EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on European Cystic Fibrosis Society Patient Registry

Summary of HTA recommendations

April 2018

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DOCUMENT HISTORY AND CONTRIBUTORS

This document represents the summary of written HTA recommendations that were adressed to the ECFSPR in the framework of the Qualification procedure on Cystic fibrosis registries as tools for pharmaco-epidemiology studies. It represents the view of the participating HTA bodies only. Only the summary of the recommendations is made public, further to applicant's agreement.

Pilot team

Responsibility/role	HTA Body/affiliation
Pilot coordinator	Haute Autorité de santé (HAS) / HTA international unit
HTA pilot participants (in alphabetical order):	The Agency for Health Quality and Assessment of Catalonia (AQuAS)
	Haute Autorité de santé (HAS) / Medicines assessment department
	National Health Care Institute of the Netherlands (ZIN)
	Portuguese National Authority of Medicines and Health Products (INFARMED)
HTA observers (in alphabetical order):	The Federal Joint Committee, Germany (G-BA)
	Italian Medicines Agency (AIFA)
	The National Institute for Health and Care Excellence (NICE)
	The Spanish Agency of Medicines and Medical Devices (AEMPS)

Conflict of interest
All participants involved in the production of this pilot have declared they have no conflicts of interest in relation to the pilot according to the EUnetHTA declaration of interest and confidentiality undertaking form.

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LIST OF ACRONYMS/ABBREVIATIONS

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (The Spanish Agency of Medicines and Medical Devices)
AIFA	L'Agenzia Italiana del Farmaco (Italian Medicines Agency)
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya (The Agency for Health Quality and Assessment of Catalonia)
CF	Cystic fibrosis
ECFSPR	European Cystic Fibrosis Society Patient Registry
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsame Bundesausschuss (The Federal Joint Committee, Germany)
HAS	Haute Autorité de Santé (French National Authority for Health)
HTA	Health Technology Assessment
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (National Authority of Medicines and Health Products, I.P., Portugal)
NICE	The National Institute for Health and Care Excellence (UK)
RWD	Real world data
UK	United Kingdom
WP	Work package
ZIN	Zorginstituut Nederland (The National Health Care Institute, Netherlands)

1. BACKGROUND INFORMATION

Real world data collection requests

At the time of initial Health Technology Assessment (HTA) of a new drug, HTA bodies may require collection of additional data in routine clinical practice, called real world data (RWD). The objective is to collect data to cover uncertainties on drug's effectiveness or long term safety, or to inform on drug's condition of use. These data are used afterwards to inform drug re-assessment.

Most HTA bodies encourage the use of already existing registries of good quality to generate the required RWD.

ECFSPR proposal

The European Cystic Fibrosis Society Patient Registry (ECFSPR) is a disease specific patient registry with its own software platform (ECFSTracker) used for the collection of cystic fibrosis (CF) data from 31 participating countries in Europe. Data from countries that have their own national registries (such as the UK, Germany, France etc.) are uploaded to the ECFSPR.

The ECFSPR consortium sent to the European Medicines Agency (EMA) a request for the **qualification** of its registry as suitable **for performing pharmacoepidemiological studies for regulatory purposes** concerning medicines intended for the treatment of CF. The proposal has been accepted within the EMA procedure for the Qualification of novel methodologies for medicine development (called Qualification procedure hereinafter). The outcome of this EMA procedure is either a Qualification **advice** or a Qualification **opinion** on the use of specific methods or drug development tools in a particular context. [1]

Other possible uses of registries (providing historical control data, supporting validation of biomarkers/surrogate endpoints) **are out of scope** of this procedure.

EUnetHTA participation

Further to an invitation from the EMA and with the agreement of the ECFSPR consortium, the procedure was undertaken as a multi-stakeholder procedure in parallel with HTA bodies, under the coordination of European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 Work package 5 Strand B (named WP5B hereinafter).

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 advice/opinion. Accordingly, the present document represents the view of the participating HTA bodies only.

It is to be noted that there is currently no equivalent of the EMA Qualification **opinion** on the EUnetHTA side. Therefore, the only possible outcome of the process from the HTA side is a Qualification **advice**, e.g. recommendations on the discussed issues. These recommendations are non-binding and do not engage HTA authorities in any possible way. **Following the rules of the EMA Qualification procedure[1], the detailed recommendations are kept confidential. Only the summary recommendations are made public (see chapter 2), further to applicant's agreement**.

[1] More details on the procedure and the outputs (qualification advice or opinion) are to be found in the EMA Guidance to applicants:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Four HTA bodies have fully participated in the procedure and their positions are presented in this document. Four other HTA bodies have participated as observers, without providing their views (see Pilot team).

Procedure overview

In order to support its proposal, the ECFSPR consortium has submitted a Briefing document with a list of questions to the EMA and HTA bodies (June 2017). The questions concerned both quality aspects and the nature (or type) of the variables recorded in the ECFSPR.

EMA and HTA bodies have in response sent their respective lists of issues.

The issues have been discussed in a tri-partite Face to face meeting (held July 3rd 2017), and were further addressed in written by the applicant (August 2017 for HTA issues).

An additional meeting was held on September 25th 2017 in order to address and clarify certain additional issues formulated by the EMA. HTA bodies did not formulate additional questions for this meeting in which they participated as observers.

The applicant received at the end of the procedure a report with the answers to the questions addressed to HTA bodies: joint answer from participating HTA bodies, when applicable, or individual answers from each HTA body, when a joint position was not reached. The EMA views were presented in a separate document.

As already specified, this document represents **the summary** of the written HTA recommendations that were adressed to the applicant.

2. SUMMARY OF RECOMMENDATIONS FROM PARTICIPATING HTA BODIES

The participating HTA bodies would like to welcome this excellent initiative proposed by the ECFSPR, to harmonize CF data collection across countries and enhance data sharing.

Moreover, they would like to acknowledge ECFSPR efforts to approach regulators and HTA bodies in order to adapt the data collections to the needs of different stakeholders.

All in all, they encourage ECFSPR objectives and further developments that are ongoing.

With regard to the variables included in the ECFSPR, HTA bodies agree on the importance of focusing on the minimal mandatory data set, rather than expanding the data collection and collecting as much data as possible. In that sense, they find the variables included in the ECFSPR registry quite comprehensive, with the exception of two types of variables that were identified as missing or incomplete by all HTA participants:

1) specific variables regarding treatments. HTA bodies emphasize that not only variables regarding CF specific therapies should be collected but also variables regarding concomitant treatments (pharmacological or not). They also underline the need to collect these variables in a detailed manner, e.g. including the evolution of the therapeutic regimen and the reasons why treatments have been changed or interrupted. This is especially important for new CF medications.

2) patient's quality of life. All HTA bodies agree on the need to collect this variable.

HTA bodies welcome the willingness of the applicant to add additional variables and emphasize the importance of introducing these variables homogeneously and with consistent quality in participating centers, in order to guarantee data exchangeability.

With regard to the frequency and the nature of data being made available by ECFSPR, as well as proposed methodology for performing post-launch studies, HTA bodies have provided individual recommendations, in accordance with their national processes. It can be noted that three out of four participating HTA bodies require/prefer having access to raw data, rather than summary data only as suggested by the applicant, especially for pharmaco-economic studies.

Finally, HTA bodies are also welcoming and encouraging the on-going internal project to enhance registry's quality of data. They would need to have the results of that project first, in order to be able to fully assess acceptability of ECFSPR's data quality control mechanisms. It should be noted that EUnetHTA WP5B is currently developing a practical tool to assess the quality of registries in the view of their use in a HTA process. Once available, this tool will help formalizing HTA bodies' requirements in terms of quality of registry data.

Disclaimer
This output corresponds to a summary of a Qualification advice and not to a Qualification opinion[1]. The recommendations presented are non-binding and do not engage HTA authorities in any possible way. They reflect the state-of-the-art of medical science and national requirements at the time of the advice.