.4. Procedures required for use of the medical device

The frequency and the duration of use of the device should be described as well as the procedure related to its use. If the use of the device requires medical or paramedical intervention or assistance at any stage this should be indicated and the procedure should be described. In case the procedure needs to be repeated in order for the treatment to be complete, the foreseen number of procedure repetitions should be stated as well as the optimal time between them. The same applies in case the procedure has to be split into more phases. Any obligations in terms of training, competence level, or level of activity for personnel should be discussed.

6.3. Status of the clinical development programme (mainly medical devices of class IIa, IIb and III)

This section should contain a summary of clinical development of the medical device and give a clear idea of the stage of development of the medical device. Evidence obtained in the field of the intended use should be mentioned. Existence of trials supporting the use of the medical device in other indications should be mentioned for completeness.

Non-clinical development programme will be summarised if adequate (on the case by case basis).

6.3.1. Clinical development up to date

Preliminary data on technical performance, efficacy and safety coming from clinical trials that are completed or ongoing should be presented if available. Safety data should address issues linked directly to the device as well as those related to the procedure needed for use of the device (if applicable). For each trial the design, comparator, number of subjects and description of studied population, results of the trial (or preliminary results of ongoing trials if available) should be given. Study reports may be provided in annexes. Cross-links to annexes are recommended.

6.3.2. Planned trials

This section should provide a comprehensive overview of all planned trials with the medical device to support its technical performance, efficacy and safety. For the trial that is to be the subject of the early dialogue, a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), comparators, endpoints (primary, secondary etc.), flowchart, follow up, methods of analysis etc. The need of a specific training or equipment for the proper use of the device should be stated and the effect of training on short-term and long-term endpoints should be discussed. All relevant information should be given at a sufficient level of detail, together with justification for the choice made and a critical discussion of key issues.

6.4. Economic aspects

If the company desires to discuss economic assessment as a part of the early dialogue, then all relevant information about the planned economic analysis should be provided.

The company should state the scope of the planned economic analysis, clearly defining the research questions.

The company should describe the main aspects of the economic analysis, in particular the type of analysis, the perspective, the time horizon, the population and the comparator(s).

An outline of the structure of the model could be provided if available. Relevant published papers could be provided as annexes to the briefing book. Expected data sources and planned sensitivity analyses should be described. Trial endpoints used to derive the model health outcome should be stated where relevant. Tools used to measure resource utilization should be described.

6.5. Regulatory status of the medical device

Information should be given on the CE marking status of the medical device (or FCC Declaration of Conformity for the USA). In case the medical device has already obtained a CE marking, its classification should be stated. For products of class II and III details about the notified body should be given and the dossier submitted to the notified body should be provided. However, strictly confidential parts of the dossier related to the device production process that are of no relevance for safety could be left out if justified by the company. In case the product is on the market, its reimbursement status should be given. The company should indicate whether a scientific advice has been received from other national or European institutions and provide minutes, or if it is planned at any further stage. Eventually, estimated timelines for market entry may be given if this information is available.

6.6. Rationale for seeking advice

The scope of the questions and the rationale for the advice request should be elaborated.

6.7. Discussion on added benefit

The company should provide arguments supporting the added benefit of the medical device in the target population in comparison with the standard of care.

7. Questions and company's positions

The company should list all questions that will be discussed during the face-to-face meeting. Any subject pertaining to relative effectiveness, economic assessment or other aspects of the development can be addressed. Both clinical and economic areas can be covered or just one of them according to the preferences of the company. The wording of questions should be clear and concise. Open questions are not acceptable. Given the timeframe, a high number of questions (i.e. more than 10) is not feasible to be discussed during the meeting. Questions should be ordered by area of expertise.

Each question should be followed by a separate explanation of the company's position including a comprehensive justification of the chosen approach. Each position description should not be longer than 3 pages. Cross-references to the relevant parts of the briefing document or to annexes can be included if additional detail is needed to support the argument.

All scales and scores that will be used for endpoint measurement should be presented and their validity should be commented.

7.1. Clinical questions

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- » population
- » comparator
- » trial design

- » endpoints to support reimbursement
- » statistical issues (trial design, power, stratification, subgroups etc.)
- » requirements for specific training or equipment

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trials.

7.2. Economic questions (if applicable)

There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- » population
- » choice of comparator
- » choice of economic model
- » data used to populate the model
- » time horizon and extrapolation hypothesis
- » perspective (societal, healthcare related etc.)
- » utility values
- » resource utilisation data

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Company's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 1.3.2 Planned trials.

8. References

This section should contain a list of all documents referenced in the text.

9. Annexes

Any of the following documents can be attached to the briefing book, if applicable:

- » Referenced articles in full text versions in English
- » Trial protocols, summaries and reports
- » Relevant clinical practice guidelines
- » Previous scientific advice received

10. Contact point

Any question or comment concerning this document or any other point related to the Early Dialogues conducted in the frame of the EUnetHTA project should be sent to:

earlydialogues@has-sante.fr

The letter of intent, and any request for additional information should be sent to the early dialogue coordinating unit at HAS:
earlydialogues@has-sante.fr