Ref. Ares(2022)719311 - 31/01/2022

Gravitate Health

innovative medicines initiative

Gravitate-Health

WP5 – Interoperability, accessibility and regulatory support

D5.1 State of the art standards of accessibility, outcomes, and APIs for ePIs, mapping of regulatory approved Product Information in common EU ePI standard

Due date	31/1/2022
Delivery date	31/1/2022
Deliverable Type	R
Dissemination Level	PU

Lead contributor	3-HL7 Europe, Catherine Chronaki

Other contributors	2-Pfizer Amy Cramer, Craig Anderson, Beverly Buckta, Giovanna Ferrari and WP5 partners

The Gravitate-Health project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 945334. This joint undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations [EFPIA]. The total budget is 18.5M€ for a project duration of 60 months.

efpia Datapharm

Document History

Version	Date	Description
0.1	23.Dec.2021	First Outline of the Deliverable
0.2	17.Jan.2022	Input from Amy Cramer on HL7 Standards
0.3	18.Jan.2022	Accessibility Standards section Catherine Chronaki, Bev Buckta
0.4	23.Jan.2022	Input from Craig Anderson, on Stylesheets
0.4	28.Jan.2022	Review by Martin Ingvar, Giovanna Ferrari, Line Løw, Anne Moen, Alan Hochberg
0.5	31.Jan.2022	Reviewer Comments Addressed
1.0	31.Jan.2022	Submitted to IMI

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Acronym / term	Full name / definition
API	Application Programming Interface
EC	European Commission
EEA	European Economic Area
EHR	Electronic health record
EMA	European Medicines Agency
ePI	Electronic product information
EU	European Union
FHIR®	Fast Healthcare Interoperability Resource
GDPR	General Data Protection Regulation
HCP	Healthcare professional
HL7	Health Level Seven
HMA	Heads of Medicines Agencies
IDMP	Identification of Medicinal Products (ISO standard)
IG	Implementation Guide (HL7 FHIR® resources)
ISO	International Organization for Standardization
MDR	Medical Device Directive
MAH	Marketing authorization holder
NIS	Network Information Security
NCA	National competent authority
QRD	Quality Review of Documents templates
PDF	Portable document format
PI	Product information
PL	Package leaflet
SME	Small or medium-sized enterprises
SmPC	Summary of product characteristics
SPOR	Substance, product, organization and referential (EMA implementation of ISO IDMP standards)

1 EXECUTIVE SUMMARY

Gravitate-Health aims at empowering and equipping Europeans with Health Information for Active, Personal Health Management and adherence to treatment using electronic Product Information. WP5 focuses on Interoperability, accessibility, and regulatory support to:

1) Provide tools for interoperability, accessibility standards and regulatory compliance that will accelerate the wide deployment of the Gravitate-Health open source federated technical platform with microservices driven by HL7 FHIR Application Programming Interfaces (APIs) combined with a robust digital health ecosystem
2) Support scale-up and broad adoption of the open-source platform and digital solutions with standards and implementation guides to ensure adoption of the common European and other electronic Product Information (ePI) standard and its connection to the health and social care system.
3) Create resources to facilitate the use of FAIR data principles to support risk minimization and use of RWD. These resources include principles that set clear standards to promote public trust in the management of data and provide high quality, inclusive and trustworthy statistical indicators. Resources also include those related among others to medication management and care transitions such as implementation guides, educational resources, and process workflows.
4) Develop tools and guidance to support EU regulatory compliance with General Data Protection Regulation (GDPR), Medical Device Regulation (MDR), Cyber Security Act, Network Information Security (NIS) and EU Pharmaceutical Products legislation and overview of potential national level variations. Provide input to policy makers on potential legislative developments to support use of new digital tools such as ePI.

This Deliverable 5.1, State of the art standards of accessibility, outcomes, and Application Programming Interfaces (APIs) for ePIs, mapping of regulatory approved Product Information in common EU ePI standard, links developments in the ePI standard and associated specifications build by EMA, to standards for accessibility, outcomes, and Application Programming Interfaces.

Based on this review and on-going work with HL7 Connectathons September 2021 and September 2022, the following recommendations are offered:

D5.1. Recommendation 1: The structure for the QRD template guidance should assessed for their ability to meet the future needs for ePI and G-lens® implementations.

D5.1 Recommendation 2: The sections and subsections for the QRD templates should be further analysed for specific groups of pharmaceutical products identifying associated dictionaries as part of the Gravitate-Health FHIR IG.

D5.1 Recommendation 3: Gravitate-Health should create style sheets which build on the EU readability guidance on design and format, at the same time address the needs (WCAG 2.1), requirements and promise of ePIs and the G-lens®.

D5.1 Recommendation 4: Gravitate-Health will adapt the testing and validation guidance of EU readability guidance to incorporate WCAG2.1, to advance real-world testing the understanding of ePIs and the application of G-lens®.

D5.1 Recommendation 5: All applications of G-lens® should take into account the WCAG2.1 guidelines for accessibility as advocated by EMA and FDA.

D5.1 Recommendation 6: The federated open-source platform (FOSP) of Gravitate-Health should offer tools to curate and validate ePIs resources and their stylesheets.

D5.1 Recommendation 7: ICHOM standards and HL7 FHIR implementation could be considered as a resource to capture patient outcomes. In a standardized manner.

D5.1 Recommendation 8: Gravitate-Health with its agile engagement in Connectathons should work to accelerate maturation of HL7 FHIR resources related to ePI, as a strategy to facilitate their adoption and alignment in collaboration with regulators globally.

2 Scope

The aim of deliverable D5.1 is to provide a review of the state of the art in accessibility, interoperability, and health outcomes standards, as well as Application Programming Interfaces (APIs) for ePIs as applicable to Gravitate-Health. Based on this review and on-going work, key recommendations are offered for the next steps. Starting from the EMA Key Principles for a common Electronic Product Information (ePI) standard [1], we also present relevant activities in progress focusing on how we envision to use standards to achieve the objectives of Gravitate-Health. Specification work that will be addressed includes: (a) the EMA ePI Setup project, (b) EMA SPOR, i.e., the IDMP implementation at EMA (c) relevant HL7 Work Groups, HL7 FHIR® Accelerators, FHIR® resources, and Connectathons (d) Standardization developments in accessibility, and (e) health outcomes. On the topic of APIs for ePIs in the broader sense that engages the vision of the G-lens® we are only offering a snapshot of what exists or is in development, since the FHIR resources associated with EMA common standard for ePI, as well as the FHIR standard itself are all work in progress.

3 Introduction

This introductory section aims to provide background information on the EMA activities directly or indirectly related to ePI, accessibility, and outcomes standards. Then, the follow-up sections will summarize the relevant standards and activities.

3.1 What is electronic Product Information?

In the European Union (EU), a medicine's product information (PI) includes the summary of product characteristics (SmPC, intended for healthcare professionals [HCPs]), labelling (outer and inner packaging information) and package leaflet (PL, for patients / consumers and generally included as a printed copy in the medicines package) [1].

The regulated and scientifically validated information included in the SmPC assists HCPs in prescribing and dispensing the medicine. PLs included in medicine package inform patients and consumers about safe use.

A report from the European Commission (EC) in March 2017, and a subsequent European Medicines Agency (EMA) action plan [2], identified areas where the SmPC and PL could be improved and developing an electronic format was identified as the most pressing priorities from a public health perspective. This is how the EMA ePI SetUP project started to develop HL7 FHIR® specification for ePI which was published for consultation in June 2021, and presented in a dedicated workshop in July 2021 [3].

ePI is authorized, statutory product information for medicines (i.e., SmPC, PL and labelling) in a semi-structured format created using the common EU electronic standard. ePI is adapted for electronic handling and allows dissemination via the world wide web, e-platforms and print. Terminology organizations, software vendors, and developers of medicinal product dictionaries and databases all participate in SPOR (ISO IDMP) task force [7].

The common EU ePI standard provides technical specifications including mark-up language, controlled vocabularies, and interoperability specifications agreed by EMA, Head of Medicines Agencies (HMA), National Competent Authorities (NCAs), and EC with

the aims of: (a) creating foundations for trustworthy regulator-authorized information that would provide patients and HCPs with an additional personalized approach to medicinal information, (b) streamline, simplify, and speed-up the regulatory processes for creation and update of PI using SPOR (i.e. substance, product, organization, and referential) data; (c) avoid coexistence of multiple standards leading to complexity that ultimately restricts data flow.

3.2 Common EU ePI standard: key principles

The report of the European Commission in 2017 outlined areas of improvement for the EU product information [3] and identified that there is a lot of room for improvement of the PL as patients and consumers especially those with low literary skills are challenged when they attempt to read and comprehend PLs. The action plan of EMA set out to address these recommendations, and included plans to explore use of electronic formats for product information, review of Guidelines for Readability, SmPC, Quality Review of Document (QRD) template, and Translation; as well as consideration of the potential value of inclusion of a key information section in the SmPC and PL. One of the actions recommended in connection with use of electronic formats was to develop key principles for use.

A joint cooperation between the European Medicine's Agency (EMA), the Heads of Medicine Agencies (HMA), and the European Commission (EC) on the key principles underpinning electronic product information for human medicines in the EU was progressed and resulted in [1]. These key principles are briefly presented below.

ePI fulfils the following key principles so that it benefits public health, creates efficiency gains for regulatory systems, aligns with the existing legislative framework and complements the paper package leaflet, serves Europe's multilingual environment, and links to ongoing digital initiatives in Europe and globally.

The key principles are as follows:

a) ePI is a **public-health priority** since it expands unbiased, up-to-date, regulator-approved PI for all medicines in the EU, provisioning the **latest 'right' information** on the medicine's safety, benefits and conditions of use, etc. at the point of need. Thus, structured ePI data will allow functionalities such as selecting information on medicines, automatic update notifications, interactive materials, and online adverse-reaction reporting tools. ePI information will be able to flow to other systems, such as electronic health records and e-prescribing systems and will provide authoritative source of the latest most up-to-date scientific and evidence-based information on EU medicines (e.g., through 2D barcode). With ePI being "**accessible by design**", medicinal product information will also be accessible to people with print, e.g., physical or sensory impairments, or learning difficulties. More accessible formats would offer large fonts or high screen contrast for partially sighted users, audible formats for blind users and those with low literacy levels, etc.
b) Administrative **regulatory procedures** will benefit from increased **efficiency** in management of ePI by reusing information and reducing or eliminating manually performed tasks. For instance, automated systems could simultaneously change, or flag for change, all locations where information needs updating, reducing the risk of error.
c) ePI will provide **information on medicines that is amenable to analysis**, and could be used to increase knowledge by facilitating study of characteristics of

current EU medicines. Data on nationally authorised medicines could provide a source of information on medicines in countries across the EU.

d) ePI **does not introduce a new legal obligation**. ePI does not substitute the paper leaflet important to patients with low literacy or limited internet access but expands the formats in which PL is available. Though not legally mandated EMA, HMA and NCAs shall commit to generation of ePI as additional information cost. The paper PL should direct to the ePI as the most up-to-date version of the PL. Meanwhile, ePI is intended for the delivery of the full and complete regulator-approved medicine PI only and should not be used for promotional information and should always be published as **freely accessible open data**. ePI itself will not include **any personal data**. In any event where processing (e.g., collecting or handling) of personal data may occur in relation to the implementation and use of ePI, subject to Regulation (EU) 2016/679 (GDPR) and Regulation (EU) 2018/1725 applicable to EU institutions.

e) In terms of **governance** an **ePI roadmap will describe the implementation process in phases**. The ePI format will be for information about human medicines authorised in the EU through EMA and NCAs, from the point of submission and throughout the evaluation process (see figure 1). The ePI will be available in EMA and member state level websites, Compendiums as well as eHealth systems such as EHRs and e-prescribing. It is envisaged that the EMA and all NCAs will be able to use ePI from the point of submission. While all stakeholders are expected to implement the common ePI standard for all medicinal products available in the EU, the implementation timelines and processes will be flexible. An HMA-EMA roadmap will define the steps of development.

f) ePI shall support **all official EU languages, as well as Icelandic and Norwegian** so that EU citizens will be able to read ePI in their preferred language when authorised ePI in that language is available. ePI will **interface and work with eHealth initiatives** within and across organizations or domains, e.g., cross-border prescription, EHRs, European medicines web portal, pharmacovigilance systems, SPOR data management services, future ePI for veterinary medicines, a future European common data model, current electronic application procedures and national ePI systems, while taking into account use of ePI in the global context. The European Interoperability Framework [1] recommends (recommendation 9) ensuring data portability, namely that data is easily transferable between systems and applications supporting the implementation and evolution of European public services without unjustified restrictions, in accordance with the legal framework. In addition, the framework outlines (recommendation 7) that, unless privacy or confidentiality restrictions apply, information and data should be shared and reused when implementing European public services.

1 https://ec.europa.eu/isa2/sites/default/files/eif_brochure_final.pdf

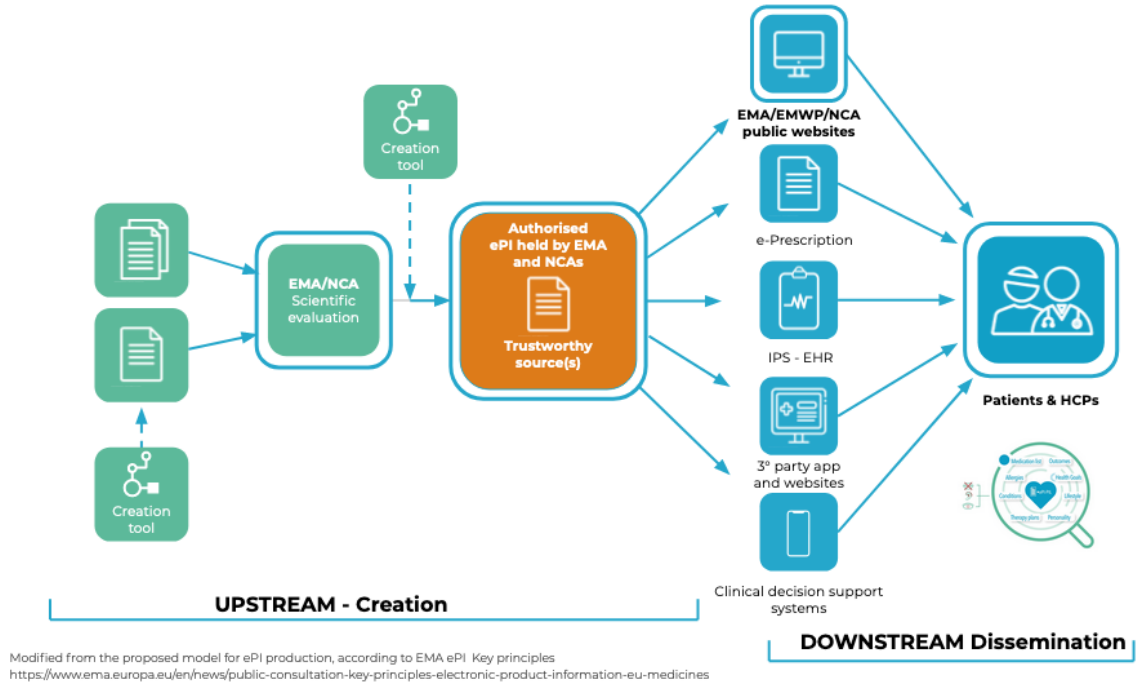


Figure 1: Possible ePI workflows.

The EMA initiated the ePI setup project early in 2021, to create a proof-of-concept EU common standard specification that can implement the key principles. The specification was published in June 2021, together with a FHIR server that hosted sample data. A hands-on workshop was organized in July 2021 [2] and a stakeholder consultation followed. Following approval of the common standard specification by the EU Data Board, the next phase in the ePI implementations started. This phase entails the ePI roadmap and ePI pilot project. The figure above describes the proposed data flow and process from the creation of ePI (upstream) to the dissemination of ePI (downstream), where the G-lens®, as main output of the Gravitate-Health project, is envisaged to accelerate progress, starting in the 'Downstream dissemination' space of the proposed model.

Unfortunately, still the primary form of delivery for Product Information is paper, and we need to find a way to smoothly inject ePI in the regulatory processes. This already has happened with Query Response (QR) codes available in many leaflets that allows users to retrieve the latest electronic version of the leaflet. One possible next step is that in the upcoming EMA ePI pilot, patient leaflets in electronic form are assessed next to paper.

3.3 The EMA implementation of IDMP: SPOR

The European Medicines Agency (EMA) has adopted the HL7 FHIR messaging standard for their EU-wide implementation of the international Identification of Medicinal Products (IDMP) standard. The EMA implemented IDMP based on the four domains of master data in pharmaceutical regulatory processes: Substance, Product, Organization, and Referential data (SPOR).

The elements of SPOR provide a vital source of information in our efforts to explore ePIs in a structured form. The European H2020 project UNICOM (www.unicom-project.eu) aims to advance the implementation of ISO/IDMP standards across Europe contributing

to harmonization worldwide. In this setting, important resources offered to Gravitate-Health are the UNICOM deliverable on gap analysis and the educational resource 'IDMP in a capsule' [8].

The ePI implementation guide of Gravitate-Health currently under development, includes information that would be expected to be retrieved from SPOR [9]. This strategic choice was made to make the implementation guide globally relevant. Gravitate-Health and UNICOM plan to engage in a shared demonstrator for May and/or September 2022. The UNICOM Project has provided global and national identifiers for medications to be stored in the Medication Section of the Patient Summary and facilitate retrieval of relevant ePI.

4 Accessibility

The key ePI principles advocate for "accessibility by design", so that medicine information should be also accessible to people with print impairments e.g., physical or sensory impairments, or learning difficulties. For this purpose, voice and video formats can complement printed information to enhance the patients' or citizen understanding of medicinal products. For those browsing the internet, compliance with web content accessibility protocols (WCAG 2.1), will all allow everyone to use preferred modality to perceive, understand, navigate and interact with the Internet.

Thus, in terms of accessibility standards, we need to examine:

a) accessibility regulations applicable in the EU
b) guidance provided by medicinal agencies applicable to patient leaflets
c) global accessibility standards.
d) accessibility of structured definitions in HL7 FHIR

Each are addressed in the sections below.

4.1 Accessibility directive and national regulations

The EU enforces the web accessibility directive [10] and has developed a strategy for web accessibility [11]. According to Art.9 of the United Nations Convention on the Rights of Persons with Disabilities (UNCRPD), to which the EU and its Member States are party, requires that appropriate measures are taken to ensure access for persons with disabilities, on equal basis with others, to information and communication technologies.

The Web Accessibility Directive (Directive (EU) 2016/2102) provides people with disabilities with better access to websites and mobile apps of public services, as it forces public web sites to conform to technical accessibility standards, (WCAG 2.1). In addition, web sites should provide an accessibility statement, users are able to provide feedback on accessibility, and countries have established a monitoring mechanism. An EU directive is not as strong as a regulation since in requires that members states transpose the regulation into national law. More generally, a directive is a legal act of the EU which does not dictate how the members states will achieving that result. This is in contrast to regulations that do not require implementation measures as they are self-executing.

Since 2019, all member states have implementation laws based on directive 2102 in place. The guidelines referred to are Web Content Accessibility Guidelines (WCAG) 2.1 [13], Level AA by taking reference to EN 301 549, PDF, Chapter 9: Web [14]

In the United States, accessibility requirements cover different disabilities, i.e., mobility, vision, hearing, cognition, independent living, and self-care. The standard to be followed is the W3C WAG2.0. [21] Best practices for accessible content advise:

- Do not rely on color as a navigational tool, or as the sole way to differentiate items
- Images should include Alt text in the markup/code; complex images should have more extensive descriptions near the image (perhaps as a caption or descriptive summaries built right into a neighboring paragraph)
- Functionality should be accessible through mouse and keyboard and be tagged to worked with voice-control systems
- Provide transcripts for podcasts
- If you have a video on your site, you must provide visual access to the audio information through in-sync captioning
- Sites should have a skip navigation feature
- Consider 508 testing to assure your site is in compliance

The laws in the United States comprise the Title III of the Americans with Disabilities Act (ADA) prohibits discrimination "on the basis of disability in the activities of public accommodations." According to Title II of the ADA applies to state and local governments are subject to Section 504 and Section 508 of the Rehabilitation Act of 1973, amended to address online resources. Section 508 website refers to universal design [22] and has the moto "buy, build, be accessible" [22].

Gravitate-Health should make sure that its demonstrations conform to WCAG 2.1 and perhaps illustrate that in part with appropriate stylesheets used in real life demonstrations or videos.

4.2 Regulatory guidance applicable to patient leaflets format

The Quality Review of Documents (QRD) template specifies the content of SmPC and patient information leaflet [15]. The actual heading of the QRD template correspond to ePI headings in the published draft standard. In Europe, the actual format and presentation of the patient information leaflet (including design considerations) should follow the guidance provided in [16] in order to be readable and user-friendly. The main points of these important documents are presented in the sections below.

Additionally, EMA has prepared a page focusing on how to prepare and review product information focusing mainly on SmPC [17]. The page has a lot of training material that could be used also for ePIs. In fact, Gravitate-Health could apply this guidance to the creation of Style Sheets appropriate for different user profiles. The presentation of ePIs would be validated using protocols inspired by the ones presented in the guidance. Alternatively, one might envision the extension of the protocols applicable to paper to include also the validation of ePIs.

4.2.1 Quality Review of Documents templates (QRD)

The QRD document first introduced in 1997 and most recently updated in 2021 includes Annexes that define title and content of the different sections of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL).Table 1.

Table 1: Basic sections and subsections of the QRD template [18]

Section		Content
1. NAME OF THE MEDICINAL PRODUCT		{(Invented) name strength pharmaceutical form}
2. QUALITATIVE AND QUANTITATIVE COMPOSITION		
2.1	General description	Name of the active substance(s)
2.2	Qualitative and quantitative composition	<Excipient(s) with known effect>
3. PHARMACEUTICAL FORM		
4. CLINICAL PARTICULARS		For 4.1: <{X} is indicated in <adults> <neonates> <infants> <children> <adolescents> <aged {x to y}><years> <months>.>
4.1	Therapeutic indications	
4.2	Posology and method of administration	For 4.2: posology for different patient groups and guidance in administration (could be considered as subsections)
4.3	Contraindications	
4.4	Special warnings and precautions for use	For 4.3: counterindications to active substances and excipients
4.5	Interaction with other medicinal products and other forms of interaction	For 4.7: <{Invented) name} has <no or negligible influence> <minor influence> <moderate influence> <major influence> on the ability to drive and use machines.>
4.6	Fertility, pregnancy, and lactation	
4.7	Effects on ability to drive and use machines	
4.8	Undesirable effects	
4.9	Overdose	
5. PHARMACOLOGICAL PROPERTIES		
5.1	Pharmacodynamic properties	For 5.1 Pharmacotherapeutic group: {group}, ATC code: <{code}><not yet assigned>
5.2	Pharmacokinetic properties	<Mechanism of action>
5.3	Preclinical safety data	<Pharmacodynamic effects>
		<Clinical efficacy and safety>
		<Paediatric population>
		For 5.2 consider keywords: <Absorption> <Distribution> <Biotransformation><Elimination> <Linearity/ non-linearity>
6. PHARMACEUTICAL PARTICULARS		
6.1	List of excipients	For 6.3: <...> <6 months> <...> <1 year> <18 months> <2 years> <30 months> <3 years> <...>
6.2	Incompatibilities	
6.3	Shelf life	
6.4	Special precautions for storage	
6.5	Nature and contents of container	
6.6	Special precautions for disposal	

7.MARKETING AUTHORISATION HOLDER	{Name and address} <{tel}> <{fax}> <{e-mail}>
8. MARKETING AUTHORISATION NUMBER(S)	
9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION	<Date of first authorisation: {DD month YYYY}> <Date of latest renewal: {DD month YYYY}>
10. DATE OF REVISION OF THE TEXT	
11. DOSIMETRY	
12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS	

D5.1. Recommendation 1: The structure for the QRD template guidance should assessed for their ability to meet the future needs for ePI and G-lens® implementations.

D5.1 Recommendation 2: The sections and subsections for the QRD templates should be further analysed for specific groups of pharmaceutical products identifying associated dictionaries as part of the Gravitate-Health FHIR IG.

4.2.2 European Guidance on Format and Content of patient leaflets

The European Commission, Enterprise and Industry Directorate General, Section of Consumer Goods and Pharmaceuticals, in 2009, delivered the first version of the "*Guideline on the readability of the labelling and package leaflet of medicinal products for human use*". To our knowledge this document has not changed since it was published, even though the review of the readability guideline was foreseen in the EMA action plan. Given the advancements since 2009, it is recommended that a modern style guide and design system be created to accompany the ePI. For example, the Government of Canada created the Aurora Design system to:

- standardize the visual language and user experience of online applications and tools.
- Make the job of developers and designers easier rather than add extra burdens or obligations to follow.
- catalogue everything that makes up a digital product including user interface elements, writing style, guiding principles, coding standards, visual design, and reusable components for easy development.
- Cover obligations such as official languages and accessibility.

Its purpose is to guide marketing authorization applicants on how to ensure that the information on the labelling and package leaflet is accessible and understood so that medicine can be used safely and appropriately, when necessary, with the help of health professionals. It refers to "Directive 2001/83/EC" which notes that medicinal products must be accompanied by outer and/or immediate packaging information (labelling) and a package leaflet that shall be easily "legible, clearly comprehensible and indelible". The main recommendations for the patient leaflet appear in the Table 2.

Table 2: European guidance for patient information leaflets [16]

Style item	Recommendation
Type size and font	- Easy to read, distinguishing letters as I, 1, l, l - Type size of 9pt, not narrow, 3mm line space - Larger if targeting visually impaired - Limited use of capitals, italics, underlining
Design and layout of information	- Justified text, 1.5 line spacing - Demarcation of different languages - Contrast background, not transparency
Headings	- Bold type face of different color - Same presentation of same level headings - No more than two levels of headings - Use separation lines - Do not include non-relevant subheadings
Print Color	- Distinguishing from the background and recognizable
Syntax	- Attend to poor reading skills, health literacy - Short sentences and paragraphs - No more 5 or 6 bullets - Side effects by frequency of occurrence - Side effects by level of risk
Style	- Use actionable statements vs style - Action to take, reasons should be provided - Use lay language before medical terms
Paper	- Weigh sufficient to avoid transparency - Folding creases not to hide important info
Use of Symbols and Pictograms	- Pictograms understood non promotional
Language	- All official languages of the country
Additional Considerations	- separate leaflet for each strength and pharmaceutical form of medicinal product.
Templates for package leaflet	- QRD template latest version [18]

Regarding people that are blind or of limited sight, the document guidance refers to presenting Braille on the label and in some cases the leaflet. It is recommended to provide the text in an audio format perceptible by hearing (e.g., CD-ROM or audio option on website). The media will have to be decided after consultation of the marketing authorization holder with representatives of organizations for the blind and partially sighted.

The document also presents guidance on the consultation process with patient groups regarding the suitability of the leaflet. Referring to the 2001 directive, article 59(3) notes:

> *"The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use."*

Such testing should be done in cooperation with relevant patient organizations. For Package Leaflet patient consultation is necessary in the first authorization, changes in legal status, new presentation and/or cases of medicinal products with particular critical safety issues.
Although the leaflet needs to be available in all relevant languages, in the centralised, decentralised and mutual recognition procedure, only the English language version of the package leaflet is considered during the scientific assessment of the Marketing Authorization Dossier by EMA or national regulator. However, the quality of translation should be the focus of a thorough review once the original package leaflet has been properly tested and modified.
The guidance on selection of users for testing guides to include:

- particular age groups such as young people and older people – especially if the
- medicine is particularly relevant to their age group;
- new users or people who do not normally use medicines, particularly for information provided with new medicines likely to be used by a wide range of people (e.g., analgesics or antihistamines);
- people who do not use written documents in their working life;
- people who find written information difficult.

The key information needs to be tested for understanding. Such information in the leaflet should include significant side effects, warnings, what the medicine is for and how to take/use the product as a minimum.

Excluding the pilot test, only small numbers of participants (e.g., 20) are needed to meet the success criteria. 12-15 questions should be enough covering general and specific issues and appear in random order. Regarding user participants, it is recommended that:

- 3-6 participants to pilot test that the questions will work in practice
- during testing review the results and make any changes to the package
- repeat tests until you have satisfactory data from a group of 10 participants
- have a final test of a further 10 to see if the success criteria are also met in this further 10 (i.e., in 20 participants in total on the final proposed package leaflet).

In preparation for the test, designed to last less than 45 minutes, create a new protocol for each medicine including questions that reflect important issues and assessment criteria that cover finding, understanding, and acting upon the provided information. A set of expected correct actions should be included. Using a written set of questions, the interviewer should adopt a conversional manner, ask questions orally, reassure participants, allowing them to read the whole leaflet, and answer in their own words. In addition to recording the answers, the interviewer should observe and record the participants' handling of the leaflet to yield information on how to improve the structure. This type of testing is conducted at key milestones in the product's lifecycle including prior to first marketing authorization, change of use, etc.

There may be some elements of the current readability guidance that are relevant to a digital format i.e., ePI, but not all. We suggest that the guidance is taken into account/assessed for relevance to digital formats in the work of the Gravitate-Health project focusing on adaptations necessary for the ePI format. For example, Gravitate-Health may create stylesheets that take into consideration those elements of the guidance in Table 2 that are pertinent to digital formats, while at the same time incorporating the latest guidelines such as WCAG 2.1.

4.2.3 United States

In the United States, FDA provides resources on labelling that are mainly concentrating on content, rather than style, as for example [19, 20]. In Canada, The Government of Canada's Aurora Design System [21] is a good modern system. The system goes into great detail about authoring style (e.g., fonts, styles, colours images, content positioning).

D5.1 Recommendation 3: Gravitate-Health should create style sheets which build on the EU readability guidance on design and format, at the same time address the needs (WCAG 2.1), requirements and promise of ePIs and the G-lens®

D5.1 Recommendation 4: Gravitate-Health will adapt the testing and validation guidance of EU readability guidance to incorporate WCAG2.1, to advance real-world testing the understanding of ePIs and the application of G-lens®.

4.3 W3C Web Accessibility Guidelines

The Web Content Accessibility Guidelines (WCAG) provide a list of recommendations to make online content more accessible to those with disabilities. It covers four main areas:

a) Perceivable so that all users, including those with impaired vision, should be able to see and read your website.
b) Operable so that websites should be responsive and easy to navigate for all users across multiple browsers and mobile devices
c) Understandable so that websites should be organized in a way that's easy to use and use language that most customers can understand.
d) Robust, so that many websites are integrated with assistive technology and tools to facilitate use by people with disabilities or just too old.

Websites should integrate with tools (Assistive Technology or AT) that are used by users with disabilities. The WAI and WCAG 2.1 Guidelines are a long list of items meant for businesses, User Experience (UX) designers, and web designers. There are tools available to test conformance to WCAG. Europe suggestions compliance to WCAG 2.1, while United States WCAG 2.0. WCAG 2.1 is not a replacement of WCAG 2.0. WCAG 2.1 is an extension of WCAG 2.0 with additional success criteria included to cater to the needs of different user groups, adding Mobile users, Low vision users, Cognitive and Learning impaired users as well as Users with motor and visual impairments. In WCAG 2.1 there are 17 new success criteria included across all the 3 conformance levels. The table below includes some additional criteria, of specific importance to Gravitate-Health tools.

Table 3: Additional criteria included in WCAG 2.1

WCAG2.1 Success Criterion	Level	Target	Explanation
Orientation	AA	Mobile users Mobility impairment Low vision	Content and functionality should be available irrespective of user's device orientation.
Identify input purpose	AA	Cognitive & learning impairments Motor impairments	Forms that collect user data should define the purpose of input fields programmatically.

Reflow	AA	Low vision to read and mobile device users.	All the page content and functionality should be available without requiring 2-D scrolling
Non text contrast:	AA	Low vision users	A contrast of 3:1 against the adjacent colors should be present for user interface control state (i.e. hover, focus etc.) and key images **Note**: WCAG 2.0 contrast requirement was present for text and in WCAG 2.1 it has been extended to include non-text content as well.
Text spacing:		low vision users, dyslexic users, and users with cognitive impairments	Content and functionality should not be lost when text spacing styles are applied.
Content on Hover or Focus:	AA	Low vision users Learning impairments	Content that becomes available on hover or focus should be 1) **Dismissible** 2) **Hoverable and focusable** 3) **Persistent**
Character key shortcuts:	A	Low vision Dexterity impairments	Web pages should not include single character key shortcuts for carrying out different tasks
Pointer gestures:	A	Motor impairments Cognitive, learning impairments	All the functionality of a web page that involves multipoint gestures or path-based gestures should provide users with alternate means to carry out the task using single point activation controls.
Pointer cancellation:	A	Visual, Motor, Learning impairments	All page functionalities should be executed on the Up event and not on Down event. If any functionality is executed on Down event, provide users with a mechanism to cancel it.
Label in Name:	A	Speech input users	Accessible name of a user interface control contains text that is present in the visual label.
Motion actuation:	A	Motor impairments	All the web page functionality that can be activated with device or user motion be also activated with user interface control.
Status messages:	AA	Users of screen readers who often go unaware about onscreen changes	Status messages can be defined programmatically to ensure that assistive technologies can render them without the status messages receiving focus

D5.1 Recommendation 5: All applications of G-lens® should take into account the WCAG2.1 guidelines for accessibility as advocated by EMA and FDA.

5 HL7® FHIR® standards

5.1 Overview of HL7 International/ HL7 Europe

Health Level Seven (HL7) is a non-for-profit, ANSI certified Standards Development Organization formed in 1987 with the vision of "A world in which everyone can securely access and use the right health data when and where they need it" [6]. The organization has grown to approximately 16,000 members that are coordinated into 48 work groups. Each work group is focused on an area of standards development. Work is often done within multiple work groups and with the growing complexity of use cases the number of work groups engaged continues to grow. FHIR approach was adopted in 2010.

HL7 Europe was established in 2010 to serve as the contact point for HL7 in Europe and collect European requirements for global HL7 standards.

When considering the healthcare landscape, there are several current HL7 workgroups engaged in interoperability standards development that can potentially impact the Gravitate-Health project are the following workgroups (includes workstreams with both short and long-term impacts): Clinical Decision support:

I. Patient Empowerment and Trust Framework
II. Biomedical Research and Regulatory
III. Pharmacy Benefits (Realtime Pharmacy Benefits Management)
IV. Clinical Decision Support
V. Questionaries (standard forms and responses) – includes PRO (Patient Reported Outcomes)
VI. Patient Care: particularly in relation to the Service Oriented Architecture (SOA) International Patient Summary (IPS) project.

5.2 Vulcan Accelerator

Stakeholders are often interested in the same use case where the work may cross over multiple HL7 work groups. To improve the coordination of these use cases, stakeholders have joined together to form HL7 FHIR® Accelerators. Gravitate-Health participates in the HL7 FHIR Accelerator®, Vulcan and coordinates a specific project on ePI/Labeling (see Figure 2).

With the Vulcan ePI project, Gravitate-Health has been utilizing Vulcan's infrastructure to participate in HL7 FHIR Connectathons that are held three times a year and check its achievements and challenges openly with the wide community of standards development, accelerating the maturation of relevant FHIR resources. This allows for more agile streamlined, efficient integration to on-going standards development that answers to the Gravitate-Health Project needs. A plan of regular participation to FHIR Connectathons from September 2021 forward has been developed.

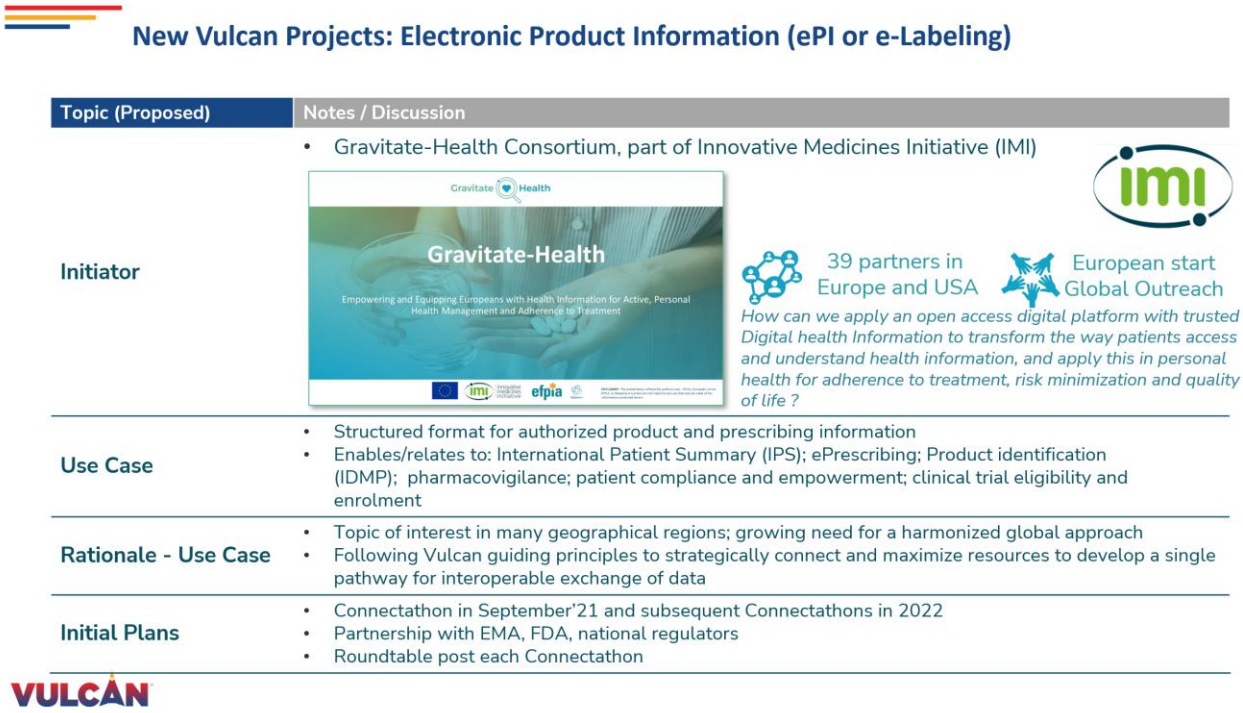


Figure 2: Overview of the HL7® FHIR® Accelerator ePI project.

5.3 HL7 FHIR Resources and Supporting Tools in use

In the context of Gravitate-Health, WP5 is responsible for the development of an HL7 Implementation Guide (IG) for the G-lens® as well as for the ePI that will allow the searching, finding and presenting patient leaflet through a G-lens® generated from a patient's IPS.

The tools that we have been using so far are in addition to the FHIR tools for the generation of the HL7 FHIR Gravitate-Health implementation guide (IG) from the GitHub repository. GitHub is a code hosting platform for version control and collaboration that can be used for teams to develop and share code together. Besides GitHub the tools used are:

2) FHIR Shorthand ("FSH" or "Shorthand") language. And its reference implementation interpreter/compiler SUSHI ("SUSHI Unshortens Shorthand Inputs") https://fshschool.org/

3) ClinFHIR is an open-source tool that provides an educational environment and also allows developers to create or search for FHIR®-based resources http://clinfhir.com/

D5.1 Recommendation 6: The federated open-source platform (FOSP) of Gravitate-Health should offer tools to curate and validate ePIs resources and their stylesheets.

5.4 EMA ePI HL7 FHIR Implementation Guide (IG)

Building on the Key ePI principles presented in section 1, the ePI-setup project at EMA started in 2021 with the aim to [23, 24]:

1) Create an EU common standard based on FHIR for ePI in the EU to support harmonised ePI across the EU and collaboration across the network

2) Provide a proof-of-concept prototype using the common standard. The prototype will be used for a design and technical feasibility study to generate some example FHIR-based documents associated with products in SPOR to publish on a website.
3) Provide a realistic medium-term vision and road map to achieve the benefits for stakeholders, HMA, EC, EMA MB, as outlined in the Key principles for ePI on the EU.

At the time of this writing, Gravitate-Health has worked with the output of activities captured in points 1 and 2, while we are waiting for the limited release of point 3. In the September 2021 and January 2022 Connectathons, we engaged and used the proof-of-concept prototype of the EMA ePI set-up project, gradually augmenting with resources that would expect in the EMA SPOR implementation, but not broadly available yet.

	EMA ePI Profile - FHIR Resource Names[1]
1	List 1
2	Bundle N
3	Composition 2 N?
4	Binary N
5	Organization 3 N?
6	RegulatedAuthorization 1
7	MedicinalProductDefinition 1
8	PackagedProductDefinition 1
9	AdministrableProductDefinition 1
10	ManufacturedItemDefinition 1
11	Ingredient 1
12	ClinicalUseDefinition 1

[1] Rows 1 to 4 make up the ePI. The ePI cross references out to SPOR which is made up of rows 5 to 11.

	Vulcan ePI Profile - FHIR Resource Names[2]
1	DocumentManifest 2
2	Bundle N
3	Composition 2 N?
4	Binary N
5	Organization 3 N?
6	RegulatedAuthorization 1
7	MedicinalProductDefinition 1
8	PackagedProductDefinition 1
9	AdministrableProductDefinition 1
10	ManufacturedItemDefinition 1
11	Ingredient 1
12	ClinicalUseDefinition 1

[2] Vulcan ePI managed as a single self-contained document.
[3] Devices in packaging (e.g., syringe)

Figure 3: HL7 FHIR resources of relevance to ePI and their relevance to EMA ePI profile.

Figure 3 above gives an overview of the FHIR resources that Gravitate-Health is working with, aiming at their gradual maturation and global relevance and reach. At the same time, Gravitate-Health works closely with the UNICOM project to achieve a sustainable strategy for medication identification.

While we work to develop the necessary APIs to connect the IPS with the ePI, we are developing the Vulcan ePI which is consistent to the EMA specification, but also includes the relevant SPOR resources as shown in Figure 3. This Vulcan ePI profile can serve as a springboard to address other markets such as the US, aligning with the Structured Product Labeling (SPL) project there. Thus, Gravitate-Health has the prospects to develop a truly global standard.

5.5 International Patient Summary

Developments in Gravitate-Health are also largely based on the HL7 FHIR IPS standard. The IPS provides the key information related to problems, allergies, and medications, as well as demographics that can be used by the G-lens® to highlight the most relevant

information in the ePI. Information on the IPS can be found in the web site www.international-patient-summary.net as well as at http://hl7.org/fhir/uv/ips/. The key elements of the IPS can be found in

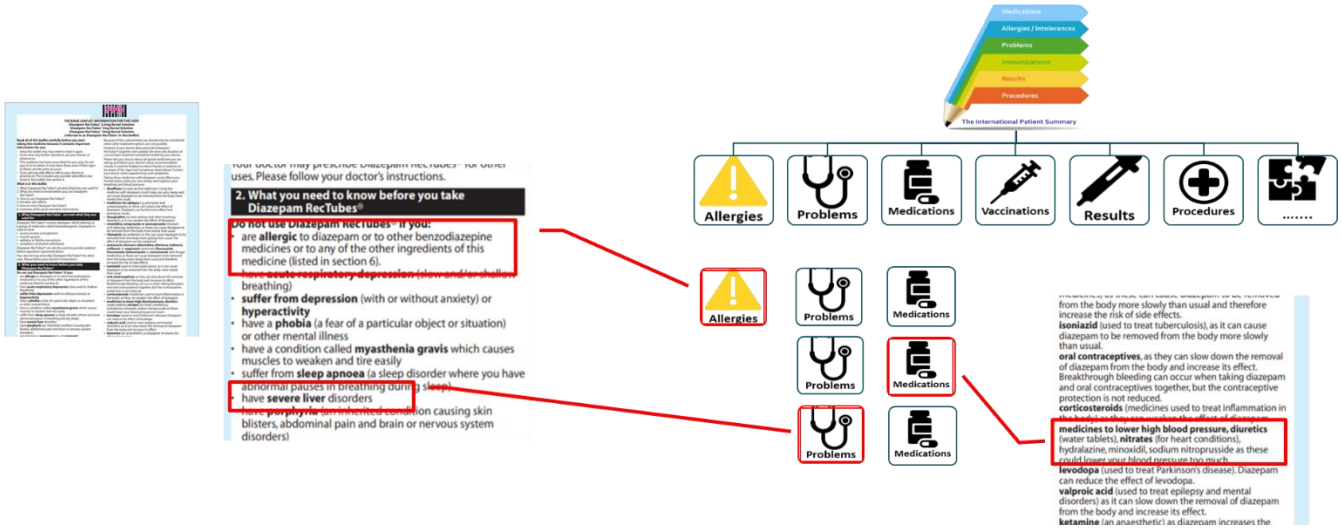


Figure 4: Key elements of the IPS (www.HL7.org/fhir/uv/ips and its function as a lens

6 Patient Outcome standards

Gravitate-Health aims to prove the hypothesis that using the G-lens® applied on a person's patient summary to highlight information on the ePI can increase the value of ePIs, by increasing access, understanding, adherence and eventually outcomes.

To achieve the first two of these objectives, namely access and understanding, the guidance provided by the European commission in testing Patient Leaflets can be extended. However, eventually we wish to prove that the use of G-lens® can improve patient outcomes. Related standards for patient outcomes are developed by International Consortium for Health Outcomes Measurements (ICHOM) (https://www.ichom.org/).

The International Consortium for Health Outcomes Measurement (ICHOM) launched in 2012, aims to create a global standard for measuring results by medical condition, in collaboration with patients, providers, and registries. So far, more that 40 standard sets targeting specific diseases and conditions have been developed.

D5.1 Recommendation 8: ICHOM standards can be considered in relation to specific testing scenarios to prove through their FHIR implementation the ability of Gravitate-Health interventions to improve patient-reported outcomes for specific conditions.

7 Standards testing and validation activities

Development of standards follows formal processes to mature a standard from inception to implementation. A key part of the maturity process is Connectathons. Connectathons are organized by different organizations and in the area of standards notably IHE and HL7. Gravitate-Health will mostly engage in HL7 FHIR Connectathons.

HL7 FHIR Connectathons (FCAT) provide a detailed implementation and testing process to enable the adoption of standards-based interoperability by vendors and users of healthcare information systems [4]. FCAT is organized into "tracks" that are dedicated to specific use cases. FCAT provides an opportunity to test the FHIR standard implementation guides using mostly synthetic data to identify gaps in the implementation guide and clarify the associated use case. In scenarios related to Gravitate-Health data is exchanged between parties using an evolving HL7 FHIR IG, which incorporates FHIR standard developments and contributes to the maturity of the resources.

As each FCAT builds on previous ones, the expectation is to expand user scenarios, while at the same time developing, testing, and validating the Gravitate-Health Federated Open-Source platform (FOSP). Moreover, in adopting an open testing strategy linked to FHIR Connectathons, we can ensure that we can gradually address not only the specific European requirements of EMA, participating national medicines agencies in Europe like Spain (AEMPS) and Norway (NoMa), but also global requirements of agencies across Europe, United States, and Asia.

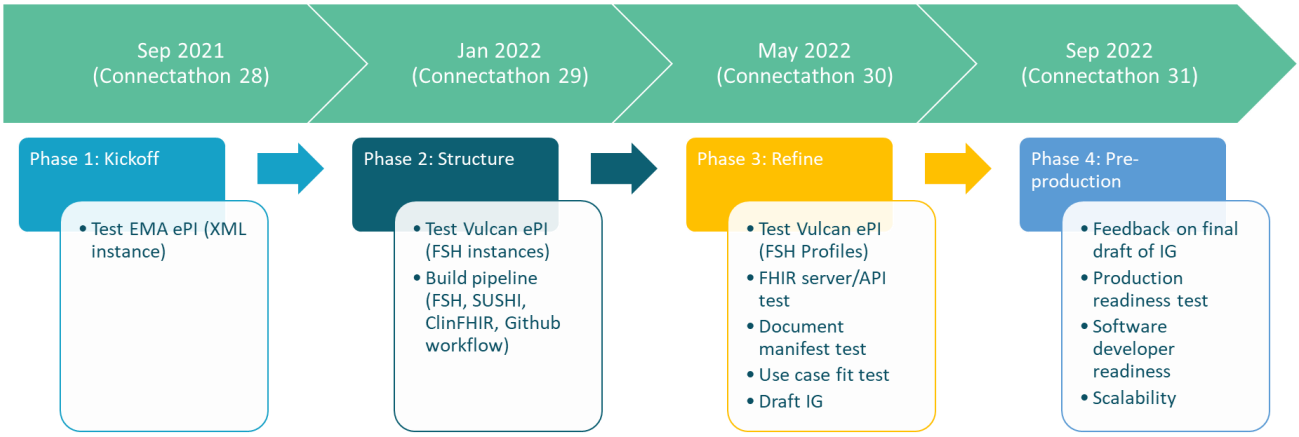


Figure 5: HL7 FCAT and Vulcan Accelerator ePI track provide the framework for the agile development of the Gravitate-Health HL7 FHIR IG.

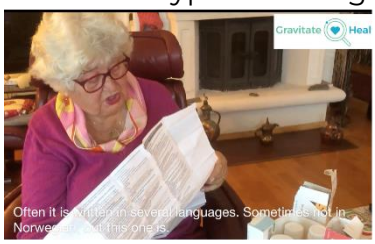
The user scenarios will continue to increase in scope and include additional medications and attributes defining those medications, as well as format to include enhanced formats in addition to text (such as educational video clips). Building on the initial work of FCAT 28 and 29, test scripts to test the evolving IG's are clearly leading to repeatable outcomes as they encourage testing interoperability across agencies and applications.

Future Connectathons should lead to additional ePI data "downstream" players (EHR vendors, handset providers, gadgets, etc.), and lend towards using FHIR resources to "pull" from other solutions and platforms in addition to those governed by regulatory agencies. Parallel to that, testing and validation will be required to be more robust. Other read and write functionalities provided to client applications using the full breadth of FHIR standard API (such as FHIR API's, ANSI SQL, and JDBC/ODBC support considerations) will need testing. Consideration and use of Testing Platforms should feature multi-version support for HL7 FHIR leveraging Natural Language Processing (NLP) for FHIR Test Script Resources. Testing will be needed both from the Client and Server Side. Along with Conformance and Interoperability, a starburst matrix illustrating

percentage of Conformance/Compatibility to the specification should be reported. Interoperability "proving grounds" should be considered in the future.
https://confluence.hl7.org/pages/viewpage.action?pageId=12009554

FCAT participants in the Gravitate-Health tracks should either understand the basics of medicinal product data (and its regulatory/healthcare context); general principles of data modeling, software development principles such as object orientation, databases; layered software design, and XML or JSON, as well as web-infrastructure protocols (HTTP, etc) or be familiar with one or a combination of these areas. As for example consider the case used in FCAT-28 in September 2021 and FCAT29 in January 2022:

Below is a typical testing scenario, reflected as one of our personas, (D1.2 for details)



In this example, Maria, who is 75 years old, Norwegian, talks about her 12 medications, that she takes every day to control her health issues. She lives with her husband in their home, and uses glasses, hearing aid and a walker when she is outside. In the scenario tested, Maria, while travelling in Cyprus, a Cypriot pharmacy/HCP recommends an OTC medication for her hay fever. Maria needs patient information in Norwegian and Greek to show her medication list to a Greek/Cypriot pharmacist/HCP. After taking the OTC, Maria sees a doctor because her legs are more swollen; has shortness of breath; walking is painful.

The goals of the ePI track in FCAT28 were to test the following data exchange:

1) Read patient information in Norwegian and Greek for her medications and new OTC medication
2) Warn if drug interactions exist between new OTC and her medications
3) Submit adverse reaction report for symptoms encountered after taking the OTC

The exchange appears in the figure below.

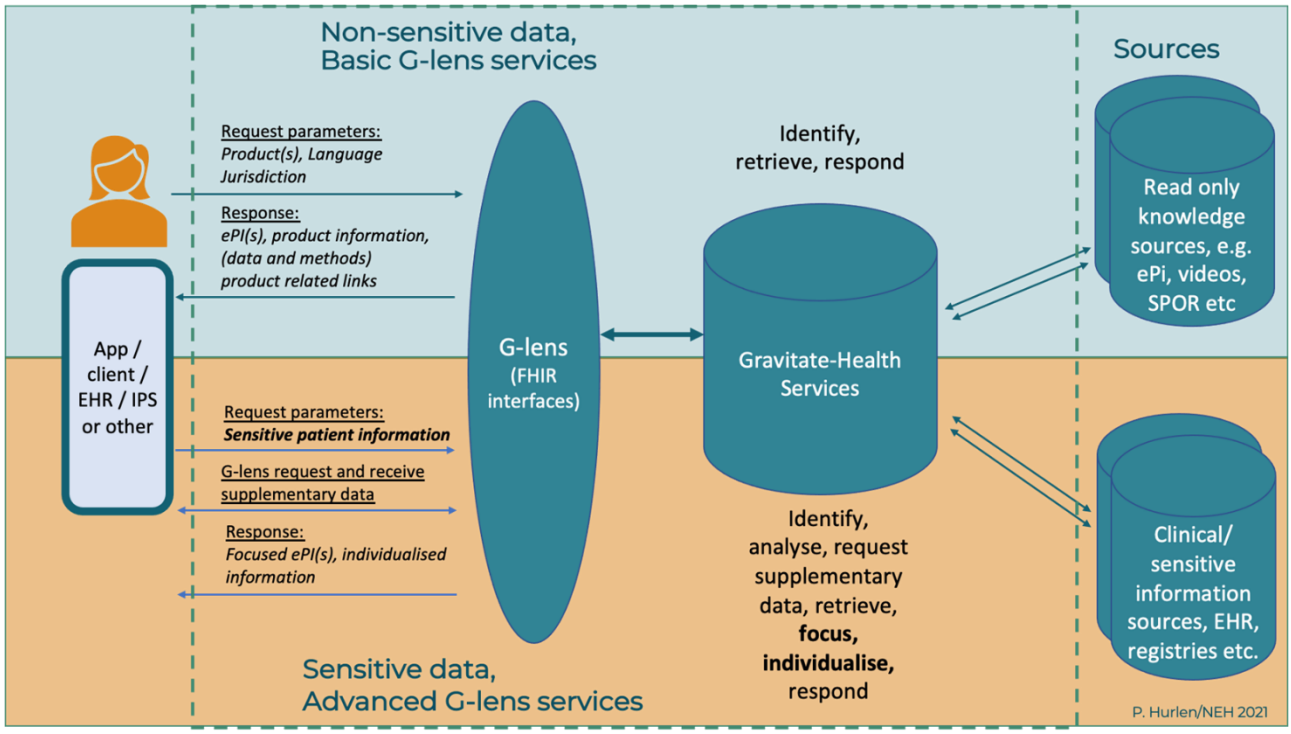


Figure 6: The work of the G-lens® supported by the HL7 FHIR Connectathons from the perspective of use case validation and HL7 FHIR IG development.

With each FHIR Connectathon, new developments will be added to the GitHub repository of Gravitate-Health https://github.com/hl7-eu/gravitate-health while the Gravitate-Health IG with relevant HL7 FHIR resources for ePI (https://build.fhir.org/ig/hl7-eu/gravitate-health/branches/master/toc.html), and the associated resources will reach higher levels of maturity.

D5.1 Recommendation 8: Gravitate-Health with its agile engagement in Connectathons should work to accelerate maturation of HL7 FHIR resources related to ePI, as a strategy to facilitate their adoption and alignment in collaboration with regulators globally

8 CONCLUSIONS

As the core IDMP architecture is better understood, along with how this relates to SPOR services, the key principles underlying the FHIR common EU standard for ePI will be further adopted [1], and the Gravitate-Health IG will describe the characteristics and contents of IDMP as expressed in FHIR. Additional "downstream" ePI aggregators, disseminators, and vendors should plan an effective strategy for IDMP implementation for their organization, or other (non-IDMP) product and substance data sources or flows using FHIR. Similar to the initial participation of the SPOR (ISO IDMP) task force established by EMA, software vendors, terminologies groups, and regulatory agencies have been involved in the HL7 FHIR Connectathons to date. Developers of the medicinal product dictionaries and Pharmacopeias are important players as well. Medicinal product dictionaries and Pharmacopeias are upstream ePI data feeds to EHRs, digital Physician Desk References, the growing number of patient data aggregators and Real-World Data Sources. There are approaches, for example, which may leverage ePI templates to allow for variations, such as adverse events, across countries, but similarities in FHIR Resources will enable interoperability.

The "why's of this work are visible from a patient perspective and in order to motivate/incentivize the uptake of ePI more broadly in the healthcare communities, considerations on the additional impact of ePI's integral to Patient Access to medication, Understanding, and Adherence and overall Outcomes will be key (https://www.ichom.org/) .

Training for National Competent Authorities (NCAs) and those who maintain central registries, who will be involved with the implementation and support of SPOR/IDMP in using FHIR will be necessary. Other areas of training include pharmaceutical companies that need support with submitting data to regional registries (or SPOR) or exporting data from their own systems or RIMS (Regulatory Information Management Systems) in a standard exchange format. Software developers or analysts will need to represent medicinal product or substance data using FHIR. This includes maintaining and sharing drug catalogues and knowledge bases to support regulatory or non-regulatory healthcare processes.

Each HL7 FHIR© Connectathon will feature new developments that will be added to GitHub repository of Gravitate-Health available at https://github.com/hl7-eu/gravitate-health. At the same time, the HL7 FHIR Gravitate-Health IG (https://build.fhir.org/ig/hl7-eu/gravitate-health/branches/master/toc.html) and the associated resources will reach higher levels of maturity. As representation in the Connectathons increase, global approaches for differences in ePI standards, additional languages, ePI creation, updating, and dissemination on a broader scale will be addressed. Future considerations must include bi-directional reporting capabilities; data interoperability in bulk and real-time,

maintaining currency and accuracy, patient education, governing responsibilities, and processes.

8.1 Recommendations

In view of the analysis above and the review of the specific standardization and specification development activities, the following recommendations are proposed to ensure that recent developments in standards for interoperability, accessibility and outcomes measurements are incorporated in the Gravitate-Health system development:

D5.1. Recommendation 1: The structure for the QRD template guidance should assessed for their ability to meet the future needs for ePI and G-lens® implementations.

D5.1 Recommendation 2: The sections and subsections for the QRD templates should be further analysed for specific groups of pharmaceutical products identifying associated dictionaries as part of the Gravitate-Health FHIR IG.

D5.1 Recommendation 3: Gravitate-Health should create style sheets which build on the EU readability guidance on design and format, at the same time address the needs (WCAG 2.1), requirements and promise of ePIs and the G-lens®.

D5.1 Recommendation 4: Gravitate-Health will adapt the testing and validation guidance of EU readability guidance to incorporate WCAG2.1, to advance real-world testing the understanding of ePIs and the application of G-lens®.

D5.1 Recommendation 5: All applications of G-lens® should take into account the WCAG2.1 guidelines for accessibility as advocated by EMA and FDA.

D5.1 Recommendation 6: The federated open-source platform (FOSP) of Gravitate-Health should offer tools to curate and validate ePIs resources and their stylesheets.

D5.1 Recommendation 7: ICHOM standards and HL7 FHIR implementation could be considered as a resource to capture patient outcomes. In a standardized manner.

D5.1 Recommendation 8: Gravitate-Health with its agile engagement in Connectathons should work to accelerate maturation of HL7 FHIR resources related to ePI, as a strategy to facilitate their adoption and alignment in collaboration with regulators globally

9 References

[1] EMA-HMA-EC Electronic product information for human medicines in the EU: key principles A joint EMA–HMA–EC collaboration. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/electronic-product-information-human-medicines-european-union-key-principles_en.pdf https://www.ema.europa.eu/en/electronic-product-information-human-medicines-european-union-key-principles (retrieved 23 December 2021)

[2] EMA action plan related to the European Commission's recommendations on product information, https://www.ema.europa.eu/en/documents/other/european-medicines-agency-action-plan-related-european-commissions-recommendations-product_en.pdf

[3] ePI information workshop and exploratory workshop https://www.ema.europa.eu/en/events/epi-information-workshop-exploratory-workshop

[4] Connectathon - IHE International. Accessed January 12, 2022.

[5] Gravitate-Health HL7 FHIR® Connect-a-ton Kick-Off Presentation. January 10, 2022. 2022-01 Vulcan/Gravitate Health - ePI (Phase 2) - FHIR - Confluence (hl7.org)

[6] About Health Level Seven International | HL7 International. Accessed January 13, 2022.

[7] EMA – SPOR (ISO-IDMP) Task Force. https://www.ema.europa.eu/en/human-regulatory/research-development/data-medicines-iso-idmp-standards/spor-master-data/spor-iso-idmp-task-force (retrieved 15 January 2022)

[8] UNICOM Project, IDMP in a capsule: https://unicom-project.eu/wp-content/uploads/2021/10/UNICOM-handboek_A4_04.pdf (retrieved 17 January 2022)

[9] Gravitate-Health Implementation Guide, https://build.fhir.org/ig/hl7-eu/gravitate-health/branches/master/toc.html

[10] Directive (EU) 2016/2102 on the accessibility of the websites and mobile applications of public sector bodies

[11] https://digital-strategy.ec.europa.eu/en/policies/web-accessibility

[12] United Nations conventions of rights of people with disabilities, (accessed January 18, 2022)https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities.html (accessed January 18, 2022)

[13] W3C Web Accessibility Guidelines 2.1 https://www.w3.org/TR/WCAG21/ (accessed January 18, 2022)

[14] ETSI, CEN/CENELEC Accessibility requirements suitable for public procurement of ICT products and services in Europe, EN 301 549 V1.1.2 (2015-04) https://www.etsi.org/deliver/etsi_en/301500_301599/301549/01.01.02_60/en_301549v010102p.pdf (accessed January 18, 2022)

[15] Heads of Medicines Agencies (HMA), QRD Templates https://www.hma.eu/126.html (accessed January 18, 2022)

[16] European Commission, Guideline on the readability of the labelling and packages leaflet of medicinal products for human use, January 2009. https://ec.europa.eu/health/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf (accessed January 18, 2022)

[17] EMA, How to prepare and review summary of product characteristics, https://www.ema.europa.eu/en/human-regulatory/marketing-

authorisation/product-information/how-prepare-review-summary-product-characteristics (accessed January 18, 2022)
[18] QRD product-information annotated template (English) version 10.2 Rev.1 First published: 03/12/1997, Last updated: 09/02/2021 10.2 Rev.1 https://www.ema.europa.eu/en/documents/template-form/qrd-product-information-annotated-template-english-version-102-rev1_en.pdf
[19] FDA, Labelling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (fda.gov) https://www.fda.gov/media/71836/download
[20] FDA, Prescription Drug labelling resources, https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[21] Universal Device and Accessibility, Section 508 https://www.section508.gov/develop/universal-design/ (accessed January 18, 2022)
[22] Electronic Product Information (ePI) for EU. Medicines https://www.ema.europa.eu/en/documents/presentation/presentation-71-update-electronic-product-information-eu-medicines-e-scanlan_en.pdf
[23] Gustavo Rodriguez FHIR and the EU common standard for ePI. Information Workshop on electronic Product Information (ePI) EMAhttps://www.ema.europa.eu/en/documents/presentation/presentation-fhir-eu-common-standard-epi-g-rodriguez_en.pdf