



X-eHealth

Exchanging Electronic Health Records
in a common framework

D5.6 – Refine PS functional specifications to account for eHN Guidelines and rare diseases

WP5 – Definition of EEHRxF functional specifications

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Abstract

The aim of Deliverable 5.6 is to refine the Patient Summary functional specifications to account for eHealth Network Guidelines and rare diseases, including cancers.

Rare diseases (RDs) are numerous (over 6,000), heterogeneous in nature, often multisystemic, and geographically disparate. At European level, the lack of data on RDs in healthcare systems represents a major issue to be addressed since the lack of visibility of a rare disease diagnosis in a patient's records can result in harmful consequences for the patient. Information in this domain is, however, particularly scattered and usually collected for different purposes, resulting in the use of different tools. Electronic health record systems able to interoperate represent the basis for data sharing and information exchange, instrumental for improving the quality and safety of patient care and boosting research.

This document addresses the specific needs in terms of data elements and semantic standards for rare diseases in general and for rare cancers as far as they differ from rare diseases. It builds on the already agreed minimum dataset for RD registries recommended by EUCERD. Recommendations are made on the importance of using ORPHA codes suitable as PS extensions, in accordance with the EU project RD-Code. Use cases refer to planned and unplanned care scenarios.

Key Words: rare cancers; rare diseases; acute health care; planned health care

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Terms and Abbreviations

Acronym	Description
RDs	Rare diseases
ePS	electronic Patient Summaries
ICD	International Classification of Diseases
CEGRD	Commission Expert Group on Rare Diseases
ICD-O	International Classification of Disease for Oncology
EUCERD	EU Committee of Experts on Rare Diseases
EHR	Electronic health records
GPs	General practitioners
ESMO	European Society of Medical Oncology
EURACAN	European Reference Network on rare adult solid cancers
MDT	Multidisciplinary teams
KPS	Karnofsky Performance Status

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Scope and Interdependencies

In scope

To analyse the specificities of Rare Diseases and Rare Cancers, identifying specific use cases for both domains, for Emergency / Unplanned care, for Planned Care, and other Use Cases, always related to the primary use of data.

Functional requirements associated with the various Use Cases will be sketched, including indications of the data sets required by each Use Case.

This will include suggestions for improvements of the current functional specifications of the MyHealth@EU Patient Summary and proposals to reshape the current Patient Summary to better fit with oncologists' needs.

Out of scope

To propose technical architectures to handle new Use Cases in which clinical documents travel “for” the patients (e.g. to request Second Opinion), and as evolutions of the current Use Case in which clinical documents are retrieved at the Point of Care, to provide assistance to the patient.

It is also not in the scope of Task 5.6 to define the Value Sets associated with the newly proposed documents, nor consider secondary use of data for scientific purposes.

Interdependencies

This document starts from the clinical analysis jointly performed in Task 5.2 - “EEHRxF and its relationship with clinical guidelines”, and the eHealth Network Guidelines on Patient Summary, Release 2, contributing to the preparation of their Release 3, and the MyHealth@EU Patient Summary implementation. It will be the main input for the WP6 Task 6.4 - Refinement of the Patient Summary (PS) technical specifications for supporting rare diseases. The main objective of said task is to refine the PS specifications to extend the use of the PS to rare diseases, starting from the requirements collected by WP5 and considering the constraints from each country involved in the action as collected by WP5, the CEF eHDSI technical specifications, and the most recent international standardisation activities (International Patient Summary). The document will be used by task T5.3 - Laboratory Domain and by task T5.5 - Hospital Discharge Report. The document will also indirectly provide input for WP7, Architecture and system specifications and specifically Task 7.1 – “X-eHealth Architecture definition to implement and deploy EEHRxF services” and Task 7.3 – “Possible upgrades of eHDSI core and generic services”.

Deliverable 5.6 will provide input in the delivery, demonstration and evaluation of proof-of-concept demonstrators for selected EEHRxF use cases for patients with rare diseases (Task 8.1).

1. Introduction

Rare diseases (RDs) are numerous (over 6,000), heterogeneous in nature, often multisystemic, and geographically disparate. Despite their heterogeneity, RDs share commonalities linked to their rarity which necessitates a comprehensive public health approach (Valdez R, et al. *Prev Chronic Dis*. 2016.^[1] The challenges that have made RD a public health priority in Europe since 2008 ^[2] ^[3] arise from their **low prevalence** and **lack of visibility in health information systems**, preventing them from providing sufficient, meaningful data to take healthcare, research and policy actions, as well as from delivering the best possible care and attention to each patient in a timely manner.

In the EU, the definition of RDs was established in the EU Regulation on Orphan Medicinal Products (1999) as conditions whose prevalence is not more than 50 per 100,000.^[4] While the definition of rare diseases is based on prevalence, 14% of them are incident diseases (Nguengang Wakap et al., 2020) (rare infectious diseases, rare diseases due to toxic effects, and rare cancers).

As incident diseases (infectious diseases and intoxication diseases) are rare in some parts of the world and common in others, they are more easily recognisable in commonly used terminologies. On the contrary, most rare diseases do not therefore require the use of a specific coding system or a set of specific data elements in health information systems, including electronic health records (EHR) and electronic Patient Summaries (ePS).

These specificities have commonalities and differences for rare diseases in general and for a particular subgroup of them, namely rare cancers, which represents around 7.5% of all rare diseases, according to the Orphanet database^[5]. Rare cancers are those with an incidence $\leq 6/100,000$ (Gatta et al., 2011) and make up one fifth of all cancer cases. In principle, there are no differences in their natural history and/or diagnosis and treatment compared to common cancers. This means that any patient summary tool conceived for rare cancers will also fit the requirements of cancer in general.

Electronic health record systems able to 'interoperate' represent the basis for data sharing and exchange of information, which is vital to improve the quality and safety of patient care and boost research. Interoperability of systems collecting data on RD entails added value, as in this domain information is particularly scattered and usually collected for different purposes, thus using different tools.

At a European level, the lack of data on RDs in healthcare systems represents a major issue to be addressed. Accordingly, recommendations have been issued stating the importance of using

[1] <http://www.eurordis.org/publication/rare-diseases-understanding-public-health-priority>).

[2] https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf;

[3] <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

[4] <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

[5] <http://www.orphadata.org/cgi-bin/index.php>

ORPHAcodes (Orphanet nomenclature of rare diseases), together with ICD, to record RD patient data in health information systems. More specifically, the Commission Expert Group on Rare Diseases (CEGRD) recommendation on “*Ways to improve codification for rare diseases in health information systems*”^[6] concluded: “*MS should consider adding Orphacodes to their country’s health information system and explore the feasibility and resources needed to do so*”. The need to use specific classifications is common in other domains, a case in point being ICD-O (International Classification of Disease for Oncology) for oncological diseases. Most recently the need to record an ORPHAcode in the Patient Summary for patients with rare diseases has been proposed as a refinement of the PS, to be considered in version 3 of the eHN guidelines.

This document will address the specific needs in terms of data elements and semantic standards for rare diseases in general and for rare cancers as far as they differ from rare diseases. It uses, as necessary, the already agreed minimum dataset for RD registries recommended by EUCERD^{[7],[8]} and the Common Data Elements for RD registries issued by the European Commission Platform for RD registration.^[9] A comparison between these datasets is given in Annex 1.

1.1 General considerations

Rare diseases in general

The lack of visibility of an RD diagnosis in a patient’s records can result in harmful consequences for the patient. In specific situations, i.e. when patients require healthcare outside their usual expert environment, identifying those suffering from a given RD, thus allowing access to useful information (particularly best practice guidelines) and to the expert centre following the patient, is crucial to the delivery of best care and avoids preventable complications.

A rare disease diagnosis is usually made at centres of expertise, now organised as European Reference Networks in Europe^[10]. Patient follow-up is usually ensured by doctors (GPs and specialists) and other health professionals, RD requiring a multidisciplinary approach, according to the recommendations of the expert centre following the patient. Since RD are clinically heterogeneous, it is not possible to describe a common healthcare pathway as in (rare) cancers. Eventually patients may encounter other professionals outside their RD follow-up environment due to unforeseen clinical situations requiring medical attention. Noteworthy, a high percentage of RD patients suffer from intellectual disability and other neurological and developmental problems. Over 70% of RD diseases exclusively affect children and up to 88% can present in the paediatric population. 72% of RD are genetic in origin (Nguengang Wakap et al., 2020). Non-expert health professionals cannot reasonably know each of the above 6,000 RD,

[6] https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

[7] http://www.rdaction.eu/eucerd/EJA/Deliverables/WP8_Registries_MDS.pdf

[8] http://www.bndmr.fr/wp-content/uploads/2020/02/MDS_v1.11-2EN.pdf

[9] https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/CDS/EU_RD_Platform_CDS_Final.pdf

[10] https://ec.europa.eu/health/ern_en

their complexity and the best management approach to RD patients. Quality and timely information on the disease, the patient and the expert centre following the patient should therefore be delivered in a reliable way at the healthcare point.

Finally, patients with RD might require treatment in another country than the one in which they live. This may be due to the lack of centres for their specific disease close to where they live, but also to people's increased mobility. This can trigger the need for data exchange on a specific person across country and language borders.

Rare cancers

From the perspective of a patient summary tool, cancer is a distinctive disease in several respects, as follows.

- The clinical history of a cancer patient can be easily divided **into one or more “phases” of treatment**, each marked by a treatment programme (for example, a patient can be treated for a primary localised tumour with surgery plus radiation therapy and chemotherapy within a first phase; then, if the disease has not been cured, after, say, months or years of follow-up, it will be treated with chemotherapy for a distant relapse within a second phase, and so forth). **Each clinical decision at the beginning of a phase should be multidisciplinary, even when the selected treatment belongs to a single medical discipline, and often different clinicians will be involved in the treatment. Each multidisciplinary team will be made up of a core of clinicians, generally within the treating institution, and other clinicians who may not belong to the centre.**
- To some degree, major clinical decisions may follow formal clinical practice guidelines, which are rather widespread in oncology, being produced by scientific/professional societies. However, any clinical decision will always be highly personalised, whereas clinical practice guidelines may simply envisage the most typical disease presentations. In other words, it is likely that a substantial proportion of patients will not be treated according to clinical practice guidelines.
- Many rare cancer patients are expected to be treated on a networking basis, i.e. within hub-and-spoke healthcare networks (generally the information, not the patient, will flow throughout the network, but sometimes even the patient may move from one centre to another).
- In principle, **any patient summary tool will need to be filled in by a clinical oncologist**. It should be readable by GPs and all other medical specialists, but **the complexity of cancer is such that only the multidisciplinary cancer team will be able to produce it appropriately**. Indeed, each member of the multidisciplinary cancer team must fill in selected sections of the patient summary. It may be assumed that at any given time a member of the multidisciplinary cancer team will be responsible for the cancer patient (on behalf of the whole team), and one may assume that they are responsible for any updates (while possibly asking other specialists to contribute). There may be professional persons (generally in the nursing domain) as case managers and the like, responsible for coordinating the flow of medical interventions, exams and clinical controls within the multidisciplinary cancer team for each cancer patient. Unfortunately, however, these people are far from being universally available.
- Finally, in any problem-oriented framework, cancer should be viewed as a permanently “active” problem.

EHRs are now widespread. However, current EHRs are highly demanding in terms of medical workload, because they claim a lot of professional time to manually input data. Overstructured fields add to this burden and often make it unnatural to input information which was previously very simple for the physician to provide (e.g. medical prescriptions and the like). Software often imposes constraints which are poorly consistent with the many rule deviations which are typical of the medical profession. Thus, the current IT scenario is very frustrating for both clinicians and patients. It is hard to believe that physicians will comply with input requirements which are felt to be excessive due to the lack of immediate usefulness of the data and degree of field structuring. In other words, fields to be actively filled in by physicians need to be minimised or must at least be perceived as immediately useful for retrieval. In addition, they need to be as little structured as possible. The complexity and unpredictability of the medical profession need to be taken into account, avoiding the imposition of IT constraints which do not correspond to real-world flows.

The patient summary as an output is essentially a clinical tool, although its data can also be useful for research or even administrative purposes. Thus, it should be readable by professionals. This means that its natural-language text should score high in terms of human readability, regarding both effectiveness and efficiency.

1.2 Objectives

To define the PS functional specifications for rare diseases including rare cancers

2. Use cases

Use cases for rare diseases

Exchange of data can be necessary for both unplanned and planned care.

Unplanned care can be necessary for intercurrent medical conditions, including non-urgent GP consultations and emergency situations. The latter can result in surgical interventions.

Planned care can include cross-border physical visits to an expert centre in a foreign country as well as cross-border expertise exchange, without making the patient travel. It can be triggered by the need to have a second opinion on the patient's diagnosis or on management of the best options.

This deliverable will propose disease specific annexes to the Patient Summary content for both unplanned and planned care.

Unplanned healthcare

Disease complications can be difficult to diagnose and very often need to be managed differently from the same situation presenting in non-RD patients. Furthermore, being unaware of the

specific needs of the RD may lead to decompensation of the RD. Anaesthesia may also require tailoring to specific needs. Less urgent or, on the opposite, emergency situations can be:

- Due to a situation directly related to the RD:
 - e.g. Aortic dissection in Marfan syndrome
 - e.g. Coma in hemiplegic migraine patients
 - e.g. Pneumothorax in tuberous sclerosis patients
 - In practice not relevant for rare cancers
- Due to a situation unrelated with the RD, but RD specificities may need special awareness and attention
 - e.g. Risk of respiratory arrest if lying an orthopedic Steinert myotonia patient down flat
 - e.g. Gentle mobilisation of Osteogenesis imperfecta patients because of risk of (new) fractures
 - e.g. Anticonvulsants: barbiturates, lamotrigine, carbamazepine, oxcarbazepine, vigabatrin, to be avoided in Dravet syndrome.
 - e.g. note of caution (e.g. myasthenic syndrome in thymic cancer)
- Due to a situation unrelated with the RD, but decisions related to RD prognosis must be clarified
 - e.g. Decision on whether to admit the patient to intensive care unit, ventilation etc. in amyotrophic lateral sclerosis for a patient having stated advanced directives for palliative care.

Use case – Unplanned care – Rare diseases (further discussed in Deliverable 7.1)

- French 15-year-old boy presents to an Italian emergency department with respiratory distress after banal bronchitis lasting for a couple of days. In addition, he complains of disabling abdominal pain. He reports to have been diagnosed with Steinert disease.
- Worst scenario:
 - Doctor does not know much about Steinert disease but wants to rule out a surgical abdomen. Patient suffers respiratory arrest when lying down for examination. Intubation is difficult and a tracheotomy should be performed
- Better scenario:
 - Doctor does not know much about Steinert disease but consults ePatient

Planned healthcare

- Second opinion/multidisciplinary consultations: To offer an RD patient the best diagnosis and/or management options, multidisciplinary consultations can be organised both physically and/or virtually. Depending on the organisation in each country, physical or virtual multidisciplinary meetings set to deliver recommendations on a particular

diagnosis workup (including the indication for genome sequencing) or to make decisions about a management protocol, can take place on the request of a physician (whether they are a RD expert or not); these second opinions can take place within ERNs, or national rare disease and rare cancer networks; or can be occasional external second-opinions.

- Concise summary for attending clinicians; for GP involvement;
- Concise summary for external consultations (e.g. a dermatological consultation in a cancer patient; a health professional consultation for an intercurrent medical problem unrelated to the RD)
- Concise summary for internal consultations (within the hospital MDT)
- Concise summary for consultations about availability of ongoing clinical studies/eligibility check
- Concise summary for patients

Use case – Planned care – Rare cancer

2013: diagnosis of gastric Gastrointestinal Stromal Tumours (GIST), size = 9 cm, MI = 9/50HPF, exon 11 KIT mutated, CT scan = negative elsewhere

Treatment phase 1.

Surgically resected (partial gastrectomy, R0) and treated with adjuvant imatinib 400 mg/d for 3 years.

Treatment phase 2.

Relapsed in January 2017, with liver metastases, KPS = 90, and treated with imatinib 400 mg/d for 2 years, with a PR, finally progressing (generalized PD to the liver and peritoneum) in January 2019.

Treatment phase 3.

Starting sunitinib 37.5 mg/d in February 2019, KPS = 90, with SD for 6 months, then progressing (generalized PD to the liver and peritoneum) in June 2019.

Treatment phase 4.

Starting regorafenib 160 mg/d-3/4w in July 2019, KPS = 90, with SD for 12 months, then progressing (generalized PD to the liver and peritoneum) in June 2020.

Treatment phase 5.

Currently ED: metastatic to the liver (10 visible lesions) and the peritoneum (several visible nodules). KPS = 90. No significant co-morbidities.

Question: Which further-line therapy?

Further details are available in D5.2

3. Data fields

Remark: these data fields are restricted to the particular elements needed to cover the specific needs of rare disease including rare cancer patients. Data fields already included in EHRs and the Patient Summary as specified by the eHealth Network (e.g. patient name and surname, administrative information, etc) are not described in this paragraph (for the full list of RD specific-items, please refer to paragraph 5).

3.1 Rare diseases in general

Unplanned care

- RD Diagnosis: Rare disease name and code
- Relevant information on the particular disease link to the Orphanet website using the following url and adding the ORPHAcode number at the end:
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Ing=EN&Expert=ORPHAcode.
This gives access to general information, links to emergency and anaesthesia guidelines and clinical practice guidelines, when they exist.
- Main alert messages about the specific risks related to the rare disease, including treatment contraindications
- Ongoing treatment(s)
- Contact information of the RD expert centre managing the patient; name of the physician/name of the centre/hospital/location/phone number(s) including emergency phone numbers, where existing.

Planned care

- RD diagnosis:
 - o Name of the disease
 - o ORPHAcode
 - o Diagnosis assertion status: suspected/confirmed/unknown (undiagnosed)
 - o Method for confirmation: clinical/genetic testing/biochemical/imaging/pathology/functional exploration/other
 - o If genetic disease,
 - gene symbol
 - variant
- RD history:
 - o Age at onset (first manifestations)
 - o Age at diagnosis
 - o Heredity (if known): sporadic/familial/dominant/recessive/X-linked
 - o Clinical manifestations
 - o Investigations (normal/positive results)
 - o Disability
- Antenatal/perinatal information (if relevant)
 - o Birth date
 - o Gender at birth
 - o Malformations detected antenatally

- Medically assisted procreation: yes/no
 - Gestational age at birth (weeks)
 - Weight at birth
 - Height at birth
 - Head circumference at birth
- Family antecedents in relation to the RD:
 - Affected member (propositus) yes/no
 - Parental relationship with the affected member
 - Consanguinity: yes/no/unknown
 - Other relevant familial antecedents (i.e. cancer)
- Treatment:
 - Treatment specific for the RD: yes/no
 - Name(s) of the ongoing treatment(s)
 - RD specific
 - Other treatment(s)
- Care pathway:
 - Name of the physician in charge of the patient:
 - Rare disease centre following the patient: name of the centre/hospital/location/phone number
 - Is the RD centre part of an ERN

3.2 Rare cancers

Unplanned healthcare

- RC Diagnosis
- Link to clinical practice guidelines (e.g. ESMO-EURACAN clinical practice guidelines)
- Main alert messages about the specific risks related to the RC, including treatment contraindications
- Short anamnesis about the specific RC
- Contact information of the RC expert centre managing the patient; name of the physician/name of the centre/hospital/location/phone number(s) including emergency phone numbers, where existing.

Planned health care

Cancer diagnosis

— Pathologic cancer diagnosis (if not available, clinical diagnosis)

- *Date of diagnosis*
- *Type of cancer*
- *Grading*
- *Relevant molecular profiling*
- *Site*
- *Stage*

Phase of the cancer disease

- Progressive number of phase (by tumour, where more than one)
- Date of onset (first pathological diagnosis or first relapse/progression after a previous phase)
- Patient performance assessment

- Updates in baseline pathological diagnosis
- Disease extent (sites of visible disease)
- Objective of the treatment programme [potentially curative/therapeutic/symptomatic]
- Treatment programme
- Rationale of the programme's choice
- Treatment modalities
 - *Surgery*
Date. Description. Potentially curative within the treatment programme/palliative/diagnostic/ reconstructive/preventive. Margin status [R0/1/2, contaminated/not contaminated].
 - *Medical therapy*
Regimen(s) or therapy(ies). Dates. Number of cycles, or duration. Chemotherapy/hormonal therapy/target therapy/immune therapy. Neoadjuvant/adjuvant/cytoreductive/therapeutic. Treatment response (if appropriate).
 - *Radiotherapy*
Start date/end date. Site. Pre-operative/post-operative/exclusive/concomitant. Photons/ electrons/protons/carbons/other (specify) or radionuclide therapy. External/brachytherapy. 2D/3D/4D/Stereotactic. Intensity modulated/adaptive. Total dose/dose per fractions/number of fractions/overall treatment time. Treatment response (if appropriate).
- Evidence of disease/no evidence of disease at the end of treatments

Last oncology contact

- Date
- Evidence of disease/No evidence of disease
- Life status (alive/dead)
- Number of the current phase of disease

Since cancer history is divided into “phases” of treatment, (e.g. a patient can be treated for a primary localised tumour with surgery plus radiation therapy and chemotherapy within a first phase; then, if the disease has not been cured, after, say, months or years of follow-up, it will be treated with chemotherapy for a distant relapse within a second phase, and so forth). The ePS should be organised in “phases” and not in problems. Thus, in any problem-oriented framework, cancer should be viewed as a permanently “active” problem.

Table 1. Summary Table of the rare cancer items required by use case for planned care

Items required	Planned care use cases					
	Second opinion/MDT consultations (e.g. ERN)	Summary for attending clinicians; for GP involvement	Concise summary for external consultations	Internal consultation (within the hospital MDT)	Availability of clinical studies	Summary for patients
Cancer diagnosis	X	X	X	X	X	X
Pathological cancer diagnosis	X	X	X	X	X	X
Date of diagnosis	X	X	X	X	X	X
Type of cancer	X	X	X	X	X	X
Grading	X	X	X	X	X	X
Relevant molecular profiling	X	X		X	X	X
Site	X	X	X	X	X	X
Stage	X	X	X	X	X	X
Phase of the cancer disease	X	X	X	X	X	X
Progressive number of phase (by tumour, where more than one)	X			X		X
Date of onset (first pathological diagnosis or first relapse/progression after a previous phase)	X			X		X
Patient performance assessment	X	X	X	X		X
Updates in baseline pathological diagnosis	X			X		X
Disease extent (sites of visible disease)	X	X	X	X	X	X
Objective of the treatment programme		X	X			X
Treatment programme		X	X			X
Rationale for choice of programme		X	X			X
Treatment modalities	X			X		
<i>Surgery</i> Date. Description. Potentially curative within the treatment programme/palliative/diagnostic/re-constructive/preventive. Margin status.	X			X		
<i>Medical therapy</i> Regimen(s) or therapy(ies). Dates. Number of cycles, or duration. Chemotherapy/ hormonal therapy/ target therapy/ immune therapy. Neoadjuvant/ adjuvant/cytoreductive/therapeutic. Treatment response (if appropriate).	X			X		
<i>Radiotherapy</i> Start date/end date. Site. Pre-operative/post-operative/exclusive/ concomitant. Photons/electrons/protons/carbons/ other (specify) or radionuclide therapy. External/brachytherapy. 2D/3D/4D/stereotactic. Intensity modulated/adaptive. Total dose/ dose per fractions/number of fractions/overall treatment time. Treatment response (if appropriate).	X			X		

Evidence of disease/No evidence of disease at the end of treatments	X	X		X	X	
Last oncology contact						
Date						
Evidence of disease/No evidence of disease						
Life status (alive/dead)						
Number of the current phase of disease						

Table 2. Summary Table of the rare disease items required by use case for unplanned and planned care

	Use case:					
	Unplanned care	Planned care				
	Unplanned care (incl. emergency/surgery)	Second opinion/MDT consultations (e.g. ERN)	Internal consultation (within the hospital MDT)	Summary for GP involvement	Availability of clinical studies	Summary for patients
RD diagnosis	X	X	X	X	X	X
Disease name	X	X	X	X	X	X
ORPHAcode	X	X	X	X	X	X
Diagnosis assertion status	X	X	X	X	X	X
Method for diagnosis confirmation		X	X	X	X	X
Causative gene (if relevant)		X	X	X	X	X
Gene variant (if relevant)		X	X	X	X	X
Disease history		X	X	X	X	X
Age of onset		X	X	X	X	X
Age at diagnosis		X	X	X	X	X
Heredity (if relevant)		X	X	X	X	X
Clinical manifestations		X	X	X	X	X
Investigations (type and results)		X	X	X	X	X
Disabilities		X	X	X	X	X
Antenatal/perinatal information (if relevant)		X	X	X	X	X
Birth date		X	X	X	X	X
Gender at birth		X	X	X	X	X
Malformation detected antenatally		X	X	X	X	
Medically assisted procreation (yes/no)		X	X	X	X	X
Gestational age at birth (weeks)		X	X	X	X	X
Weight at birth		X	X	X	X	X
Height at birth		X	X	X	X	X
Head circumference at birth		X	X	X	X	X
Family antecedents in relation with the RD		X	X	X	X	X
Affected member (propositus) yes/no		X	X	X	X	X
Parental relationship with the affected member		X	X	X	X	X
Consanguinity: yes/no/unknown		X	X	X	X	X
Other relevant familial antecedents (i.e. cancer)		X	X	X	X	X
Treatments	X	X	X	X	X	X
Treatment specific for the RD: yes/no	X	X	X	X	X	X
Name and posology of the ongoing treatment(s) (RD specific; others)	X	X	X	X	X	X
Care pathway	X	X	X	X	X	X
Name of the physician in charge of the patient:	X	X	X	X	X	X
Rare disease centre following the patient: name of the centre/hospital/	X	X	X	X	X	X

location/phone number (incl. emergency phone number)						
Is the RD centre part of an ERN (yes/no)	X	X	X	X	X	X
ERN name	X	X	X	X	X	X
Useful information	X	X	X	X		X
url leading to information on the disease, including CPGs, emergency and anaesthesia guidelines	X	X	X	X		X
Main alert messages	X	X	X	X		X

4. Existing standards and terminologies

4.1 Rare diseases

fields	definition	standards
Rare disease	Defines a medical condition whose prevalence is <50/100,000 in the general population in Europe.	Orphanet nomenclature of rare diseases (ORPHAcode) www.orphadata.com
Phenotypic abnormality	Clinical signs and symptoms observed in the patient	Human Phenotype Ontology (HPO) https://hpo.jax.org ICD-10/ICD-11 https://icd.who.int/browse10/2019/en#/ https://icd.who.int/en
Gene name	Symbol of the gene which is causative of the genetic rare disease	HGNC https://www.genenames.org
Variant	Genetic anomaly in the causative gene	HGVS https://varnomen.hgvs.org
Disability	Patient's activity limitation(s) and/or participation restriction(s) (functional consequences)	ICF https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health

4.2 Rare cancers

Fields	definition	standards
Type of cancer	Describes the tumour morphology (also the site of the primary site is coded)	ICD-O3 International classification of disease for oncology Morphology and Topography https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology ICC3 International classification for childhood Cancer https://seer.cancer.gov/iccc/ SNOMED https://www.snomed.org/
Grading	Describes the biological aggressiveness of the tumour. In general, a lower grade indicates a slower-growing cancer and a higher grade indicates a faster-growing one. Grading systems differ depending on the type of cancer. In general, tumours are graded as 1, 2, 3, or 4, depending on the amount of abnormality. GX: grading cannot be accessed	ICD-O3 grading
Staging	Describes the tumour extent at the time of the first definitive treatment (depending on the tumour, other factors can be incorporated beyond tumour extent)	TNM https://www.uicc.org/resources/tnm
Treatment response	A standard way to measure how well a cancer patient responds to treatment. It is based on whether tumours shrink, stay the same, or get bigger. To use RECIST, there must be at least one tumour that can be measured on x-rays, CT scans, or MRI scans. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD). Also called Response Evaluation Criteria In Solid Tumours.	RECIST (Response Evaluation Criteria in Solid Tumours) https://recist.eortc.org/

Implementation example (Patient Summary functional specifications for rare diseases including rare cancers)

Table 3. New items specific for rare disease and rare cancer patients vs ePS version 3

	New items for rare diseases	New items for rare cancers	New items for rare diseases and rare cancers	Variable to be integrated in an already available variable of ePS V3	New variable to be recorded in Annex to PS
ERN to which the rare disease/rare cancer expert centre information belongs			X	X To add to preferred HP to contact	
Healthcare alert description in relation to the rare disease	X			X To add to medical alert information	
Diagnosis assertion	X				X
Heredity	X			Maybe add to medical history	
Family history	X			Maybe add to medical history	
Antenatal/perinatal history	X			Maybe add to medical history	
Clinical signs and symptoms (phenotype)	X			X To add to physical findings	
Disabilities	X			X To add to functional status	
Genetic testing	X			To add to list of current problems	
Pathological cancer diagnosis, or clinical cancer diagnosis		X		X To add to list of current problems	
Type of cancer		X		X	

				To add to list of current problems	
	New items for rare diseases	New items for rare cancers	New items for rare diseases and rare cancers	Variable to be integrated in an already available variable of ePS V3	New variable to be recorded in Annex to PS
Cancer grading		X		X To add to list of current problems	
Relevant molecular profiling		X		X To add to list of current problems	
Risk stratification or stage		X		X To add to list of current problems	
Phase of the cancer		X			X
Patient performance assessment		X		X To add to current functional status	
Updates in baseline pathological diagnosis		X			X
Disease extent (sites of visible diseases)		X			X
Objective of the treatment programme		X			X
Treatment programme		X			X
Rationale for the choice of programme		X			X

Description of the surgical procedures (free text)		X		X To add among procedures	
Objective of the surgical procedures		X		X To add among procedures	
Margin status after surgery		X		X To add among procedures	
	New items for rare diseases	New items for rare cancers	New items for rare diseases and rare cancers	Variable to be integrated in an already available variable of the ePS V3	New variable to be recorded in Annex to PS
Medical Therapy (Number of cycles, duration, setting)		X		X To add to the current medication summary	
Radiotherapy (site, setting, type, dose, treatment response)		X		X To add to the current medication summary enlarging the scope of this section to radiotherapeutic treatment	
Evidence of Disease		X			X

Summary and Discussion

The aim of this document is to address the specific needs in terms of data elements and semantic standards for rare diseases in general and for rare cancers as far as they differ from rare diseases, in relation to well-defined use cases for both planned and unplanned care. Data elements are based both on previously agreed minimum data sets for rare disease patient registration, which are in some cases implemented in health records in some countries, and on the experience of European Reference Networks on rare cancers. Identified data elements will be used as functional specifications to adapt the PS and European Electronic Health Record exchange format (EEHRxF) to these specific groups of diseases.

The exercise resulted in three types of specifications:

- New data fields not yet considered in the PS
- New items to be included in already existing data fields in the PS, to extend them
- New terminological standards to be implemented in the PS
-

Some consideration is needed concerning the ePS for rare diseases and rare cancers.

- Who should write the ePS for RD including RC

RDs and rare cancers are rare and complex types of disease requiring highly specialised expertise and a multidisciplinary approach. In Europe, this expertise is organised in European Reference Networks, but some countries have their own national policy to recognise such expertise. Therefore, we recommend that, where possible, PS be filled in by an expert in the case of RD/RC and that data fields related to RD/RC be retrieved from EHRs from expert centres.

- Format of the ePS (structured vs. free text)

The patient summary as an output is essentially a clinical tool, ensuring continuity of care, although its data can also be useful for research or even administrative purposes. Thus, it should be readable by professionals. This means that its natural-language text should score high in terms of human readability, regarding both effectiveness and efficiency. The risk of mistakes should be minimised, leaving the physician full control of something which he/she will have to undersign and may be used at any time by other physicians, also in emergency conditions, when the original data cannot be verified. EHRs are now widespread. However, current EHRs are highly demanding in terms of medical workload, because they claim a lot of professional time to manually input data. Overstructured fields add to this burden and make it often unnatural to input information which was previously very simple for the physician to provide (for instance, medical prescriptions). Software often imposes constraints which are poorly consistent with the many rule deviations which are typical of the medical profession. One may expect formidable technological improvements in the near future in terms of human-machine interfaces (which on average are highly suboptimal, also in comparison to many everyday-life interfaces, such as online newspapers, etc.). In addition, AI may make it more fluent for physicians to input data and to retrieve them. However, the current IT scenario is very frustrating for both clinicians and patients. It is hard to believe that physicians will comply with input requirements considered

excessive in terms of usefulness of data and degree of field structuring. If ePS is produced manually, the fields to be actively filled in by physicians need to be minimised or perceived as immediately useful for retrieval. In addition, they need to be structured as little as possible. A free-text field should therefore always be available, particularly in use cases for planned care.

- ePS vs EHR

In principle, data envisaged for a patient summary tool should be already available inside current EHRs, enabling them to be transferred automatically. This is particularly relevant for unplanned use cases, at which ePS was originally intended. However, the content to be exchanged is constrained to what is available in source records and a comprehensive data exchange may not be available due to the maturity of systems involved. Thus, the ePS is a valuable solution for unplanned care but not for planned care, with the relaxed time frame and the ideas of completeness and higher granularity, the whole EHR should be exchanged. We suggest that any additional data requests to be included in EHR IT implementation should be previously discussed with a sample of clinicians, to check the additional burden they may impose on routine care, all the more so when their use is foreseen for unlikely events (such as emergencies while the patient is abroad, etc.). Whenever new technologies, namely AI, can be exploited to minimise manual data input and/or data structuring, they should be exploited.

- Exploitability of ePS for rare diseases

Patients with RD might require treatment in another country from the one in which they live. This may be due to the lack of centres for their specific disease close to where they live, but also to people's increased mobility within and outside the EU. However, all healthcare professionals who are not RD experts may not always be familiar with RDs and timely, accurate medical information on a particular RD and the individual patient is required to provide adequate medical care, particularly in unplanned situations. RD patients will greatly benefit from the implementation of the specifications suggested in this document.

- Exploitability of ePS for cancers

Rare cancers make up one fifth of all cancer cases. In principle, there are no distinctive characteristics in their natural history and/or diagnosis and treatment as compared to common cancers. This means that any patient summary tool conceived for rare cancers will also fit the requirements of cancer in general. On the other side, from the perspective of a patient summary tool, cancer is a distinctive disease in several respects, as follows.

- The clinical history of a cancer patient can be easily divided into one or more “phases” of treatment. Thus, the ePS should be organised in “phases” and not in problems. In any problem-oriented framework, cancer should be viewed as a permanently “active” problem.
- Every clinical decision at the beginning of a phase should be multidisciplinary, even when the selected treatment will then belong to a single medical discipline.
- Any clinical decision will always be highly personalised whereas clinical practice guidelines simply foresee the most typical disease presentations.

Annex 2 exemplifies challenges and possible solutions for identifying cancer patients and treatment phase in EHRs.

References

Valdez R, Ouyang L, Bolen J. Public health and rare diseases: Oxymoron no more. *Prev Chronic Dis.* 2016;13:E05.

Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* 28, 165–173 (2020). <https://doi.org/10.1038/s41431-019-0508-0>

Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, Otter R, Licitra L, Mallone S, Tavilla A, Trama A, Capocaccia R; RARECARE working group. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer.* 2011 Nov;47(17):2493-511. doi: 10.1016/j.ejca.2011.08.008. Epub 2011 Oct 25. PMID: 22033323.

EUCERD Minimum Data Set for rare diseases registries. January 2015. http://www.rd-action.eu/eucerd/EJA/Deliverables/WP8_Registries_MDS.pdf

BNDMR Minimum Dataset http://www.bndmr.fr/wp-content/uploads/2020/02/MDS_v1.11-2EN.pdf

RD Common data elements for RD registries. Joint Research Center https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/CDS/EU_RD_Platform_CDS_Final.pdf

Annex 1

Comparison of RD datasets with PS items

	Minimum dataset for RD registries EUCERD recommendation		BNDMR MDS (French National Rare Diseases Minimum Data Set)		Common Data Elements for RD registries		ePS unplanned *		ePS planned care*
1. Consent	Patient consent								
	Patient nonopposition to the reuse of data		Patient's non-opposition for data reuse		Consent to the reuse of data				
	Consent by legal guardian								
2. Patient identification	International rare disease identifier GUID (Global Unique Identifier)				Pseudonym (EUPID)				
	National anonymous RD patient ID		Health national identifier						
	other national identifier Patient ID		Patient's local hospital identifier						
			Patient is affected with a rare disease Y/N						
	Foetus (if applicable) Whether information is recorded for a foetus		foetus						
3. Administrative information	Patient's maiden name		Patient's patronymic name (surname at birth)						
	Patient's (married) last name		Patient's commonly used last name						
	Patient's first name		Patient's first name						
	Patient's date of birth		Patient's date of birth		Date of birth				Date of birth
	Gender		Patient's gender		Sex				Gender at birth
	Country of birth		Country of birth						
	Patient's city of birth		City of birth						
	Country of residence		Country of residence						
	Patient's city of residence		City of residence						
Parents information (if foetus)			Mother's patronymic name (surname at birth)						
			Mother's commonly used last name						
			Mother's first name						
			Date of pregnancy						
			Multiple pregnancy						
			foetus' gender						
			foetus' first name						
			Country of residence						
			City of residence						
4. Family information	Propositus?		Propositus						
			Propositus identifier						
	Relationship with the propositus		Parental relationship with the propositus						
	Patient born from a relationship between related parties		Inbreeding (consanguinity)						
5. Vital status	Patient's vital status Is the patient still alive?		Patient's vital status		Patient's status				
	Patient's date of death		Patient's date of death		Date of death				
	Death due to the rare disease		Death due to the rare disease						
	If death is not linked to the rare disease, main cause of death		Main cause of death						
6. Care pathway	Patient addressed by		Patient referred by						
	Patient's date of inclusion in the RD center		Patient's date of inclusion in the RD reference centre		First contact with specialised centre				
			Name of the physician in charge of the patient						

			RD centre(s) of the patient				Contact information of the rare disease expert centre that follows the patient; name of the physician/name of the centre/hospital/location/ phone number(s) including emergency phone numbers if exists		Contact information of the rare disease expert centre that follows the patient; name of the physician/name of the centre/hospital/location/ phone number(s) including emergency phone numbers if exists
			Not included in the label terms						
7. Care activities	Date of care performed by the patient		Date of the performed rare disease care						
	Context of the care activity		Context of the rare disease care activity						
	Objectives of the care activity		Objectives of the rare disease care activity						
	Occupation of the personnel performing the care activity		Occupation of the personnel performing the declared care activity						
	Personnel performing the activity (Name)		Personnel performing the declared activity						
			RD Centre for which the activity is declared						
			Location of medical consultation						
8-10. Diagnosis									
	Age at onset		Age at onset of first signs		Age at onset				Age at onset
			Specification of the age at onset of first signs (months)						
	Assessment of the diagnosis at center admission (appropriateness)		Assessment of the diagnosis at first admission in the rare disease centre						
	Age at diagnosis		Age at diagnosis		Age at diagnosis				Age at diagnosis
			Specification of the age at diagnosis (months)						
	Current state of the diagnosis (Ongoing,Likely,Confirmed,Undetermined)		Current status of the diagnosis						Diagnosis assertion
	Diagnosis of the rare disease (Diagnosis retained by the RD center Orphanet code)		Patient's rare disease diagnosis (Orpha code)		Diagnosis of the rare disease		RD Diagnosis: Rare disease name and code (Orphacode)		RD Diagnosis: Rare disease name and code (Orphacode)
							url of generic website with relevant information on the particular disease (Orphanet)		
							main alert messages about the specific risks related to the rare disease, including treatment counterindications		
	Additional or unusual signs associated with the rare disease (HPO code)		Additional signs associated with the rare disease						Clinical manifestations
			Unusual signs associated with the rare disease						
	Sporadic or familial disease		Sporadic or familial case						Heredity
	Confirmation method of the diagnosis		Method(s) used for diagnosis investigation.						Method(s) used for diagnosis investigation/confirmation.

	Biological method used to assess the diagnosis (if applicable)		Method used to assess the diagnosis (if applicable)						
	Genetics Gene identified?		Genes (HGNC)		Genetic diagnosis				Genetic diagnosis: gene,variant (HGNC,HGVS)
					Undiagnosed case (HPO, HGVS)				
	Mutation (if applicable)		Other genetic description						
	Penetrance (if applicable for a seemingly healthy patient)		Subject seemingly healthy (mutation carrier) Y/N						
	Weight								
	Height								
	Disabilities				Classification of functioning/disability				Disabilities
	QoL								
11. Treatment									
	Is a specific treatment for the rare disease in process?		Is a treatment specific to the rare disease in progress?			Ongoing treatments			Ongoing treatments
	Ongoing treatment for the rare disease		Ongoing treatment for the rare disease						
12. Ante- and neonatal									
	Medically assisted procreation		Medically assisted procreation						Medically assisted procreation
	Does the patient have a prenatal malformation?		Presence of antenatal malformation						Presence of antenatal malformation
	Full-term (if else, clarify the term)		Full-term birth?						Full-term birth?
			Term (if premature birth)						Term (if premature birth)
	Height at birth		Height at birth						Height at birth
	Weight at birth		Weight at birth						Weight at birth
	Head circumference		Head circumference at birth						Head circumference at birth
	Has a foetopathological examination been performed?		Foetopathology						
13. Research	Patient participating in a protocol		Patient involved in a protocol						
	Agreement to be contacted for a protocol		Agreement to be contacted for a protocol		Agreement to be contacted for research purposes				
	Patient having previously given a biological sample for research		Patient having previously given a biological sample for RD research		Biological sample				
	Patient having previously given a biological sample for molecular diagnosis		Patient having previously given a biological sample for molecular diagnosis						
	Link to a biobank				Link to a biobank				

* only specific items are listed; generic items (i.e. administrative information) are not to be excluded

Is the present subject (i.e. the subject of this collection of information), who carries the mutation, sick or not?

Annex 2 - Selection of cancer patients and treatment phase (an example from the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (INT)).

The following example exemplifies challenges and possible solutions for identifying cancer patients and treatment phase in EHRs.

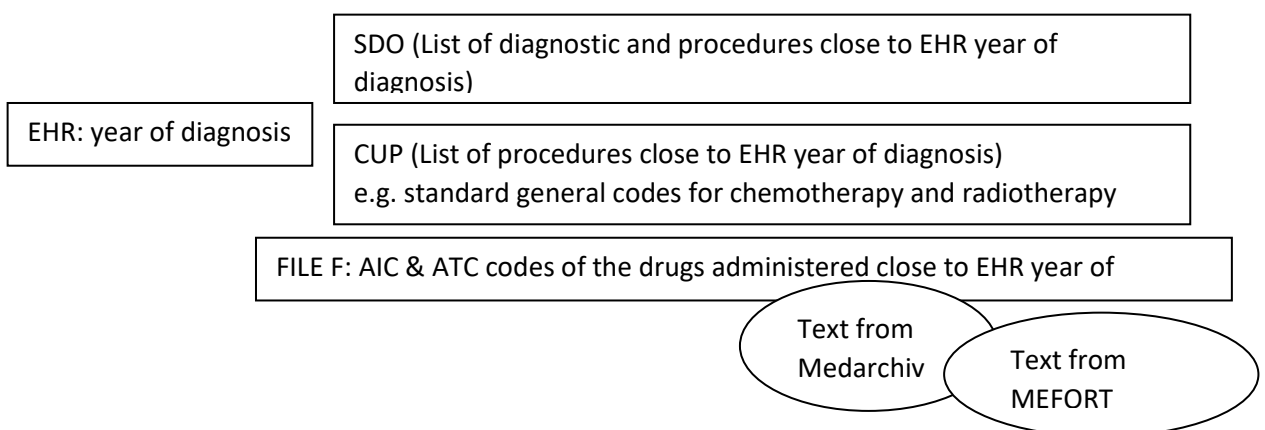
Step 1: patient selection using the electronic health record (EHR)

EHR: year of diagnosis + diagnosis (structured text variable)

Step 2: identification of the primary treatment using EHR + additional electronic databases.

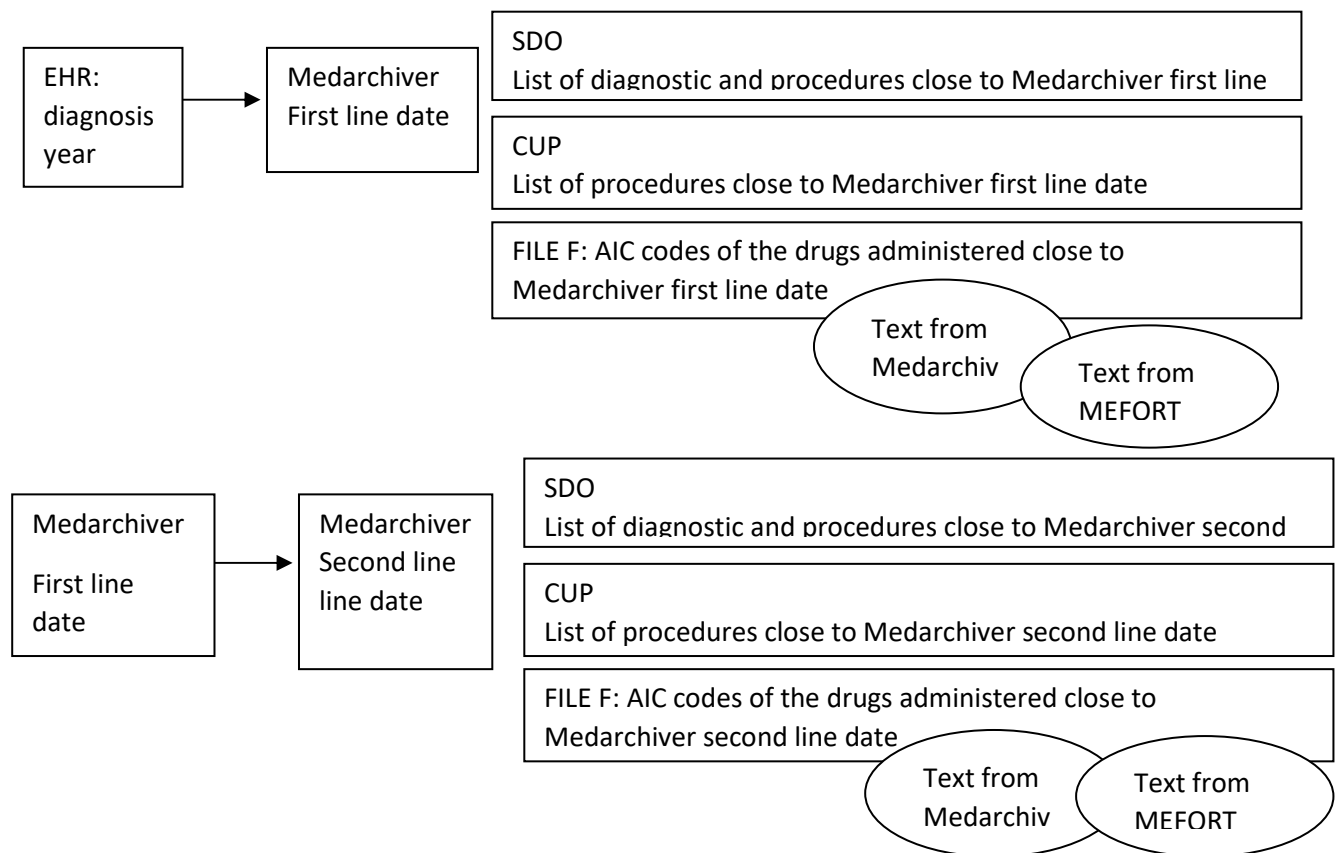
The EHR does not include structured information for this purpose but only textual information. Additional electronic database linked to the EHR have structured data coded according to international classification standard. To define the primary treatment, it is necessary to query the SDO (Hospital discharge), the CUP (Booking center) and the FILE F (Administrative pharmaceutical reimbursement) first, in order to identify the procedures performed in a date close to the year of diagnosis of the EHR. If there is an interest to report chemotherapy regimens, the only chance is to use the Medarchiver (Chemotherapy app) which, however, contains the information in text format. This text format could be linked to the FILE F that includes ATC codes.

Note: Additional electronic databases include only treatments and procedures performed in INT. Treatments performed outside INT can only be described in text filed in the EHR



Step 3: identification of subsequent phase of the disease

Option 1. Use Medarchiver as pointer of treatment phase since it provides the information on whether the chemotherapy is a first, second or third line. Again, this variable is in text format. There are some quality problems and there is the need to standardise the definition of the use of first, second third line across the different cancers. Medarchiver is linked with all the other DB thus, using the date of the therapy in Medarchiver, queries should be developed to identify in the other DB the details of the procedures performed close to Medarchiver therapy date



Option 2. Use the EHR as pointer of treatment phase. The EHR include an item about the cancer phase. This variable is in text format and the options of this variable should be reviewed to properly be used as a pointer. This would be a suggestion for EHR dedicated to cancer. Once identified the treatment phase, additional information can be exported only from the other DB as explained in option1.

Selected/relevant electronic information sources at the INT

- hospital discharge (inpatient and day-hospital) database containing information about primary diagnosis, coexisting conditions, provided procedures (coded according to ICD-9CM) and clinical condensed stage (1. tumour confined to organ of origin; 2. tumour beyond organ of origin; 3. metastases to regional lymph node; 4. tumour beyond organ of origin + metastases to regional lymph nodes; 5. distant metastases; 6. distant lymph nodes; 7. not confined to organ of origin but unknown if 2,3,4,5 or 6; 8. No distant organs invasions but unknown if 1,2,3 or 4; 9. Unknown); clinical discharge records (SDO) coded in ICD-9CM
- outpatients booking centre (CUP), including visits and procedures performed in specialist ambulatories (coded according to the regional outpatients services coding);
- DB of chemotherapy performed (Medarchiver),
- DB of radiotherapy performed (MEFORT),
- drug prescription database (File F) providing information on all the drugs reimbursed by the National Health System (coded according to the AIC / ATC classification system);