eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Joint Action 3

DELIVERABLE

Deliverable D5.6 Recommendations and tools for post-launch evidence generation

Date of submission	June 2021
Work package	WP5
Author(s)	WP5B LP and ACs
Dissemination level	Public

Co-funded by the Health Programme of the European Union

EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

Recommendations and tools for post-launch evidence generation

Final version – June2021

This document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020).

DOCUMENT HISTORY AND CONTRIBUTORS

Version number	Date	Description
V1	28.09.2020	1st draft
V2	5.10.2020	Text modifications ; chapter 3.4
V3	27.10.2020	Inclusion comments from NICE, TLV, HAS, AVALIA-T
V4	04-12-2020	Review of recommendations
Final	06-2021	Update with finalisation of PLEG pilot and inclusion of AIFA and RedETS comments

Authors

Responsibility/role	HTA Body/affiliation	Name
Author	HAS	Irena Guzina, Chantal Bélorgey, Chantal Guilhaume, Amélie Meillassoux
Co-author	AIFA	Agnese Cangini
	Avalia-t	Leonor Varela Lema; Maria Jose Faraldo Valles; Janet Punal Riobóo
	NICE (for the section on REQueST)	Helen Powell. Hannah Patrick
	TLV	Johan Ponten

How to cite this document
Please cite this document as follows:

Deliverable D5.6 Recommendations and tools for post-launch evidence generation. Diemen (The Netherlands): EUnetHTA; 2021. [Date of citation]. Available from: https://www.eunethta.eu

TABLE OF CONTENTS

List of abbreviations

AC	Activity centre(s)
DOI	Declaration of Interest
CU	Confidentiality undertaking
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
EVIDENT	Evidence database on New Technologies
FtF	Face to face
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
HTAb	HTA body
PARENT	Cross Border Patient Registries Initiative
PLEG	Post-launch evidence generation
REA	Relative Effectiveness Assessment
REQueST	Registry Quality Standards tool
RWD	Real world data
RWE	Real World Evidence
WP	Work package

1 INTRODUCTION

EUnetHTA Joint Action 3 (JA3) General Objective

The general objective of this action is to support cooperation at scientific and technical level between Health Technology Assessment (HTA) Bodies to validate the model for joint work to be continued after EU funding under the Health Programme ends. The JA3 aims to increase the use, quality and efficiency of joint HTA work at European level to support evidence-based, sustainable and equitable choices in healthcare and health technologies and ensure re-use in regional and national HTA reports and activities, in order notably to avoid duplication of work.

The Joint action 3 started in 2016 and will end in 2021.

JA3 Work package 5 – Life cycle approach to improve Evidence generation

The objective of Work package (WP) 5 is to help generate optimal and robust evidence for health technologies (pharmaceuticals or others) throughout the technology lifecycle, bringing benefits for patient access and public health.

The WP5 consists of two strands: strand A focuses on initial evidence generation and the activity of Early Dialogues, while strand B focuses on Post-Launch Evidence Generation (PLEG).

PLEG is an umbrella term for evidence generated after the launch or licensure of a health technology within its approved or intended indication. **Its role is not to replace but to complement evidence generation already undertaken for marketing authorisation or HTA appraisal, addressing remaining uncertainties but also potentially covering wider questions of disease management and healthcare delivery.** It contributes therefore to the overall and accumulating evidence about a health technology during the life cycle.

Despite this particularity of JA3 pilots, WP5B wants to stress that PLEG in general is not limited to a specific type of data collection but can encompass a wide range of study designs (both interventional and observational). The most adapted type of data collection/study depends on the evidence gap(s) that need(s) to be filled in.

As per the JA3 Grant agreement and the work plan, the specific objectives of WP5 Strand B are to:

1) Promote collaboration on PLEG, between HTA bodies, but also other actors in the field
2) Enhance the use of high-quality registries in HTA
3) Develop a tool/document to support permanent collaboration on PLEG.

Purpose of this document

This report is being produced in order to meet the above-mentioned objective of supporting permanent collaboration on PLEG.

The report aims at providing an overview and summarizing the results and lessons learned from all PLEG activities carried out in the framework of JA3 WP5. Its objective is to help understand possible levels of and best means for joint work on PLEG.

Its conclusions will further inform the work of the EUnetHTA Task Group on Future Model for Cooperation, aiming to develop a complete blueprint for future European cooperation on HTA post-2021.

Structure of this document

The document recalls first national (individual) PLEG practices of WP5B partners (chapter 2). Results and lessons learned from joint PLEG activities are presented next (chapter 3).

2 PLEG PRACTICES OF EUNETHTA PARTNERS ON NATIONAL LEVEL

2.1. Survey among WP5B partners

2.1.1 Description of the survey

A survey to understand PLEG practice in various countries was conducted in December 2019 as practices have evolved in many countries recently.

A 9-questions questionnaire was sent to the WP5B partners. The topics addressed were mainly about the PLEG practices in each country, their general timelines, the data ownership and the resulting opportunities for a European collaboration for a common protocol for collecting and sharing data.

The survey was sent to work package 5B partners (25 partners). Twelve agencies completed the survey (AIFA; Azienda-zero; Fimea; G-BA; HAS; INFARMED; NICE; NOMA; SNHTA; Spanish medical device HTA network; TLV; ZIN).

Most of the responders assess only medicinal products, but some also evaluate medical devices.

The scope of evaluation from the responding agencies is presented in the table below. In bold, the agencies evaluating both medicines and medical devices.

Agencies evaluating medicines	Agencies evaluating medical devices
AIFA, G-BA, **HAS**, Infarmed, Fimea, NICE, NOMA, **SNHTA**, TLV, ZIN	Aziendra zero, **HAS,** Spanish HTA Network (RedETS), **SNHTA**

For Spain, a common response was given by AQuAS and Avalia-t on behalf of RedETS, the network of HTA Spanish agencies in charge of evaluating the non pharmacological health technologies.

Despite NICE assesses both medicines and medical devices, the HTAb only completed the survey for medicines.

2.1.2 Summary of survey results

Detailed results of the survey are reported here:
https://eunethta.sharepoint.com/:f:/g/Work%20Packages/WP5/StrandB/plegpilotsstrandb1/EiaW6-sWY8NKqqHiPKcYwWwBhoS4EZmIPUxu-510Em34dg?e=QzaHNv

In December 2019 more than half of HTAb have procedures in place with official requests made by the HTAb for PLEG. Given that this is a growing field, this percentage should increase. In more than 75% of cases, the PLEG request is made at the time of the assessment/appraisal but details of the request are usually defined later on, they can even be part of the pricing & reimbursement negotiations.

In the majority of cases, PLEG is used for re-assessment of the added value of technology but it can also contribute solely to the monitoring of good usage of the health technology.

The responsibility for setting up the data collection and running the analyses mainly lies with manufacturers for pharma while it is more the HTAb's responsibility with support of scientific societies for MD. In connection with data collection responsibilities, companies are generally the data owners of PLEG, especially for pharma. The exception is AIFA who is the sole owner of post-launch data at the national level. In a few cases, the Ministry of Health is in charge of implementing post-launch data and is the data owner. Despite this, some agencies can help the manufacturer in defining the protocol for PLEG, in order to insure it will be consistent with the agency's evaluation standards. They can also advise on the source to collect post-launch data.

In case of a European collaboration, a majority of the agencies evaluating drugs estimate that the collaboration could take place even before the HTA has started; this is not the case for the medical device agencies, where the vast majority have no opinion on the timelines of a potential collaboration. Most agencies are not in favour of collaboration starting during the production of the HTA report but recommend starting once the evidence gaps have been defined for instance after national appraisal. When the collaboration follows a European joint assessment, the process can start during the production of the HTA report, once the evidence gaps have been defined. In case the technology is assessed at national level only, collaboration can only start once the HTA report has been published.

Some agencies are still developing a formal PLEG request procedure. Their practices will be implemented soon but some of them are already willing to participate in a possible EUnetHTA process.

At the date of the F2F meeting, some agencies are working on national PLEG process improvement.

Some agencies have different practices for PLEG, depending on the topic concerned, but most of them refer to the usage of registry (mainly disease registry). They are also, most of the time, involved in the discussion or decision in the method for development of post-launch data by developing the protocol or reviewing protocol proposed by manufacturer, research centre, Ministry of Health. The earlier the PLEG request can be anticipated and formalized, the easier it will be for the agencies to exchange on their request, on the protocol under study, and on potential opportunities to share data. Data sharing in particular should be anticipated as only a few agencies own the data and are able exchange them without asking permission.

2.2 Overview of differents agencies'practices

In addition to the survey, the national PLEG practices were discussed during the face-to-face meeting for WP5B partners (12 December 2019) and the transcript is summarised below. The same HTAb as the ones completing the survey were involved with the exception of the HZIZ who additionally shared Croatian experience.

PLEG practice for drugs in Italy, based on AIFA feedback

The main instrument applied in the PLEG practice is the AIFA monitoring registry system, a web-based platform which enables all stakeholders to use product registries. The main objective of the registry is to promote the appropriate use of drugs in the approved indication (and/or subpopulation where the medicine has proven to be cost-effective) and to apply the managed entry agreements established with each company during the P&R process. AIFA generates incoming data from product registries during the re-assessment process of a specific medicinal product. There are two main objectives required by the application of this technical instrument: setting up the framework of a drug use, defined during the place in therapy process, and allowing all committees, in the post-marketing setting, to evaluate the real impact of a drug in the market. AIFA implements drug registries with the systematic collection of patient characteristics, drug usage and clinical outcomes at different time points. The registries are defined by AIFA after interaction with company, clinical experts and scientific associations. Data are collected via local hospital/regional databases/networks.

PLEG practice for drugs in Finland, based on Fimea feedback:

During assessment, Fimea identifies and reports uncertainties and evidence gaps as a part of the public HTA report. There is, however, no mandatory PLEG request to the company. Fimea does not implement post-launch studies but can get access to these data by applying for a permission and submitting data requests. In Finland, Findata issues permits and delivers data for use cases that need data resources from a number of different data controllers (e.g. health care service providers and Social insurance institution).

PLEG practice for drugs in Sweden, based on feedback from TLV:

TLV's scope is mainly pharma and some OT, although the main part of OT assessment is regional. Hospital drugs are assessed at a regional level while outpatient drugs are assessed only by TLV. The decision on pricing is taken by the TLV board. TLV can use the assessment produced by other stakeholders. When there is a financial risk, the board can request to have both national and regional bodies around table. When TLV is not confident during the initial assessment they will formulate a formal request to monitor drug condition of use for 18 to 30 months. The requests are mostly made to the manufacturer but TLV can also manage development

of post-launch data itself. TLV can exchange with company but this has little influence on TLV re-assessment decision. They will also search for existing registries and investigate their content. Until now, most registries could not retrieve data needed for TLV. Interaction with research field/clinicians is not always easy as TLV is not perceived as a research agency.

PLEG practice for drugs in Germany, based on G-BA feedback:

There is an official request for PLEG in Germany, and it will be used for re-assessment. GBA is not responsible for generating data, that responsibility lies with manufacturer. They can develop evidence in collaboration with a registry. G-BA will be in charge of making strict recommendations on study design for PLEG. This procedure is to be further developed/decided next year. In between, IQWIG is responsible for developing a recommendation for a valid PLEG method (recommendations were published January 24, 2020)[1]. In any case, the manufacturer will be legally responsible for PLEG and will be the data owner. In case no data are developed, a price cut could be applied. There should be a possibility for manufacturer to discuss PLEG design with G-BA. G-BA is also planning to interact with BfArM (The Federal Institute for Drugs and Medical Devices).

PLEG practice for drugs in the UK, based on NICE feedback:

There is an official request for PLEG in the UK during the assessment, only for pharma, even if they wish to move forward to device diagnostic within the next year or 2. The official PLEG request happens at the time of the appraisal but the NICE assessment team works with the NICE technical team to formulate the request to industry. NICE assessors have a meeting with the committee where all the requirements for the PLEG process are defined.

The entity responsible for setting up the data collection and analysis depends on the topic. It could be academic centres, hospitals, patient organisations, or the manufacturers. They work in partnership with NHS England and other payers in England, such as Public Health England.

The company is always asked to do the data collection and analysis but NICE works closely with them and they meet every 6 months to check the data recorded for quality etc. The same procedure applies when data are collected via a registry.

The company owns the output and if the data comes from a public health registry, it belongs to Public Health England. The raw data, before being analysed, belongs to the organisation that collects the data and when the analysis is carried out it belongs to the company as they pay for it. Currently only aggregated data could be shared with other EUnetHTA partners. A new process is under consideration to be able to share the raw data.

Re-assessment for cancer drugs occurs between 2 years and up to 5 years after launch. For rare conditions re-assessment is usually done after 5 years. Timing of the re-assessment is part of the agreement made with companies.

NICE makes approximately between 15 to 20 PLEG recommendations a year but only half of the companies come back with the requested data. PLEG are mandatory when the committee thinks there are key uncertainties. In that case, it is part of the conditional authorisation.

In case of a EUnetHTA pilot, the collaboration could start even before the production of the HTA has started, because the PLEG topics are identified during the scoping phase and the manufacturer can proactively come with PLEG proposal before submitting the drug file for appraisal. The Medicine and Healthcare Products Regulatory Agency can also ask for PLEG data in case of licensing decision.

PLEG practice for drugs in Portugal, based on Infarmed feedback:

Request for PLEG could happen at the moment of the assessment while the definition of data to be collected is made during pricing and reimbursement negotiation. Post-launch data are used during re-assessment that

[1] [A19-43] Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V – rapid report (iqwig.de)

occurs 2 years later. Only two requests for PLEG have been made so far as there is not enough funding to do as much PLEG as wished. The owner of the data is Infarmed as they have two disease registries (spinal muscular atrophy and hepatitis C). For oncology products, PLEG can also be requested at the time of re-assessment with usage of the National Oncology Registry (RON) data. The Ministry of Health is the owner of RON and only aggregated data are available for sharing.

In total around 10 PLEG requests per year are made in Portugal.

PLEG practice for drugs in the Netherland, based on ZIN feedback:

There is no official request for PLEG in Netherlands but they have started two additional programmes in 2019.

- Managed entry agreement focused on orphan drugs, with access conditional to data collection. It can take place any time between 7 and 15 years. For this process PLEG will be established with the company and is based on product registry.

- Patient registry for expensive drugs using disease-based registry a combination of public and private funding. There are ongoing discussions on the source to finance these disease registries between government and clinicians or a combined funding.

Soon ZIN will ask for PLEG with the intention of re-assessment. They participate actively to the follow-up of the drugs, but in that follow-up, they do not often ask for additional evidence.

PLEG practice for drugs in France, based on HAS feedback

There are some common steps in the PLEG process in France for drugs and MD: PLEG is requested by HAS with several objectives : for re-assessment of the added value of technology (evidence gap...) but also in order to contribute to the monitoring of good health technology usage, the place of the product in the clinical practice. HAS exchanges once or twice with the company on what they expect from PLEG (protocol reviewed by HAS assessment teams). For MD, the pricing committee can force the company to provide post-launch data as part of the negotiation; there is a meeting between the pricing committee, HAS, and the company during the negotiation phase on pricing decision to define together the timelines of PLEG and the potential difficulties related to the set-up of the study. Accordingly, the company will propose HAS a protocol for review. 5 years later, at the time of the re-assessment, the company will submit PLEG data to HAS and the Pricing Committee (CEPS).

Once recommendations are formulated, they become binding, with a re-evaluation scheduled in the initial opinions. If the manufacturers do not follow the recommendations, the pricing committee CEPS can take financial sanctions. These sanctions are more pronounced in the context of medical devices.

HAS can be the agency requesting for PLEG, but it is not the only one, as the CEPS, the ANSM, the CPAM, or the INCA can also make the request or conduct PLEG.

HAS guidelines on PLEG (https://www.has-sante.fr/jcms/c_1191960/fr/les-etudes-post-inscription-sur-les-technologies-de-sante-medicaments-dispositifs-medicaux-et-actes) are currently under review. All ongoing PLEG are listed here: https://www.has-sante.fr/jcms/p_3113800/fr/les-etudes-post-inscription-pour-les-medicaments

PLEG practice for MD in Spain, based on the Spanish HTA Network of agencies feedback:

The RedETS currently have five MS on-going. Some of them are in the analysis phase. Although regional health authorities support participant hospitals by reimbursing all involved costs, including the technology under assessment and data gathering, the Ministry of Health funds the RedETS participation.

All MS are applied under an investigational protocol, limiting the provision of the assessed technology and guiding its indication to a previously selected set of referral centers.

At least each three months the HTA agencies have to complete a short summary about the assessed products, including how many patients are treated and if there is a special safety issue, they have to highlight it and

communicate it to Ministry of Health in order to ensure that PLEG protocol requirements are fulfillment. Once the data collection is finished, a final report with statistical analysis of data and new evidence published will be made.

The number of PLEG requests depends of the evidence gaps identified in the assessment reports in the working annual plan of RedETS. The current agencies involved in the MS program are Osteba, SESCS, AETS-ISCIII and Avalia-t.

The commission that decides the approval has a representation of the Autonomous Communities. The commission approvals the protocol that included the selection criteria/requirements that have to be fulfilled by centers to participate in the MS.

Regions could also propose PLEG subjects to the Ministry of Health, but for now all the PLEG that have been done has come from National Commission of Provision, Insurance and Financing (CPAF) requests.

The set-up of PLEG in the monitoring studies program is done by the Ministry of Health, but the HTA agencies are responsible for defining the protocol, with clinicians and a group is created to discuss the proposed protocol and reach a consensus. Stakeholders i.e. industry and patients representative are encouraged to provide feedback to PLEG protocol. The Ministry of Health owns the data, and if agencies want to share the data, they have to ask permission from the Ministry of Health.

PLEG practices in Switzerland, based on feedback from SNHTA:

Every three years the Federal Office of Public Health reviews all pharmaceuticals on the specialities list to check whether they still meet the requirements for listing. The review is conducted according to a list of rules that cover the HTA domains of efficacy and cost-effectiveness. It also covers the criterion appropriateness. The appropriateness of a technology can be defined as:

- relevant to patient care in comparison with alternative technologies,
- consistent with legal requirements, social and ethical aspects or values of the society,
- the quality and appropriate use of the technology in the Swiss practice setting.

In parallel to these triennial reviews, some pharmaceuticals present on the specialties list are selected for a full or short HTA report. This has happened since 2015, as part of the federal government's HTA programme that aims to re-evaluate benefits already being reimbursed by the obligatory health insurance system. The requests for a HTA report can be filed any time after the initial assessment, appraisal, and inclusion of the drug on the specialties list.

When the presented evidence of the PLEG review is considered insufficient, the commission can decide to delist or conditionally reimburse the drug. Data collection for PLEG reviews typically relies on published data rather than raw data.

For medical devices, a PLEG request can be defined at the moment of the initial appraisal of the device. This will include a description of the goals to be addressed, the type of PLEG (clinical study, registry, review of published data) and responsibilities. It will also define requirements of reporting and the time frame for a planned re-assessment. Usually a yearly status report is requested for each PLEG activity. Coverage conditions or PLEG modalities might be amended during a PLEG period if deemed necessary in view of the information from regular update reports.

PLEG practice for medical device, based on Azienda zero feedback:

PLEG are implemented by regional agencies as needed for re-assessment purposes with the collection of both clinical and resource use data.

PLEG practices in Croatia, based on feedback from HZJZ

There is no PLEG process within HZJZ, as they are not doing HTA. In Croatia, there was a separate government body called Agency for Quality and Accreditation in Health and Social Care that used to do it, and

now the Ministry of Health has taken over the task. The Ministry is then in charge of requesting the collection of any additional data on drugs or MDs.

3 PLEG PRACTICES ON JOINT LEVEL – RESULTS OF EUNETHTA JA3 WP5B WORK

3.1. Introduction – general organization of work within Work package 5B

Main objectives of JA3 WP5B included promoting collaboration on PLEG (between HTA bodies and other actors in the field) and enhancing the use of high-quality registries in HTA. For that reason, WP5B work was initially broken down into two activities:

- piloting joint work on PLEG requirements and data sharing for specific product or disease - *PLEG pilots (main activity)*;
- developing a tool to guide and assess the quality of registries – *REQueST tool (supporting activity)*.

In technical reporting, these two activities were respectively referred to as WP5B1 and WP5B2. The development of REQueST was performed in the beginning of the project as a separate, yet closely linked activity to pilot production. In the later phase of the project, REQueST tool was directly used in PLEG pilots.[2]

3.1.1 Governance: distribution of work and establishment of activity centres

Firstly, HAS as WP5 lead partner (LP) has been assigned the role of global coordination and project management of WP5B ; participation in the preparatory work for pilots (see here below) ; supportive role in the production of PLEG pilots ; production of the final WP5B deliverable (present report). During the course of the project, HAS was brought in to author and coordinate some PLEG pilots (see chapter 3.2).

Secondly, a dedicated task force composed by HAS and 4 activity centers was set up

- in order to make best use of the national experiences of WP5B partners, specific activity centers (AC) for pilot production have been established. Three agencies have been assigned the roles of activity centres, with each agency covering a specific type of products[3], in accordance with their national PLEG expertise: AIFA hospital drugs, TLV ambulatory drugs and avalia-t medical devices. In practice, this role implied the following tasks: participation in the preparatory work for pilot production (see here below); active participation in the pilot topic selection; main authorship and coordination of PLEG pilots for products in the domain of expertise; and participation in the production of the final WP5B deliverable (present report).
- NICE has been assigned the role of the lead of the production of the REQueST tool, thus becoming the fourth activity centre of WP5B. NICE has also participated in the production of the final WP5B deliverable (present report).

Finally a WP5B working group was established composed by 14 partners (AIFA; AQUAS, AETSA, AVALIA-T, NICE, ZIN, AGENAS, HZJZ, FIMEA, NOMA, INFARMED, OSTEBA, SNHTA, TLV) who were regularly informed on PLEG projets and were systematically invited to review PLEG procedure & guidelines and to participate in pilots.

3.1.2 Two phases of work on PLEG pilots in Joint action 3

EUnetHTA had a wide range of PLEG related activities since 2010, yet these were almost exclusively of theoretical nature in the previous Joint actions. The first examples of setting-up practical collaboration were to begin in Joint action 3. In order to best prepare this new collaborative activity, the work was split in two phases: preparatory work for pilot production in the first year of the project (2016-2017) and pilot production strictly speaking, from mid-2017.

---

[2] The use of REQueST is presented in more details in the chapter 3.3.

[3] It is to be noted that, whilst these technologies share common issues concerning development, they could have substantial differences concerning reimbursement pathways and evidence requirements, requiring differential management and additionally justify the creation of activity centers.

The objective of the preparatory work was to lay out particular aspects of PLEG collaboration, to be then considered in the phase of pilot production. The preparatory work consisted in identifying/analysing:

a) projects to collaborate with or to build on (through internet search of finalized or on-going projects/initiatives in the field)
b) stakeholders to involve in PLEG collaborations and the added value of engaging them (based on national experiences of WP5B partners and findings of other projects)
c) legal and practical barriers to set-up croos-broder data collection and/or exchanging data across registries and countries (again, based on national experiences of WP5B partners and findings of other projects).

The preparatory work was performed by the three AC (AIFA, TLV, avalia-t) and the LP (HAS). Its results were compiled in a report that was reviewed by WP5B partners (AETSA, AQuAS, CIPH/HZJZ, CRUF, Fimea, HAS, HDir, Infarmed, JAZMP, MPA, NICE, Osteba, SNHTA, ZIN). The report is available as a standalone internal document (MS 5.9-https://eunethta.sharepoint.com/:w:/s/EvGen/EWLta7uMaVVEqRu3A0FGAuIBBoN-m9yzIlKnQABdnsG5zQ?e=cKi9QW); its main findings are also incorporated in the present report.

The work on the pilot production strictly speaking started once the preparatory work was finalized, with the selection of topics for pilots. This and other phases of the pilot production are presented in the next chapters.

Of note, the WP5B work plan initially foresaw that the pilot production be carried out in two rounds (first and second round, with an intermediate analysis of lessons learned in between). That planning was abandoned in the course of the project for feasibility reasons (different start dates and duration of first pilots). All the lessons learned are analysed jointly, in the present report.

3.2. Cross-border collaboration on PLEG - EUnetHTA PLEG pilots

3.2.1. General characteristics of JA3 PLEG pilots

As of September 2020, two types of collaboration on PLEG have been carried out by WP5B:

1. Product-specific PLEG pilots arising from HTA
2. Registry-specific PLEG pilots.

3.2.1.1 PRODUCT-SPECIFIC PLEG PILOTS ARISING FROM HTA

Product-specific PLEG pilots can arise from evidence gaps identified either in national assessments of EUnetHTA partners or directly in EUnetHTA assessments.

Figure 1 presents the PLEG flow in general on the left side, and the corresponding outputs of JA3 product specific PLEG pilots on the right side.

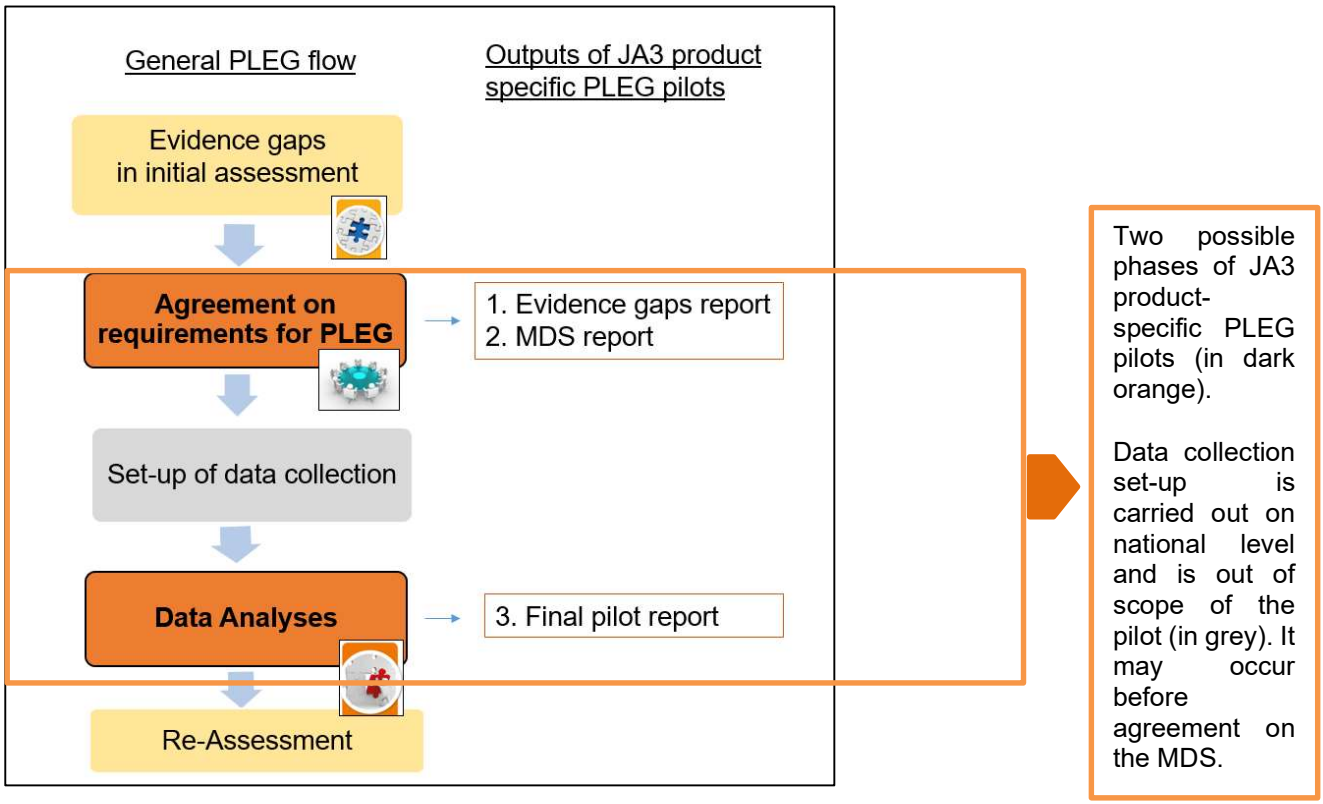


Figure 1: General PLEG flow and corresponding outputs of JA3 product specific PLEG pilots

The pilots consist in agreeing, among participating agencies, on the common requirements for PLEG (common evidence gaps, minimum data set and quality requirements) for a specific product, in order to fill in the gaps identified at the moment of the assessment of the product and inform its re-assessment.

→ These jointly defined requirements are presented in two reports: the evidence gaps report and the minimum data set (MDS) report.
→ Subsequent data collections are organized and implemented locally, on national level. The jointly defined requirements from PLEG pilots reflect or serve as the basis for the data collection set-up on national level.

Whenever possible, these common data (from different jurisdictions) are shared, compiled and analysed in a second phase of the pilot. The results are presented in a separate (third) report, along with the main lessons learned from the collaboration.

The reports represent the outputs of product-specific pilots and are published on EUnetHTA website (https://eunethta.eu/pleg/).

The added value of defining PLEG requirements jointly lies in harmonizing the structure of PLEG requirements and aligning them as much as possible, in order to create the possibility of obtaining **comparable** and **consistent da**ta on a **higher number of patients**.

As of September 2020, WP5B has performed three product specific pilots, led by the three pilot activity centres and all arising from evidence gaps identified in the respective **national** assessments (see table 1). More details on the topic selection, the exact organisation of work and the available results and lessons learned are presented in the following chapters.

Table 1: WP5B product-specific PLEG pilots as of September 2020

Name of the product	Indication	Agencies involved	Data sources used
Spinraza	Spinal muscular atrophy	AIFA (pilot lead), AAZ, FIMEA, INFARMED, NOMA, ZIN	Product or disease registries
Ibrance	Metastatic breast cancer	TLV (pilot lead), INFARMED, NIPN, NOMA *UCSC (observer)	Registries and claims databases
Left ventricular Assist Devices	End-stage heart failure	Avalia-t (pilot lead), NICE *Agenas, KCE (reviewers of the Evidence Gaps report)	Registries

3.2.2 REGISTRY-SPECIFIC PLEG PILOTS

Registry-specific pilots are performed in collaboration with registry owners and consist in assessing the suitability of existing data sources (most often registries) for HTA PLEG purposes, in terms of variables collected (minimum data set) and the quality of data collection. Since 2019, the latter is being assessed with the help of the REQueST tool.

The output of the pilot is one single report that contains non-binding recommendations from participating agencies on the discussed aspects (variables collected, data quality). It is published on EUnetHTA website (https://eunethta.eu/pleg/).

WP5B has performed two registry-specific pilots (see table 2). The second pilot on EBMT registry specifically focused on the suitability of this registry for post-launch follow-up of CAR T therapies. Of note, a third registry-specific pilot was supposed to be launched in April 2020 but had to be suspended because of the Covid-19 outbreak. The pilot was supposed to be performed together with the EMA and concerned the International Niemann-Pick Disease Registry (INPDR).

Table 2: WP5B Registry-specific PLEG pilots

Name of the registry	Indication	Agencies involved
European Cystic fibrosis society patient registry (ECFSPR)*	Cystic fibrosis	AQUAS, HAS, INFARMED, ZIN Observers: AEMPS, AIFA, G-BA, NICE Pilot coordination: HAS
European Society for Blood and Marrow Transplantation (EBMT) registry	CAR-T products in ALL[4], DLBCL[5] and PMBCL[6]	Avalia-t, AIFA, G-BA, HAS, INFARMED, NICE, NOMA, ZIN Observer: SNHTA Pilot coordination: HAS

* Pilot performed in collaboration with the EMA.

Additional observational pilots

Of note, WP5B partners have also participated as observers in two regulatory PLEG collaborations:

- in one EMA scientific advice on a Post Authorisation Safety Study (one pilot AC and WP5B LP);
- in the EMA qualification of the EBMT registry (six HTA bodies and WP5B LP). HTA bodies could not engage actively when the EMA qualification started because none of the CAR-T (specific objective of the EMA qualification) were assessed at that moment. The HTA-EBMT collaboration took place later, under a distinct form (see chapter 3.2.3.2).

3.2.2. Selection of topics and launch of collaborations

The selection of topics for the PLEG pilots was guided by the following general principles:

- in order to be selected, topics had to fulfil EUnetHTA Selection-prioritization criteria for PLEG ;
- a number of pilots were expected to arise from HTA reports, but collaborations initiated by other actors was also planned to be tested (in order to meet WP5B specific objective n°1, see Introduction);
- a number of pilots were expected to use data from registries (in order to meet WP5B specific objective n°2, see Introduction), but using data from sources other than registries was planned to be tested as well (given the raising interest in the use of prescription databases notably).

EUnetHTA selection-prioritization criteria for PLEG[7] were developed in Joint action 1, with the objective of helping HTA bodies, but also other organisations, determine if PLEG is really worth performing and feasible. The selection criteria are split in two categories: five primary criteria, all of which need to be met for a topic to be considered eligible, and four secondary criteria, allowing further selection and prioritization. The primary criteria question the need, the suitability and the feasibility of PLEG (by

[4] B-cell acute lymphoblastic leukaemia

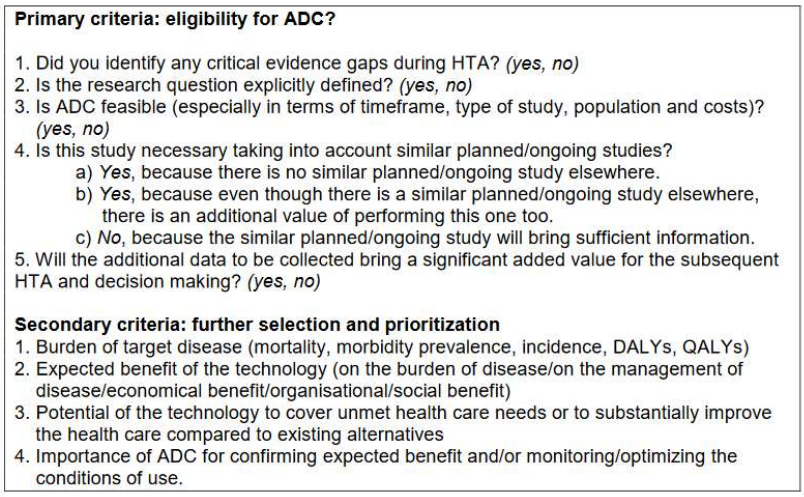
[5] Diffuse large B-cell lymphoma

[6] Primary mediastinal large B-cell lymphoma

[7] Called « AEG » (Additional Evidence Generation) in JA1

considering the existence of critical evidence gaps; how well they are defined and the need and the added value of setting up a new data collection)(see Figure 2).

Figure 2: JA1 selection prioritization criteria

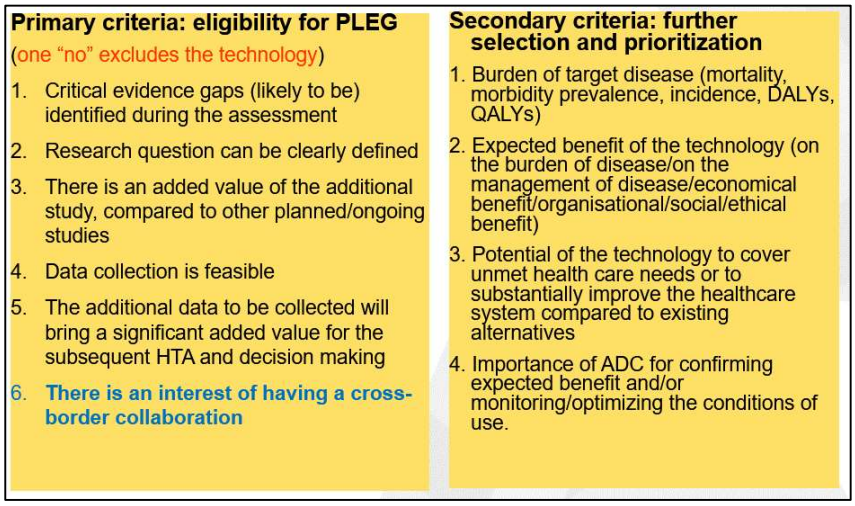


* ADC: Additional Data Collection

The JA1 criteria were considered valid and suitable for JA3 PLEG pilots, with the addition of two points specific to the context of JA3 activities:

- given the cross-border nature of the collaboration to be put in place, the interest of having a cross-border collaboration was also taken into account when selecting the topics for PLEG pilots (addition of a six criterion, see Figure 3);
- given the specific experience of the three pilot activity centers in developing/using observational data (collection) for PLEG purposes, JA3 pilots focused on observational data collection.

Figure 3: JA3 selection prioritisation criteria, adapted from JA1 criteria



Topic selection in practice

The selection of topics for the first product specific pilots was based on proposals made by the three pilot AC. The discussions were opened mid-2017, and the three agencies have suggested in total seven topics for drugs and nine topics for medical devices. Each proposal contained a description of the need, the suitability and the feasibility of PLEG, as required in the above presented criteria. All the proposals were arising from **national HTA** reports (of the three agencies).

After a primary selection by HAS and AC (notably prioritization of those proposals for which the national PLEG within the lead agency had not started yet) the final selection of the pilot topics was carried out at the annual WP5B WG meeting. Each activity centre then launched a call for collaboration for one topic selected among their proposals (see next section)[8].

Registry specific pilots in JA3 were initiated further to the application from registry holders. The applications were assessed against the same criteria (Figure 3), with the fourth criterion being automatically fulfilled (since data collections were already in place). In case of disease registries, these considerations were applied to the class of available or upcoming treatments. In case registries were to be assessed for their suitability for the follow-up of treatments that are still in development or for which HTA has not yet been performed, it was deemed necessary to have at least some evidence available on these treatments in order to select the collaboration.

The selection of topics for the last pilots of JA3 could start once the first product-specific pilots have sufficiently progressed (for resource reasons). The discussions with the AC therefore started in the second half of the year 4 of the project but had to be stopped during the peak of the Covid-19 outbreak. The discussions resumed during the summer of 2020 and covered both types of pilots, with a focus on Covid-19 related topics (in line with EUnetHTA's prioritization for the last year of the project). Final selection of topics took place in September 2020. As the pilots must be finalized before May 2020, they could only follow a rapid production process focusing on the minimum data set. Finally the two potential pilots identified for the continuation period of JA3 (one on COVID convalescent plasma and one on Zolgensma) could not be launched for lack of human resources.

Launch of collaboration and responses received

Once the topics have passed the selection process, call for collaborations were sent. This was done by using specific WP5B templates developed for this step, for both types of pilots (see 3.3). Templates were filled-in by the agency coordinating the pilot. In case of registry specific pilots, the call could be accompanied by the letter of intent submitted by the applicant. For product-specific pilots, responses were submitted through a specific questionnaire developed for that purpose (see 3.3).

All calls for collaboration specified that, in principle, pilot participants should be a) HTA bodies b) that could use the data covered by the pilot for re-assessment purposes.

The deadlines to respond to the calls were usually 10-15 working days, but the deadlines were extended when needed.

All JA3 WP5B calls for collaboration were successful, resulting in pilot launch. The number of responses varied, depending on the topic:

- A specifically low response rate was encountered for the medical device pilot (five responses in total), with the number of negative responses outnumbering the number of positive responses (one positive, four negative). This low rate could be explained by the fact that for the moment only few agencies have experience with PLEG on medical devices. Most of the partners do not actually run registries, do not have the remit to request PLEG or have problems accessing real world data on medical devices. As for the agencies that have experience with PLEG MDs, differences in national PLEG timelines for the MD in question were noted for some agencies, preventing these agencies to take part in the collaboration.
- Registry-specific pilots or drug specific pilots recorded more total responses, with the number of positive responses varying from three to nine (see tables 1 and 2).

[8] For the medical device pilot, the launch could not take place immediately after the annual meeting but several months later due to specific PLEG requirements for the leading agency on national level.

For each pilot, partners not being able to take part in the collaboration were asked to briefly explain the reasons why, along with their response. Lack of resources and no or limited possibility in having access to real world data (in case of product specific pilots) were among the most cited responses.

3.2.3. Conduct of the collaboration and encountered challenges

3.2.3.1. Distribution of work

- Product-specific pilots

As foreseen in the general distribution of work within WP5B (see section 3.1), the three pilot AC were coordinating the production of their respective pilots and have been the main authors of the pilot reports.

WP5B partners that responded positively to the call for collaboration participated in different pilot steps as described here below and participated in the production of the pilot reports, by providing necessary information and reviewing the drafts of the reports.

For some pilots, observers have been added to the team for capacity building (see Table 1).

HAS as WP5B lead provided support in the different pilot steps (see here below) and acted also as the internal reviewer of pilot reports.

- Registry-specific pilots

Unlike the product-specific pilots, the coordinators for registry-specific pilots were not pre-defined in advance within the general distribution of work, since no agency had specific previous experience with this type of collaborations. Each time, the role of the coordinator was discussed and agreed with partners having expressed interest in the collaboration.
For the two registry-specific pilots carried out, it is the HAS that took the role of pilot coordination and was the main author of pilot documents.
WP5B partners that responded positively to the call for collaboration participated in different pilot steps as described here below and in the production of the pilot report by reviewing the report drafts.
In both pilots, there have been agencies participating as observers, for capacity building (see Table 2).

3.2.3.2. Pilot steps[9]

This section presents general pilot steps. Challenges encountered and lessons learned from the JA3 pilots are presented in the following section; details on stakeholder involvement can be found in the chapter 3.2.4.

- Product-specific pilots

After a successful launch of the call for collaboration, general pilot steps include:

1) Establishment of pilot team and pilot start a) Confirmation of and distribution of tasks among pilot participants. If needed, further discussion on any legal/practical issues highlighted by the pilot participants in their responses to the call for collaboration b) Gathering/sharing of project management information (collection of DOI+CU for each participant and their validation by EUnetHTA COI committee; creation of specific pilot folder on the intranet; provision of a specific code to declare hours spent on the pilot in the timesheet) c) Informing relevant stakeholders on the pilot (manufacturer, patient associations and other stakeholders, see 3.2.4)	First (main) pilot phase

[9] For the general description of the pilots and related outputs, see 3.2.1.

d) Entering the pilot information in EVIDENT database (see 3.3) **2) Agreement on common evidence gaps** a) Collection of information on evidence gaps and research needs identified by pilot participants in their national HTA via the Questionnaire on evidence gaps (see 3.3) b) Based on the responses received, identification and highlight of commonalities. Presentation of common evidence gaps and subsequent research recommendations (in the PICO format) c) Production of the **Evidence gaps report** (using a specific template, see 3.3) Of note, all evidence gaps and research recommendations, regardless of the subsequent data collection setting (i.e. clinical studies or RW setting), can be reported in this step (step 2). Further distinction between the two settings is to be made at the level of agreeing on the data set and research methods (step 3). **3) Agreement on common minimum data set and research methods with quality requirements** a) Based on the results of the step 2, definition of the minimum data set (outcomes and variables) to be collected. This step can be performed in collaboration with stakeholders (see 3.2.4) b) Specification of the research methods (study design, statistical aspects etc.) c) When applicable, check/application of registry quality requirements by using REQueST (see 3.3) d) Production of the **Minimum data set report** (using a specific template, see 3.3) Of note, the minimum data set should reflect **all** outcomes and variables that need to be collected in a specific setting, to fill-in the evidence gaps. In case some of the common outcomes and variables could not be collected in practice in a certain country, this is to be reported in the final pilot report.	
Data collection period	
4) Exchange of data, data analysis and production of the final report a) Update on the possibility to share data among pilot participants b) Compilation of common (aggregate) data from pilot participants (whenever possible) c) Analysis of common (aggregate) data (whenever possible) d) Production of the **Final report** (using a specific template, see 3.3) including lessons learnt from the collaboration	Second pilot phase

The progress of the different pilot steps can be followed via the Checklist for different PLEG pilot steps (see 3.3).

Of note, in JA3 pilots, all pilot participants participated in the steps 2-4. The charge of Step 1 was split between the pilot coordinator and WP5B LP as follows: pilot coordinator in charge of steps 1a), 1c) and 1d), with possible help and support from WP5B LP; WP5B LP in charge of the step 1b.

Pilot participants are invited to provide feedback on the pilot once it is finalized.

- Registry-specific pilots

The two registry-specific pilots carried out until September 2020 followed a slightly different process, since one was performed in collaboration with the EMA, and the other was an HTA-only pilot in the context of specific drugs assessment. Both were performed in collaboration with registry owners and relied, for some or all steps (see here below), on the input and material provided by the registry owners.

The pilot performed together with the EMA on ECFSPR followed the EMA procedure for the Qualification of novel methodologies for drug development. Consequently, pilot steps included in brief:

1) Topic identification following request from registry holder
2) Establishment of pilot team and pilot start (step including the same sub-steps as for product-specific pilots (see here above), except the sub-step 1c)
3) Submission of the final briefing document with a list of questions to the EMA and the HTAb (by the applicant). **Points discussed: quality aspects and variables collected in the registry.**
4) Production of EMA and HTAb list of issues on the briefing document (by EMA and EUnetHTA, separately)
5) Tri-partite FtF meeting to discuss the issues. Meeting minutes produced by the applicant.
6) Final written applicant responses to the List of issues (by the applicant)
7) Production of the **Pilot report** (for more details see here below) (by EMA and EUnetHTA, separately)

This procedure gives the applicant the possibility to receive advice from both regulators and HTA bodies at the same time. It allows exchanges between regulators and HTA bodies but does not intend to produce a joint output. Accordingly, as specified above as well, EMA and HTA produced separate list of issues and final reports.

Moreover, the final outputs from the EMA and HTA side are different:

- From the EMA side, there are two possible outputs for the qualification procedure in general: **public Qualification opinion** (on the acceptability of a specific use of the proposed registry, based on the assessment of submitted data), or **confidential Qualification advice**[10] (on the measures to be taken by the registry holders to improve the quality and the usefulness of data).
- From the EUnetHTA side, pending clarifications and agreement on what a qualification opinion would mean in practice (e.g. exact reach of the decision, duration of the validity of the opinion etc.), it was agreed to have only one possible outcome of the process from the HTA side - the **Qualification advice**, i.e. non-binding recommendations from the participating HTA bodies on the discussed issues. They reflect the joint position of participating HTA bodies, when applicable, or individual positions of each HTAb, when joint position cannot be reached.
  The EMA Qualification procedure foresees that the detailed recommendations are shared with the applicant but not published (kept confidential) and that only the summary recommendations are made public. Accordingly, detailed EUnetHTA recommendations were shared with the applicant and the only the summary recommendations were published in the EUnetHTA pilot report.

It is to be noted that the ECFSPR qualification was the first time a qualification was performed for a registry, both for the EMA and for EUnetHTA.

In practice, the pilot coordinator had the charge of the general pilot coordination, the step 1, the communication with the EMA and the applicant, and the production of pilot documents. Pilot participants provided their input for the HTA list of issues, participated in the FtF meeting and reviewed the final pilot report. Pilot participants were invited to provide feedback on the pilot when it was finalized.

The second pilot on EBMT registry was an HTA-only pilot, which followed the next steps:

1) Establishment of pilot team and pilot start (step including the same sub-steps as for product-specific pilots (see here above), except the sub-step 1c)
2) In parallel:
   a) HTA agreement on the variables to be collected in the registry (HTA minimum data set) - drafted on the basis of conclusions of national HTA reports (and national data sets when available), provided by the pilot participants

[10] Qualification advice is a confidential document shared only with the applicant. The latter can be accompanied by a letter of support that can be made publicly available subject to applicant's agreement. The objective of the letter of support is to encourage the efforts for data sharing and facilitate the improvements to be made.

b) HTA Registry quality analysis via REQueST – on the basis of the information provided by the registry holders in REQueST forms
3) Production of the HTA list of questions arising from 2a) and 2b) for the registry holder
4) FtF meeting with the registry holderto discuss the issues. Meeting minutes produced by EUnetHTA pilot coordinator.
5) Agreement between HTA participants on the final versions of the HTA minimum data set (2a) and the registry quality analysis via REQueST (2b). Additional exchanges in written with the registry holder, if needed.
6) Production of the **Final report** (incorporating the HTA minimum data set and the results of the REQueST quality analysis). As in the case of an EMA-HTA pilot, the content of the final report represents non-binding recommendations from the participating HTA bodies on the issues discussed (variables and data quality). They reflect the joint position of participating HTA bodies, when applicable, or individual positions of each HTAb, when joint position cannot be reached.

In practice, the pilot coordinator had the charge of the general pilot coordination, the step 1, the communication with the applicant and the production of minutes and other pilot documents. All pilot participants participated in the task of defining the HTA minimum data set. The task of performing the quality analysis via REQueST was carried-out by three agencies separately, their input was consolidated by the pilot coordinator and then reviewed and further discussed with all pilot participants. All pilot participants participated in the FtF meeting and reviewed the final pilot report.

It is to be noted that in both processes (i.e. EMA-HTA and HTA only), the main content of exchanges was the same (i.e. the variables collected in the registry and the quality of the data collection). The main difference between the two is that in the EMA procedure, the process mainly relies on the documentation provided by the applicant (through the briefing document) and that the exchanges are structured around applicant's questions to the EMA and the HTA. In the HTA only pilot, the registry holder did not submit a briefing document, or specific questions to HTA at the beginning of the procedure; the information was provided through the REQueST tool, and the discussions were structured around REQueST items and the HTA minimum data set. Of note, at the time the ECFSPR pilot with EMA was performed, REQueST tool was not yet available.

3.2.4 Challenges in the conduct of PLEG pilots

3.2.4.1 Challenges anticipated during preparatory work

The preparatory work (https://eunethta.sharepoint.com/:w:/s/EvGen/EWLta7uMaVVEqRu3A0FGAuIBBoN-m9yzilKnQABdnsG5zQ?e=cKi9QW) for pilot production included an establishment of a list of potential **practical and legal barriers** in setting-up cross-border data collection and/or exchanging data across registries and countries.

The list was developed by AIFA by consulting the inventory of initiatives/projects of interest for PLEG work (also developed during the preparatory work) and analysing publications and material produced by those initiatives/projects. An additional literature search of international and European projects and initiatives specifically covering the topic of the registries or the broader topic of cross-border sharing of health data, has been carried out. Finally, EU regulation available or under revision at the moment of the production of the preparatory work, has been analysed. These findings were supplemented with the experience of WP5B partners, and notably that of pilot activity centers. The preparatory work document was reviewed in the end by WP5B partners.

The established list was divided in two sections: 1) practical barriers and 2) legal barriers (further sorted as privacy and confidentiality of data, and as multi points and multi-stakeholders responsibilities).

As for practical barriers, twelve barriers in total were identified (see annex 1). Besides presenting the barriers, the list also aimed at identifying possible solutions to be implemented for each barrier, with a further attempt to indicate, when applicable, also possible alternative solutions in addition. In further discussions, WP5B partners agreed that **data comparability, interoperability, data access, patient mobility and different IT system standards could be the main practical issues for PLEG pilots** (especially the step of data exchange). Data quality issues were expected to be addressed with the development of the REQueST tool.

As for legal barriers, nine barriers in total were identified (see annex 1). Besides presenting the barriers, the list also aimed at identifying possible solutions to be implemented for each barrier, with a further attempt to

indicate, when applicable, also possible alternative solutions in addition. In further discussions, WP5B partners agreed that **privacy and data protection rights were the main legal issues** for PLEG pilots.

3.2.4.2 Learnings from the performed pilots

- **In general**

1) Differences in national HTA and PLEG timelines

National HTA and subsequent PLEG can be performed at different time points after marketing authorization or CE approval. In addition, PLEG process can have different durations in different countries. This had a particular impact on the conduct of JA3 product-specific PLEG pilots. In some cases, some national PLEGs have started and/or moved faster than others, which caused challenges in aligning and following the pilot timelines. Likewise, if national PLEGs were facing delays, clock stops in pilot production were sometimes required. These issues could be overcome as general timeline alignments among partners' progress. Of note, these differences did not have an impact on conduct of the two registry-specific pilots.

2) Differences in national PLEG processes

As illustrated in the Chapter 2, existing PLEG processes vary among WP5B partners. For JA3 pilots, these differences had an impact on the timing for the start of the collaboration (e.g. some partners could get involved only once the national PLEG was officially issued) but also on the conduct of the collaboration for product-specific pilots (e.g. involvement of stakeholders, access to data – these aspects are further discussed on the next pages). These issues could be overcome as PLEG processes among partners become more aligned.

3) Resources issues

The conduct of PLEG pilots was affected by internal resource constraints among WP5B partners. Following points were particularly noted: a) periods of limited partner availability (e.g. because of concomitant national emergences, particularly noted during the Covid-19 outbreak); b) changes in the staff allocated to the pilot, with replacements not always found on time or not being in a position to commit equally. These lessons show the importance of continuous commitment of participating agencies to contribute actively to the work.

- **Product-specific pilots**

Except the above-mentioned timeline and resources constraints, which resulted in delaying the production, no particular difficulties were encountered with the tasks themselves in the phase 1 of pilot production. Agreement on common evidence gaps was always reached, as well as the agreement on the common minimum data set. Partners agreed that the minimum data set should reflect all variables of interest for HTA and arising from the common evidence gaps; in case some variable is not collected in a certain country that is to be reflected in the final pilot report, but should not lead to the exclusion of the variable from the common minimum data set.

Last pilot phase (exchange of data, data analysis and production of the final report), and especially the step of accessing and sharing data, cannot be conducted. In average, in each product-specific pilot, only few agencies (1 or 2 maximum) could access and share data.
Learnings from the pilots regarding data availability, access and sharing can be summarized as follows:

1) Differences in infrastructures for use of and access to data among HTAb

Important differences in access to PLEG data were noted. Some HTA bodies planned to rely on existing data sources and have encountered the following challenges:
- difficulties in establishing contact with data owners,
- specific application process in place in order to get access to data, requiring extra work and additional documentation, with lengthy application and approval procedures (several months),
- need to pay for data access or data sharing.

All these obstacles impeded these pilot participants to access and share their national data - at all or by the end of JA3. These access problems were encountered in countries in which PLEG processes are still in development and not completely established. A link was also observed between the binding character of the PLEG for the re-assessment and the access to data – HTAb whose PLEG recommendations were not officially linked with re-assessments have encountered more difficulties in actually obtaining the data.

2) Difficulties with data sharing

Given the findings from the preparatory work, it was expected that the data sharing step would be the most challenging step of product-specific PLEG pilots. For that reason, it was assumed that the sharing of data

would be limited to aggregate data and that consequently, only the qualitative analysis of the results from different countries would be possible.
The experience from the product-specific pilots confirmed that, for those partners who had access to data, sharing aggregate data was much less problematic than sharing patient level data. Whereas aggregate data were considered sufficient for some outcomes, it was found regrettable in principle not to have the possibility to pool the data from different countries and perform a quantitative analysis.
In one pilot, one participant reported having access to aggregate data but not being able to share them, for legal reasons but also timing issues (data to be received after the end of JA3).

3) Missing outcomes/variables in registries

HTA bodies relying on existing registries reported that, in some cases, not all outcomes and variables from the jointly defined minimum data set were collected through the data source they planned to use (e.g. QoL).

These findings from the pilots confirmed the results of the preparatory work, which also identified variations in the healthcare's organization and governance and organizational aspects related to data access as possible obstacles for the step of data exchanging. The options for establishing specific procedures/agreements to grant HTAb easier access to data should be further explored.
The possibilities to improve data sharing should also be further discussed in the future. A legal consultation and support on this element would be recommended. The options for establishing specific agreements for data sharing should be further explored.
If these aspects are improved, future PLEG collaborations could include the step of performing a quantitative analysis of common data.

- **Registry-specific pilots**

Unlike product-specific pilots, no particular difficulties were encountered with the pilot tasks. As for the agreement on the HTA minimum data set (the variables to be collected), agreement on the core outcomes was reached among HTAb. Some differences in the level of details required or regarding the importance of a specific variable were noted (e.g. variables relevant for economic but not for clinical assessment). QoL questionnaires recommended by HTAb could also be different.
Like in the product-specific pilots, it was noted that some HTA relevant variables (e.g. QoL) were not collected in the registries.

Even though these pilots do not include the actual step of sharing data, the possibilities to share data - in this case between the registry and the HTAb- were mentioned during the exchanges (since these aspects are covered by REQueST items). In general, HTAb preference of patient level vs. aggregate data depended on national PLEG processes. Naturally, those HTAb that perform some or entire analysis on their own expressed the wish to receive patient level data, in order to be able to perform subgroup analysis or pharmaco-economic analysis in particular. For registry holders, sharing individual patient level data was perceived as much more stringent legislation wise and necessitating changes in patient consent planning.

As for REQueST analysis, agreement was reached among HTAb on all scores (in the pilot in which REQueST was used).

The use of REQueST not only helped structure the discussions around data quality but also, thanks to the comprehensiveness of its items, allowed to discuss with the registry representatives other important aspects relative to data sharing and analysis highlighted during the preparatory work, such as interoperability, patient mobility etc.

3.2.5 Stakeholder involvement

3.2.5.1 Results from preparatory work on identification of relevant stakeholders and their roles

It is acknowledged that building an efficient system for PLEG activities depends on the engagement of several stakeholders. For that reason, the preparatory work for pilot production (annex 2) included a stakeholder analysis, aiming to gather relevant information about different stakeholders of relevance for PLEG, and to formulate, for each of them, the added value of engaging in PLEG activities.

The list was developed by TLV and supplemented with input from a sample of relevant Swedish partners, WP5B AC and findings from other projects with similar or broader scope. The preparatory work document was reviewed in the end by WP5B partners.

The work resulted in a list of twenty-five stakeholders that might be involved in different PLEG activities in different settings summarized in annex 2. Most important characteristics and information of relevance for WP5B pilots are presented in different columns: how does the stakeholder contribute to PLEG, what does the stakeholder expect from PLEG, what are the "risks" for the stakeholder to get involved in PLEG, what would be the expected work load for the stakeholder in PLEG, what does PLEG bring to the stakeholder ("added value"). The importance of each stakeholder may vary depending on the exact purpose of PLEG, the exact setting etc. In further discussions, WP5B partners agreed that for the JA3 pilots **the most relevant stakeholders to include would be: health professionals, patients / patient organizations, product manufacturers, registry holders, as well as, when applicable and depending on the context, other health organizations: regulators, Ministry of health, etc.**

3.2.5.2 Learnings from the performed pilots

In practice, WP5B explored possibilities to collaborate with various stakeholders when conducting PLEG pilots.

Registry-specific pilots were always performed in collaboration with the registry holders, one was performed in collaboration with the EMA as well. In the HTA-only pilot, the registry holder will be invited to provide feedback on the pilot once it is finalized.

As for product-specific pilots, due to the current differences in national practices regarding stakeholder involvement (see chapter 2), the decisions on how to involve stakeholders were made separately for each pilot (since depending on the participants' practices). Following principles were defined: a) prior to establishing contact with stakeholders, preparatory work stakeholder list was consulted, in order to make sure that all relevant stakeholders are included; b) stakeholders could be involved either on **pilot (joint) level** (i.e. contacted by the pilot lead) or on **national level** (i.e. contacted individually by each participant, at the moment of national uptake).

Each pilot report (i.e. Evidence gaps, MDS, Final report) contains the details on stakeholder involvement on pilot level at the stage of the production of the report.

The involvement of the main stakeholders in JA3 product-specific pilots can be summarised as follows:

- For the three product-specific pilots, manufacturers were always contacted on pilot level and, when responded, kept informed about different pilot steps and outputs
- Health professionals were involved on pilot level in one pilot (LVAD), in which they were informed on the pilot and also participated in the step of agreeing on the common minimum data set (step 3), as external experts who reviewed the HTA dataset via Delphi survey. Their involvement followed the general EUnetHTA rules for involvement of external experts. Before confirming their involvement, experts' Declarations of interest were examined and approved by the EUnetHTA DOI Committee
- Patient involvement was handled on national level (when part of national PLEG practices)
- Registry holder involvement was handled on national level (when part of national PLEG practices)
- Regulators were not involved in the pilots, since, when applicable, their PLEG requirements were already defined.

3.2.5.3 Engagement with stakeholders and other actors outside the pilot production

Engagement with regulators

WP5B closely collaborated with the EMA throughout Joint action 3.

EUnetHTA has established collaboration with the EMA on specific activities that are described in the EUnetHTA-EMA work plan. For WP5 Strand B these include gaining experience with late dialogues and optimising the use of post-licensing evidence generation for decision making, collaboration in requirements for data collection and analysis of real-world data including registries. Mutual activities in the field were regularly discussed at bi-annual EMA-EUnetHTA meetings.

In addition, besides the previously described collaborative registry-specific pilot, WP5B partners also participated in five workshops organised by the EMA Patient registries initiative: on Cystic fibrosis (June 2017), Multiple sclerosis (July 2017), CAR T cells (February 2018), Haemophilia (June 2018) and on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features (November 2019). WP5B partners' participation was always on individual basis, coordinated by WP5B LP (HAS). The WP5B LP has in addition, for the November 2019 workshop, provided input on EUnetHTA quality requirements for registries, on the basis of the requirements outlined in the REQueST tool.

Finally, WP5B partners have also contributed to the public consultation on the EMA Discussion paper on the use of patient registries for regulatory purposes in June 2019. Input from eleven WP5B partners was collated by WP5B LP (HAS) and submitted to the EMA.

WP5B has also established contact with representatives of the International Medical Device Regulators Forum (IMDRF) and attended their meeting in early 2018 in order to present the work on REQueST.

Engagement with EUnetHTA stakeholders

WP5B has involved EUnetHTA stakeholders in the development of the REQueST tool and its vision paper, in the framework of a stakeholder consultation on the draft versions in November/December 2018 (seven responses received) and in the framework of the public consultation on the near final versions in June 2019 (five responses received).

Moreover, regular updates on WP5B activities were provided at annual EUnetHTA Assemblies and Forums, as well as at EUnetHTA-EFPIA meetings.

Engagement with other projects/initiatives on RWD

WP5B has continuously exchanged and contributed to several other projects and initiatives related to RWD/RWE. Can be cited in particular:

- participation in European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) qualitative survey on the ENCePP Code of Conduct Revision 4 (June 2018)
- contribution to the INAHTA Real world evidence task force activity on revising Real World Data/Real world evidence definitions (September 2018)
- revision of the HTAi Policy forum paper "How to deal with the inevitable; generating real-world data and using real-world evidence for HTA purposes. The role of HTA agencies, industry and other stakeholders" (March 2019).

3.3. Tools for collaboration on PLEG

This chapter recalls all available material for joint work on PLEG that was produced during JA3 or previous joint actions. Of note, the general guidance and the IT tools can also be used for national PLEGs.

3.3.1 Templates for different collaboration steps

All of the listed templates were developed in JA3 and are stored on EUnetHTA intranet https://eunethta.sharepoint.com/:f:/g/Work%20Packages/WP5/StrandB/plegpilotsstrandb1/EltUX68pgU5Dr32eGZZ54JAB4GSWmtdma48QHfQGG5kmtw?e=8AliNa (for internal use only). Their use in specific pilot steps is cited in the previous chapter (3.2). The Evidence gaps template in REA reports is presented in more details at the end of this chapter.

Template	Step to be used in	Additional comment
Selection/prioritization criteria for the topic of collaboration	Topic selection	JA3 adaptation of JA1 criteria, for the specific context of cross-border collaboration (see 3.2.2)
Evidence gaps template in REA reports **(for PLEG arising from JCAs)**	Topic selection and agreement on common evidence gaps	Presented in more details at the end of this chapter
Call for Collaboration	Launch of collaboration	Three templates available: for product-specific pilots, for HTA-only registry specific pilots, for HTA-EMA registry specific pilots
Questionnaire for the expression of interest for participation to pilots **(for product-specific pilots)**	Launch of collaboration	
Checklist for different PLEG pilot steps (pilot steps follow-up template)	All along the pilot production	Two templates available: for product-specific pilots and for HTA-only registry specific pilots
Questionnaire on evidence gaps	Agreement on common evidence gaps (product-specific pilots)	Based on JA2 position paper on research recommendations (see next list)
Report on common evidence gaps	Agreement on common evidence gaps (product-specific pilots)	Based on JA2 position paper on research recommendations (see next list)
Minimum Data Set report	Agreement on the minimum data set and research methods with quality requirements (product-specific pilots)	Based on JA2 Core protocol (see next list)
Final PLEG report	Finalization of the pilot	Draft available – might be upgraded after the first use in pilots
Form to collect feedback from Registry holders **on usage of REQueST**	Post-pilot phase (for registry-specific pilots)	Being drafted – might be upgraded after the first use in pilots

3.3.2 Procedures, guidance and IT tools for collaboration

Except for the present document and the REQueST tool, all other documents and the database were developed in previous joint actions. Except EVIDENT database, all are publicly accessible.

The present document is specifically focusing on joint work, all **other outputs listed here below can also be used for national PLEGs.**

REQueST tool and EVIDENT database are presented in more details at the end of this chapter.

Name	Short description	Available at	Collaboration step to be used in
Criteria to select and prioritize health technologies for additional evidence generation	Criteria aiming to help HTA doers, research funders and other stakeholders to select technologies for which additional studies are really worth performing	https://eunethta.eu/wp-content/uploads/2019/10/Selection-prioritisation-criteria-1.pdf	This version to be used when considering PLEG in general, and on national level In a context of a cross-border collaboration, JA3 adaptation (see previous list) to be used
Position paper on how to best formulate research recommendations for primary research arising from HTA reports	Document aiming to provide a structured, harmonized and transparent approach in identifying evidence gaps and formulating subsequent research recommendations	https://eunethta.eu/wp-content/uploads/2019/10/EUnetHTA-Position-Paper-on-research-recommendations.pdf	Agreement on common evidence gaps[11] (as additional guidance to the corresponding templates from the previous list)
Position paper on how to decide on the appropriate study design for primary research arising from HTA reports	Document providing consideration of various issues around the choice of the appropriate study design	https://eunethta.eu/wp-content/uploads/2019/10/EUnetHTA-Position-Paper-on-study-design_0.pdf	Agreement on the minimum data set and research methods with quality requirements (as additional guidance to the corresponding template from the previous list)
Core protocol for Additional Evidence Generation	Document defining the "core elements" of a study protocol for Additional Evidence Generation, and developing a template, based on these core elements, that could be used in different countries	https://eunethta.eu/wp-content/uploads/2019/10/EUnetHTA_Core-protocol-Pilot-for-AEG_0.pdf	Agreement on the minimum data set and research methods with quality requirements (as additional guidance to the corresponding template from the previous list)

[11] Or whenever it is required to present evidence gaps and subsequent research recommendations in a structured, harmonized and transparent manner.

Name	Short description	Available at	Collaboration step to be used in
REQueST tool **(excel and online version)**	Practical tool aiming at guiding and evaluating the quality of registries.	• Excel version : https://eunethta.eu/request-tool-and-its-vision-paper/ • https://eunethta.sharepoint.com/sites/REQuest	• Agreement on the minimum data set and research methods with quality requirements (product-specific pilots) • Registry quality assessment step (registry-specific pilot)
EVIDENT database	• Allows to share and store information on national and joint (EUnetHTA) PLEG activities • Contains information on both PLEG requirements and subsequent data collections	https://eunethta.dimdi.de/EVIDENT/login.xhtml Access restricted to EUnetHTA partners having an EUnetHTA ID and password.	All along the collaboration (see the specific description here below)

3.3.3 REA evidence gaps table

In collaboration with WP4 LP and CoLPs, WP5B has started to investigate mid-2018 possible links between the evidence gaps identified in EUnetHTA assessments with the WP5B work. This inter-WP collaboration resulted in a co-development of the Evidence gaps table template, which aims to allow to present the evidence gaps identified during EUnetHTA assessments in a structured and harmonised way. These common evidence gaps could be the starting point of a national or joint PLEG, in which further requirements for PLEG would be defined (dataset to be collected, quality requirements). This collaboration therefore contributes to the lifecycle approach of EUnetHTA´s work.

The development of the template was based on the JA2 Position paper on how to best formulate research recommendations for primary research arising from HTA reports and notably the Table n°3. Some format and structural adjustments were made to the table and thus created template was shared with WP5B and WP4 partners for comments. The near-final version of the tables was presented at the EUnetHTA-EFPIA meeting in December 2019, and the final version was published in the EUnetHTA Companion Guide in February 2020.

The template comprises three parts: the first part (“Evidence profile of the technology”) summarizes the main information about the rationale, the research question(s) and the PICO of the assessment; the second part (“Assessment results”) presents the outcomes where evidence is currently lacking or is considered insufficient (on the basis of assessment results); the third part (“Additional evidence generation needs”) presents the subsequent additional evidence generation needs, structured according to the EPICOT format. The appropriate study design as well as ongoing studies likely to fill-in the identified gaps can also be indicated in the third part.

In practice, the WP4 assessment team completes the table template during the internal review of the first draft assessment and sends it to WP5B. The third part of the table (“Additional evidence generation needs”) is also published in the appendix of the assessment report.

Since its publication in the Companion guide, the use of the template was piloted in ongoing REA. WP5B received first tables in August 2020. Specific meetings were organized with WP4 to feedback on the usefulness and practical use of the template. WP4 project teams found the tables quite complex to fill in in absence of

dedicated guidance with rational and explanations (illustrated with examples) for tables completion. The tables are easier to grasp for agencies with the experience of requesting PLEG at national level. Therefore a guidance was developed in collaboration with WP4 (https://eunethta.sharepoint.com/:b:/s/EvGen/EXIg58Y2bPJGs4F0GhFrwxMBkY-nqJ35xzFxPSoXvt7hlg?e=yf8GX2)

3.3.4 REQueST tool

The Registry Evaluation and Quality Standards Tool (REQueST) is a practical tool aiming to support HTA bodies in guiding and assessing the quality of registries.

REQueST is specific to registries as data collection systems, which are defined as "organised system that collect data and information on a group of people defined by a particular disease, condition, exposure or health-related service and followed over time, and that serves a pre-determined scientific, clinical and/or public health (policy) purpose" (adopted from PARENT). As for registry-based studies (i.e. investigation set up to answer a research question that uses data collected in a registry), they will benefit from quality assessment of the registry platform via REQueST but will have other specific requirements that need additional review by other tools.

REQueST can be used in all joint EUnetHTA or individual national activities in which the quality of registry data for HTA purposes is to be defined or assessed. A widespread adoption of the tool (i.e. by other HTA and regulatory organisations) should contribute to an even more effective usage of good quality registry data. Likewise, the tool can be used by evidence developers to guide or self-assess the quality of their registry.

The standards set out in the tool are universal and essential elements of good practice and evidence quality that are, therefore, relevant for different types of registries. They are divided in three sections:
8 'methodological' (descriptive) items relating to suitability of the registry for a specific purpose (in terms of the type and nature of the data collection), 12 'essential' quality standards relevant to any registry for HTA purposes, used to assess the quality of the data collection *stricto sensu* and 3 'additional' considerations for specific purposes. REQueSt - Home (shahttps://eunethta.sharepoint.com/:f:/g/Work%20Packages/WP5/StrandB/plegpilotsstrandb1/EltUX68pgU5Dr32eGZZ54JAB4GSWmtdma48QHfQGG5kmtw?e=8AliNarepoint.com)

To WP5's knowledge, it is the only tool currently available to bring together textual guidance into the form of criteria and feedback to registry owners. It sits alongside the existing guidance on registry quality as a tool for its implementation. The purpose is to highlight areas of a registry that need improvement in order to maximize the quality of its data and ensure that those data can be used for HTA purposes and beyond.

3.3.4.1 Development of REQueST

REQueST was developed in the framework of JA3 WP5B. NICE and CIPH (HZJZ) were the main authors of the tool drafts.

At the beginning of REQueST development, a Report on current use of registry data by HTA agencies was produced. This report was based on a) document and web-based search of partners' published HTA process information where available (performed by NICE) and b) a survey of EUnetHTA partners and follow-up interviews (performed in January 2017, 33 responses received). The final version of the report was shared with partners in March 2017. The report showed that many agencies do use registry data in their everyday work but that few employ criteria or standards to assess the quality of registry data. In addition, the criteria used were unformal or not specifically developed for registries. (https://www.cambridge.org/core/services/aop-cambridge-core/content/view/B1829150772A2D02796A1A4719C997FF/S0266462318000478a.pdf/quality_assurance_of_registries_for_health_technology_assessment.pdf)

(https://eunethta.sharepoint.com/:b:/s/EvGen/EfkY2OHi2jdPqSfPzu6mMqkBmxpJ6VR5YXlqpR4g9bWjkQ?e=bFyMVd)

Based on the above-mentioned report and notably the results of the PARENT Joint action, a draft standards tool was prepared. The draft tool went through an extensive review and testing phase, and each time the feedback gathered was used to produce an upgraded version:

- the first consultation targeted WP5 partners and was carried out in April/May 2018, with twelve partners responding;
- the second consultation targeted WP5 partners, EUnetHTA stakeholders and the EMA, and was carried out in November/December 2018. Thirteen WP5 partners, seven external partners (stakeholders) and the EMA have responded;
- in parallel, three volunteering agencies (avalia-t, AQuAS and INFARMED) have tested the use of the draft tool in their HTA activities, on three specific registries (one each), from October 2017 until January 2019. The testing phase has confirmed the usefulness of the tool, and the gathered recommendations for changes have been implemented in order to improve its utility;
- finally, the near-final version was submitted for public consultation. In total, 17 organisations responded, including HTA bodies (of which three were WP5 partners), regulators, patient organisations, industry, health professionals, academia, and CROs.

All comments received during the different consultations were each time collated in a document together with responses from the REQueST development team and shared with the consultees. Likewise, a specific report with the results of the testing phase was produced.

The final version of the tool and of the accompanying vision paper (see here below) was published on EUnetHTA website in October 2019. (https://www.eunethta.eu/wp-content/uploads/2019/10/Registry-Evaluation-and-Quality-Standards-Tool-REQueST-1.xlsm)

3.3.4.2 Use of REQueST

As already specified, REQueST can be used by:

- evidence developers (e.g. registry holders) to develop the quality of their registry,
- international organisations (HTA bodies) considering whether to use registry data for HTA and regulatory purposes.

In practice, since its publication, the tool has been used in two EUnetHTA PLEG pilots, in EUnetHTA Early dialogues (3 Eds until October 2020) as well as in several national PLEG activities.

As for EUnetHTA PLEG pilots, REQueST was used by participating HTAb in the registry-specific pilot with EBMT, in order to assess the quality of an existing registry (EBMT), and in the product-specific PLEG pilot on LVAD, in order to guide the set-up of a new registry. It is to be noted that both possible uses of REQueST were covered by these pilots.

Likewise, in EUnetHTA Early dialogues, HTAb use REQueST standards to give recommendations on usage of a specific registry for PLEG, whereas manufacturers use REQueST standards to discuss rational for choosing one specific registry for future PLEG.

REQueST was also used in national PLEG activities. NICE reported two examples of use of REQueST on national level, with very positive feedback from registry holders on the purpose of the tool and the defined standards. On the other hand, the format of the tool (excel sheet) was found not very user-friendly by the registry holders.

It is to be noted also that REQueST was referenced as registry quality standard in the Report of the EMA workshop on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features (held in November 2019).

WP5B has also been made aware of the use of REQueST by registry holders for self-assessment of the quality of their registry.

3.3.4.3 Vision on the options for the sustainable availability and use of REQueST after the end of JA3

In parallel with the development of the REQueST tool, a vision paper on the options for its long-term delivery, use, and sustainability was drafted. The paper was revised through the aforementioned WP5, stakeholder and public consultations. A phased approach to tool implementation with learning from experience has been advised. WP5B partners agreed that training or assistance for tool use should be ensured. The ownership, the

continued development of the tool after JA3 as well as a broadening of the vision for future use of REQueST, allowing third parties to use and perform assessments via REQueST, are still to be agreed.

The subsequent use of REQueST after its publication indicated that an on-line version of the tool would be more useful and user-friendly than the current excel version. A SharePoint version using PowerApps functionalities was therefore developed in 2020 and should be released soon for testing last quarter of 2020. The funding for the PowerApps licences and the maintenance of the tool should be considered for the launch of the online version and its use after JA3.

3.3.4.4 EVIDENT database

EVIDENT database was released in 2012, with the objective to allow sharing and storage of information on joint or national PLEG projects of EUnetHTA partners.

There is no restriction regarding the health technology covered by the PLEG project, the type of data collection or the phase of the project. The database can indeed contain information on all types of health technologies (drugs, MDs, procedures) and on planned, ongoing or finalized PLEGs.

In practice, the database allows to:

- share/search information on ***PLEG recommendations/requests*** (details on evidence gaps and subsequent research needs)
- share/search information on the ***progress of the PLEG*** (with the possibility to upload the study protocol and share study results, when available)
- express ***interest in a collaboration on PLEG*** – additional functionality
- share/search information on the ***HTA and reimbursement "status" among EUnetHTA partners for innovative technologies*** for which there is a record in EVIDENT – additional functionality.

The database can therefore be used in all stages of joint/national PLEG work. To WP5B knowledge, it is the only database gathering information on HTA-originated PLEG for all types of health technologies and for different types of data collection (both trials and observational studies). It is also the only database allowing to both share information on evidence gaps and to follow-up the progress of subsequent studies (set-up to fill-in these evidence gaps).

The database was offline for a long period during JA3, due to transfer of IT hosting and the requirements for security fixes.

Since its re-opening at the end of 2019, the database was fed with information on EUnetHTA PLEG pilots and with information on recent national PLEG projects from some WP5B partners.

A specific work group was set-up within WP6 to perform an analysis of EVIDENT functionalities; the suitability of the database and possible improvements were also discussed with WP5B partners. Following conclusions arose from the two pieces of work:

- EVIDENT is adapted for entering information on current EUnetHTA PLEG pilots ((i.e. product specific pilots and registry-specific pilots). In addition, there is an interest among EUnetHTA partners to share information on national/EU registries and their use for PLEG, EVIDENT database can be used for that purpose.
- A balance should be found between the time needed to enter information and the gain from doing it. The information to be entered in EVIDENT can be limited to the mandatory items only, other items can be left empty or completed in a second time[12].
- As for additional functionalities (see here above), and notably the collection of information on the reimbursement status of innovative technologies, it was agreed that, while this information can be of great importance in some cases, its collection on a systematic basis is too burdensome. It was therefore agreed

[12] The database manual was upgraded in the meantime, in order to better highlight the fact that only few database items are mandatory and must be filled-in in order to submit the forms. The mandatory items are now presented in a separate list, in order to be easily distinguished from the rest of the items. The updated manual can be found here

that this functionality should be activated and used only in specific situations -e.g. emerging HT of great interest for EUnetHTA partners.

3.4. Summary of lessons learned and recommendations for the future

3.4.1 General

- A common definition of PLEGs is proposed: PLEG is an umbrella term for evidence generated after the launch or licensure of a health technology within its approved or intended indication. Its role is not to replace but to complement evidence generation already undertaken for marketing authorisation or HTA appraisal, addressing remaining uncertainties but also potentially covering wider questions of disease management and healthcare delivery. It contributes therefore to the overall and accumulating evidence about a health technology during the life cycle. PLEG in general is not limited to a specific type of data collection but can encompass a wide range of study designs (both interventional and observational)
- Various PLEG pilots have been carried out in JA3, with different objectives and data sources used, sometimes even within the same pilot.
  WP5B therefore met its objective of conducting a number of pilots using registry data, but also testing the use of other data sources.
- WP5B also met its objectives of performing both pilots initiated by HTAb and pilots initiated by other bodies. The main objectives and steps of collaboration on PLEGs have been to identify the need for common PLEGs (topic identification), to agree on common evidence gaps and common minimum data set. Having a common analysis of data collected locally was also considered in order to support future re-assessment. Sharing common quality requirements has been a strong will and WP5B succeeded in establishing a tool for assessing quality of registries (REQueST). Those principles should be maintained.
- The added value of jointly defining PLEG requirements lies in providing well structured, transparent and aligned requirements from several HTA bodies, with the ultimate goal of obtaining comparable and consistent data on a higher number of patients.
  The JA3 experience showed also that some HTA relevant variables are not always collected in routine data collection (e.g. QoL). The added value of joint PLEG work is to jointly communicate and raise awareness on essential variables to be collected for HTA PLEG purposes.

  👉 *Transparency and regular exchange with external stakeholders on common PLEGs is recommended.*

  👉 *Conflict of Interest (CoI) management in the field of PLEGs is recommended, as for any common HTA activities*

- Since the beginning of the JA3, experience in PLEG and REQueST use has been growing among WP5B partners. This should enable continuation of joint work after 2021, within an enlarged pool of agencies to lead or participate in joint work. As for other EUnetHTA joint activities,

  👉 *the future joint work on PLEG could be divided into two strands: one for pharmaceuticals and one for other technologies (mostly medical devices).*

- Due to the increasing needs for PLEGs data and their use in life cycle approach assessment, quality is key,

  👉 *the use of REQueST for any common PLEG activity should be highly recommended. The consolidation of the tool and its governance should be insured*

- WP5B topics were always discussed within a dedicated group of experts (lead and activity centers). This organisation was relevant to build and conduct the activities and to have a referent contact.

  👉 *Having a dedicated group of PLEGs' experts in the network is valuable*

3.4.2 Selection of topics for common PLEGs

- JA3 pilots focused on observational data collection, given the specific experience of the three agencies that held the role of pilot activity centers.
  WP5B recalls however that PLEG in general is not limited to a specific type of data collection but can encompass a wide range of study designs (both interventional and observational). The most adapted type of data collection/study depends on the evidence gap(s) that need(s) to be filled in.

  👉 Provided sufficient resources and opportunities for collaboration, *future joint work on defining requirements for PLEG would not need to focus on observational data collection only*.

- The experience from JA3 showed that JA1 selection-prioritization criteria are still valid when considering PLEG in general, and especially when considering PLEG on national level but needs to be completed asking to consider the interest of having a cross-border collaboration on the topic.

  👉 *In a context of a cross-border collaboration to be set-up, criteria for topics selection are proposed* (see chapter 3.2.2 Figure 3 and chapter 3.3).

- Product-specific PLEG pilots can arise from evidence gaps identified either in national assessments of EUnetHTA partners or directly in EUnetHTA assessments. In JA3, only pilots arising from national assessments were carried out.

  👉 *Product-specific PLEG collaborations arising from evidence gaps identified in EUnetHTA joint assessments should also be carried out*

- For the moment, most agencies do not have the remit to request PLEG for MDs, nor can run registries or have easy access to real world data on MDs.

  👉 *Until these constraints are solved, PLEG collaboration on MDs could be restricted to the sole step of agreeing on the common requirements for PLEG (i.e. common evidence gaps, minimum data set and quality requirements). The added value of the collaboration would be that of providing joint HTA requirements from several HTAb in a harmonized, structured and transparent manner, for a PLEG for a medical device of particular interest.*

3.4.3 Conduct of the collaboration

General

- In JA3, the conduct of JA3 PLEG pilots was affected by internal resource constraints among WP5B partners (periods of limited availability, changes in staff).

  👉 *Continuous commitment of participating agencies to contribute actively to the work is of outmost importance for a good progress of the PLEG collaboration. Having experienced HTAb in requesting/assessing/using PLEG at national level in the EU network is also recommended.*

- JA3 experience showed that differences in **national timelines** for HTA and PLEG can impede the participation in the joint work on PLEG or impact the organisation and the progress of the collaboration. Likewise, differences in national PLEG **processes** can have an impact on the timing for the start of the collaboration (e.g. some partners could get involved in pilots only once the national PLEG was officially issued, because of the process confidentiality) but also on the conduct of the collaboration for product-specific pilots (e.g. involvement of stakeholders depending on national practices).

  👉 *These obstacles could be overcome as HTA and PLEG timelines and processes become more aligned among different HTAb*.

  👉 Moreover, it is expected that *PLEG collaborations that would arise from joint EUnetHTA assessment instead of individual national assessments, would be less subject to timeline variations, facilitating the organization of the collaboration. Thus technologies which go through the joint assessment process should be prioritised.*

Product-specific pilots

- No particular difficulties were encountered with the steps of agreeing on common evidence gaps or common minimum data set in JA3 pilots. However, timeline and resources constraints (see above) resulted in delaying the work and the publication of pilot reports.

  👉 *In future PLEG collaborations, timeline and resource constraints should be solved (see above) by better anticipation (before start of assessment process) in order to have collaboration outputs accessible in a timely manner.*

  👉 *Joint work on topic identification and agreeing on PLEG requirements for specific products should be done as early as possible, in order to allow exchanges with external stakeholders and a timely national uptake.*

  👉 *It is expected that PLEG collaborations that would arise from joint EUnetHTA assessment, instead of individual national assessments, would allow to have PLEG requirements defined earlier.*

- The step of accessing and sharing PLEG data was the most challenging step in the conduct of product-specific PLEG pilots. Differences in national PLEG mechanisms and data access infrastructures were noted; moreover PLEG mechanisms do not seem to be completely established in some countries. Finally, it was also observed that HTAb whose PLEG recommendations were not officially linked with re-assessments had encountered more difficulties in actually obtaining the data.

  👉 *These obstacles could be overcome as PLEG mechanisms and access to data get further developed and improved. The link between PLEG data and re-assessments should be reinforced*.

  👉 *The options for establishing specific procedures/agreements to grant HTAb easier access to PLEG data should be further explored by HTAb including exchanges with external stakeholders (registry owners, industry).*

Registry-specific pilots

- Registry-specific pilots have generated particular interest among WP5B partners in JA3. No partner has a formal process for assessing registries on national level pilots, hence a more formal process on joint level seems of great value, especially in case of cross-border registries/registries i.e.for orphan diseases.

  👉 *Due to the development of health data use in the field of RWE, registry-specific PLEG collaborations are supposed to represent the largest part of joint work on PLEG after 2021.Enlarging specialised resources (in particular on use of data) and capacity to perform the activity should be envisaged.*

  👉 *As for product-specific PLEG collaborations, registry-specific PLEG collaborations should also be performed as early as possible, in order to set-up the necessary data collection in a timely manner.*

- JA3 Registry-specific pilots were performed either in collaboration with the EMA or as HTA-only pilots. No similar activity for registries has been performed before JA3, either on EMA or EUnetHTA side; the processes were defined during the course of the project. It was agreed that the output from the HTA side always be a Qualification advice, i.e. non-binding recommendations from the participating HTA bodies on the discussed issues.

  👉 *JA3 processes for registry-specific collaborations could be further refined in future collaborations. The procedure on registry-based PLEGs could be inspired by the early dialogues'one.*

- As for pilot conduct, no particular difficulties were encountered with the pilot tasks. The use of REQueST not only helped structure the discussions around data quality but also, thanks to the comprehensiveness of its items, allowed to discuss other important aspects relative to data sharing and analysis.

  👉 *REQueST should continue to be used in future registry-specific collaborations*.

👉 ***In total, WP5B recommends that the cooperation between different joint activities are further developed and reinforced, so that they are carried out as a continuum throughout the life cycle of a health technology. Notably, the opportunity to build PLEG work on the findings of REA should be***

further developed. Likewise, the possibilities to perform joint re-assessments using data generated through PLEG work should be discussed. Finally, the opportunities to establish links between horizon scanning activities to identify potential health technologies requiring PLEG with existing registries available for the corresponding indication should be explored.

3.4.4 Stakeholder involvement

- JA3 preparatory work resulted in an establishment of a list of twenty-five stakeholders that might be involved in different PLEG activities in different settings. JA3 work showed that for the HTA cross-border PLEG collaborations most relevant stakeholders to include would be: patients / patient organizations, health professionals, registry holders, product manufacturers, as well as, when applicable and depending on the context, other health organizations: regulators, Ministry of health etc.
- In JA3 product-specific pilots, there were two possible ways to include stakeholders in the pilot production: on pilot (joint) level (i.e. contacted by the pilot lead) or on national level (i.e. contacted individually by each participant, at the moment of national uptake. On pilot level, the involvement should always consist in information exchange on the pilot and in reviewing the HTA minimum data set at least by patients. Due to the existing differences in national practices regarding stakeholder involvement, the decisions on which stakeholders to involve and how were made separately for each JA3 product-specific pilot (since depending on the participants' practices).

👉 *In future PLEG collaborations, JA3 stakeholder list can still be used as a check-list of all possible stakeholders to involve.*

👉 *A systematic stakeholder information on joint level should be envisaged for future PLEG collaborations; Patients and health professionals involvement at the different steps of the project (identification of PLEG, gap analyses, minimum data set, data analyses) should systematically be discussed.*

3.4.5 Legal barriers

- The results of JA3 preparatory work indicated that privacy and data protection rights could be the main legal issues for PLEG pilots, making the data sharing step the most challenging step of product-specific PLEG pilots. Consequently, only sharing of aggregate data and their qualitative analysis was targeted for JA3 product-specific pilots.
- The experience from the product-specific pilots confirmed that, for those partners who had access to data, sharing aggregate data was much less problematic than sharing patient level data. Whereas aggregate data were considered sufficient for some outcomes, it was found regrettable in principle not to have the possibility to pool the data from different countries and perform a quantitative analysis.

👉 *Possibilities to improve data sharing should be further discussed in the future. The options for establishing specific agreements for data sharing should be further explored. A legal consultation and support on this element is recommended.*

👉 *If aspects around data sharing are improved, future PLEG collaborations could include the step of performing a quantitative analysis of common data.*

3.4.6 Tools for collaboration on PLEG

- Specific templates for joint work on PLEG were developed in JA3, on the basis of the general PLEG guidance developed in previous Joint actions. Most of the previous guidances was found suitable for current PLEG joint work, for some a few adaptations were made.

👉 *JA3 templates developed for product specific PLEG (Call for collaboration, Check list for different steps, Evidence gap template, Minimum data set report, Final PLEG report) and for Registry Qualification (Check list for different steps, Form to collect feedback from Registry holders) can be used for future*

PLEG collaborations, and further refined if needed. A procedure detailing ideal timing for each steps could be developed based on the check list document and experience of JA3 pilots.

👉 *JA2 guidance on identification of PLEG and development of adapted protocol (JA2 position paper on research recommendation and JA2 Core protocol) can be used as a support material for the use of JA3 templates in future joint work on PLEG. This general guidance can also be used for national PLEG work.*

👉 *An update of the Position paper on how to decide on the appropriate study design is recommended (given the evolutions in the PLEG domain since the end of the JA2, like the raising interest in the use of prescription databases etc.).*

- Among the JA3 templates, a specific one was co-developed in collaboration with WP4 LP and CoLPs, the "REA evidence gaps table", allowing to present in the JA report, the evidence gaps identified during EUnetHTA assessments in a structured and harmonised way. This table was included in the JA report template. These common evidence gaps could be the starting point of a national or joint PLEG, in which further requirements for PLEG would be defined (dataset to be collected, quality requirements). A guidance for WP4 is under development.

  👉 *REA evidence gaps tables should continue to be used after 2021, in order to allow to link joint assessments and PLEG work.*

- One of the main outputs of the JA3 WP5B work is the development of the Registry Evaluation and Quality Standards Tool (REQueST). To WP5's knowledge, it is the only tool currently available to bring together textual guidance into the form of criteria and feedback to registry owners. The purpose is to highlight areas of a registry that need improvement in order to maximize the quality of its data and ensure that those data can be used for HTA purposes and beyond. A phased approach to tool implementation with learning from experience has been advised.

  👉 *The use of REQueST is recommended in all future joint (or individual national) activities in which the quality of registry data for HTA purposes is to be defined or assessed (e.g. ED on PLEG, PLEG collaborations).*

  👉 *A widespread adoption of REQueST (i.e. by other HTA and regulatory organisations) should contribute to an even more effective usage of good quality registry data. Likewise, the tool can also be used by evidence developers to guide or self-assess the quality of their registry.*

- EVIDENT database's functionalities were reviewed in JA3 and were found adapted for current joint PLEG activities (i.e. product specific pilots and registry-specific pilots). In addition, a need among EUnetHTA partners to share information on national registries and their use for PLEG was highlighted - EVIDENT database was found suitable or that purpose as well.
  It was agreed that the information to be entered in the database can be limited to the mandatory items only.

  👉 *EVIDENT database can be used to share information on future PLEG collaborations, as well as on national PLEG activities after 2021. Simplification can be considered.*

  👉 *In order to ensure the general principle of transparency, having a public repository of PLEGs and national and EU registries should be further explored*

Annex 1: List of practical and legal barriers and possible solutions – results of WP5B preparatory work, 2017

	Barriers	Details	Possible solutions	Alternative Solution
	1. Practical barriers			
A	Data collection is purpose-dependent	Characteristics of data collection depend on the scope. It is important to keep in mind the scope for the implementation of the different registries, in order to evaluate data pooling.	To apply joint methodologies to systematically select and integrate information from different sources: interoperability is necessary.	In case of existing Registries with different scope and interoperability is not allowed, overlapping data could be sorted, pooled and analysed
B	Compatibility	The compatibility means that data created by one registry can be imported into another, without manual data manipulation. In order to be compatible registry data needs the following requirements: 1. Technical compatibility (identical or convertible data structures, formats, coding schemes etc.) 2. Comparability 3. Double counting exclusion	Develop and implement ITC systems allowing intercommunication based on common software/programming languages and shared compatibility parameters.	In case of lack of compatibility between systems, a procedure of data extraction and harmonization and integration is required before proceeding to analysis
C	Comparability	Comparability issues may arise from different definitions and categorizations (e.g. 'hospital', 'hospital bed', 'long term care', 'community care'). It is relevant to identify in advance comparability issues in order to correctly interpret differences across registries. It would also be important to develop harmonization protocols allowing an efficient alignment and integration of data originating from different sources.	Develop a process of semantic harmonization. Set ex ante parameters using international standards (e.g. MESH terms) for disease and health status categorization and classification to allow a more efficient comparability of data. Adapt existing registries to standard definition to allow ex post comparison	See B
D	Linguistic barriers	In order to make datasets comparable between registries, meta-data should be standardized according to validated and widely used classifications.	To explore the opportunity of generating registries in a double language: a common language (English is preferable) and country specific language	Accurate translation could be performed when languages of registries are not matching

	Barriers	Details	Possible solutions	Alternative Solution
E	Interoperability	The interoperability implies that different systems can operate each other. Both functional and semantic interoperability are essential. The functional interoperability implies the possibility for one system (sender) to transmit data to another. Semantic interoperability between registries implies that the recipient system is not only able to handle the received information but also able to automatically interpret it. It is possible that registries that collect data for the same disease use different disease coding systems.	See B	See B
F	Population	The comparability of data of population-based registries requires clear definition of the given population. To generate comparable data on a population level, the same set of inclusion and exclusion criteria are required. Without such a clear definition it cannot be certain, for example, that there is no overlap between the populations of the registries. This is especially true within the EU, where free mobility of people increases the probability that the same person is registered in different registries.	Apply international standard classification of disease. Develop data collection process and ICT solution able to flag possible sample duplication.	
G	Mobility	Free mobility within and across borders makes the establishment of population-based registries (especially in a smaller geographical area) and comparison of data between other registries without the risk of having the same person recorded in two or more databases challenging. This means in terms of patients recruitment and also expected outcomes (whatever their definition). Consequently, without this first requirement, seems difficult to capture in a correct way the information for a patient especially subject of mobility: it is known that the free mobility of people in EU (within and across borders) is an increasing phenomenon. The desiderata must be data collection without the risk of duplication in case of patient moving.	To explore possibilities on interconnection data including widening of the legal framework.	
H	Socio-demographic, genetic factors	Variations and differences in socio-demographic and genetic factors such as ethnicity, genetic mutations in certain populations could make it difficult or even nearly impossible to compare some specific data among populations.	Include genetic/molecular (biomarkers) information with impact on specific health conditions	
I	Healthcare organization	Variations in the healthcare's organization and governance across countries should be adequately considered when comparing data coming from different contexts.	See A, E, H	

	Barriers	Details	Possible solutions	Alternative Solution
L	Data quality	The use and analysis of pooled data must be based on accurate and high-quality data, which is a necessary condition for generating value from cross-border registries. Requirements for data collection and quality assurance should be identified during the registry planning phase. Differences among registries may occur due to different rules for collection of data and quality assurance. Before pooling data, quality across different registries should be evaluated. The challenge is to assess the quality (which dimensions should be considered? e.g. accuracy, completeness, accessibility, relevance and coherence) and to identify acceptable level of quality of data. Also, quality control procedures for on-going registries should be defined.	Use methodologies to provide structure and common procedures for the assessment of data quality, facilitating a comprehensive view of data quality, recognizing interrelations among elements and allows variation's emphasis across countries. The literature differs on a definition of data quality, but one thing is certain: data quality depends not only on its own features but also on the business environment using the data, including business processes and business users. Also, suggestions emerging from Big data might be taken into account, also if academia hasn't yet provided a uniform definition of data quality and quality criteria. Indeed, Big data quality faces many challenges due to its characteristics (the so called 4Vs: Volume, Velocity, Variety, and Value).	• Monitoring level of data quality within the registries • Data quality audits
M	Organizational aspects	There is need to develop specific procedure to grant researchers the access to registries		
N	IT system standard	Patient registries among European countries might operate on deeply diverse IT infrastructures, for ensuring interoperability use and data pooling the interconnection and sharing of existing IT systems (cloud capacities, building shared infrastructure, or EU modelled infrastructure) should be explored.		To explore MSs' experiences

	Barriers	Details	Possible solutions	Alternative Solution
	2. Legal barriers			
	Privacy and confidentiality of data			
O	Privacy and data protection rights[13]	Collection, processing and distribution of personal data are regulated by the Data Protection Directive - DPD (95/46/EC). A legislative process for a new harmonization of Data Protection framework is still ongoing: in 2011 the proposal of the Commission for a Regulation on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) has been presented. the General Data Protection Regulation - being an EU Regulation - will come directly into effect within all EU Member States, and national law in the scope of the Regulation will have to be repealed. Indeed, currently the implementations and interpretations of the Data Protection Directive largely differ depending on the specific MS context. Also, the roles of Data Protection Authorities and Ethical Committees differ greatly across MSs. The pooling data process might be affected by these differences.	A *Data Controller* of the patient registry (-ies) should be identified. According to the DPD he can be a natural or legal person, a public authority, an agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data. Where the purposes and means of processing are determined by national or Community laws or regulations, the controller or the specific nomination criteria may be designated by national or Community law. Same rules are valid for Data Processor according to DPD. Furthermore, the DPD provides also the definition of: • *Third party* any natural or legal person, public authority, agency or any other body other than the data subject, the controller, the processor and the persons who, under the direct authority of the controller or the processor, are authorized to process the data. • *The recipient* means a natural or legal person, public authority, agency or any other body to whom data are disclosed, whether a third party or not.	A legal consultation is advised in order to clarify if a Data Controller is required for the WP5 strand B activities.

[13] The data privacy and data protection rights have likely changed since the entry into force of the GDPR Regulation

	Barriers	Details	Possible solutions	Alternative Solution
P	Legal instruments for establishing a registry	Two legal instruments can be utilized to establish a registry (or other studies): by formal and explicit consent of the patient; or based on law.	As Clinical trials and Cross Border Health Care are increasing the need for patient registry data, new opportunities for establishing alternative legal instruments, such as Agreements on data sharing and transferability will stem. Also, the forthcoming General Data Protection Regulation will introduce further instruments for registry implementation.	Legal consultation is advised on the need to obtain further patient consents (in addition to the one obtained at the national level) when data are shared across countries.
Q	Patient Consent Planning	Several aspects might affect data pooling if not pre-planned in the informed consent • All concepts of the Data Protection Directive should be fulfilled; • The adoption of a consent model requires the planning of each purpose of the registry • it is advisable that the consent is given in written form • The content of informed consent varies between Member States, requiring consulting local Data Protection Authorities and/or ethical committees	Information and consent on processing and transferability of data to other subjects or other countries need to be covered with the aim of pooling data	See P
R	Legal protection of registry holder and researchers	The acquisition of an explicit informed consent is aimed also at guaranteeing legal protection of registry holders and researchers. If the establishment of the registry is based on law or on specific Agreements of countries/stakeholders how to guarantee legal security of registry holder and researchers?		See P

	Barriers	Details	Possible solutions	Alternative Solution
S	Data and information security	In order to ensure privacy of patients and legal protection of registry holders, researchers, health care professionals and other stakeholders the data confidentiality management should be implemented.	The data confidentiality management should describe several elements: security risks, policies, measures and procedures. Also, physical and technical safeguards (data encryption/anonymization/pseudo-nominization, restriction of data access, data back-ups, and methods/software for de-identification of local data) should be incorporated in the collection, storage, data transfer and access to data. It is remarkable that pseudonymous and encrypted data are considered to be personal data and therefore Data Protection Law applies to them, while anonymised data are not personal data. In order to guarantee data anonymization, Data sharing agreements might offer additional safeguard against inappropriate/incorrect/unsafe use of information.	See P
T	Legal issue on primary and secondary use of data	General privacy or data protection legislation provide the legislative requirements regarding the secondary use of data. These provisions may differ between Member States and should need to deliver information to the patients and written consent for the collection, use or disclosure of information for purposes outside the direct one of the registry.	During the planning program for implementing a (cross-border/shared?) Registry, the circumstances where data gathered will be used for secondary reasons (e.g. testing the pooling of data) should be clearly defined and different measures should be implemented for security and data/legal protection purposes. Different approaches will be needed depending on the typology of use of data: e.g. data collected and being kept by the registry holder for direct purposes of the registry (primary use) or uses for purposes other than those for which it was originally collected as further research, MEAs, performance monitoring, service planning, audit and quality assurance purposes (secondary use).	
	Multi points and multi-stakeholders responsibilities			

	Barriers	Details	Possible solutions	Alternative Solution
U	Legal issues related to national and/or regional health systems	Implementation, development and maintenance of registries (and other PLEG studies), as well as data operations are dependent on country specific health care system organization. Health data resources, therefore, could have different relevance and positioning in national strategic prioritization. Furthermore, registries may be part of national and/or regional infrastructures.	Different stakeholders with different roles, rights and responsibilities may be involved in registries, with ample differences among countries. The stakeholders' list can include: • Physicians • Pharmacists • Pharmaceutical companies • Regulatory bodies • Price and reimbursement bodies • HTA bodies • Payers • Patients organizations • Scientific societies • Health managers (Hospital or territory) • Regions referees The critical point is how to involve in a better way? Explain the responsibility and competences. And also, which is the interaction between them and the level of confidentiality to share information. Roles and responsibilities should be deeply analysed in this context with reference to data pooling	

	Barriers	Details	Possible solutions	Alternative Solution
V	Multipoint and multi-stakeholder data exchange	Different stakeholders with different roles and rights among countries are involved in registries activities (and other types of PLEG). Country specific legislation might forbid cross-border data exchange, generally limiting the use the data among different stakeholders, requiring the definition of legally acceptable options.	Check domestic legislation and EU regulations on exchange of registry data (e.g. property of collected data could be advocated by manufacturers? manufacturers could require controlling data, quality audits?)	A legal consultation on this element is strongly advised. The option to arrange a specific agreement with the manufacturer(s) of the product(s) to be monitored by the Pilot registry should be explored. To explore MSs' experiences especially regarding the legal framework that could help organize a potential stakeholders' network.
Z	Operational responsibility and roles	Operational responsibilities, roles, outcomes, services and data exchanges should be clearly examined from a legal perspective and agreed for each process (i.e. governance, quality control, traceability, risk management measures).	Differences in MSs and agreement for who should be responsible for a process will be needed	Legal consultation is advised.

Annex 2 : Upstream and downstream stakeholder analysis and added value concept – results of WP5B preparatory work, 2017

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
1	Patient	Gives or doesn't give informed consent. Informs about disease history, symptoms etc. Contribute to the development of the research question (especially in choosing outcomes of interest)	More information about own disease and treatment.	Privacy and Data Protection. Personal integrity. Subject to rationing.	Medium	Earlier introduction of treatment. Surveillance on effectiveness and safety. Theoretically, an improved QoL if PLEG well implemented.
2	Relative/ informal care giver	Sometimes, gives or doesn't give informed consent if patient is not able to. Same as for patient.	Same as for patient.	Same as for patient. (Personal integrity).	None or medium	Same as for patient. Theoretically, decreased physical and mental burden due to their patient/relative having an improved QoL.
3	Patient organisation (eg EURORDIS and others)	Inform patients, collect and coordinate patient feedback. Take an active part as advisor or partner in setting up studies etc. Facilitate processes with informed consent etc. Contribute to reporting of effects and side effects outside monitored studies.	Information on group level about safety, effectiveness, indication for treatment etc. Information and learnings about introduction and organizational factors (drivers and stoppers in the health care).	Increased knowledge might give potential for tougher priorities between patient groups and for rationing.	Small	Early and equal introduction. Better possibility to evaluate treatment introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge and better system for treating the next generation of patients.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
4	Prescriber N.B. With **medical devices/procedures** the person that decides on the treatment could be different from the person who will actually deliver it (please see the column below)	Meet the patient. Diagnose and decide about treatment. Fill in the patient data into the journal/registry. Contributes to the definition, motivation (and any variation) of indication.	Information about treatment/therapy (dosage, type of devices, operational procedure, accompanying tests, etc.) Information about patient characteristics & outcomes on both individual and group level. Information about own prescription patterns/operational procedures compared to colleagues.	Risk (or at least concern) for disclosure of patient data. Risk for providing data that will be used for control or audit purposes or for financial follow-up and budgetary measures. Risk of getting an extra workload without having extra resources.	High	Reliable and timely surveillance of effectiveness and safety on individual basis. Better possibility to evaluate treatment introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge and capacity to manage future introductions within treatment area (new comparators/ competitors etc.)
5	Health Care Professional who delivers treatment (could be prescriber in some cases)	Follows up the patient Fills in the treatment & patient outcome data into the journal/registry.	Information about treatment/therapy (dosage, type of devices, operational procedure, accompanying tests, etc.) Information about own prescription patterns/ operational procedures compared to colleagues.	Same as prescriber.		Same as prescriber.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
6	Registry Holder (might be an authority, health care provider, individual researcher or Pharma/ Device company)	Responsible for the set-up of the registry. Responsible for managing and facilitating the data input. Has the power to decide over access of data and procedures for data deliveries (In some settings) Has the responsibility of identifying and overcoming barriers to successful data input.	Information about treatment effects and side effects on group level. Information about prescription patterns in different areas/regions etc. Identification of future research areas and data input to these. Need clear definitions. Need clear rules for data sharing, patient integrity, secrecy etc. Potential financing of registry and future work.	Risk (or at least concern) for disclosure of patient data. Risk for misuse of spread patient data. Risk for providing data that will be used for control or audit purposes or for financial follow up and budgetary measures. Might also differ depending on private or public registry holder	High	Equal introduction. Better possibility to evaluate treatment introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge and better system for treating the next generation of patients. Increased knowledge and capacity to manage future introductions within treatment area (new comparators/competitors etc.)

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
7	Health care Provider	Is responsible for delivering health care. Depending on the setting: a, employs the prescriber or b, is the prescriber. Gives permission for employees to perform studies during work time, etc. When also ensuring process for ethical committee approval: responsible for data collection in own organization and allocating appropriate resources. When applicable responsibility for risk management.	Responsible for quality assurance of the care provided. Need for a cost control perspective (depending on payment structure). Need to improve health care over time. Need to provide equal care.	Risk of being responsible for disclosure of patient data. Risk for colliding interests on patient quality and cost control.	High	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Delivery of data needed for quality assurance and development of care.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
8	Health care Professional organizations (e.g., CPME - Standing Committee of European Doctors, for therapy specific see also link to EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/q_and_a/q_and_a_detail_000130.jsp&mid=WC0b01ac05805c0cad)	Diverse, but might include: Writing treatment guidelines. Take an active part as advisor, primarily within the scientific committee of the register. (standardization of definitions and characterizations, datasets, relevant outcomes, etc.) Driving research within therapeutic area. Opinion leading.	Information about treatment effects and side effects on group level. Information about prescription patterns in different areas/regions etc. Identification of future research areas and data input to these. Need clear definitions. Need clear rules for data sharing, patient integrity, secrecy etc. Potential financing of registry and future work.	Risk that data will be used for control purposes or for financial follow up and budgetary measures.	Small or none depending on whether they are considered as advisor or not	Equal introduction. Better possibility to evaluate treatment introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge and better system for treating the next generation of patients. Increased knowledge and capacity to manage future introductions within treatment area (new comparators/competitors etc.)
9	Pharma Company (e.g. EFPIA member companies)	Owns patent right etc. for NCE. Owns data in some registries. Designs, drives and finances studies (RCT and follow up studies).	Increased knowledge of its own product or competitor. Knowledge about existing data/ databases. Knowledge about legal aspects of access rights etc. Need for follow up data to base risk sharing agreements on.	Risk for providing data that will be used for control purposes in health care and for financial follow up and budgetary measures.	High, small or none if not driving the study	Potentially earlier introduction. Better possibility to evaluate treatment, introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge for future introductions within treatment area (new comparators/competitors etc.)

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
10	Device Company (e.g. EUCOMED, COCIR or EDMA member companies)	Owns patent right etc. for NCE. Owns data in some registries. Designs, drives and finances studies (RCT and follow up studies).	Increased knowledge of its own product or competitor. Knowledge about existing data/databases. Knowledge about legal aspects of access rights etc. Increased understanding on how device is used. Information about clinical usability. Need for follow up data to base risk sharing agreements on.	Risk for providing data that will be used for control purposes in health care and for financial follow up and budgetary measures.	High, small or none if not driving the study	Potentially earlier introduction. Better possibility to evaluate treatment, introduction and results in relevant patient groups. Increased knowledge on indication for use etc. Increased knowledge for future introductions within treatment area (new comparators/competitors etc.)
11	Device or pharmaceutical branch organization e.g. EFPIA, EUCOMED, COCIR or EDMA themselves	Owns data in some registries. Designs, drives and finances guidelines and practices.	Increased knowledge of products and use. Knowledge about existing data/databases. Knowledge about legal aspects of access rights etc. Increased understanding on how devices are used. Information about clinical usability.	Risk for providing data that will be used for control purposes in health care and for financial follow up and budgetary measures.	Small	Increased knowledge on use of product, indication for use etc.
12	CRO (contract research organization)	Designs and drives studies.	Knowledge about existing data/databases. Knowledge about legal aspects of access rights etc.		High	Increased knowledge for future introductions within treatment area (new comparators/ competitors etc.)

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
13	Payer/ Insurer (e.g. ESIP or AIM (International Association of Mutual benefit societies)	Pays for the care delivered. Pays for the pharmaceuticals. Ask for tenders. Call for auctions. Evaluates its business through follow up and evidence generation.	Need for quality assurance and evaluation of the care given. Cost control. Horizon scanning and budget prognosis. Data input to price negotiations. Need for promises about follow up data to base risk sharing agreements on.	Risk for colliding interests: patient quality vs. cost control. Risk for being mistrusted by patients and prescribers. (to only look for cost cuts).	Small	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.
14	Regulatory Body (e.g. EMA)	Gives ethical permission for clinical studies (depending on the country). Approves clinical studies. Keeps track of ongoing studies. Evaluates and approves new pharmaceutical products. Formulates requirements for post-authorization studies.	Information about treatment effects on group level, often connected to different kinds of conditional approval. Information about long term safety and adverse events on individual and group level. Indication for use. Information about prescription patterns in different areas/regions etc.	Risk, data from non RCT environments are judged to have evidence that is too weak to evaluate effectiveness but robust enough to evaluate risks and that interest for safety measures dominate over effectiveness measures. Do normally not make priorities between products.	Medium	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use (and cost effectiveness). Increased knowledge on indication for use etc.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
15	Committee or agency for ethical approval (might not exist in all health systems as a separate entity, see also n°14)	Gives ethical permission for clinical studies (depending on the country).		Risk for unethical behavior and patient integrity interference when setting up or performing studies and/or when handling personal health data.		
16	Body for health care revision	Evaluates and makes audits on healthcare providers and health care professionals.	Potential need to go back and see which method was used on which indication. Need to see if, where, when and possibly why mistakes were made.	Most registries are not set up with the aim to serve these needs. There might even be legal hindrance to use registry data for these purposes.	None	
17	HTA body	Makes assessments (and appraisals) of new and existing technologies. May be involved in defining requirements for PLEG studies.	Information about treatment effects and side effects on group level. Need for comparative effectiveness data. Need for cost effectiveness measures as well as ethical and organizational info about the new treatment, when available and applicable.	Do data from non RCT environments have evidence that is strong enough?	Depending on system	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
18	P&R body (might not exist in all health systems as such, see n°19 and 20)	Appraises new technologies, especially pharmaceuticals. Depending on the country/setting: could approve PLEG studies and be responsible for appraisal of PLEG study results Decides on coverage/reimbursement **and/or** pricing. Performs price negotiations. Establishes reference prices.	Information about treatment effects and side effects on group level. Need for comparative effectiveness data. Need for cost effectiveness measures as well as ethical and organizational info about the new treatment. Need for promises about follow up data to base risk sharing agreements on. Information about covered indications/conditions on group level Access to data and its analysis for evaluating the performance of MEA.	Risk for being mistrusted by patients and prescribers. (to only look for cost cuts)	Small	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
19	Coverage body (might not exist in all health systems as such, see also n°18)	Grants coverage/financing approval Depending on the country/setting can approve PLEG studies; participate in the assessment and appraisal of PLEG study results. Responsible for re-evaluation of coverage indications	Information about covered indications/conditions on group level			
20	Pricing body (might not exist in all health systems as such, see also n°18)	Grants/sets price level, responsible for follow up of budget and for re-evaluation of pricing decisions	Information about sales volume, drug utilization, covered indications/ conditions on group level			
20	National/ Regional Health Care Provision Body	Depending on the country/setting: (please see above), can be responsible for health care organization (defining reference centers, etc.)	Facilitates implementation Practical information on organization of health care.	Risk of being responsible for disclosure of health care data. Risk for audit & quality control Risk for being mistrusted by patients & providers.	Small	Better organization of health care.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
21	Statistic agency	Collects data. Keeps registries, health databases etc. Makes statistical analyses and provides/sells analysis results.	Needs to have easy (automatic) ways to collect data. Needs interoperability between data sources. Needs clear definitions. Needs clear rules for data sharing, patient integrity, secrecy etc.	Is data available for the purposes of the study and the different stakeholders? Risk of being too technical. All analysis results may not be fully understood by users.	Medium	National standards for registries/PLEG etc. A stable organization for registries. Sustainable financing models for registries.
22	Public health agency	Keeps records of public health and analyses background data in health data registries compared to outcomes etc. Makes recommendations on public health interventions and measures.	Needs national health data registries to be up to date and have high coverage. Needs data from individual registries to cover gaps in health data registries. Access to data and its analysis for evaluating the performance of MEA		Small	Information on drug use in population, differences across social groups, regions etc.
23	Academia/ Researchers	Initiates some of the registries. Important in setting scientific standards for evidence and methods.	Information about treatment effects and side effects on group level. Information about prescription patterns in different areas/regions etc. Identification of future research areas and data input to these. Potential financing of registries and future work.	Risk for early publication of results that makes it more difficult to get a peer scientific review.	Potentially high	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.

	Stakeholder (relevant example when applicable)	**Contribution** What does the stakeholder contribute with?	**Need** What does the stakeholder want to see?	**Risk** Which are the risks for the stakeholder?	**Workload (none, small, medium or high)**	**Added value** What can increased knowledge about new technologies bring to the stakeholder?
24	Pharmacies	Delivers pharmaceutical products and can potentially collect data in the personal meeting with the patient/customer.	Information about treatment effects and side effects on group level. Information about distribution (and prescription) patterns in different areas/regions etc.		Small	Better possibility to evaluate treatment access, introduction and equity between patient groups. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.
25	Ministry of Health	Depending on country and system. Makes the final decision with regards to coverage. Decides on the budget for pharmaceuticals. Decision makers with regards to the implementation of PLEG.	Information about treatment effects and side effects on group level. Need for comparative effectiveness data. Need for cost effectiveness measures as well as ethical and organizational info about the new treatment. Need for promises about follow up data to base risk sharing agreements on. Need to follow up budget and spending.		Depending on system	Better possibility to evaluate treatment, introduction and results in relevant patient groups. Comparison of efficacy from RCT and effectiveness from PLEG. Information on drug use and cost effectiveness Increased knowledge on indication for use etc.