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Electronic model-driven health computing platforms in the management of chronicity: contributions to integration and harmonization of e-health standards and modelling efficient e-ophthalmology services

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Abstract

To date, most health services worldwide have been organized to treat acute episodes, whereas chronic conditions consume as much as 80% of national healthcare's budgets due to a suboptimal management of chronicity. In parallel, the proliferation of health-related devices able to share clinical information over communication networks has unleashed new horizons in the clinical practice. This new scenario of electronic healthcare leads to reconsider traditional clinical practices toward more accurate diagnoses and a more efficient redistribution of resources, both material and human. Therefore, in order to adapt the existing health services in a coherent, comprehensive, and reusable manner, a number of needs arise that must be efficiently solved, which are described as follows.

First, theoretically, e-health standards arena must guarantee standardization at different levels of interoperability to achieve a faithful exchange of health information. And yet, there is no unified solution for interoperability, indeed, even the e-health standards available nowadays are not directly interoperable with each other. To bridge this gap, this Thesis proposes a comprehensive methodology for formalizing clinical information in accordance with technical, syntactic, semantic, process/organizational, and presentation layers of interoperability, that will guide experts on clinical domain to actively engage in modelling their own clinical processes into model-driven information systems.

Second, given the heterogeneity of the information systems that must interoperate in a conventional health service, there is a need of integrating new technologies and new devices into the legacy information systems. In this context, this Thesis identifies the different information systems involved on the management of patient-centred clinical processes, to propose an architecture that connects them all into an open health computing platform.

Third, although the advantages of cutting-edge e-health standards – which differentiate data structures and domain-related knowledge when modelling clinical information – are well-known, there is still a clear need to make contributions to the existing corpus of electronic models, given the current scarcity of knowledge artefacts available so far. Such contributions would help in widening the range of healthcare scenarios to which the dual-model approach could be applied. Therefore, this Thesis formalizes a number of electronic models for real healthcare scenarios. More specifically, models are provided for three eye conditions considered strategic for the management of chronicity in ophthalmology, since they correspond to the most frequent causes of avoidable blindness in Europe and their associated clinical processes threaten to overload the waiting lists of health services, due to the scarcity of specialists available to handle the revisions within recommended intervals: Diabetic Retinopathy (DR), Age-related Macular Degeneration (AMD), and Chronic Glaucoma (CG). Consequently, this Thesis proposes the modelling of the clinical processes associated to these three conditions, based on the methodology and in compliance with the open health computing platform proposed before. Although in principle the models provided are created for Health Service of Navarre (Servicio Navarro de Salud - Osasunbidea [SNS-O]), this Thesis pursues the reusability of the electronic resources that comprise these models.

In summary, this Thesis proves that a definition of a comprehensive methodology for formalizing clinical practice into information systems, the design of a model-driven, standard-based, open e-health platform and the creation of semantically enabled electronic models improves the management of electronic information in healthcare, the interoperability as well as the reutilization of the resources.

Resumen

En general, los servicios de salud se diseñan para tratar episodios agudos, mientras que las enfermedades crónicas consumen cerca del 80% del presupuesto de los servicios nacionales de salud debido a una gestión subóptima de la cronicidad. En paralelo, la proliferación de dispositivos en el ámbito clínico con la capacidad de intercambiar información a través de redes de comunicación ha abierto nuevos horizontes en la práctica clínica. Este nuevo escenario de salud electrónica nos lleva a reconsiderar la práctica clínica tradicional en pro de la precisión diagnóstica y una redistribución más eficiente de los recursos disponibles, ya sean materiales o humanos. De modo que, con el fin de adaptar los servicios de salud ya existentes de forma coherente, integral y reutilizable, surgen una serie de necesidades a considerar, tal y como se describe a continuación.

En primer lugar, para lograr un intercambio fiable de la información clínica, las normas de salud electrónica deben garantizar la estandarización a diferentes niveles de interoperabilidad. Y sin embargo, de momento no hay una solución integral para alcanzar dicha interoperabilidad. De hecho, incluso los diferentes estándares de salud electrónica disponibles hoy día no son directamente interoperables entre sí. Para suplir dicha carencia, esta tesis proporciona una metodología integral para formalizar la información clínica de acuerdo a los niveles de interoperabilidad técnica, sintáctica, semántica, de proceso/organizativa y de presentación. Esta metodología guiará a los expertos del dominio clínico a participar activamente en el modelado de procesos clínicos para que sean integrados en sistemas de información clínicos.

En segundo lugar, dada la heterogeneidad de los sistemas de información que deben interoperar en un servicio de salud convencional, existe la necesidad de integrar nuevas tecnologías y nuevos dispositivos en los sistemas de información ya existentes. En este contexto, esta tesis identifica los diferentes sistemas de información que participan en la gestión de los procesos clínicos centrados en el paciente y propone una arquitectura que conecta dichos sistemas en una plataforma abierta de salud electrónica.

En tercer lugar, es cierto que las ventajas de los estándares actuales en salud electrónica (los cuales diferencian entre la estructura de los datos y el conocimiento del dominio a la hora de modelar la información clínica) son patentes. Sin embargo, en vista de la escasez de artefactos de conocimiento disponibles hasta la fecha, se percibe una clara necesidad de contribuir al corpus de modelos electrónicos existente. Tal contribución ayudaría a ampliar el abanico de escenarios clínicos en los cuales se puede aplicar el enfoque del modelo dual. Por consiguiente, en el marco de esta tesis se formalizan una serie de modelos electrónicos que se corresponden con escenarios clínicos reales. Más específicamente, se proporcionan modelos para tres afecciones oculares estratégicas en la gestión de la cronicidad en oftalmología: retinopatía diabética, degeneración macular asociada a la edad y glaucoma crónico. Éstas se corresponden con las causas más frecuentes de ceguera evitable en Europa y sus procesos clínicos asociados amenazan con sobrecargar las listas de espera de los servicios de salud debido a la escasez de especialistas disponibles para hacer el seguimiento de los pacientes dentro de los intervalos recomendados. En consecuencia, esta tesis propone el modelado de los procesos clínicos asociados a estas tres afecciones, basándose en la metodología y de acuerdo a la plataforma abierta de salud electrónica anteriormente propuestas. Aunque los modelos resultantes se crean para el Servicio Navarro de Salud - Osasunbidea (SNS-O), esta tesis fomenta la reutilización de los recursos electrónicos que los componen.

En definitiva, esta tesis demuestra que la definición de una metodología integral para formalizar la práctica clínica dentro de los sistemas de información, el diseño de una plataforma abierta basada en modelos y estándares de salud electrónica y la creación de modelos electrónicos estructurados semánticamente mejora la gestión de la información electrónica, la interoperabilidad, así como la reutilización de los recursos en el ámbito de la salud.

Publications

The methodology and proposals made along this Thesis are the result of the expertise acquired from applying electronic health strategies to ophthalmology. In that respect, the scientific publications worth highlighting of our research group are listed below:

Publications in international journals

- J. Andonegui, D. Aliseda, L. Serrano, A. Eguzkiza, N. Arruti, L. Arias, A. Alcaine. Evaluation of a telemedicine model to follow up patients with exudative age-related macular degeneration. Retina 2016; 36(2):279-84.
- A. Eguzkiza, J.D. Trigo, M. Martínez-Espronceda, L. Serrano, J. Andonegui. Formalize clinical processes into electronic health information systems: modelling a screening service for diabetic retinopathy. Journal of Biomedical Informatics 2015; 56:112-26.
- J.D. Trigo, C.D. Kohl, A. Eguzkiza, M. Martínez-Espronceda, A. Alesanco, L. Serrano, J. García, P. Knaup. On the seamless, harmonized use of ISO/IEEE 11073 and openEHR. IEEE Journal of Biomedical and Health Informatics 2014; 18(3):872-84.
- M. Pérez-de-Arcelus, J. Andonegui, L. Serrano, A. Eguzkiza, J. Maya. Diabetic retinopathy screening by general practitioners using non-mydriatic retinography. Current Diabetes Reviews 2013; 9(1):2-6.
- J. Andonegui, A. Zurutuza, M.P. de Arcelus, L. Serrano, A. Eguzkiza, M. Auzmendi, et al. Diabetic retinopathy screening with non-mydriatic retinography by general practitioners: 2-Year results. Primary Care Diabetes 2012; 6(3):201-5.
- J. Andonegui, L. Serrano, A. Eguzkiza, L. Berastegui, L. Jimenez-Lasanta, D. Aliseda, et al. Diabetic retinopathy screening using tele-ophthalmology in a primary care setting. Journal of Telemedicine and Telecare 2010; 16(8):429-32.

Book chapters

- J. Andonegui, A. Eguzkiza, M. Auzmendi, L. Serrano, A. Zurutuza, M. Pérez de Arzelus. E-ophthalmology in the diagnosis and follow-up of chronic glaucoma. In: M.M Cruz-Cunha, I. Miranda, P. Gonçalves (Eds.). Handbook of Research on ICTs and Management Systems for Improving Efficiency in Healthcare and Social Care: IGI Global; 2013, p. 88-108.
- J. Andonegui, L. Serrano, A. Eguzkiza, M. Auzmendi, A. Zurutuza, M.P. Arcelus. Diabetic retinopathy screening with nonmydriatic retinography by general practitioners. In: K. Yogesan, L. Goldschmidt, J. Cuadros (Eds.). Digital Teleretinal Screening - Teleophthalmology in Practice: Springer Berlin Heidelberg; 2012, p. 157-66.
- J. Andonegui, L. Serrano, A. Eguzkiza. E-Health Applications in Ophthalmic Diseases: Ongoing Developments. In: M.M. Cruz-Cunha, A.J. Tavares, R. Simões (Eds.). Handbook of Research on Developments in E-Health and Telemedicine: Technological and Social Perspectives: IGI Global; 2010, p. 1088-115.

Publications in national journals

- J. Andonegui, L. Serrano, A. Eguzkiza, D. Aliseda, S. Led, M. Galarraga, et al. Evaluación de un sistema de e-Oftalmología para el seguimiento de la DMAE exudativa. Anales del Sistema Sanitario de Navarra 2012; 35(2):339-40.
- J. Andonegui, L. Serrano, A. Eguzkiza. eOphthalmology: current and future tendencies [article in Spanish]. Anales del Sistema Sanitario de Navarra 2010; 33(1):79-91.
- J. Andonegui, L. Berástegui, L. Serrano, A. Eguzkiza, I. Gaminde, D. Aliseda. Agreement among ophthalmologists and primary care physicians in the evaluation of retinographies of diabetic patients [article in Spanish]. Archivos de la Sociedad Española de Oftalmología 2008; 83(9):527-31.

Selected international conference proceedings

- J. Andonegui, N. Arruti, D. Aliseda, A. Eguzkiza, L. Serrano, A. Alcaine. Evaluation of a telemedicine model for exudative age related macular degeneration follow-up. The Association for Research in Vision and ophthalmology (ARVO) annual meeting, Florida 2014.
- J. Andonegui, D. Aliseda, A. Eguzkiza, L. Serrano, J. Maya. Evaluation of a telemedicine model for exudative age related macular degeneration follow-up. 13 European Society of Retina Specialists (EURETINA) congress, Hamburg 2013.
- J. Andonegui, D. Aliseda, L. Serrano, A. Eguzkiza. Evaluation of a telemedicine model for exudative AMD follow-up. American Academy of Ophthalmology, Chicago 2012.

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Acronyms

AAO	American Academy of Ophthalmology
ADL	Archetype Definition Language
AMD	Age-related Macular Degeneration
Anti-VEGF	Antivascular Endothelial Growth Factor
AOM	Archetype Object Model
API	Application Programming Interfaces
AREDS	Age-Related Eye Disease Study Group
CDA	Clinical Document Architecture
CDR	Clinical Data Repository
CDS	Clinical Decision Support
CEN	European Committee for Standardization (Comité Européen de Normalisation)
CG	Chronic Glaucoma
CHN	Hospitalary Complex of Navarre
CIPNA	Personal Identification Code of Navarre (Código de Identificación Personal de Navarra)
CKB	Clinical Knowledge Base
CKM	Clinical Knowledge Manager
CPOE	Computerized Physician Order Entry
DICOM	Digital Imaging and Communications in Medicine
DIMSE	DICOM Message Service Elements
DCM	Detailed Clinical Models
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
EHR	Electronic Health Record
EMR	Electronic Medical Record
ESB	Enterprise Service Bus
ETDRS	Early Treatment Diabetic Retinopathy Study
ETSI	European Telecommunication Standards Institute
GDL	Guideline Definition Language
GP	General Practitioner
HL7	Health Level 7
HUB	Bellvitge University Hospital
HTML	Hyper Text Markup Language
HTTP	Hyper-Text Transfer Protocol
ICD-x	International Statistical Classification of Diseases and Related Health Problems
ICPC	International Classification of Primary Care
ICT	Information and Communication Technologies
IEEE	Institute of Electrical and Electronics Engineers
IHE	Integrating the Healthcare Enterprise
IOP	Intraocular Pressure
ISM	Instruction State Machine
ISO	International Standards Organization
IRMA	Intra-Retinal Microvascular Abnormalities
JSON	JavaScript Object Notation
LIMS	Laboratory Information Management System
logMAR	Logarithm of the Minimum Angle of Resolution
LOINC	Logical Observation Identifiers Names and Codes

ME	Macular Edema
NHS	National Health Service
NMR	Non-Mydriatic Retinography
NPDR	Non-Proliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
OMP	Pharmacy/Treatment Order
ONH	Optic Nerve Head
OPT	Operational Template
ORU	Unsolicited transmission of an Observation or Result
OUL	Unsolicited Laboratory Observation
PACG	Primary Angle-Closure Glaucoma
PACS	Picture Archiving and Communication System
PDQ	Patient Demographics Query
PDR	Proliferative Diabetic Retinopathy
PDT	Photodynamic Therapy
PIX	Patient Identifier Cross-reference
PMI	Patient Master Index
POAG	Primary Open-Angle Glaucoma
PRP	Pan-Retinal Photocoagulation
RDS	Pharmacy/Treatment Dispense Messages
REST	Representational State Transfer
RIS	Radiology Information System
RNFL	Retinal Nerve Fiber Layer
RPC	Remote Procedure Call
RPM	Remote Patient Monitoring
SITA	Swedish Interactive Thresholding Algorithm
SNOMED-CT	Systematic Nomenclature of Medicine, Clinical Terms
SNS-O	Health Service of Navarre (Servicio Navarro de Salud - Osasunbidea)
SOA	Service-Oriented Architecture
SOAP	Simple Object Access Protocol
TC	Technical Committee
TCP/IP	Transmission Control Protocol/Internet Protocol
UI	User Interface
UMLS	Unified Medical Language System
VA	Visual Acuity
VF	Visual Field
WfMS	Workflow Management System

Content

Chapter 1:

Introduction

This Chapter provides general background of the work discussed along this PhD dissertation. First, the current sociotechnical scenario in healthcare is introduced, discussing the advent of digital Information and Communication Technologies (ICTs) into clinical environments and how adoption of e-health standards entails a great potential in terms of interoperability among healthcare-related information systems and technologies. Second, the importance of the standardization of Electronic Health Records (EHR) systems is highlighted, given the need for an integrated management of patients' clinical information, and bearing in mind the emerging trend in e-health toward development of semantic-enabled vendor-independent health computing platforms. Third, the situation on the Health Service of Navarre (Servicio Navarro de Salud - Osasunbidea [SNS-O]) is presented with regard to recent implementations concerning e-health. Fourth, the Chapter focuses on the context of our research group in the field of e-health projects which gave rise to this Thesis. Fifth, a set of hypotheses are proposed, and the general and detailed objectives are defined, primarily to optimize the management of chronic diseases in the ophthalmology department of the SNS-O through implementation of new e-health services. Finally, the outline of this Thesis is defined.

1.1 CURRENT SOCIOTECHNICAL SCENARIO IN HEALTHCARE

Over the past 15 years, the Information and Communication Technologies (ICTs) revolution has driven global development in an unprecedented way. In 2016, the International Telecommunication Union determined that 7 billion people (95% of the world's population) live within an area covered by a mobile-cellular network, and 3.5 billion people (nearly 47% of population) are using the internet [1]. Given the information society in which we live, the increasing success of Web 2.0 and social-media has empowered citizens in the management of their own health information [2].

In medicine, this new "sociotechnical" environment has been reflected in well informed citizens asking for an active participation on the clinical decisions and procedures concerning their healthcare [3]. This fact has shifted the doctor-patient relationship as we knew it: in contrast with the unquestionable authority that doctors had in the past, patients today have access to diverse information sources which can differ with doctor's guidelines.

In fact, usually there is not only one way to manage a specific medical issue. And therefore, numerous care alternatives must be considered so as to find the one which best suits the context found for each healthcare scenario. So accordingly, clinicians must assist patients to make sense of a confusing cornucopia of information and advice available due to the information age [4].

Modern society expects the highest level of quality in their healthcare, so clinical processes must incorporate leading edge technology and the latest advances in clinical practice. Yet, the problem is that the investment of healthcare organizations is limited, especially since the global economic crisis started in 2008, which forced to reduce the financial resources earmarked for healthcare in many countries. And meanwhile, the population ageing occurring in developed countries entails a growth in prevalence of age-related diseases, especially chronic conditions, which in turn, results in an increasing healthcare expenditure [5].

1.1.1 MANAGEMENT OF CHRONICITY

Nowadays, most health services in the world have hitherto been organized to treat acute episodes, whereas chronic conditions consume as much as 80% of national healthcare's budgets due to a suboptimal management of chronicity [6]. The reason for this is that chronic conditions present special features not addressed by the clinical practices focused on treatment of acute episodes: first of all, the advance of many chronic conditions is gradual and often presents no symptoms until the patient presents advanced stages of the disease, so in many cases patients are treated too late with the consequent increase in healthcare costs and the irreversible consequences for health. In addition, the healthcare resources necessary to cope with chronic conditions grow exponentially as their level of severity increases. Second, as chronic diseases eventually may lead to multimorbidity, most of healthcare expenses are concentrated in the last period of patient's life. Thus, few patients with complex healthcare needs consume a high percentage of health resources [5, 7]. Finally, we must not forget the impact that chronic conditions cause on patient's quality of life. In addition, to cover the emerging needs of patients affected by chronic conditions will incur in indirect costs for the society. For instance, in the case of ophthalmology, the population in working age affected with blindness or severe visual impairment will require special support for their reintegration into the labour market, hence the importance of an early diagnosis.

At this point, a paradigm shift is needed, otherwise the costs arising from chronic conditions will continue increasing unless health services adapt their care strategies from reactive to preventive. The good news is that new models of chronic care provision, which monitor periodically risk patients and adjusts the treatment to the specific needs of each patient, can optimize considerably the health expenditure. Hence, specific preventive strategies such as screening and follow-up services must be launched so as to take care of patients before acute episodes occur.

However, unlike treating acute episodes, these strategies must guarantee the continuity of care for chronic patients. This means that health services must consider new issues linked to the long-term care not covered so far. For instance, with regard to citizens' mobility needs nowadays, patients might live in a different city in which they work, or they could suffer episodes of recurring illness during vacation. In such cases, healthcare providers should be able to attend patients wherever they are.

1.1.2 ELECTRONIC HEALTHCARE OR E-HEALTH

At this point, the electronic healthcare, also known as e-health, takes on special relevance. The proliferation of ICTs and health devices connectable to data networks facilitates the exchange of relevant diagnostic information among health facilities. In this regard, the amalgam of papers and diagnostic tests in physical format has led to Electronic Medical Records (EMR). Therefore, while traditionally, patients living in regions with inadequate health services required to be physically present at health facilities properly equipped or else accept substandard care services, conversely, e-health provides analogous services in which clinicians can access medical records remotely [8]. Through e-health, distance and time are becoming trivial, so the healthcare facilities in which the care of patients is carried out turns irrelevant. Thus, healthcare providers can decentralize care services, and still offer patient-centred clinical processes [9].

This new context of electronic healthcare leads to reconsider traditional clinical practices toward more accurate diagnoses and a more efficient redistribution of resources, both material and human. Accordingly, many e-health services emerged, generally to cover the shortcomings of traditional care procedures. However, due to the lack of standardization of clinical information, most of these proposals would be limited to very specific local healthcare scenarios. And meanwhile, many clinical processes hitherto applied are becoming obsolete given the potential of ICTs, and yet these will remain in force while a seamless integration of e-health is not achieved. Actually, that is one of the main challenges of e-health nowadays.

Although novel therapeutic strategies/mechanisms keep in constant evolution toward efficient healthcare strategies, most health services do not reconsider traditional clinical procedures because of the intense efforts required to remodel their static and vendor-specific electronic health information systems [10]. Moreover, even if the system is finally modified, the healthcare providers are error prone, so they must overcome a training process until they get familiar with the new software tools [11].

Obviously, there is a gap when putting these proposals into practice due to lack of normalization when applying them, because healthcare facilities need for additional effort to adapt new strategies to the requirements and resources of the specific healthcare scenarios. At best, the technological ecosystem on which e-health services are implemented nowadays entails heterogeneous information systems compliant to multitudinous health information standards which even are not interoperable with each other [12]. According to this, the common breeding ground for new e-health proposals are either research projects specifically designed for the diagnostic devices and information systems available on the health service, or turnkey services installed by a given manufacturer which provides all infrastructure necessary.

Either way, any novel contribution upon medical practice must contemplate the enormous base of technologies, information systems, and medical devices, often based upon proprietary specifications, installed in the health service concerned. Therefore, the future of healthcare will be determined by a holistic management for the arising new electronic clinical information.

In this sense, the normalization of information and communications in medicine are considered strategic, as they facilitate the development of new e-health services that coordinate devices from different manufacturers. Those e-health services, in turn, will provide software tools that, relying on objective parameters, would facilitate an efficient management of healthcare resources [13, 14].

1.2 STANDARDIZATION OF EHR SYSTEMS

To share clinical information among health facilities, EHR systems are a cornerstone of any e-health service. Likewise, those systems have demonstrated to be a powerful tool to organize healthcare, especially when it comes to clinical processes centred on patients [15].

Nevertheless, the healthcare industry has an enormous installed base of legacy systems based on proprietary technologies, so the lack of normalization of EHRs makes it difficult, if not impossible, to exchange information. To address this, some EHRs have adopted interoperability standards that define common data architectures to reach an agreement during message exchange among heterogeneous systems [14, 16, 17]. In this context, the standards development organizations – such as the International Standards Organization (ISO), the European Committee for Standardization (Comité Européen de Normalisation [CEN]), Health Level 7 (HL7), the Institute of Electrical and Electronics Engineers (IEEE), or the European Telecommunication Standards Institute (ETSI) – are key in the normalization of the clinical information.

In this regard, irrespective of the standards chosen, ETSI distinguishes four categories of interoperability which must be covered to achieve an efficient understanding during information interchange among EHR systems: *technical*, *syntactic*, *semantic*, and *clinical process* [18]. Nowadays, beyond simply ensuring a faithful data interchange among different EHRs (technical and syntactic interoperability), the challenge now lies in finding an efficient way to preserve the clinical meaning of that information (semantic interoperability) and maintain the integrity of workflow among all health institutions involved in a specific clinical process (clinical process interoperability) [19, 20]. Therefore, the study of the current ecosystem of standards and specifications for EHR systems which cover the aforementioned levels of interoperability would be the starting point of this Thesis.

By focusing on semantic and clinical process interoperability, the EHRs involved in the communication must share the same knowledge base from clinical domain, where every clinical concept and procedure would be defined. At this point, some standardization organizations made attempts to formalize the whole healthcare domain into pervasive reference models, but the size and complexity of medicine hindered the proliferation of this approach.

In principle, EHR systems are meant to record patient's health information longitudinally to its life [21]. And as such, they must guarantee the continuity of patient's care beyond health institutions. For that reason, EHRs must be flexible enough to handle complex and constantly changing social information and clinical workflows, forever.

However, most EHR systems used so far in healthcare are not adequately prepared to keep pace with the rapidly changing body of knowledge plus the non-deterministic nature of medicine. First, there is an important interdisciplinary gap in reaching an agreement among software developers and clinicians, when knowledge from clinical domain must be transcribed into electronic health information systems. Second, EHRs must handle a huge variety of medical records, given the broad and complex knowledge domain of medicine. Further, each EHR system should be adapted bearing in mind the specific requirements reliant on the local context of final users. Thus, clinical specialities with very specific requirements, such as ophthalmology, are not covered by pervasive information systems [22]. Hence the consequent developmental costs resulting from an endless redesign of this magnitude would become unaffordable for any health service. And consequently, health services must deal with outdated legacy systems, based on proprietary technologies, which can hardly be dismantled since they contain sensitive information about patients' health.

This is mainly because, given the classical software engineering, up to 90% of the cost related to the life of software developed for healthcare could correspond to the maintenance phase [10, 23]. Therefore, this background has led to a search for more adaptive strategies for modelling the clinical knowledge inside information systems [24].

1.2.1 MULTI-LEVEL APPROACH ON MODELLING THE CLINICAL KNOWLEDGE

The advent of health information standards based on dual-model layered architectures, such as the EN/ISO 13606 or openEHR, has simplified all of those factors, i.e., agreement among clinicians and software developers, continuous need to adapt the information system, and system customization to specific healthcare scenarios. These new information standards have simplified the management of the clinical knowledge inside the EHR [17, 25].

This architecture defines two conceptual levels: on the one hand, a reference model that standardizes the way the information is handled inside the software, and, on the other hand, an archetype model that gathers knowledge about the clinical process to be managed. The former defines the structure and semantics of information in terms of information models, which are handled inside the software to register the clinical data in a normalized form. By contrast, the latter is constituted by archetypes and templates which define formally the clinical knowledge to be registered about a clinical domain. Experts in the clinical domain customize the information in their own EHR systems, whereas software developers work independently toward better tools to achieve interoperability among information systems [14, 26, 27].

Traditionally, all casuistry is planned before implementation, whereas two-level modelling can face the changes to the model on the fly [28], which is why this strategy has significantly improved the maintainability regarding time, cost, and simplicity of the software [24]. In essence, this architecture combines formal clinical modelling, terminology and a services infrastructure, thus providing a basis for implementation of semantic-enabled vendor-independent health computing platforms [29].

1.2.2 MODEL-DRIVEN OPEN PLATFORM ARCHITECTURE

With consideration of all the above, it is expected that EHR systems will evolve from monolithic information islands toward open health computing platforms in which even legacy systems are integrated into a distributed but interoperable collection of information systems. This would ensure, on the one hand, the collaboration among different healthcare providers, whilst health services retain control and ownership of the data in the long term; and on the other hand, the progressive incorporation of software tools responding to the specific needs of each health service at any given time, maintaining the interoperation with institutions that manage different configurations.

However, nowadays, proposals toward development of open health computing platform architectures are actually hindered by the scantiness of electronic models corresponding to healthcare scenarios already covered by the foregoing health information standards. In that respect, building new knowledge models is not the major concern. Clinical knowledge is already accessible in diverse information sources, whether explicit or implicit, resulting from previous efforts in developing novel clinical practices, building medical guidelines, specifying technical standards in the clinical setting, and gathering experiences of numerous domain experts. The real issue becomes how to gather, organize, and incorporate methodologically such knowledge to produce high-quality up-to-date electronic models. Therefore, at this point it is imperative to work forward on better modelling software tools and define guidelines that would encourage domain experts to participate actively in formalizing clinical processes into electronic platforms.

1.3 STATE OF THE ART ON THE SNS-O

From previous experiences conducted in the SNS-O, we learnt that innovative healthcare procedures involving e-health are easily adopted locally, but when the service has to be extended to new healthcare scenarios, it is necessary to deal with different information systems, clinical guidelines, and healthcare resources [30-32]. In this regard, unless a clear strategy is defined to normalize the medical records, and the way these are exchanged among health facilities, the resulting e-health projects will depend to a large extent on the healthcare scenario for which they were originally

implemented. Thus, in the event that the underlying healthcare scenario evolves, the respective e-health projects would be at risk of becoming obsolete accordingly. For this reason, the lifespan of e-health projects is very short, hence their implementation ends up being very costly for the health service.

Moreover, because of lack of consensus among standard-setting institutions, and without strong government or cross-border institutional regulations, it is usual to suffer data loss and duplication of diagnostic tests among different organizations. Which is, in fact, unacceptable to achieve high-performance healthcare models, since this increases the cost, whilst it does not revert to any improvement for the service [14].

Presently, on the service of ophthalmology of the SNS-O, there is an opportunity to leverage ICTs to redistribute more efficiently the workload derived from the chronic diseases consuming most time from specialists. Within this health service, very interesting proposals have been made during the last years, with regard to management of the chronic diseases corresponding to the most frequent causes of avoidable blindness in Europe, namely, Diabetic Retinopathy (DR) [30, 31], Age-related Macular Degeneration (AMD) [32], and Chronic Glaucoma (CG) [33]. Thus, by formalizing these healthcare scenarios in compliance with multi-level modelling standards, and the ensuing management using semantically enabled model-driven health computing platforms, should therefore serve to better adjust the responsibilities and assign the workload according to specific training and capabilities of the care providers available in the health service. Hence, given the scarcity of specialists in ophthalmology, this initiative should alleviate the overall waiting lists in the service.

Further, if the resulting electronic models are provided in open-access repositories, any health service interested in adopting the same clinical processes could easily reproduce or adapt this strategy to its needs.

1.4 BACKGROUND OF THE RESEARCH

This section contains a brief description of the research projects of our research group, as the work developed at those projects is the kernel of this Thesis. Each project presented different objectives, all of them aimed at improving specific aspects of the health service. As the projects were implemented in real healthcare scenarios, new possibilities were identified in terms of the use of ICTs. Thus, the experience we acquired in each project was progressively incorporated to new proposals, constituting the starting point for the present proposal of this PhD dissertation.

Our first research project proposed the implementation of a screening service of DR using non-mydriatic funduscopy in a primary care setting:

> **2008-2009: "REDIAP Project: Diabetic Retinopathy in a Primary Care Setting"**. Collaborative project among the ophthalmology department of the Hospital of Navarre (HN), the Public University of Navarre (UPNA) and the Primary Health Care department of the Health Service of Navarre (SNS-O), and funded by the health department of the Government of Navarre.

To that end, a software tool was designed using funduscopic images labelled beforehand by ophthalmologists, firstly to support the training of General Practitioners (GPs) on the analysis of non-mydriatic retinographies, and secondly to evaluate the agreement between GPs and ophthalmologists in DR screening [34]. Thus, it was proved that specifically trained GPs can reliably identify signs of DR by reviewing non-mydriatic retinal photographs. Therefore, ever since practitioners joined the DR screening, only patients presenting symptoms of DR were referred to ophthalmologists, thus alleviating the waiting lists of specialists in retina [30, 35].

The new DR screening service was successfully implemented in the SNS-O. Indeed, that year it was considered the best research project in Navarre in the area of health system management and it was

awarded with the "Mikel Larumbe Zazu" grant by the health department of the Government of Navarre. However, all diagnostic test acquisitions and clinical data had to be exploited manually, hence monitoring the outcomes from the screening service was slow and laborious. This stems from the fact that the diagnostic devices available used proprietary implementations to model clinical information. In consequence, it was not possible to interconnect devices from different manufacturers. Moreover, the worklist was managed using referral notes in paper, so the flexibility of the DR screening service was conditioned by outdated administrative procedures.

Our next research project proposed a normalized management for exchange of diagnostic images in ophthalmology regardless of device manufacturers:

2009-2010: "OPHTIMA: Ophthalmologic Image Management". Funded by the innovation, business and employment department of the Government of Navarre.

The ophthalmic devices had to be adapted so as to provide clinicians a comprehensive access to imaging studies. Therefore, ubiquitous access to diverse diagnostic tests would improve accurateness of diagnoses, and agility in clinical practice [31, 36].

Digital Imaging and Communications in Medicine (DICOM) standard was established to achieve interoperability among the heterogeneous diagnostic imaging devices involved in ophthalmology. In this sense, installation of a Picture Archiving and Communication System (PACS) was proposed to handle all medical imaging studies acquired by ophthalmic devices. Nonetheless, clinical information relating to diagnostic tests not based on medical imaging and medical reports from clinicians were beyond the scope of the DICOM standard.

Our third research project leveraged the work on standardisation for DR, and extended the use of ICTs to other healthcare scenarios within ophthalmology:

2010-2011: "Evaluation of an e-ophthalmology system for monitoring wet AMD". A two year-long project that involved HN and UPNA, was coordinated by the Miguel Servet foundation, and funded by the health department of the GN.

The use of e-health strategies was studied to manage the monitoring of patients with wet AMD. This proposal would allow clinicians to adapt the treatment of wet AMD according to the progression of symptoms identified on images assessed remotely to diagnostic devices [37].

However, before implementation of the e-health approach, the remote assessment proposed must be validated with respect to traditional face-to-face consultations. To that end, both procedures functioned in parallel during an evaluation period, and meanwhile, diagnostic decisions resulting from both approaches were registered in a web platform specifically set up for the project. After using the platform to analyse the results, we determined that e-health proposal might be a useful alternative for the follow-up of wet AMD [38].

However, creating a framework from scratch to handle the results of this specific project of research involved a huge effort on coding. Moreover, the clinical process should be adapted as clinical knowledge evolves, but applying modifications into this platform was too slow due to the lack of standardization of the information registered. Therefore, it was not worth adapting this platform to include new requisites or to be reused in future studies.

Our last project proposed modelling the clinical process designed to monitor wet AMD in compliance with openEHR norm:

> **2012-2014: "Evaluation of an e-ophthalmology model for monitoring exudative AMD"** code PI11/02797. Funded within the "Fondo de Investigación Sanitaria" (FIS) by the Spanish Ministry of Economy and Competitiveness, this project involved the Hospitalary Complex of Navarre (CHN), the Bellvitge University Hospital (HUB) and the UPNA.

The model-driven standardized information system used would be more adaptive than the non-standardized proprietary systems used in previous projects. Besides, the results of the clinical process could be managed by any EHR system compliant to that modelling standard. Thus, using this strategy, the clinical knowledge modelled would be reusable for different healthcare scenarios.

One could say that this PhD dissertation stems from this last project, although the scope of this thesis work goes beyond that. As we will see later, modelling will be extended to include three clinical processes we considered strategic based on the experience acquired in the domain of ophthalmology. To that end, the ICT infrastructure deployed for the aforementioned projects must be adapted to the new scenario. Finally, based on the two-level modelling seen so far, a semantically enabled model-driven health computing platform will be proposed to manage patient-centred clinical processes.

1.5 HYPOTHESIS AND OBJECTIVES

The first major aim of this Thesis, is to research into, and make contributions toward interoperability among information systems applied to e-health. And, secondly, this work seeks to gather the experience that our research group acquired during the last decade in the clinical domain of ophthalmology, and transcribe it into computerized models. In this way, other researchers would be able to progress from that point onward.

Thus, bearing in mind the two pillars of this Thesis, the focal aim is on the one hand to investigate major e-health standards so as to find solutions toward interoperability among information systems used in ophthalmic environments; and, on the other hand, to make contributions on development and normalization of efficient e-health services in ophthalmology. This approach suggests the following foremost underlying hypotheses:

- A clearly defined methodology to build semantically computable electronic models would prompt domain experts to contribute to formalize the management of specific clinical processes.
- The definition of an open health computing platform in ophthalmology would, on the one hand, empower healthcare facilities on a flexible choice of Application Programming Interfaces (APIs) and services, incorporated incrementally according to the needs of the health service at any given time, and on the other hand sustain the usefulness of the electronic medical records over the long-term, by guaranteeing backward compatibility with legacy systems.
- Building electronic models (including archetypes, templates, terminology subsets, guideline rules, and User Interface (UI) forms) for the main chronic diseases threatening to overload the waiting lists of ophthalmology services would enhance the management of patients through complex healthcare procedures, and by extension, would save time and costs for all parties involved: patients, clinicians, and health services.

Thus, the major aim of the Thesis, together with the abovementioned hypotheses, leads us to the overall objectives:

1. To deeply study the ecosystem of standards and specifications pervasive in e-health, remarking initiatives focused on interoperability among EHR systems, e.g. openEHR, EN/ISO 13606, DICOM, HL7 (HL7v2, HL7v3, HL7 Clinical Document Architecture or CDA, and more recently HL7 FHIR), and standard medical terminologies (Logical Observation Identifiers Names and Codes – LOINC, Systematic Nomenclature of Medicine - Clinical Terms – SNOMED-CT, International Statistical Classification of Diseases and Related Health Problems – ICD-x or International Classification of Primary Care – ICPC).
2. To design a methodology that would guide domain experts to actively engage in modelling their own electronic models compliant to model-driven e-health standards.
3. To propose an open architecture for building health computing platforms based on the e-health standards mentioned above, so as to coordinate heterogeneous information systems toward a comprehensive management of patient-centred clinical processes and guaranteeing the continuity of care of patients.
4. To contribute to the design of new e-health services in the SNS-O that would optimize clinical practice in chronic diseases threatening to overload the waiting lists of the ophthalmology department (DR, wet AMD, and CG).
5. To formalize into electronic models the clinical processes devised in the previous point, i.e. a DR screening service, a service monitoring the intravitreal antivascular endothelial growth factor (anti-VEGF) therapy used to treat wet AMD, and a follow-up service for CG.
6. To collaborate closely with standard-setting institutions and to use open platforms to share the experience gained during this Thesis.
7. To prepare the ophthalmology department to implement e-health proposals: standardization of the diagnostic tests and information systems involved in the clinical processes proposed above.

At a deeper level, the following objectives regarding contributions to the DR screening service deserved mention:

- To consolidate a standardized, future-proof solution to manage the clinical information handled in the DR screening service, given the continuous evolution of the clinical knowledge.
- To build an electronic model for the DR screening service which proved to be a success in the SNS-O, so as to facilitate implementation for this clinical process in other healthcare facilities and organizations.

Regarding the service monitoring the intravitreal anti-VEGF therapy used to treat wet AMD:

- To provide a solution to adjust the therapeutic strategy, as well as the health resources allocated to each patient depending on the state of the disease presented at any time.
- To design a high resolution consultation model that would address the revision and treatment of patients diagnosed with wet AMD throughout a single outpatient visit in order to alleviate the waiting lists of the service.

Finally, regarding the follow-up service for CG:

- To design a health computing system to analyse all diagnostic studies transversal to the disease of each patient, thus facilitating the implementation of software tools able to identify any sign of evolution in CG.

1.6 THESIS OUTLINE

The rest of this Thesis has been organized as follows: background on the main topics addressed further on along this Thesis is presented in Chapter 2. To this end, first, the clinical domain is addressed, with a special focus on management of chronic diseases in ophthalmology; second, background upon e-health standards and EHR architectures is provided; third, the strategies found in literature which address the design and implementation of electronic models are discussed; fourth, the state of the art of open health computing platform architectures is described; fifth, the management of clinical information within the SNS-O is depicted, emphasizing the needs identified for such healthcare service; and finally, an overall analysis of the knowledge artefacts modelled so far in the clinical domain of ophthalmology is provided as a starting point for the electronic models proposed along this Thesis.

Next, the guidelines toward integration of e-health systems into pervasive clinical practices are outlined in Chapter 3. To start with, a methodology is proposed to guide domain experts to participate actively in building their own electronic models compliant to model-driven e-health standards. Then, an architecture is provided to build an open health computing platform that would integrate the installed base of heterogeneous information systems of an entire health service, in order to implement the electronic models resulting from that methodology applied to a seamless management of patient-centred clinical processes.

Then, given the open health computing platform and the modelling guidelines mentioned above, specific electronic models are presented along Chapter 4 as proof of concept. These models correspond to specific healthcare scenarios identified in the SNS-O, with regard to the management of chronic ophthalmologic diseases responsible for the most frequent causes of avoidable blindness in Europe. Accordingly, electronic models for a remote screening for DR, a high resolution consultation to monitor the treatment in AMD, and a follow-up service for patients diagnosed with CG who are medically stable are provided in this chapter.

Along Chapter 5, the topics covered along the Thesis are discussed: on the one hand, the implications of applying the methodology, and the architecture proposed in Chapter 3 are outlined. On the other hand, the conclusions reached from modelling the three clinical processes proposed in Chapter 4 are discussed.

Subsequently, in Chapter 6 the objectives achieved along this PhD dissertation are summarised and, suggestions for future research lines are described briefly.

To conclude, two additional appendixes have been added at the end of the present Thesis: one for listing all elements involved in the electronic models defined along this Thesis, and other for setting out the outcomes of a use case for one of the electronic models provided.

Chapter 2:

Background

This chapter introduces the main topics addressed along this PhD dissertation, i.e. ophthalmology and interoperability on e-health. To start with, the three major ophthalmologic diseases are studied as concerns the most frequent causes of avoidable blindness and visual impairment in Europe. Second, this chapter provides an in-depth analysis of the current management strategies for electronic information in healthcare. In this regard, different levels of interoperability have been identified to guarantee a faithful communication among heterogeneous information systems. Thus, given the aforementioned interoperability levels, primary standards bodies doing specific work in e-health standards and specifications applicable to EHR systems are presented. Third, the state of the art related to the design and implementation of electronic models that could cover the aforementioned interoperability levels is reviewed. Fourth, the open health computing architectures are presented as a solution to face the main challenges nowadays with regard to management of clinical information and interoperability in e-health. Fifth, in contrast to that architecture, the chapter focuses on the specific scenario found in the SNS-O, in terms of the base of information systems installed for the management of clinical information. To conclude the present chapter, the knowledge artefacts compliant to dual-model layered architecture, and specifically modelled for the clinical domain of ophthalmology are identified. This would establish a starting point for the subsequent electronic models.

2.1 THREE MAJOR CHRONIC DISEASES IN OPHTHALMOLOGY

AMD (26%), glaucoma (20.5%) and DR (8.9%) are the most frequent causes of avoidable blindness in Europe. Although there are even more frequent ophthalmic conditions, such as cataract, because of the chronicity of the aforementioned diseases, they cause severe and irreversible loss of vision when patients are not early treated [39, 40]. The visual loss resulting from these affections will accompany patients throughout their lives, whereby the prevalence of visual impairment increases with patients' ageing.

To avoid that scenario, the management of such chronic conditions should entail the continued care of patients. However, given the traditional clinical procedures, there are not enough specialists in health services to handle the increasing workload arising from periodic revisions necessary to guarantee a suitable management of chronicity in ophthalmology. What's more, due to the increasing life expectancy in developed countries, the occurrence of blindness or visual impairment will become even more common the coming years [41].

For this reason, research into efficient management for DR, AMD, and CG is becoming critical in the area of ophthalmology. Thus, in line with that research, this section introduces briefly the aetiology as well as generalized strategies used worldwide to manage each of these chronic affections.

2.1.1 DIABETIC RETINOPATHY (DR)

Diabetic retinopathy is one of the most feared complications of diabetes mellitus, and an important cause of visual loss worldwide among middle-aged and therefore economically active people [42].

The International Diabetes Federation estimated the worldwide prevalence of diabetes in 8.8% (415 million) of adults aged 20-79 in 2015. And according to the projections for 2040, this figure is expected to increase to 10.4% (642 million) of adults worldwide [43]. From these figures, approximately one-third of people with diabetes develop nowadays some degree of diabetes-related eye damage. Thus, as the global prevalence of diabetes increases, so will the population affected with vision-threatening DR, namely, severe Non-Proliferative DR (NPDR), Proliferative DR (PDR) and Diabetic Macular Edema (DME) [44].

Classification system

When it comes to establish normalized diagnoses and consequent therapeutic procedures concerning DR and DME, the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale became the gold standard for many years. However, the precise description of symptoms, and the definition of more severity levels than necessary made this scale too complex to be used in daily clinical practice. Consequently, the American Academy of Ophthalmology (AAO) proposed the "international clinical Diabetic Retinopathy and Diabetic Macular Edema disease severity scales", which simplified the ETDRS severity scale toward a more generalized clinical applicability [45, 46].

Based on scientific evidence, this new classification distinguished different levels depending on clinical findings easily recognized upon eye fundus. As a result, five severity stages were identified for DR as described by Wilkinson CP, Ferris FL III, et al [45]:

- *No apparent DR* (ETDRS levels 10, 14, 15): No abnormalities.
- *Mild NPDR* (ETDRS level 20): Microaneurysms only.
- *Moderate NPDR* (ETDRS levels 35, 43, 47): More than just microaneurysms but less than severe NPDR (less than 4:2:1 rule described below).
- *Severe NPDR* (ETDRS levels 53A-E): Any of the following (4:2:1 rule) and no signs of proliferative retinopathy:
    - Extensive (>20) intraretinal haemorrhages in each of 4 quadrants.
    - Definite venous beading in 2 or more quadrants.
    - Prominent Intra-Retinal Microvascular Abnormalities (IRMA) in 1 or more quadrants.
- *PDR* (Preliminary PDR: ETDRS levels 61 & 65, High-risk PDR: ETDRS levels 71 & 75, Very severe or advanced PDR: ETDRS levels 81 & 85): One or more of the following:
    - Neovascularization.
    - Vitreous/preretinal haemorrhage.

Any stage of NPDR can lead to DME, which can cause rapid vision loss to patients. For this reason, it is important for ophthalmologists to classify the severity of DME along with the diagnosis of DR. To that end, first, it is checked whether Macular Edema (ME) is present or not and, if so, the severity is classified as mild, moderate, or severe, according to its location relative to the macula. Indeed, DME involving the centre of the macula implies major consequences concerning visual loss compared to the same findings but distant from the macula.

Accordingly, Wilkinson CP et al. identified four severity stages to classify DME [45]:

- *DME apparently absent:* No apparent retinal thickening or hard exudates in posterior pole.
- *Mild DME:* Some retinal thickening or hard exudates in posterior pole but distant from the centre of the macula. Not clinically significant ME.
- *Moderate DME:* Retinal thickening or hard exudates approaching but not involving the centre of the macula. Clinically significant ME.
- *Severe DME:* Retinal thickening or hard exudates involving the centre of the macula. Clinically significant ME.

Given the severity scales above, it should be noted that patients can still be assessed using different levels of precision, depending on the purpose of the study. For example, whereas differentiating patients presenting signs of DR from those with no evidence of DR (ETDRS value $\leq$20) is sufficient for screening purposes, the assessment of ophthalmologists for patients with confirmed DR must be more fine-grained, including levels of severity either for DR and DME. In this sense, the American Telemedicine Association recognizes four categories of validation for DR e-health programs, all of them based on the severity scales seen above [47].

Strategy for diagnosis and follow-up

DR progresses over a long period before it becomes symptomatic, so early detection and prompt treatment enables preventing up to 98% of diabetes-related visual impairment [48]. According to this, most authorities recommend that retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually to avoid irreversible damage at eye fundus: patients with type 1 diabetes should undergo fundus examination 5 years after their diagnosis and then annually, whereas patients with type 2 diabetes should be examined as soon as diabetes is diagnosed and then annually. Only if no sign or evidence of retinopathy is found for one or more annual eye exams, exams every 2 years may be considered [49].

Consequently, due to the high prevalence of the disease and the scarcity of ophthalmologists, many patients do not benefit from an eye examination within the recommended periods. In that respect, today, there is an ongoing debate regarding the choice of the best protocol to conduct a screening to detect DR. First of all, which care professionals should be involved in the DR screening is a subject of

discussion: ophthalmologists, optometrists, GPs, screening technicians, or clinical photographers [42]. Second, in case of DR classifications not made by ophthalmologists, there are variations concerning the training method chosen for the personnel, or how the resulting clinical decisions are validated (whether or not evaluated by peer-review) [50].

Third, a screening method must be chosen: direct ophthalmoscopy, dilated slit lamp bio-microscopy with a hand-held lens, mydriatic or non-mydriatic retinal photography, or retinal video recording [42]. Beyond these methods, the International Council of Ophthalmology also considers including the Visual Acuity (VA) exam and a thorough diabetes history to assure appropriate referral [51].

Given the foregoing methods, Non-Mydriatic Retinography (NMR) has become a widely accepted alternative to identify signs of DR, since it has similar reliability to the classical methods of ocular examination [52-54], but at a greater cost-effectiveness [55]. Moreover, it requires less time for each patient, it can be applied to populations at a distance from the specialist, and it does not require pupillary dilation. In other words, this diagnostic method complies with all requirements for development of e-health programs that would alleviate the burden of DR screening.

With regard to NMR, different authors propose variations in number and size (angle of view) of the ETDRS fields acquired for each eye [56]. Moreover, although pupillary dilation is rarely necessary, this possibility may be considered for specific cases [50].

Therapeutic recommendation

Management of patients varies depending on the severity of the DR, hence the importance of preventive screening to avoid irreversible damage on eye fundus. In that respect, intraocular steroids and anti-VEGF agents have the greatest potential in treatment of DME and proliferative disease. Likewise, grid laser photocoagulation is recommended in the setting of clinically significant ME when macular ischemia is absent. Conversely, Pan-Retinal Photocoagulation (PRP) and vitrectomy are indicated to treat patients presenting advanced stages of DR [57].

Thus, considering scatter PRP laser, focal and/or grid laser photocoagulation, intravitreal anti-VEGF therapy, intravitreal corticosteroids, and vitrectomy surgery as main procedures to treat DR, the AAO defined a set of therapeutic recommendations depending on the diagnoses established. Therefore, the aforementioned recommendations made by the AAO are summarized in Table 1, in connection with the stages used to classify severity of DR and DME [58].

2.1.2 AGE-RELATED MACULAR DEGENERATION (AMD)

Age-related macular degeneration is a degenerative process of the central retina that develops in elderly people. The macula covers the central area of the retina which actually is responsible for detecting high-acuity details of central vision. Therefore, when it gets damaged, the VA decreases drastically, especially in central areas of the Visual Field (VF).

The visual impairment due to AMD has devastating effects on the quality of life of patients. Consequently, daily activities such as reading, driving, watching television, recognizing faces or doing housework become great challenges for them [59, 60]. The severity of those consequences sets the AMD as the leading cause of blindness in people over 65 years. Indeed, its prevalence in people over 40 years in the United States is 6.5%, and more than one out of every 10 Americans over 80 has advanced symptoms of AMD at least in one eye [61]. Studies in other developed countries concluded that the increase of AMD depends on the age of patients [62]. Consequently, as AMD is a process strongly associated with age, the prevalence of AMD would increase in the coming years proportionally with the ageing population.

Table 1: *Management recommendations defined by the AAO for patients with diabetes.*

Severity of Retinopathy	Presence of ME	Scatter PRP laser	Focal and/or grid laser photocoagulation	Intravitreal anti-VEGF therapy
No apparent DR	No	No	No	No
Mild NPDR	No Non-clinically significant ME Clinically significant ME	No No No	No No Sometimes	No No Sometimes
Moderate NPDR	No Non-clinically significant ME Clinically significant ME	No No No	No No Sometimes	No No Sometimes
Severe NPDR	No Non-clinically significant ME Clinically significant ME	Sometimes Sometimes Sometimes	No No Sometimes	No No Sometimes
PDR	No Non-clinically significant ME Clinically significant ME	Recommended Recommended Recommended	No Sometimes Sometimes	Considered Usually Usually

Classification system

AMD is divided into two subtypes: atrophic (dry) and exudative (wet) [63]. The former is more frequent and it has not treatment yet, but its consequences are less visually debilitating for patients, whereas the latter occurs less frequently and is treatable, but its consequences are more severe for the vision. It is worth mentioning that the prevalence of wet AMD represents 10-15% of all cases of AMD, but accounts 90% of severe visual loss due to AMD [64].

One of the main classification systems for AMD was proposed by the Age-Related Eye Disease Study Group (AREDS) to define different categories according to progression of the disease [65, 66]. These categories established for AMD are further described in Table 2:

Table 2: *Classification of the severity of AMD according to the AREDS scale.*

AREDS Category	Severity of AMD	Description
Category 1	No AMD	No or a few small (<63 micrometres in diameter) drusen.
Category 2	Early AMD	Many small drusen, a few intermediate-sized drusen (63-124 micrometres in diameter), or pigmentary changes on the macula.
Category 3	Intermediate AMD	Many intermediate drusen or at least one large drusen (≥125 micrometres), or geographic atrophy not involving the centre of fovea.
Category 4	Advanced or late AMD	Dry: Drusen and geographic atrophy involving the foveal centre. Wet: Choroidal neovascularisation or evidence for neovascular maculopathy.

Strategy for diagnosis and follow-up

The visual loss due to wet AMD progresses rapidly compared to dry AMD. As per wet AMD, a study of the natural progression showed that during 28 days elapsed between initial diagnosis and treatment, 44% of patients investigated had some degree of visual loss, and 16% lost more than 3 lines of distance VA [64]. Meanwhile, the appearance of geographic atrophy ranges from 2.5 to 5.9 years depending on the type of lesion [67]. Thus, to minimize the risk of visual loss, wet AMD has to be continuously monitored in short periods of time. Furthermore, the treatment is significantly more effective when applied at first stages of the disease, since the VA deterioration caused by delaying the therapy can become irreversible [68]. Nevertheless, the symptoms are imperceptible in the initial stages of AMD, so the population at risk, which usually consists on elderly patients, should be included into follow-up circuits guaranteeing the detection of the disease. Concerning those follow-up processes, the study of different viewpoints of the macula is required. Consequently, the tests of NMR, combined with either the diagnostic tests of fluorescein angiography or Optical Coherence Tomography (OCT) are involved in monitoring the progression of wet AMD [69].

Therapeutic recommendation

Once the diagnosis of wet AMD has been confirmed, the progression of subretinal neovascularization which characterizes this condition can be retarded by repeated injections of anti-VEGF agents into the vitreous cavity [70]. Originally, all patients were treated equally by applying them monthly intravitreal injections. Actually, great results were achieved in terms of VA, but at the expense of a huge number of monitoring visits and invasive therapeutic procedures [71-73]. Therefore, considering that not all

patients respond similarly to the same treatment, as we shall see later, more personalized treatment approaches are suggested in literature.

In that respect, in order to reduce the number of unnecessary treatments and clinical encounters, some authors recommend, after the three first monthly injections, including an evaluation for further treatment as part of the therapy. Consequently, the treatment could be adapted for patients not responding to the injections, and so the anti-VEGF agents are used only when they are effective [69, 74, 75]. In the same way, by reducing unnecessary interventions, the adverse complications resulting from intravitreal injections are minimized too.

Infectious endophthalmitis is regarded to be the most adverse postoperative complication of anti-VEGF intraocular injections, due to its vision-threatening potential [76]. Thus, when the intervention is considered necessary, it must undergo in compliance with procedure guidelines specially designed to guarantee the safety of patients. In this sense, the choices made according to the location where the procedure takes place, the strategy for ventilation, the sterilization of surgical equipment and barriers used to prevent the infection, the method employed to apply anesthesia, the preparation of antiseptics, the use of post-injection antibiotics, and the anti-VEGF agents used are critical to reduce the risk of infection to the greatest extent possible [77, 78].

Taking into consideration the pharmaceutical agents used for intravitreal injection, ranibizumab (Lucentis®, Genentech/Roche, Inc., South San Francisco, CA) is the most cost-effective among treatments for neovascular AMD approved by the United States Food and Drug Administration agency [79]. However, bevacizumab (Avastin®, Genentech/Roche, Inc., South San Francisco, CA) has to be considered as an alternative to ranibizumab, since both are anti-VEGF compounds whose effectiveness has been proved for AMD before ranibizumab was licensed [80]. Indeed, the use of bevacizumab was approved in the USA in 2005 and in Europe in 2006 as a systemic anticancer therapy, but it is still being debated whether it is safe enough for intravitreal injections. In that respect, compared to bevacizumab, ranibizumab presents decreased risks of ocular inflammation and venous thrombotic events [81]. Even so, latest publications and guidelines support the safety of using bevacizumab within AMD, since the effectiveness is similar to ranibizumab but at lower cost [70, 81, 82]. Aflibercept (Eylea®, Regeneron Pharmaceuticals Inc., Tarrytown, NY) is proposed as salvage therapy when the patient does not respond to ranibizumab and bevacizumab [83, 84]. Other medications such as pegaptanib sodium (Macugen®, Eyetech, Inc., Cedar Knolls, NJ), or alternative treatments such as antioxidant and vitamin supplement intake, Photodynamic Therapy (PDT), and thermal laser photocoagulation surgery are used when patients do not respond to those primary therapies [84, 85].

2.1.3 CHRONIC GLAUCOMA (CG)

Chronic glaucoma is an optic neuropathy associated with a progressive loss of the VF that often but not necessarily is associated with high intraocular pressure (IOP). As a consequence of the progression of glaucoma, patients may present acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons [86]. Consequently, the progressive damage on Retinal Nerve Fiber Layer (RNFL) may become clinically manifest in nerve fiber layer thinning (Figure 1), increased cupping of the Optic Nerve Head (ONH) (Figure 2), and glaucomatous VF loss (Figure 3), or any combination of these:

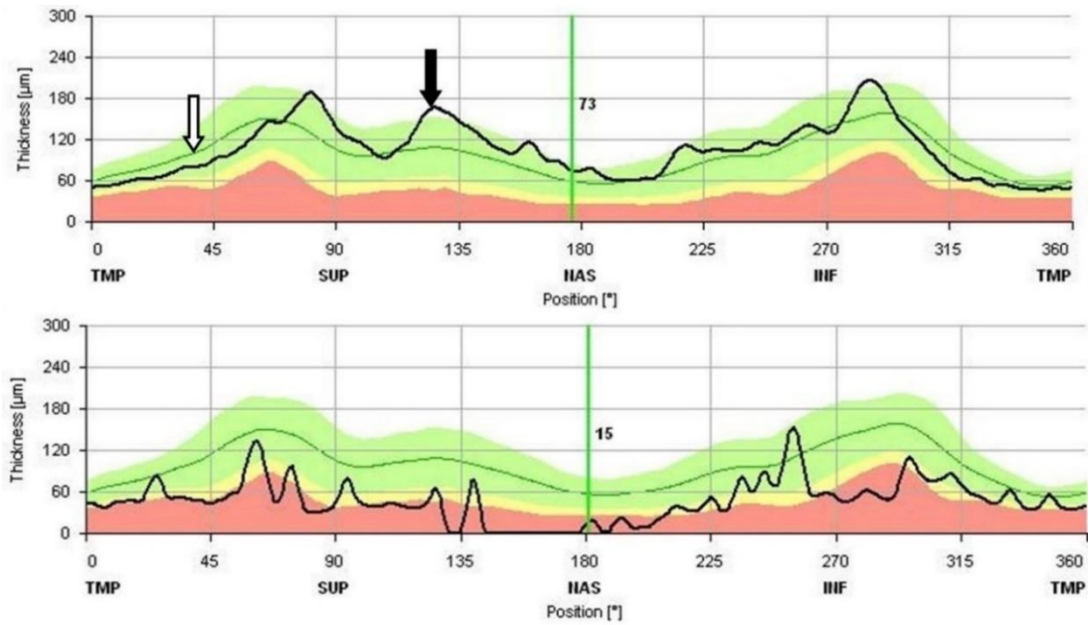

Figure 1: *OCT measurement of the RNFL thickness measured around the ONH.*

First of all, the black line in Figure 1 indicates the RNFL thickness measured for a specific patient, while the dark green line draws the average value obtained statistically from healthy subjects consistent with that patient's age. Thus, the upper chart shows the measurement in a patient with no signs of thickness reduction. On the contrary, the second measurement presents a marked reduction of the RNFL thickness. In this case, the line corresponding to the patient measurement goes into red zone, which means that the thickness is clearly under the average value.

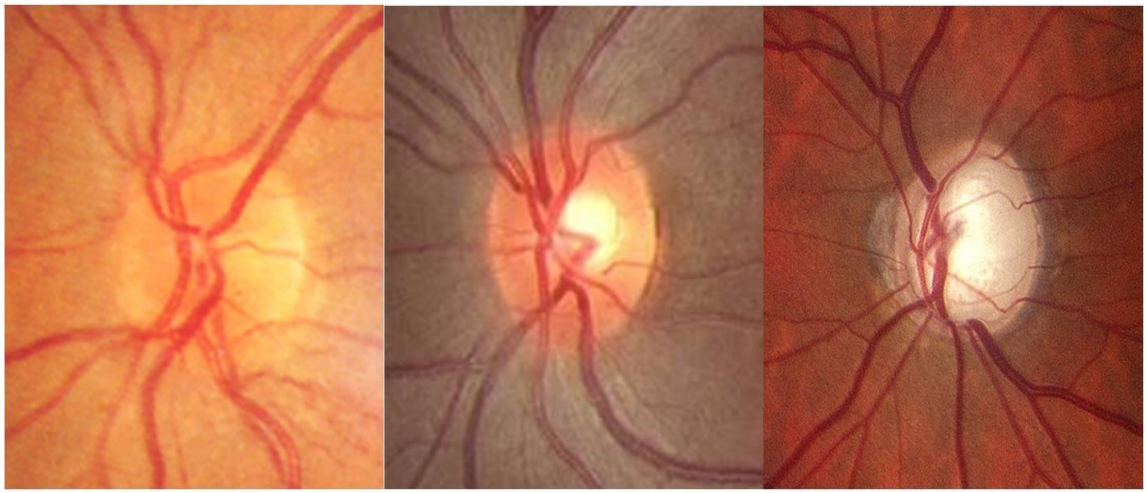

Figure 2: *Different degrees of optic disc cupping.*

Second, three eye fundus photographs centred on the ONH appear in Figure 2 to show different degrees of optic disc cupping. The fundus image on the left presents an optic disc with no cupping. The one in the middle, is affected by an intermediate cupping, whereas the one on the right corresponds to an optic disc with complete cupping.

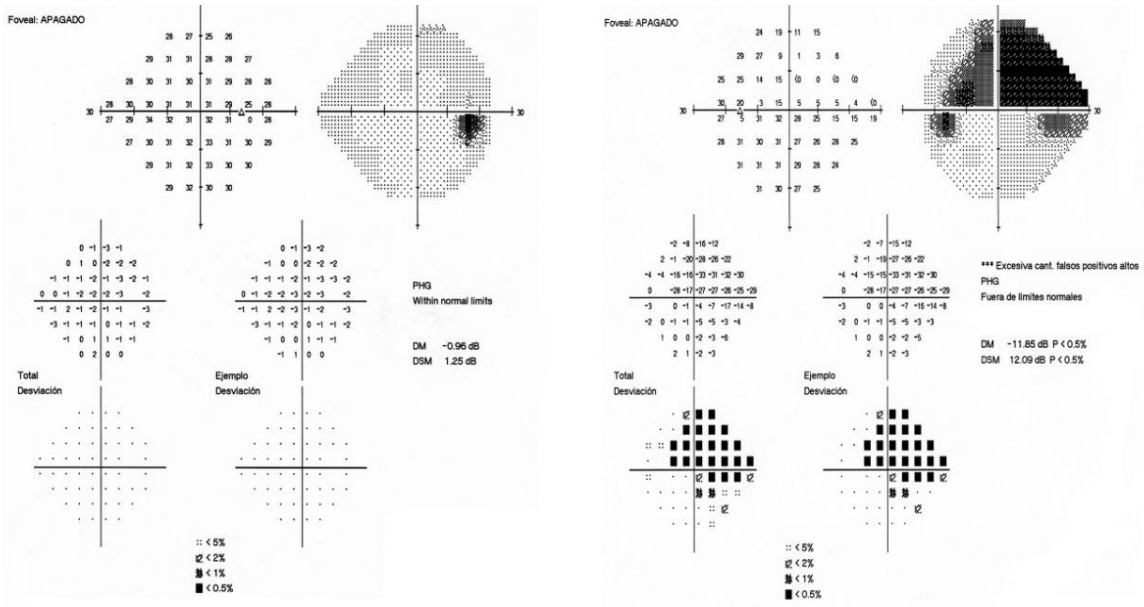

Figure 3: *Comparison of a VFs of a patient with no signs of glaucomatous damage (image on the left), and a patient presenting advanced glaucomatous damage (image on the right).*

Finally, the dark spots visible on the VF at the right of Figure 3 represent areas of irreversible VF loss characteristic of glaucomatous damage.

These manifestations of progressive damage make chronic glaucoma an important cause of irreversible visual loss which generates an important demand for ophthalmologic consultations. Indeed, the prevalence of adults (aged between 40-80 years) worldwide diagnosed with glaucoma in 2013 was estimated in 3.54% (64.26 million people), from which open-angle glaucoma accounts for 86.16% of all glaucoma cases. In this regard, even though most cases present open-angle glaucoma, angle-closure glaucoma is more aggressive, hence it is responsible for a disproportionate number of patients with severe vision loss [87]. Besides, it is expected that the number of people with glaucoma worldwide will increase by 74% from 2013 (64.26 million) to 2040 (111.8 million) [88]. This trend is mainly due to the increase of life expectancy, so in developing regions such as Asia and Africa, the epidemiology of glaucoma will move up more dramatically in the years ahead, compared to the leading nations in terms of the ageing of the population (Europe and North America) [88].

In view of these figures, and given that affected individuals require lifelong ophthalmic care, CG represents an important problem for health authorities due to the increased number of consultations required to manage this disease.

Classification system

Glaucoma can be classified into two broad categories: open-angle and (acute) angle-closure glaucoma, each of which can be categorized as primary and secondary.

Open-angle glaucoma is usually but not always in the presence of elevated IOP, perhaps in part related to increased aqueous production and decreased outflow. The main feature distinguishing Primary Angle-Closure Glaucoma (PACG) from Primary Open-Angle Glaucoma (POAG) is that the angle, the site of aqueous outflow in the eye, is obstructed by apposition of the iris, resulting in an anatomically closed angle (defined if at least 270° of the angle is occluded).

Both open-angle and angle-closure glaucoma can be primary diseases, whereas secondary glaucoma results from trauma, certain medications such as corticosteroids, inflammation, tumour, or conditions such as pigment dispersion or pseudoexfoliation [87].

As can be seen in Table 3, many types of glaucoma are distinguished, even if we only consider primary types. In fact, there is an ongoing debate on the best classification approach to determine the prognosis or optimal management. This stems from the fact that the biological basis of this condition is poorly understood and the factors contributing to its progression have not been fully characterized. Anyway, once CG has been confirmed and a treatment has been established, the follow-up process would be limited to identify whether glaucoma is stable or progressive so as to adapt the treatment accordingly [89].

Table 3: *Classification of primary types of glaucoma for assessment and follow-up protocols.*

Category	Description
Ocular Hypertension (OHT)	IOP > 21 mmHg without treatment, whereas the study of VF, optic disc and RNFL, family history, and gonioscopy is normal. It can be classified as low-risk or high-risk OHT, depending on the severity of risk factors (e.g. IOP, cup/disc ration, central corneal thickness).
POAG Suspect	Given the study of VF, optic disc and RNFL, at least one is suspicious. Besides, IOP can be normal or increased. Thus, risks and benefits of treatment need to be weighed against the risk of the development of glaucomatous disc damage.
POAG (also known as chronic glaucoma)	It is defined by elevated outflow resistance in the trabecular meshwork outflow pathways. As a result, the patient presents acquired characteristic glaucomatous damage on ONH, optic disc haemorrhages, and even RNFL changes. Accordingly, glaucomatous defects corresponding to the optic disc damage may be present on VF. To rule out any type of PACG, gonioscopy must show an open anterior chamber angle. In some cases, the central corneal thickness may be thinner than average. For diagnostic purposes, POAG can be subdivided into high-pressure (IOP > 21 mmHg) and normal-pressure (IOP < 21 mmHg) types. Once the diagnosis has been confirmed, the follow-up focuses on identifying any sign of progression could lead to reconsider the therapeutic strategy.
PACG Suspect	Normal IOP, no VF defect, nor glaucomatous optic neuropathy, but two or more quadrants of iridotrabecular contact found on gonioscopy.
PACG (also known as acute glaucoma)	PACG is defined by the presence of iridotrabecular contact, hence it is generally classified by the type of contact it presents, to wit, acute angle-closure, intermittent angle-closure, chronic angle-closure and status post-acute angle-closure attack. The follow-up service must rule out PACG. The follow-up service must rule out any type of PACG.

Strategy for diagnosis and follow-up

The detection and follow-up of patients with glaucoma are more complex processes compared to DR and AMD. Firstly, identifying symptoms of glaucoma is not obvious in its early stages, when treatment can be the most beneficial [40]. Secondly, once diagnosed, the clinical course of glaucoma is usually slow, and with the currently available treatments, symptoms of glaucoma progression are not easily identifiable.

No single test has demonstrated an adequate balance of sensitivity, specificity, and positive predictive value in this regard, that is why diagnosis and follow-up of glaucoma must combine the assessment of various diagnostic techniques simultaneously [33]. Correspondingly, the diagnosis and follow-up of glaucoma entails measurement of IOP, inspection using gonioscopy of anterior chamber angle,

examination of the optic disc at fundus photographs, determination of the status of the VF through campimetry, and monitorization of the loss of RNFL by means of confocal scanning laser ophthalmoscopy, OCT, or scanning laser polarimetry [86].

Therapeutic recommendation

Therapy in glaucoma management aims to lower IOP to slow the rate of visual field deterioration. In this regard, the upper limit of the IOP estimated to be compatible with a rate of progression sufficiently slow to maintain vision-related quality of life in the expected lifetime of a patient is established by the target IOP. Given that there is no single IOP level appropriate for every patient, this parameter should be re-evaluated regularly and, additionally, when progression of disease is identified or when ocular or systemic comorbidities develop.

Once target IOP is determined, most forms of open-angle glaucoma and many types of chronic angle-closure glaucoma are initially treated with topical and occasionally orally administrated agents that act either on the reduction of aqueous humour production or enhancement of the aqueous outflow or on both. In this regard, there are drugs presenting higher IOP reduction rates than others, so the choice of specific medication would depend on the pre-treatment baseline IOP plus the patient's tolerance to each drug. If the initial therapy reduces IOP to the target and is well tolerated, therapy can be left unchanged, but the patient needs to be monitored with regular checking of endpoints. Otherwise, switching to another monotherapy or applying combination therapy (add a second drug) would be considered. Alternatively, laser trabeculoplasty would be indicated when IOP is not satisfactorily controlled with medications. Laser treatment may also be suitable for patients with known intolerance or allergy to topical agents or suspected poor compliance [89].

Finally, incisional glaucoma surgery, and cyclodestructive procedures should be considered to slow down the progression of the disease whenever medical or laser treatment appear unlikely to maintain sight in the glaucomatous eye. Especially for eyes with a very high level of IOP at presentation causing an immediate threat to sight [87].

2.2 MANAGEMENT OF CLINICAL INFORMATION AND INTEROPERABILITY OF INFORMATION SYSTEMS ON E-HEALTH

As a result of the chronicity of the diseases described in the preceding section, patients affected need a continuous management of their condition. To that end, a significant part of patients' management includes the documentation of clinical information that could help in future medical decisions. Until quite recently, the use of medical records in paper limited the availability of patients' information within a geographic area, and consequently, the responsibility of managing almost the whole clinical procedure often would fall on a single clinician. With the advent of electronic management of medical records, clinicians gained ubiquitous and instant access to patients' clinical information, so many health providers were able to coordinate their work toward a specific care plan.

Although this approach did work at a small scale, each healthcare provider – hospitals, administrative entities such as government agencies or insurance companies, pharmaceutical services, or primary care physicians or medical specialists – had its own installed base of proprietary systems, technologies, and information systems which lacked interoperability with the systems used by other providers.

Therefore, the coordination of healthcare providers equipped with systems made by different manufacturers can be accomplished by means of e-health standards. Numerous standardization entities work to address this issue, but they are still far from reaching a common solution to achieve full interoperability among information systems in healthcare. Instead of that, each standard-setting institution provides its own solutions for interoperability, so there is a wide ecosystem of e-health standards available nowadays to electronically exchange clinical information among healthcare

service providers. In contrast, any of these standards provides comprehensive interoperability, indeed, in most cases they are not even interoperable with each other. This stems from the fact that e-health standardization must guarantee interoperability at different layers which currently are not covered by a unique standard. Thus, the success of interoperability on e-health will be determined by the understanding and an effective combination of pervasive standards.

2.2.1 LAYERS OF INTEROPERABILITY

As mentioned above, none of the information systems in use nowadays in healthcare implements full interoperability. Most of them are compliant on some level, but to achieve an understanding among heterogeneous systems, first, the concept itself has to be clarified. There are many views on how to define interoperability, for instance, Stroetmann defined interoperability in its most basic form [90]:

> "Interoperability refers to the ability to communicate and exchange data and information such that a common understanding of their meaning is possible."

We can even narrow down the definition considering interoperability applied into the field of ICTs. This concept is not new in computer science, in 1990 the IEEE defined interoperability in that context [91]:

> "The ability of telecommunications and digital systems - and the processes they support - to exchange data and to enable the sharing of information and knowledge."

Although the original idea was clear, during the last years the definitions for interoperability have continued to evolve along with development of ICTs and computing [90, 92]:

> "The ability of two or more systems or components to exchange information and to use the information that has been exchanged." **– Stroetmann**
>
> "Interoperability' means the ability of disparate and diverse organizations to interact towards mutually beneficial and agreed common goals, involving the sharing of information and knowledge between organizations, through the business process they support, by means of data between their respective ICT systems." **– European Parliament**

According to these definitions, this concept can be equally valid for information systems in healthcare. Many authors were more specific on that direction and described interoperability in healthcare as follows [21, 90, 93]:

> "E-Health area interoperability refers to facilitating and safeguarding the exchange, understanding and acting on patient and other health information and knowledge among linguistically and culturally disparate medical professionals, patients and other actors within and across health systems in a collaborative manner." **– Stroetmann**
>
> "An EHR system consolidates patients' healthcare data generated from various healthcare systems. Hence, it should be capable of integrating data from all such systems. Moreover, it should enable interoperability among various healthcare applications and systems that are developed independently." **– Sinha et al.**
>
> "In healthcare, interoperability is the ability of different information technology systems and software applications to communicate, exchange data, and use the information that has been exchanged." **– Healthcare Information and Management Systems Society**

In short, the level of interoperability implemented would be inversely proportional to the effort it takes to use and invoke services among different systems. Thus, to achieve an efficient understanding

among healthcare-related information systems, it is necessary to establish common specifications that would serve as conformance points to address the exchange of information.

In this regard, the ETSI distinguishes four layers to structure interoperability for a faithful data exchange among information systems: technical interoperability (which supports the physical connection among systems), syntactic interoperability (which allows those systems to exchange information), semantic interoperability (which provides to those systems the ability to interpret the information received, and act accordingly), and process/organizational interoperability (which defines the necessary context for organizations to cooperate) [18].

Besides the aforementioned layers, given the trend of e-health toward an ecosystem, in which information from clinical information systems would be accessed from increasingly variety of electronic terminals, some authors propose standardising the way the information is presented to end-users [29, 94, 95]. Along this Thesis, this new layer of interoperability among systems has been named "presentation interoperability".

The aforementioned layers of interoperability have been briefly described in Table 4, which actually has been adapted from the layers of interoperability proposed by Kubicek et al. toward "Organizational interoperability in e-government" [92]:

Table 4: *Description of the five layers of interoperability.*

Layer of interoperability	Aim	Objects	Solutions	State of knowledge
Technical interoperability	Technically secure data transfer	Signals	Protocols of data transfer	Fully developed
Syntactic interoperability	Processing received data	Data	Standardized data exchange formats	Fully developed, still must evolve in healthcare domain
Semantic interoperability	Processing and interpretation of received data	Information	Terminologies, reference models, archetypes, Detailed Clinical Models (DCM), ontologies	Theoretically developed, but practical implementation problems
Organizational interoperability	Automatic linkage of processes among different systems	Processes (workflow)	Architectural models, standardized process elements	Still lack of conceptual clarity, vague concepts with large scope of interpretation
Presentation interoperability	Normalize representation of information	UI views	UI markup languages, UI forms	Theoretical approach

Technical or functional interoperability

Technical interoperability defines the interfaces, either logical or physical toward harmonization of data exchange among systems. Therefore, the technical issues toward linking up information systems, the definition of open interfaces, data formats and protocols, including the physical devices necessary to guarantee the communication are formalized at this level. Basically, technical interoperability is responsible of a faithful delivery of bytes from one system to another.

The current state of development of technical interoperability is very advanced compared to the rest of the layers, given that this has been extensively implemented in systems other than healthcare. This enables establishing advanced pervasive standards which cover all possible scenarios concerning data exchange among systems, e.g. IEEE 802.3, IEEE 802.11, Transmission Control Protocol/Internet Protocol (TCP/IP), Hyper-Text Transfer Protocol (HTTP), Bluetooth, ZigBee, lower levels of ISO/IEEE 11073, etc. [19].

Syntactic interoperability

Whereas technical interoperability must guarantee the exchange of bytes, the syntactic interoperability is responsible for the delivery of documents. It ensures that documents or messages exchanged are correctly structured at arrival, so the file formats used and the data types they contain are built in compliance with well-defined syntax and encoding specifications. For example, a system could be able to make transformations from one file or data format to another depending on the requirements of the receiving system, while the coherence and the information contained inside files is preserved unaltered. However, systems that uniquely implement this level of interoperability would provide messaging services but do not intervene in the content of the files exchanged, and therefore they are unable to react accordingly. There would be a need for an additional level of interoperability, to enable the interpretation of the information handled by computerized systems.

This level of interoperability has been developed to a considerable degree too, but still must evolve as regards the area of healthcare. At this point, the most widely used specifications which provide for the syntactic interoperability in healthcare environments could include: XML, specifications for data types such as CEN TS 14796 or ISO 21090, DICOM message specifications, 2.x versions of HL7, ISO/IEEE 11073, or even GS1 (for automatic identification and data capture). Reference information models from HL7 v3, HL7 FHIR or EN/ISO 13606 standards could also be considered, but these would implement semantic interoperability as well [19].

Semantic interoperability

Whereas syntactic interoperability specifies clearly defined classes of data for the information delivered, the semantic interoperability concerns the meaning of the information exchanged. Thus, systems semantically interoperable must ensure a univocal understanding of data in both sides of the communication. In fact, according to IEEE, semantic interoperability responds to the following description [91]:

> "Is the ability of two or more systems or elements to exchange information and to use the information that has been exchanged."

This means that, whenever there is data exchange, the receiving system must be able to interpret the information delivered in such a way that that system could react accordingly without external intervention of an operator. Thus, considering the current healthcare scenario where clinical processes should be centred on patients, and yet clinical information is scattered among heterogeneous information systems each covering specific clinical practices, semantic interoperability will contribute to organize the amalgam of data generated toward a comprehensive management of healthcare. Furthermore, semantic interoperability would facilitate building secondary services upon that information, such as ubiquitous access of healthcare providers to the whole of clinical data corresponding to specific patient-centred clinical procedures, or data mining services either for research or epidemiologic purposes.

Terminologies, ontologies, and classification systems stand central to achieve semantic interoperability. However, these terms can lead to confusion, as different authors used these terms differently in scientific literature. For this reason, in this Thesis the glossary of terms proposed by SemanticHEALTH European project was taken as a basis so as to clarify this point [96]:

- **Controlled Vocabulary:** A list of specified items to be used for some purpose, usually in an information system to reduce ambiguity, misspellings, etc.
- **System of identifiers ("codes"):** Controlled vocabularies, and many lexicons, ontologies, and thesauri, are usually accompanied by systems of identifiers for their units, e.g., identifiers act as the primary unambiguous means of referring to the entities in the system for computational purposes with the text form being used for communication with users. Examples are the "Concept Unique Identifiers from the Unified Medical Language System (UMLS), SNOMED-CT identifiers, etc.
- **Lexicon:** A list of linguistic units that may be attached to a controlled vocabulary or ontology, in a specific language or sublanguage, often including linguistic information such as synonyms, preferred terms, parts of speech, inflections and other grammatical material. Example: terms and lexical material in UMLS identified by Lexical Unique Identifiers.
- **Ontology:** A symbolic logical model of some part of the meanings of the notions used in a field, i.e. those things which are universally true or true by definition. The key relationship in an ontology is "subsumption" or "kind-of". Every instance of a subkind must be an instance of the kind, without exception. Typically ontologies are implemented in logic languages such as Ontylog or OWL or frame systems such as Protégé-Frames. Examples: The GALEN Core Model, the stated form of SNOMED-CT.
- **Classification:** An organisation of entities into classes for a specific purpose such as international reporting or remuneration. Examples ICD and Diagnosis Related Groups.
- **Thesaurus:** A system of terms organised for navigation with the primary relationship being "broader than"/"narrower than". Examples MeSH, WordNet.
- **Background knowledge base (or "Knowledge Representation System"):** The common knowledge to be assumed by the system, including both the ontology – what is universally true – and generalisations about what is typically true.
- **Terminology:** Any or all of the above in various combinations. Most heath terminologies consist, at a minimum, of a controlled vocabulary and a system of identifiers. They may include extended lexicons, ontologies, thesauri or background knowledge base. This definition is deliberately broader and less specific than that in most of the standard references and intended to approximate common usage.
- **Coding system:** A terminology with attached identifiers or "codes".

Nonetheless, contrary to widespread belief in this regard, semantic interoperability cannot be achieved only through the use of normalized terminologies. In fact, terminologies do not contain definitions of domain content (e.g. "microbiology result"), but rather facts about the real world (e.g. kinds of microbes and the effects of infection in humans). Thus, to faithfully represent semantics of clinical domain, terminology services – such as SNOMED-CT [97], ICD-x [98], or LOINC [99] which codify the clinical information using normalized clinical terms – must be combined with additional information intended to contextualize these terms into specific healthcare scenarios. Normalized reference models can be used to that end (EN/ISO 13606:1, HL7 RIM or CDA, etc.), whereas mechanisms such as archetypes (EN/ISO 13606:2) or DCM would be used to formalize and to exchange the resultant clinical concepts [19].

Process level or organizational interoperability

Organizational interoperability refers to when two or more healthcare providers must coordinate their clinical procedures and work processes to achieve a seamless collaboration among institutions. To that end, the healthcare services and care policies provided by each party must be well-known by the

rest of organizations concerned. In this regard, business rules are usually the means of maintaining all systems up-to-date on the workflow they have in common [100].

Although there is still much work to be done in that respect, there are already some attempts to normalize this area: the EN/ISO 12967 HISA (Health informatics – Service architecture) and EN/ISO 13940 (Health informatics – System of concepts to support continuity of care) standards, for instance [101, 102]. In this context, some key concepts have been listed below, as provided by the EN/ISO 13940 standard. These, in fact, correspond to the conformance points on which different systems should reach an agreement for guaranteeing their interoperability at organizational level [101, 103]:

- **Care plan:** Dynamic, personalized plan including identified needed *healthcare activities*, *health objectives* and *healthcare goals*, relating to one or more specified health issues in a *healthcare process*.
- **Health objective:** Desired ultimate achievement of a *healthcare process* addressing health needs.
- **Healthcare goal:** Desired achievement of one or more healthcare activities, considered as an intermediate operational step to reach a specific *health objective*.
- **Clinical guideline:** Set of systematically developed statements to assist the decisions made by healthcare actors about *healthcare activities* to be performed with regard to specified health issues.
- **Protocol:** Customized *clinical guidelines* in conformance with the *health policies* of an organization or person participating in healthcare.
- **Clinical pathway:** Pathway for the *healthcare activities* informing the content of core *care plans*.
- **Workflow:** Depiction of the actual sequence of the operations or actions taken in a *process*.
- **Healthcare process:** Set of interrelated or interacting *healthcare activities* which transform inputs into outputs.

These concepts were found to have many similarities; even they overlap to some degree. In this regard, Figure 4 illustrates the overall relationship between the concepts in order to clarify the scope of each of them [103].

Presentation level interoperability

Traditionally, the UI is integrated in the source code of applications, so it has to be customized for each application according to the requirements of end-users. Thus, whenever the content of the application is modified, the UI specifications have to be re-engineered accordingly.

There is an emerging trend toward connecting health information systems to countless electronic terminals, from which the clinical personnel must have access to the same clinical information. Thus, the need arises for presenting the information in a consistent manner irrespective of the different technologies and APIs implemented. In this regard, the latest proposals on standardization suggest to go one step further and normalize how the information is presented to end-users [95].

On the basis of an information model strongly standardized in compliance with technical, syntactic, semantic and even process levels of interoperability, the normalization at presentation level is essentially about mapping the information elements into the UI definitions of the target technology. Taking this into account, it would be possible to model the UI specifications outside the source code of the software. Thus, each clinician could even customize the views depending on its working procedures, in a way that this change would take place accordingly to every electronic terminal accessible by that individual.

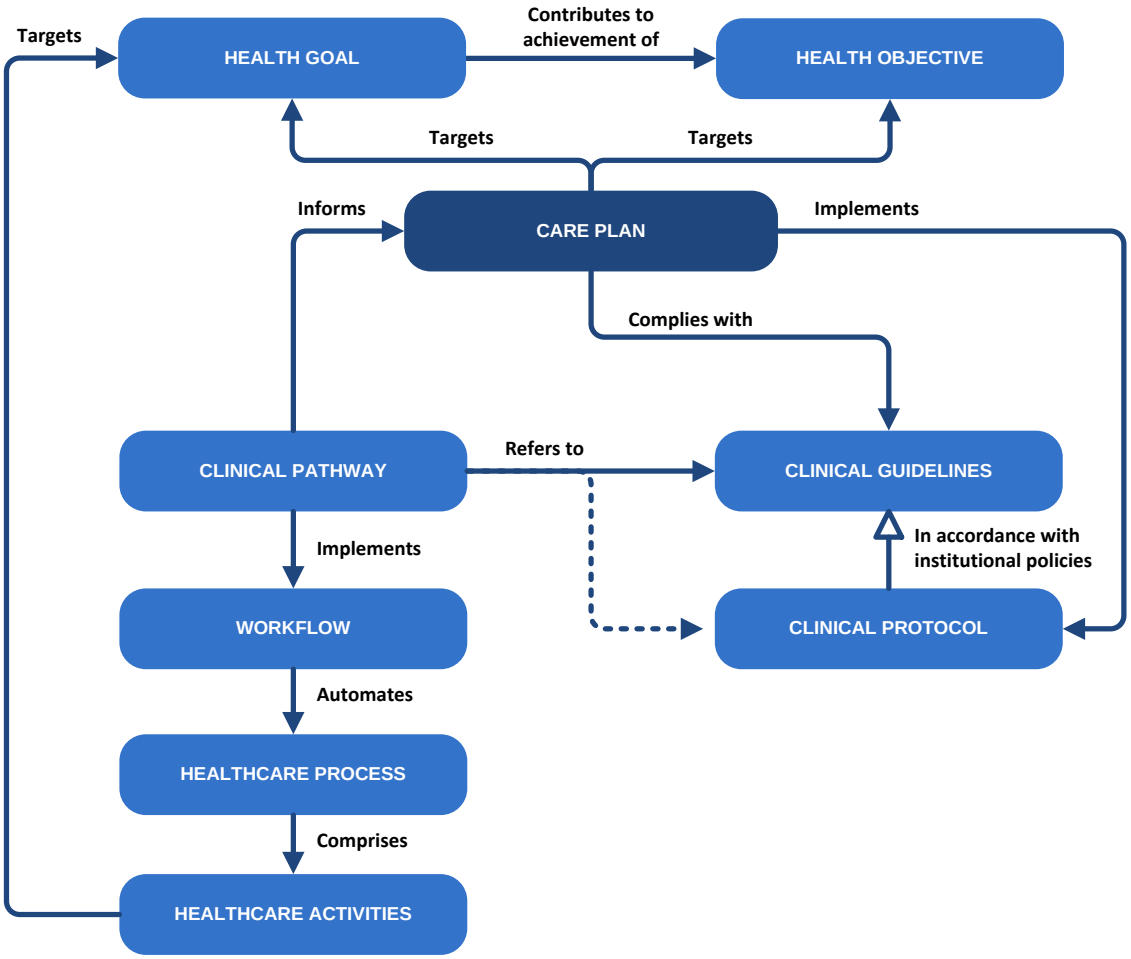

Figure 4: *Relationship between the key concepts studied to guarantee the organizational interoperability conforming to the ISO 13940 standard.*

2.2.2 ELECTRONIC HEALTH RECORDS

When implementing a standalone e-health system, the different levels of interoperability described along previous section must be considered for every component involved in the exchange of health information. But, with regard to patient-centred healthcare guaranteeing the continuity of care, e.g., for management of chronic conditions, EHR systems are definitely the cornerstone in the management of medical records of individuals.

At present, the ISO/TR 20514:2005 standard defines an EHR as [104]:

> "A repository of information regarding the health of a subject of care in computer processable form, stored and transmitted securely, and accessible by multiple authorized users. It has a commonly agreed logical information model which is independent of EHR systems."

The ISO also states that an EHR should record the complete healthcare information longitudinal to patient's life-long medical history, irrespective of the organisations or different kinds of specialists involved. Thus, insofar healthcare is increasingly producing and consuming large amounts of information from heterogeneous origins, EHR systems must be able to include all these contributions to patient's history. Which is why most e-health standards converge into this point, and thus a comprehensive strategy is needed to interconnect all sources of clinical information with the EHR systems.

In this regard, given the architecture of any modern e-health system on which the EHR is the centrepiece, we must contemplate the implementation of the standards necessary to support the services needing a safe, secure, reliable exchange of information with the rest of system components concerned, such as [14]:

- Demographic information system: Manages the Patient Master Index (PMI), and overall demographic data records of the hospital, both for patients and for clinical personnel. Data exchanged with the EHR: univocal identifier for patients in different clinical settings.
- Hospital information system: Manages administrative data of hospitals, including patient's affiliation, agenda, human resources, and patient admission. Data exchanged with the EHR: administrative data such as patient registration and identification, clinic appointments, admissions, discharges and transfers (ADT). May also provide commissioning, billing and accountancy data.
- Laboratory information management system: Manages the investigation requests for laboratory tests and generates the corresponding reports. Data exchanged with the EHR: requests for laboratory tests, and the resulting investigation reports.
- Medical image management system: Schedules medical imaging tests, and refers the corresponding radiology reports back. Data exchanged with the EHR: requests for imaging investigations, and the resulting diagnostic reports.
- Pharmacy administration system: Manages drug prescriptions, supervises the dispensation of medications, and monitors the stock in pharmacy at all times. Data exchanged with the EHR: prescriptions for medication.
- Remote Patient Monitoring (RPM) system: Manages the information submitted by personal health devices located outside the healthcare facility, and analyses such data to generate medical reports from remote monitoring and trend analysis of patient's physiological parameters. Data exchanged with the EHR: monitoring reports, and clinically significant events.
- Other EHR systems: Manages medical records associated to a clinical activity addressed in a different healthcare facility. Services associated with the EHR: Transfer and merging of EMRs between hospitals.

To achieve a faithful communication with all these e-health components, currently there are several international organizations working on standards relating to EHRs:

- The Technical Committee (TC) 215 of the International Standards Organization: It is the peak international standards body for EHR and other e-health standards. Although some standards such as ISO 18308 are produced "de novo", it commonly works on integrate existing standards from other national and international standards development organizations so as to pool pervasive standards on e-health, e.g. IEEE, CEN, HL7, etc. For this reason, for research purposes the source standardization organizations confer greater agility to standards, whereas ISO provides greater stability necessary for implementations in healthcare industry [105].
- The TC 251 of the CEN: It corresponds to the health informatics committee of CEN, which is the peak European standards organization that transcends the national standards organizations of the 33 member countries it comprises. TC 251 developed the EN/ISO 13606 standard (currently accepted by ISO) for the communication of the EHR, as well as EN/ISO 12967 HISA (Health informatics – Service architecture), that was subsequently adopted in 2009 by the International Standards Organization within the ISO 12967 norm [106].
- Health Level 7 (HL7): Although HL7 standardization focuses primarily on U.S., it nowadays comprises over 20 international affiliates. It defined standards for communicating data between different systems through messaging (HL7v2.x and HL7 v3 messages) and also a

model that defines the structure and semantics of medical documents (HL7 CDA, FHIR) [107].

- Other entities working on EHR standardization: With the archetype specification in common with EN/ISO 13606 standard, the "openEHR foundation" published the specifications of a complete EHR architecture designed to support distributed, patient-centred, life-long, and shared care health records [108]. "Clinical Data Interchange Standards Consortium" is an open organization that develops data standards that enable information system interoperability to improve medical research and related areas of healthcare [109]. "Continua health Alliance" is dedicated to establishing a system of interoperable personal connected health solutions with more than 230 member companies around the world [110].

Messaging standards

Until recently, the main efforts toward interoperability in healthcare were focused on messaging standards developed for normalized information exchange between EHR and non-EHR systems (e.g. laboratory, imaging, and pharmacy systems), and between EHR systems which did not share the same information model, e.g. HL7 (HL7v2.x and HL7 v3 messages), DICOM (approved as the ISO 12052 standard), UN/Edifact (approved as the ISO 9735 standard), or even ISO/IEEE 11073 (medical/health device communication standards).

However, these messaging standards are limited to well-known healthcare scenarios for both parties of communication, since the same message transmitted in different healthcare contexts may acquire different meaning. In this regard, normalized profiles are routinely used to specify unambiguously how a specific application or project conforms to the messaging standard. Furthermore, in the case of EHR extracts, it would be much more efficient to exchange those directly using lower level interoperability protocols (Simple Object Access Protocol (SOAP), Remote Procedure Call (RPC), etc.), although this is only possible with EHR systems compliant to the same information model and independent of the EHR systems architecture.

Consequently, to move forward on interoperability in e-health, specific standards were developed for defining the information models and architecture of EHRs. The standard setting organizations stated above proposed different approaches to normalize the clinical information handled by EHRs at the semantic level, which in turn would facilitate the development of high-level services able to achieve a seamless coordination and cooperation between EHR systems (process level interoperability).

EHR architectures

The international standards development organization ISO/TC 215 defined the "Requirements for an EHR Architecture", which have been reflected in the ISO 18308 standard [111]. This standard establishes the following requirements to exchange safely the information accommodated within the EHR [17]:

- Content structure model: The requirements for the content structure model that an EHR system should conform to are established by the standard.
- Inclusion of clinical and record processes: An EHR will implement services supporting either clinical or record processes. While clinical processes include orders, care plans, clinical guidelines, decision support, and so on, record processes include processes for capturing, editing, updating, querying, and presentation of data.
- Content exchange: It should be possible to exchange partial or complete records between healthcare systems having different medical record structures, while maintaining integrity and context of EHR data.
- Privacy and security: An EHR should support authentication, data integrity, confidentiality, nonrepudiation, and audit trail for the accessed information.

- Legal considerations: It is mandatory to record every action (read, write, insert, update, verify, transmit) performed by an actor to the EHR to enable auditing and recreation of the EHR at any specific point in the past.
- Ethical, consumer/ cultural aspects: The actors must access and share only the specific parts of the EHR records it corresponds, depending on different levels of permissions.
- Future-proof framework: An EHR should be able to represent new types of data, incorporate new record types, and generally be extensible in nature.

Aligned with these principles, the following standards for interoperable EHR can be found in literature:

- EN/ISO 13606: It is a five-part standard for EHR communication. The first part provides a reference model that defines generic data structures and their relationships to represent any kind of information which may be registered as part or totality of an individual's EHR. The second part proposes an archetype specification, which consists of a generic information model to define re-usable models of a domain concept built from the reference model. The third part specifies reference archetypes and term lists; the former represent how other standards can be expressed with this norm, and the latter the local terminology used by the reference model of the standard. In the fourth part the security framework specifies the security and access policies for the EHR. And finally, the fifth part defines the minimal messaging specification and service interfaces to enable the communication between EHR systems [112].
- OpenEHR: It is an open standard specification of a technology-independent and patient-centred EHR architecture consisting of a reference model, an archetype model and a service model. It conforms to EN/ISO 13606, given that its reference model is closely related to ISO 13606-1, and the openEHR archetype model was adopted "as is" within ISO 13606-2. In contrast to EN/ISO 13606, openEHR standard is more focused on providing an EHR architecture rather than on ensure the data exchange between systems [108].
- HL7 CDA: It was the first HL7 standard relating to EHRs. CDA is a schema standard that specifies the structure and semantics of the clinical documents to be exchanged between EHR systems. For this purpose, CDA represents medical records as XML documents based on the normalized information model of HL7v3 RIM. Even if HL7 CDA is not a full EHR specification, it covers the issue of defining clinical documents for the purpose of exchange and is compatible with the equivalent components in openEHR and EN/ISO 13606 [17].
- HL7 EHR-S Functional Model (approved as ISO/HL7 10781): The HL7 EHR-S DSTU project is HL7's first conscious move into EHR standards development. It describes the various functional profiles categorized as Direct Care, Supportive Functions, and Information Infrastructure that individually enlist the various functions involved in patient care management, Clinical Decision Support (CDS), administration and financial management, security, record management, registry, and standard terminology and related services.

In brief, to achieve semantic interoperability between EHR systems, each of the standards described above specifies its own reference model for EHR communication. Then, concepts from clinical domain are defined using different clinical models. Examples of such models are openEHR or EN/ISO 13606 archetypes [113], CDA templates [17], and DCM [16]. And clinical vocabularies, e.g. terminologies, ontologies and classification systems, are used to provide precise description about the elements used to define the clinical domain. Provided that reference models have been normalized, even though differently, harmonization and therefore the exchange of information is possible even between different standards. To that end, clinical models must be shared among all parties beforehand, so as to achieve semantic interoperability among the EHR systems involved in the communication. Finally, the use of clinical vocabularies should foster computerization of medical guidelines, as they contribute to connect the abstract clinical models with objects in the real world.

At this point, considering the complexity and the continuous evolution of the health domain, the flexibility that provides the archetype model of openEHR or EN/ISO 13606 on modelling the domain knowledge is very interesting compared to the pre-established clinical models presented by other standards. This architecture approach for EHRs is known as dual-model layered architecture since it differentiates a reference information model representing technical properties settled for interoperable EHRs on the one hand, and the formal clinical modelling represented by archetypes on the other. Although it is preferable that the archetype model should be defined under the aegis of the health professional colleges in conjunction with standards development organizations (ISO, CEN, or HL7), this approach enables clinicians or other domain experts to adapt the EHRs to their domain-specific needs, while IT specialists work upon the reference model to ensure interoperability and propose new services for EHR systems.

Consequently, using EHR systems compliant to dual-model layered architecture would facilitate organizing the heterogeneous information managed in specific healthcare scenarios, irrespective of the diversity of components connected in the e-health system. Likewise, this architecture gives rise to the empowerment of EHR users on the clinical information they use.

2.3 DESIGN AND IMPLEMENTATION OF ELECTRONIC MODELS AND THE INTEGRATION THEREOF INTO HEALTH INFORMATION SYSTEMS

Due to the recent advent of health information systems based on dual-model layered architectures, the content model of these systems is still limited compared to previously established e-health implementations. Therefore, in order to extend the two-level modelling approach into a broad range of healthcare scenarios, experts of the clinical domain should actively engage in modelling their own clinical processes. And, to facilitate this process, a clear strategy is needed to produce high-quality electronic models.

In this regard, modelling new healthcare procedures is not the major concern; the clinical knowledge is usually already available in many information sources, either explicit or implicit, having been built thanks to previous efforts in medical guidelines, clinical practice, healthcare technical standards, and the experiences of other domain experts. The real issue is how to gather, order, and incorporate methodologically that knowledge into electronic models.

Different strategies can be found in literature to address the modelling of clinical processes. A good starting point could be the analysis of Rosenbrand et al. about the procedure for development of evidence-based clinical practice guidelines [114]. This work presents an overview of the history of clinical guidelines development. These guidelines aim at analyzing and organizing the clinical practice according to validated scientific methodologies. However, this proposal does not explain how to transcribe these theoretical guidelines into the electronic models.

In that respect, considering the amalgam of information systems and e-health standards available, the report about semantic interoperability published by the Institute of Health Carlos III [19] introduces us on design practices when modelling specific components of electronic models. Likewise, publications focused on describing methodologies for development and maintenance of archetypes can be found in the literature [115-118]. In practice, examples applying such types of archetype modelling methodologies can also be identified for specific healthcare scenarios [119-121]. Some publications have gone one step further and have considered the use of standard terminology services to support the semantic interoperability among heterogeneous information systems [122-124].

Based on a semantically enabled definition of clinical information, other studies propose using the information registered during clinical encounters to provide computerized decision support to clinicians [125-128]. To that end, the rules that trigger a specific action or another depending on pre-established medical guidelines must be modelled. However, the conditions governing these guideline rules depend strongly on the context information registered in the information system. Therefore, these

guideline definitions were solutions designed to satisfy the specific requirements of particular implementations. Alternatively, Chen et al. presented the Guideline Definition Language (GDL) that leverages the archetype model of information systems compliant to the two-level modelling approach to normalize the clinical content included within the guideline rules [129].

The aforementioned guideline rules were originally devised to trigger CDS services depending on specific events observed during clinical practice. But, theoretically, these guidelines rules could also be used to manage the workflow of clinical processes. Nonetheless, the workflow modelling strategies found in the literature do not contemplate using a formal workflow to coordinate model-driven EHR systems [130, 131].

Aligned with the presentation layer of interoperability, a recent inclusion into the design of electronic models is the definition of UI specifications as part of the clinical process. A related article was that in which Palau et al. presented the UI forms as a solution to normalize the presentation of healthcare information into heterogeneous visualization front-ends [95]. However, there is no consensus on how these UI forms should be defined. In fact, although some health information systems implement this approach in practice (see EhrScape form definitions on the API explorer) [132], current modelling methodologies still do not contemplate UI specifications as part of the modelling guidelines.

All said, no previous work has created a comprehensive methodology taking into account the different layers of interoperability identified in e-health (technical, syntactic, semantic, process/organizational, and presentation). Thus, it is required to define a methodology based on the knowledge from the state-of-the-art modelling experiences to cover all the necessary steps to build electronic models from the clinical concept to the presentation layer. This approach would guide experts on clinical domain to build their own clinical processes into model-driven information systems.

In Subsection 3.1., a novel methodology for defining clinical concepts, archetypes, termsets, templates, guideline definition rules, and UI forms within its steps is presented.

2.4 OPEN HEALTH COMPUTING ARCHITECTURES

Traditionally, the development of EHR systems responded to the need for gathering the clinical information generated by the increasing electronic diagnostic devices in specific clinical areas. Many of these systems were built on proprietary technology, so ended up being information silos which use was confined to the department of origin [29]. Therefore, when e-health standards provided solutions to interconnect heterogeneous information systems, not-standardized legacy systems had to be adapted, in order to connect them all by means of a common Clinical Data Repository (CDR). However, many features provided by these systems could not be integrated into the main information systems, since the development of proprietary systems focused on meeting the requirements of specific clinical scenarios.

Today, there are many initiatives of governments worldwide to integrate the management of clinical data beyond health institutions [17]. But, given the predominant strategy of centralizing the clinical information into monolithic information systems, the enormous base of hierarchically connected proprietary technologies must synchronize the clinical data regularly. Thus, the comprehensive management of clinical information would increase in complexity as it integrates more and more healthcare organisations and systems.

To face this issue, open health computing architectures propose building health computing platforms presenting a modular design. Each module would comply with a set of specifications agreed by manufacturers to connect compatible components. Thus, despite the modules that comprise a health computing platform would be commercial solutions supplied by different manufacturers, the customer would retain at any time the control and ownership of the data managed within the platform. In other words, an architecture based on open standards should prevent technical incompatibilities among

purchased components, due for instance to proprietary implementations, which could lead to lock-in or unexpected costs in the future. In fact, a proposal in this regard would contribute to face the main challenges nowadays in managing clinical information in e-health [29].

Moreover, this platform-based e-health ecosystem would unleash the decentralization of healthcare into care networks, hence it will provide access to normalized clinical data, regardless the information system where it was originally registered. As a result, each health department could implement dedicated health information systems compliant to the requirements of specific clinical specialties, and yet maintain interoperability with information systems nationwide, even internationally. In this way, a health service implementing the open health computing platform approach could incorporate progressively clinical models, terminologies, and service infrastructure tailored to the unique needs of the service at any given time. Thus, an e-health ecosystem comprised by domain specific information systems, e.g. OpenEyes which provides a rich set of tools focused solely on eye care, would be feasible [133].

In that respect, the advent of dual-model layered architecture has led to the development of semantically enabled, open health computing platforms in e-health. On the premise that the information inside the EHR has been semantically enabled, a fully-fledged service infrastructure could be built upon normalized data, giving rise to endless possibilities in the management of clinical information.

In [134], Frade et al. identify different dual-model-based system implementations (particularly EN/ISO 13606- or openEHR-based approaches). This paper includes both proposals from R&D institutions and companies around the world. For example, Pazos proposes an architecture to build a standard-based open source EHR platform compliant to openEHR specifications [94]. Furthermore, Maldonado et al. focus on an EHR architecture for integrating the dual-model approach into non-standardized EHRs in compliance with EN/ISO 13606 (this proposal includes editing domain concepts, mapping EHR data to electronic models, and automatically transform source data into archetype instances) [135]. Marco-Ruiz et al. used the same approach to normalize into standardized data repositories the proprietary data from a Laboratory Information Management System (LIMS) in Norway. Implementations like this would foster integration of proprietary EHR systems into open health computing platforms [136]. Mandl et al., in turn, puts into practice the health computing platform concept, by proposing the SMART platform (Substitutable Medical Applications, Reusable Technologies). This platform presents a modular architecture, upon which different applications or apps are attached. In this regard, different manufacturers would have a common API at their disposal for implementing healthcare applications compatible with the platform. As the platform functionally separates the core system from the third party apps, the customers or final users would customize their workspace depending on the apps chosen [137].

Nonetheless, the architectures surveyed are focused on specific EHR implementations. Given the heterogeneity of the information systems that must interoperate in a conventional health service, there is a need of guidelines on the basics of building health computing platforms based on open standards. Such recommendations would facilitate the manufacturers to develop new e-health proposals along this line. In this context, this Thesis will identify the different information systems involved on the management of patient-centred clinical processes, to propose an architecture that would connect them all into an open health computing platform approach. This topic is approached in Subsection 3.2.

2.5 MANAGEMENT OF CLINICAL INFORMATION IN THE SNS-O

Currently, the SNS-O covers 3 health areas divided into 56 basic health zones: 41 health zones on the health area of Pamplona, 8 health zones on the health area of Estella, and 7 health zones on the health area of Tudela. These health areas are covered by a hospital complex (grouping together 3 public hospitals from the health area of Pamplona), 2 additional public hospitals, 58 primary care centres and 232 local practices [138].

To connect all these health facilities, the Government of Navarre deployed a corporate network that provides service to the aforementioned points of care (except for 22 local practices located in geographic areas of difficult access). An overview of the information systems for the management of clinical information within the SNS-O network can be seen in Figure 5.

2.5.1 IDENTIFICATION OF PATIENTS

To manage patient admission on all these facilities, the SNS-O issues a health card that enables a unique identification of patients. In this way, it is possible to access to the clinical and administrative information of a specific patient, although spread throughout the corporate network of the Government of Navarre. In the SNS-O there are three stand-alone patient databases using their own identification codes to conduct admission depending on where the patient was registered: first, patient admission services in hospitals assign a unique identifier for the EHR system of specialized care. Second, the primary care centres provide another unique identifier corresponding to the basic health zone where the patient want to be attended. Third, the health card office registers patients through administrative channels, and generates the Personal Identification Code of Navarre (Código de Identificación Personal de Navarra [CIPNA]) for all patients using any service from the SNS-O. The latter code prevails over the others, so the patient databases are synchronized accordingly to maintain coherence of the information about patients' admission in the SNS-O [139].

During 2007, the SNS-O collaborated with the National Health Service (NHS) to synchronize their personal health card databases. Consequently, today, information about admissions and discharges of patients resident in Navarra are automatically updated in both databases. Thus, patients attended in other health services can be uniquely identified along the country using the CIPNA or the personal identification code provided by the NHS (CIP-SNS) indistinctly [140].

2.5.2 ELECTRONIC HEALTH RECORD

To manage the clinical information generated along the health service, the SNS-O combines the use of two interoperable EHR solutions. At this point, the unique identification of patients facilitated the coordination of these EHR systems when it comes to assemble all clinical information pertaining to each patient.

On the one hand, there is an EHR system accessible from every primary care centre in Navarre. In this regard, the commercial solution OMI-AP was adapted to manage the clinical practice specific to primary care, taking the name of “Atenea” [139].

On the other hand, there is another EHR system devised to manage the medical records submitted on specialized care. This one was an own development of the Government of Navarre, based on the original design of an EHR originally created for the hospital "Reina Sofia" in the city of Tudela, so it was adapted and extended to the rest of Navarre. This EHR should cover the needs of every clinical specialty on specialized care on the same platform.

As an exception, in 2007 an EMR system was launched to record solely the nursing care practices that take place on specialized care. This software was named “Irati”, and it was designed by nurses from the SNS-O in collaboration with teachers in nursing from the UPNA, and implemented by experts in development of EHR systems from the Government of Navarre and the SNS-O [140].

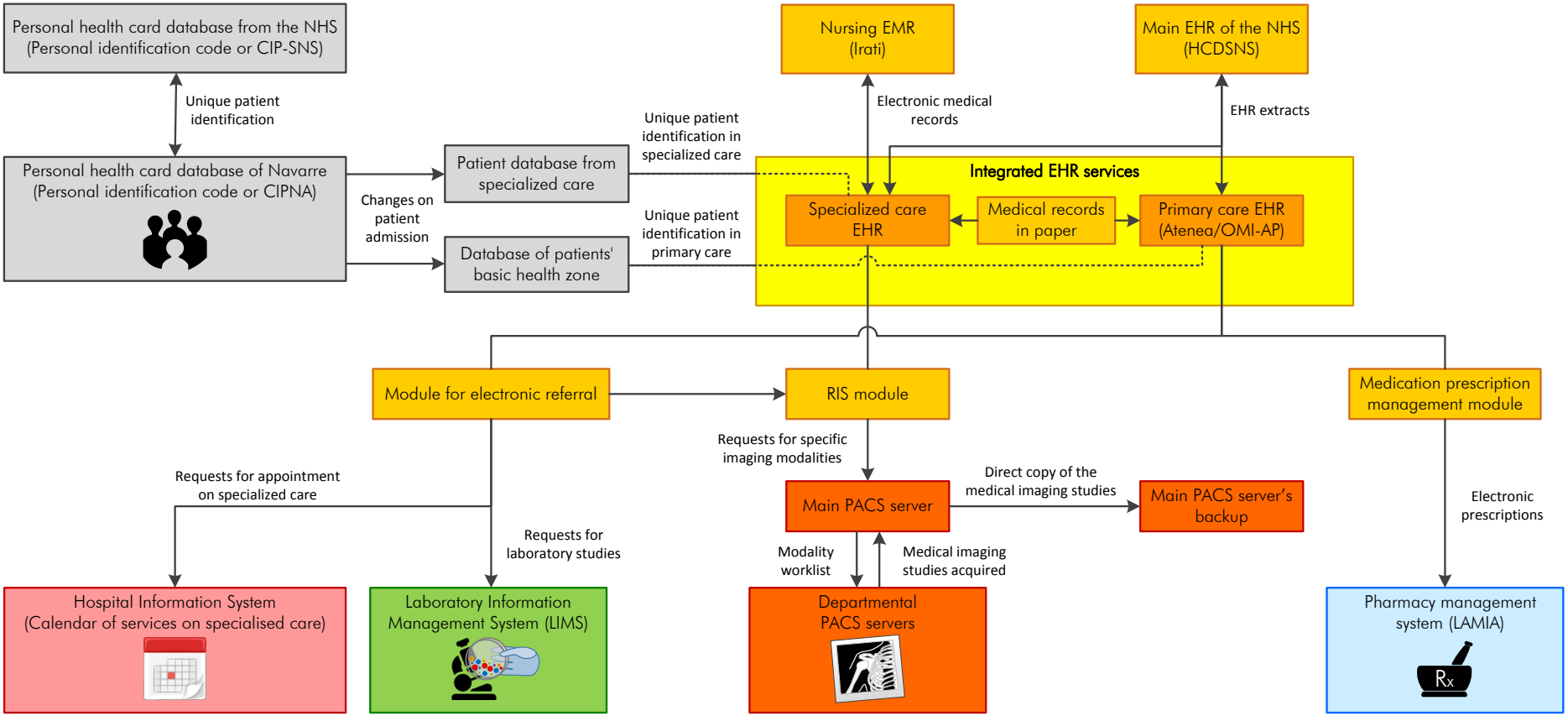

Figure 5: *Setting of information systems in the SNS-O for the management of clinical information.*

Exceptionally, medical records in paper are also used: on the one hand, the diagnostic devices not yet integrated on the EHR system continue producing clinical information in paper form. But generally, medical records are still used in paper when it comes to review studies previous to the comprehensive implementation of the EHR. Anyway, this is no longer an issue, since they have been scanned and uploaded to the EHR. Therefore, currently these medical records can be accessed indistinctly on paper or electronically [139].

The NHS developed an EHR (HCDSNS) that would access to the summarized patient's clinical record from EHR systems implemented on regional health services. The EHR systems from the SNS-O were successfully connected to that server, so they would exchange EHR extracts defined by the NHS as relevant data sets. This makes it possible reviewing medical reports registered outside Navarre, along with those originally belonging to the SNS-O [141].

However, although predefined EHR extracts can be exchanged nationwide, inside the SNS-O the installed base of EHR systems does not support the data richness actually required by clinicians. Thus, specialists have to deploy parallel databases, for example for research purposes. To face this issue, it would be necessary to implement software tools compatible with the existing EHR systems, each covering the requirements of specific clinical specialties. Nonetheless, to that end, as in the case of the EMR "Irati", it would be necessary to redesign the knowledge base and the service catalogue.

For the same reason, at present, the software tools for analyzing the clinical information registered in EHRs are limited by the lack of standardization of their knowledge model. In this regard, a complementary EHR solution implementing dual-model layered architecture would provide flexibility to attach new features upon the existing base of medical records. Indeed, this would enable deploying an ecosystem of tailor-made applications for each clinical specialty, while maintaining interoperability with the original EHR servers of the SNS-O.

Besides registering clinical information, the EHR systems of SNS-O provide modules to interoperate with other information systems available on the health service, such as digital medical imaging, electronic referral, or medication prescriptions (Figure 5).

Digital medical imaging

The EHR servers incorporate a Radiology Information System (RIS) module which manages the requests for specific diagnostic imaging modalities, and refers them as a work list addressed to the main PACS server available in the SNS-O.

The main PACS is in turn connected to departmental PACS servers, so the orders are redirected through them toward the appropriate imaging modality. As a result, the work lists are loaded into each diagnostic imaging device, where the responsible clinician undertakes the imaging studies as requested. Then, once the imaging studies have been completed, they are sent back to the corresponding departmental PACS.

At this point, the studies stored in departmental PACS servers are copied immediately into the main PACS, which in turn comprises a backup server located in a different data processing centre. Therefore, the SNS-O relies on two layers of backup. Taking advantage of this architecture, to improve performance of the searches, clinicians access first to the PACS server of the department where they are located, and, if the imaging study requested cannot be found, then the request is automatically redirected to the main PACS.

The implementation of the DICOM network of the SNS-O, and the subsequent integration with the EHR servers accelerated considerably the clinical practice, as both request and examination of imaging studies can be conducted ubiquitously today. Anyway, DICOM is a standard which compliance does not always imply the same level of conformance of the norm. Thus, in the SNS-O there are still many imaging modalities and features to be integrated into the DICOM network.

Consequently, in many cases, clinicians must go directly to the diagnostic device to retrieve specific data from an imaging study [139].

Management of care service referrals

In order to put an end to the use of referral notes in paper, the SNS-O implemented a module for electronic referral, aimed at managing the requests for provision of a specified service by means of telematics. Besides the request of specific services, the electronic referral would also monitor the status of these requests, i.e. it would provide information about the procedures completed, pending and remaining at any given time. For example, the request for radiodiagnosis and laboratory tests are triggered by electronic referral notes, and the service is completed when the test results are returned.

To implement such module, first, a common catalogue had to be defined listing all the care services provided on the SNS-O. Specifically, the services provided by the following clinical specialties were included in that catalogue: allergology, digestive system, cardiology, general surgery, pediatric surgery, genetics, haematology and haemotherapy, internal medicine, nuclear medicine, pneumology, neurophysiology, gynecology and obstetrics, ophthalmology, radiodiagnosis, rehabilitation, sleep unit and urology. Thus, all specialists had to reach an agreement in specifying the requirements of each service considered.

Furthermore, the electronic referral modules of primary care and specialized care EHRs have been integrated, so a service request ordered from primary care can schedule an appointment on the calendar of services from specialized care [139, 140].

Electronic prescription

In 2010, the SNS-O implemented a module integrated in the front-end of the EHR systems to manage electronic prescriptions. This module was connected to a pharmacy management system that registers, in a central server, every prescription and the consequent dispense of medications associated to patients from the SNS-O. At the other end, pharmacies from Navarre installed a different module to register which medications were dispensed due to these electronic prescriptions. The whole system devised to manage the electronic prescriptions in the SNS-O was named "Lamia".

When patients arrive to a pharmacy, they are uniquely identified using the personal health card, so that they can receive their corresponding medications. Likewise, healthcare professionals can instantly supervise the medication regimen prescribed for each patient, and pharmacists keep track of the quantity of subsidized medications delivered.

The integration of this mise en scène entailed a great challenge, not technically but due to the conflicts of interest among personnel from the public health service and pharmacists owning a private business that must delimit their competences. Today, this service has replaced the traditional prescription in paper [139].

2.5.3 OPHTHALMOLOGY IN THE SNS-O

To date, the ophthalmology service of the SNS-O makes use of the specialized care EHR to register the information electronically. However, the information defined within the medical reports is mostly text-based and not structured. Consequently, the later exploitation of clinical information is unpractical.

Alternately, in order to partially solve the gaps of the main EHR system, our research group proposed several projects to research on specific healthcare procedures taking place in the service [34, 38]. However, this research work implied the duplication of information in the main database. Additionally, these projects had a limited lifespan and the effort invested was aimed at solving very specific issues, which could not be reused.

In any case, no previous work has achieved to model the clinical practices in ophthalmology while guaranteeing interoperability with the existing EHR. In this regard, in Chapter 4 of this Thesis, the integration of the dual-model layered architecture into the SNS-O to semantically enable the clinical information contained in the non-standardized EHR is proposed.

2.6 ELECTRONIC MODELS IN OPHTHALMOLOGY

As said before, there are two main standards supporting dual-model layered architectures, namely EN/ISO 13606 and openEHR. Both of them have repositories for electronic models. The former has recently launched the Clinical Information Model Manager (CIMM) [142], but to date, there is only one archetype defined (*CEN-EN13606-ENTRY.Blood_pressure.v1*). Additionally, the HCDSNS implemented a number of semantic resources to enable interoperability among the health services nationwide. However, it is a reduced set (10 compositions, 7 sections, 38 entries, 3 clusters, making a total of 58 EN/ISO 13606 archetypes) and none of them are related to ophthalmology [141]. The latter, openEHR, launched the Clinical Knowledge Manager (CKM), which includes 499 archetypes, 78 templates and 29 termsets [113]. Among them, the electronic models related to ophthalmology are the following:

- openEHR-EHR-OBSERVATION.visual_acuity.v1
- openEHR-EHR-OBSERVATION.fundoscopic_examination.v1
- openEHR-EHR-OBSERVATION.visual_field_measurement.v1
- openEHR-EHR-OBSERVATION.refraction.v1
- openEHR-EHR-CLUSTER.refraction_details.v1
- openEHR-EHR-OBSERVATION.intraocular_pressure.v0

In addition, the openEHR CKM includes a specific project to author ophthalmology models. However, to date, there are no electronic models for the most frequent causes of avoidable blindness and visual impairment in developed countries: DR, AMD, and CG.

Consequently, this Thesis will propose in Chapter 4 the modelling of the clinical processes associated to these three conditions, based on the methodology proposed in Section 3.1.

Chapter 3:

Guidelines toward the integration of e-health systems into pervasive clinical practices

First of all, this chapter describes a comprehensive methodology to guide experts on clinical domain to actively engage in modelling their own clinical processes into model-driven information systems. To this end, technical, syntactic, semantic, process/organizational, and presentation layers of interoperability were covered by the guidelines devised for clinical knowledge modelling.

In connection with that methodology, the second half of this chapter presents a health computing architecture based on open standards and good design practices, for setting up the e-health environment necessary to manage the electronic models resulting from the above guidelines.

3.1 METHODOLOGY PROPOSED TO FORMALIZE CLINICAL PRACTICE INTO INFORMATION SYSTEMS

The modelling experiences reviewed along section 2.3 were refined and then unified into a comprehensive methodology. This methodology therefore goes one step further than merely computerizing the domain knowledge using the two-level modelling approach. On top of that, it proposes using standardized terminology services, modelling computerized medical guidelines, managing workflow pathways of the clinical process, and formalizing the specifications for the UI (how that information is presented to users).

That would guarantee a suitable level of quality for the electronic models designed with the aim of ensuring continuity of care in patient-centred clinical processes that require tight coordination among multidisciplinary care providers. Considering all this, the modelling strategy proposed is comprised of three main phases (Figure 6):

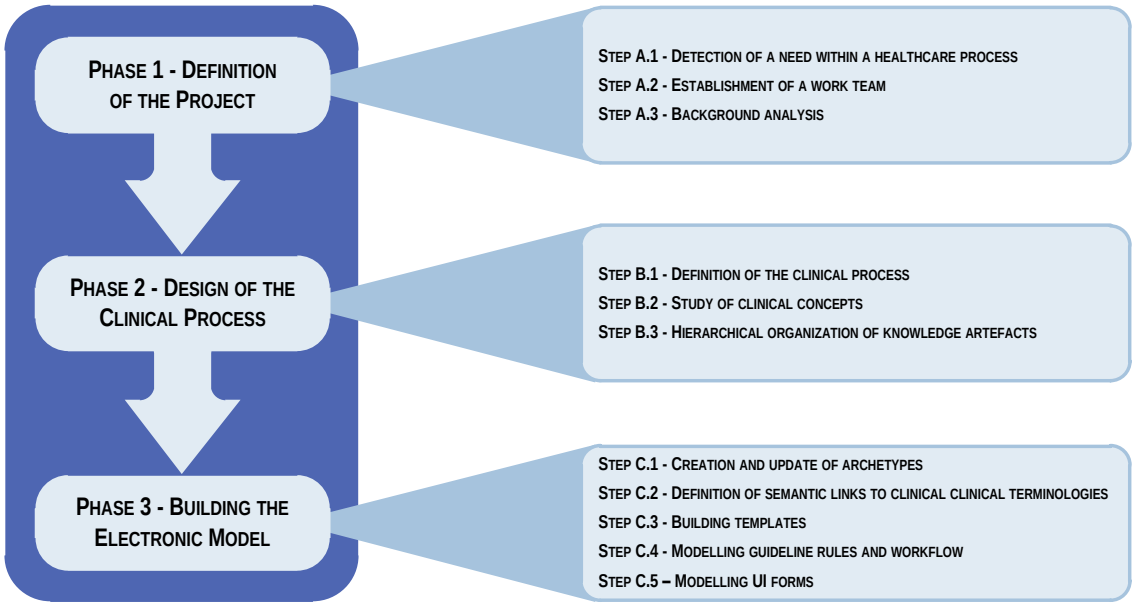

Figure 6: *Methodology proposed for modelling the clinical knowledge into electronic models.*

3.1.1 DEFINITION OF THE PROJECT

In this first phase, a work team is convened to analyse available information resources and define requirements to redesign a clinical procedure in response to deficiencies detected in daily clinical practice for a particular healthcare scenario.

Detection of a need within a healthcare process (step A.1)

The process of modelling healthcare guidelines into standardized knowledge repositories begins when healthcare providers identify in their daily practice the absence of formally described domain knowledge specifications for a particular healthcare scenario.

Establishment of a work team (step A.2)

When this occurs, a work team is established to determine the objectives and scope of the project initiated. As shown in Figure 7, such work team would be comprised of multidisciplinary experts who assume different roles depending on their capabilities. In this way, the work team will be able to cover broad viewpoints about the healthcare scenario to be modelled [19]:

- *Discussion Committee*: Healthcare experts are convened to expose the information and requirements of the clinical process to be modelled. On the other hand, experts in technical domain guide them to efficiently transcribe their knowledge into electronic knowledge repositories. The collaboration of experts from other domains is welcome depending on the scope of the project (engineers, statisticians, economists…).
- *Convenor*: A convenor is elected for each discussion committee. This role manages and registers every decision made by the committee and distributes the workload among the participants. In case of collaboration meetings with multiple discussion committees, the convenor is also the representative of his/her own discussion committee.
- *Experts in clinical domain*: Experts with broad knowledge about the clinical domain under study. Thus, they direct the decisions made by the discussion committee and then validate the information gathered.
- *Experts in technical domain*: Specialists in ICTs, with expertise in standards defining the interoperability between the electronic information systems used in healthcare. This role is the responsible of guaranteeing the compliance of technical standards when the information agreed by the discussion committee is transferred into electronic knowledge repositories.
- *Expert terminologists*: They are engaged to supply detailed terminologies and ontologies for the artefacts modelled by the discussion committee.
- *Subgroups*: When a clinical process involves many healthcare areas, the meetings of the work team can become overcrowded, and hence they can lose efficiency. Thus, the experts are distributed in smaller groups (preferable multidisciplinary) and then, the aforementioned roles are shared for each one of those. Meanwhile, the main discussion committee – composed of the convenors from each subgroup – coordinates the overall modelling. Thereby, each convenor would share in the main group a summary of the achievements and executive decisions made in their corresponding subgroups.

Once the work team is established, this organizational structure facilitates coordination of project's workload among the work team members. At this point, *Agile* mindset-based project management approaches, e.g. *SCRUM*, could be applied to ensure sustainable development for projects with continuously changing requirements [143].

Background analysis (step A.3)

Then, the work team proposes a solution for the issue identified during clinical practice, but it must be supported by reliable sources of information resulting from a comprehensive review of the state of the art. In that respect, three different information sources should be reviewed:

- Work experience in clinical practice: It is comprised of clinical knowledge obtained from evidence based medicine experiences in local scenarios. These experiences are based on the service procedures used to date (healthcare protocols and guidelines, medical forms, data field) and are the basis of service modelling due to the extensive expertise of the work team.
- Scientific literature: Peer-reviewed scientific journals, internationally validated clinical guidelines, and technical standard specifications shall be periodically reviewed to complete and/or update locally used healthcare procedures whenever they become outdated.
- International clinical knowledge repositories: These offer clinical knowledge which has been already electronically modelled. Repositories of archetypes such as the clinical knowledge manager (CKM) for openEHRs must be considered, including both published models and drafts [113]. Clinical terminologies such as SNOMED-CT, LOINC, or ICD-x provide univocal meaning for specific clinical concepts [122]. Other useful sources of information can be reference information models from technical standards used in healthcare, e.g., DICOM or ISO/IEEE [14, 144].

As a result of reviewing the state of the art, a list of the information sources identified shall be documented; all members of the work team can access that information.

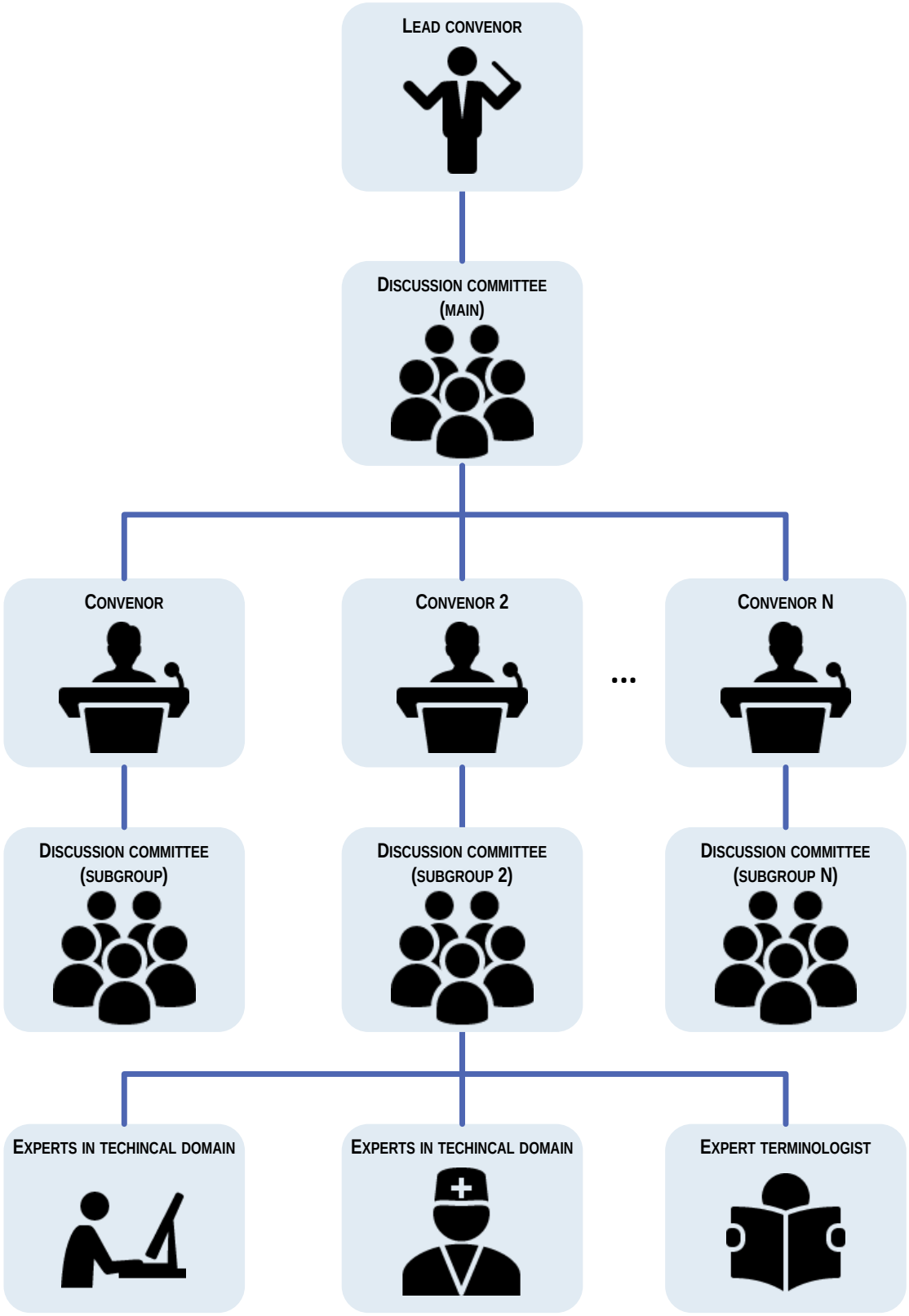

Figure 7: *Organizational chart of the roles defined within a work team.*

3.1.2 DESIGN OF THE CLINICAL PROCESS

At this phase, the methodology proposed must satisfy the requirements of the project described previously. The clinical process is defined as a combination of activities, decisions, and conditions that constitute the clinical pathways in the healthcare service. Those pathways are completed with the clinical concepts identified and then organized hierarchically according to the healthcare scenario chosen.

Definition of the clinical process (step B.1)

The work team proposes a clinical process in conformance with the specifications defined during the previous phase of the modelling. That process constitutes the workflow between the stages corresponding to different clinical encounters a patient has to go through to receive continuous clinical care. So first of all, the overall clinical process is agreed in a set of healthcare activities, conditions and decisions that represent the pathways between clinical stages. In this regard, activity diagrams in UML provides a suitable way to represent that workflow according to the definition of Martin Fowler [145]:

> "Activity diagrams are a technique to describe procedural logic, business process, and workflow."

Moreover, collaborative and on-line diagramming tools are recommended to reduce the number of meetings of the work team, since each expert can contribute remotely on the design of the activity diagrams [146, 147].

To conclude this step, the work team defines a project report that specifies every clinical practice conducted inside each one of the clinical stages identified on that activity diagram.

Study of clinical concepts (step B.2)

The stages identified in the clinical process are reviewed at this point, looking for reusable patterns of information that correspond to the clinical concepts to be modelled. And consequently, every clinical concept of interest to the clinical service is listed in a table which is added to the project report to keep every domain expert up-to-date about which parameters have to be included in the modelling.

In that respect, given that archetypes are used to register clinical knowledge in a standardized and reusable manner, some of those clinical concepts could be already modelled and validated as archetypes [26]. In this way, the contributions of previous projects are reusable for subsequent modelling. Thus, reuse of appropriate archetypes will avoid modelling every clinical concepts from scratch.

For this reason, the work team must review the archetypes available in the clinical knowledge repositories identified during the analysis of resources. Therefore, three situations can be distinguished: some archetypes will perfectly fit the concepts consulted, so they will be downloaded from the corresponding knowledge repository and used directly in the model; other archetypes will require modifications to match the needs of the current model; and other concepts will be new, so their archetypes have to be created from scratch.

Hierarchical organization of knowledge artefacts (step B.3)

The clinical concepts identified in the last step will be combined to build diverse knowledge artefacts hierarchically related to each other. Specifically, the knowledge will be structured within the electronic models according to the hierarchy that Skyrme defined in 1999 for modelling knowledge [148] (see Figure 8).

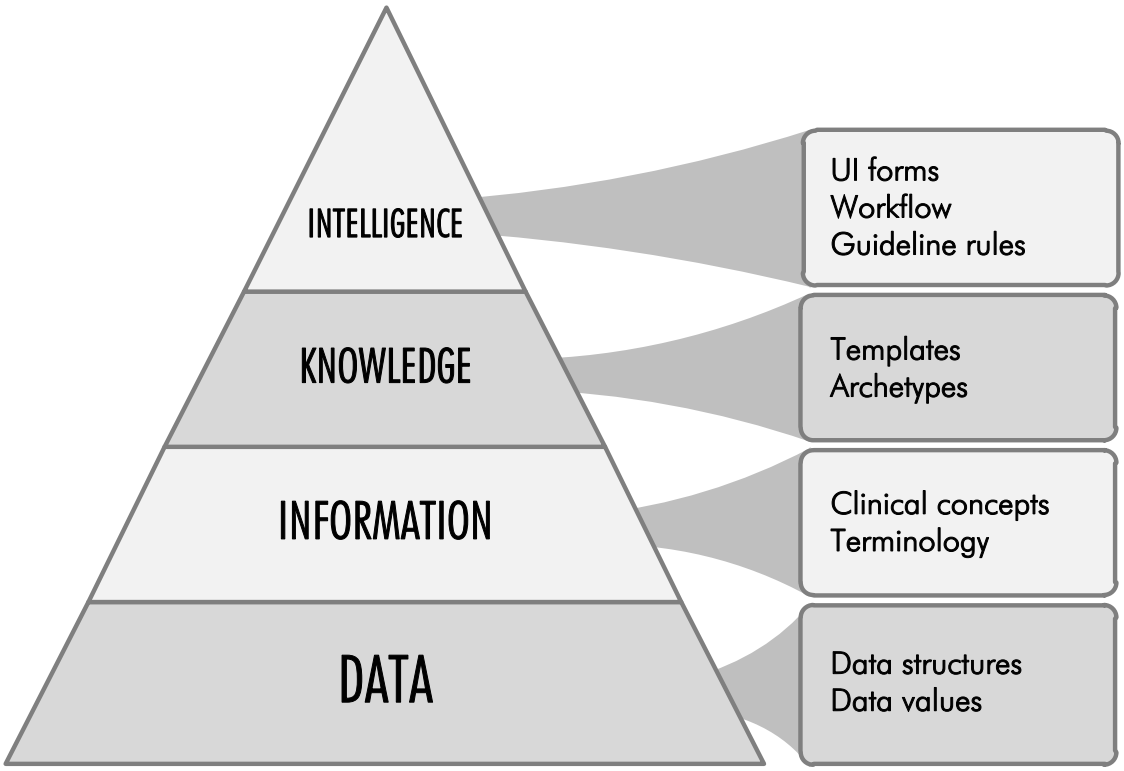

Figure 8: *Knowledge hierarchy proposed by Skyrme compared to archetype-based models.*

According to this, the work team will design a tree-type diagram in which the relationships among different knowledge artefacts involved on the computerized management of a specific clinical process are defined. Therefore, for each healthcare scenario to be modelled, the knowledge artefacts described below will be structured given the following hierarchy (see Figure 9):

- UI forms: Set of rules that determine how the knowledge artefacts modelled in the content model – defined by archetypes, templates, and bindings to standard terminologies – will be displayed to clinicians.
- Workflow: The dynamic side of clinical care; the process that guides patient healthcare through the stages of the clinical process [149, 150].
- Guideline rules: These rules based on medical evidence or by consensus from domain experts, provide notification services to support clinicians toward best healthcare practices. Guideline rules also can be used to manage other guidelines, e.g., alerts, unit conversion, and automatic filling out of data among archetypes. For now, the only rules defined here are those concerning the stages of patient flow through the clinical process [150].
- Stages and roles: Each stage is a clinical scene inside the healthcare process handled by personnel with specific capabilities (roles).
- Templates: They constrain the concepts and terminology from the archetypes they contain to define a form in which clinicians register the results of clinical encounters [151, 152].
- Archetypes: Archetypes are formal definitions of knowledge about a clinical domain. Thus, the data handled by an archetype-based EHR would be registered through the following categories of archetypes [26, 27]:
  - Compositions or thematic archetypes: They are the smallest units for data exchange between information systems. They include all clinical and administrative information of a clinical care session. As such, they must include meta-information to contextualize the healthcare session regardless of the EHR system. In this sense, when a contribution to a specific composition is filled out, it is signed by the responsible professional; hence

compositions have the same medico-legal validity as paper clinical documents. The extra information in compositions guarantees the ACID characteristics of transactions: Atomicity, Consistency, Isolation, Durability, indelibility, modification, and traceability [149].

- Sections or organizational archetypes: They organize the information inside compositions for human readability. They usually are used to arrange archetypes, but they also can enclose templates [149].
- Entry type or descriptive archetypes: These define the semantics for the information to be recorded in the information system. Five subtypes of entry are distinguished depending on their function in the iterative clinical problem-solving cycle used in medicine: admin entry (for non-clinically relevant administrative information), and four types of care entry archetypes (observation, evaluation, instruction, and action) [149, 153].
- Groupable archetypes: Clusters and structures are used embedded in different entry type archetypes to reuse context information they have in common.

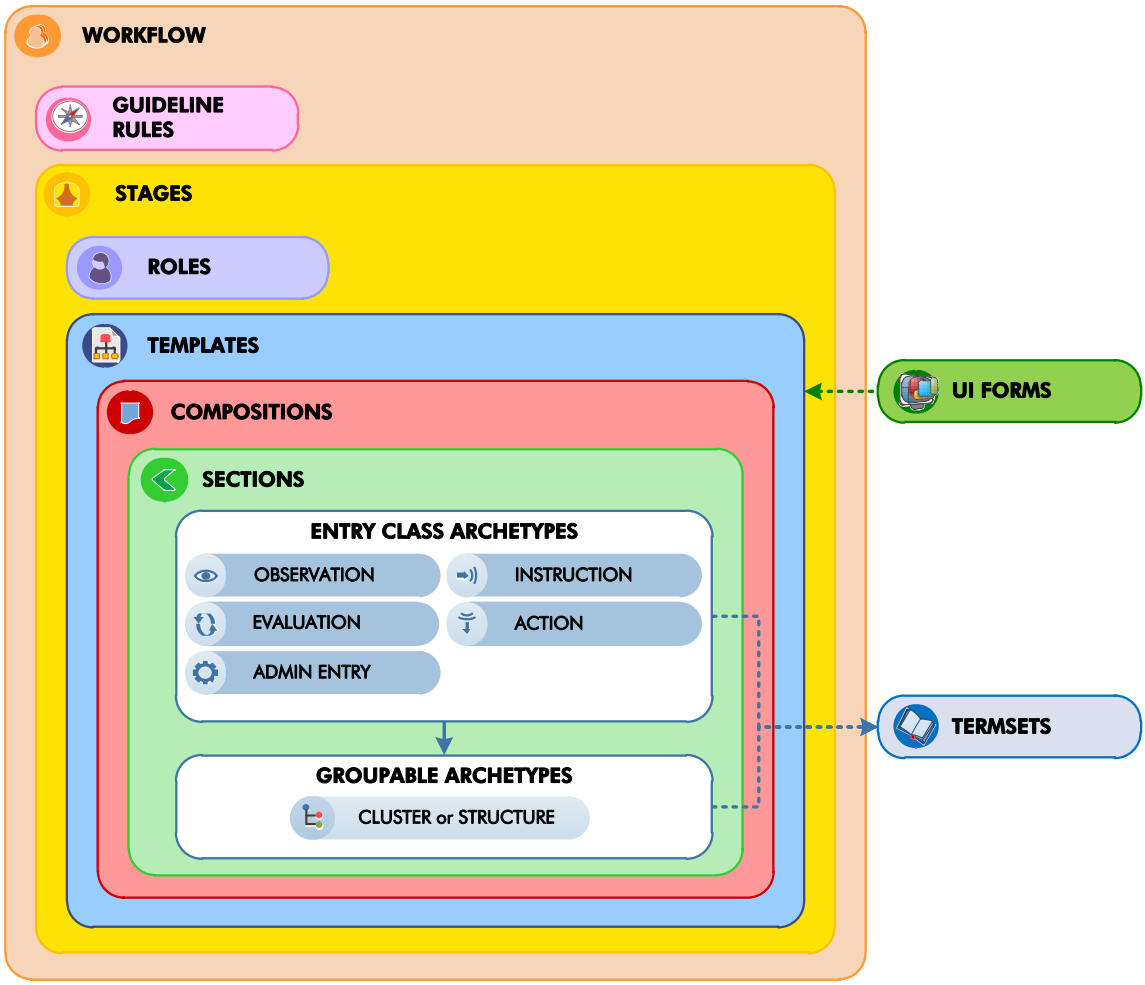

Figure 9: *Conceptual diagram of the overall hierarchy among the knowledge artefacts considered in the proposed modelling.*

3.1.3 BUILDING THE ELECTRONIC MODEL

At the third phase, all information necessary to build the electronic model has been already documented. Consequently, it is time to formalize the different aspects of healthcare for the clinical process designed in the previous phases. This section, therefore, would guide domain experts in building the knowledge artefacts considered by the proposed methodology: archetypes, templates, terminology bindings, guideline rules, and UI form specifications.

Creation and update of archetypes (step C.1)

At this point, the clinical concepts identified in step B.2 are defined into archetypes. Based on experience with archetype creation in the literature, the work team uses the following procedure to create or update archetypes when necessary [19, 115-117, 153]:

- Definition of the scope: Archetypes must be created with the aim of promoting their reusability. However, the first versions are focused on the definition of the information considered essential for the specific use case the archetype is created for. Thus, archetypes will adopt broader definitions to the extent that they are versioned for different use cases.
- Naming archetypes: The name of archetypes describing new concepts must be unique and it must follow the naming conventions defined by the standard used.
- Languages: A primary language is defined, so translations will be based on this unique reference.
- Elicitation of content: The clinical concepts identified in the clinical process (section 3.1.2) are dismantled into primary data elements. Then, each one of data elements identified must adopt at least one data type to represent the information they contain. Thus, those data types must be assigned according to the reference model of the standard chosen to build the archetypes. Next, in step C.2, the resulting data elements may be connected to equivalent clinical concepts defined by standardized terminologies.
- Content organization: The structure of archetypes is defined by establishing connections among those data elements. Mind-mapping diagrams offer precise representation of those relationships, providing a key tool to manage the contributions of different work team members [146, 147].
- Assignments of constraints to data elements: The properties of existence, cardinality, and occurrences must be established for each data element of the archetype [154].
- Building archetypes: The clinical concepts already designed at a theoretical level must be electronically registered. In case of openEHR, for example, the archetype editor of Ocean Informatics is used to develop and parse the code expressed in the Archetype Definition Language (ADL) defined by the standard [155].
- Publishing and validating the archetypes: Once archetypes have been uploaded into a Clinical Knowledge Base (CKB) system, they must follow the authoring process defined by the standard. For instance, the archetypes hosted in openEHR's CKM, have to overcome different states of the archetype development lifecycle. So, this authoring process fosters peer-review procedures to guarantee archetypes in line with the evolution of knowledge on the clinical domain concerned [117, 156, 157].

Definition of semantic links to clinical terminologies (step C.2)

This section was established simultaneously with the creation of archetypes and templates (step C.1). First, the semantics of data elements must be established for local use; at the same time, those data elements will be bound to their equivalent terms defined univocally in standardized terminology services in accordance with the following steps:

- Selection of terminologies: As seen in section 2.2.1, different terminologies, nomenclatures and coding systems are available for this purpose. Thus, the appropriate terminologies must be chosen to cover the knowledge structured within the archetypes to be modelled. In some cases we will find concepts covered by several terminologies, although this overlapping is solved by binding the same concept to as many terminologies as considered necessary.
- Semantic description of the structure of knowledge: Then, the terminologies chosen are analyzed looking for the concepts that best suit the knowledge elements formalized within the archetypes, templates, even guideline definition rules that comprise the model. Therefore, each knowledge or data element must include notations and links to international terminologies that will describe them unambiguously.
- Association of data values: In addition to the definition of data elements, those that define their content as coded data values or term lists must be referred to standardized terminologies as well, to constrain the set of possible values they can adopt [122]. At this point, different approaches must be considered to determine the connections among the information model and terminology services, depending on the scope expected for the value sets:
    - Binding the concepts within the archetypes: Value sets can be directly modelled inside the archetypes, and then, bound one by one to equivalent concepts in terminology services. This is possible when the value sets handled in the archetypes are small, manageable and universally applicable. For example, in ophthalmology the data element "laterality" would be always limited to: left eye, right eye, or both eyes.
    - Binding at template level: In some cases, the value sets identified toward pervasive use of archetypes can differ from the requirements of specific use case scenarios. Thus, those value sets must be constrained at template level, providing that they are small and locally applicable and the need for coding is not present. For example for registering new compounds used in clinical trials that have not yet been adopted on pervasive clinical guidelines
    - Create independent termsets: If the value sets are large or may be modified over time, involve different levels of hierarchy among concepts, and their use is widespread in the clinical domain, then it may be sensible to define them as normalized termsets to foster the semantic interoperability. The definition of termsets is comprised of queries addressed to a specific subset of concepts defined in a terminology service. Those are managed as a separate resource to archetypes and templates, providing them broad applicability with no need of additional modifications. For example, the list of substances used in anaesthesia which use is extended in many clinical practices, but still may incorporate new compounds and/or doses in the future. Another typical example is the termset that defines blood groups: A, B, AB, 0, plus the combinations of these due to Rh positive or negative.

Building templates (step C.3)

Considering that templates are local representations of the stages of the clinical process, they are responsible for composing the archetypes modelled in step C.1 into larger structures analogous to medical forms in paper [26]. In light of this, this step of the methodology is focused on modelling templates for a specific clinical process, which would register significant information obtained during clinical encounters:

- Identification of templates in the healthcare process: First of all, the clinical process is analyzed to determine which templates must be modelled to cover the information handled in clinical encounters. In this regard, the workflow of such clinical process should be divided into clinical stages corresponding to each clinical encounter planned

for patients. Then, at least one template must be modelled for each one of the clinical stages identified. Nevertheless, the more clinical concepts are involved in a clinical encounter, the more laborious becomes maintaining updated all the archetypes within the resulting template. Thus, to avoid building too complex templates, it is recommended to distribute the clinical concepts to be managed in a single encounter among small templates which would require a simpler maintenance. In addition, the use of smaller templates fosters their reusability in similar healthcare scenarios, in contrast with complex templates which are more use-case dependent. Section-type archetypes, also known as organizational archetypes can be used to that end. Those are capable to enclose templates as well as archetypes, so they are really useful to arrange the different templates concerning a clinical stage.

- Determine source archetypes: Templates do not change the structure of archetypes other than deleting or mandating certain branches, so it is essential to choose properly the archetypes to be included into templates. The choice as well as the hierarchy of the elements enclosed in the template should already have been described along the design of the clinical process. Therefore, the internal structure of templates will be formalized according to the hierarchy defined in step B.3.
- Applying constraints: Given that archetypes contain generic data elements to support their use within broad healthcare scenarios, further constraints must be defined at template level to adapt the information managed so as to be applicable in local healthcare scenarios [151, 152]. Optional nodes of the archetypes can be included, removed or turned into mandatory as required; the language in which the resulting forms will be generated is chosen at template level; terminologies associated to elements in the archetypes are specified to local usage; terminologies or occurrences already defined in archetypes, can be restricted so as to register just the information required in a local healthcare scenario; default values can be defined for data elements depending on the most used options for a local use case.
- Publication and authoring process: Finally, all previous specifications are formalized using the definition language provided for templates by the standards chosen. In this sense, templates can be considered as specialized archetypes, so the languages used to define archetypes and templates tend to merge into the same. Furthermore, design tools can be used to build archetype-based templates disregarding the definition language used. In case of openEHR, the templates can be built using the template designer developed by Ocean Informatics, and then are published into the CKM [155]. Once templates have been published into a clinical knowledge repository, they will follow the same authoring process applied for archetypes [152, 157].

Modelling guideline rules and workflow (step C.4)

The computerized guideline rules, and consequently the workflow are formalized at this point. First of all, clinical guidelines and recommendations established along section 3.1.2 – on the basis of local resources and settings within a specific healthcare service – must be formalized through computerized decision rules.

Then, further elements must be considered in addition to those guideline rules, to devise a workflow model. In fact, while guideline rules are modelled to execute specific events found during clinical practice, the workflow model considers the whole events triggered as the context information from a specific healthcare scenario. As a result, the workflow model would determine patients' pathway through the clinical process, based on the overall analysis of the context found at any given time. The main concepts that comprise clinical guideline and workflow models are further described below:

- Clinical pathway: They will provide, depending on the conditions met during clinical practice, a route through clinical process for patients. Those pathways are comprised of the healthcare activities, conditions and decisions identified in step B.1. Therefore, at this stage, the aforementioned pathways are formalized as business process models, to be processed by the corresponding workflow engine.
- Guideline rules: Among all guideline rules modelled, those determining the transitions between the clinical stages will be used to govern the workflow. Hence, the clinical stages defined along section 3.1.2 will be considered as the baseline when modelling those rules. According to these stages, the guideline rules modelled will specify a set of conditions determined by the pathways that trigger different actions or events depending on the context-data registered during the clinical practice.
- Conditions: The conditions defined in guideline rules must therefore interact dynamically with data registered in clinical records to trigger new activities addressed to specific roles. To that end, all entities that have impact on the clinical practice must be accessible to give a context to those rules, so the use of medical ontologies should be considered at this point. In this regard, the use of GDL language is recommended, as it leverages the knowledge base provided by multi-level modelling standards, to determine the context for the rules. In addition to the conditions defined in guideline rules, the workflow engine implements its own conditions to determine the next healthcare activity to be addressed. Provided an event listener detecting all guideline rules fired within the clinical process, the workflow model must define the process-level rules, which depending on the events triggered by the aforementioned guideline rules would determine the clinical pathway for each patient.

  In this way, the workflow engine will assess the set of queued events resulting from healthcare scenarios in which diverse guideline rules coexist and interact with each other. Thus, the conditions established at the process-level will resolve, for example, priority between conflicting rules, coordination of activities running in parallel, or placing time restrictions before specific events are launched.
- Activities: Traditionally, guideline rules were aimed at producing reminders, alerts, and recommendations to guide clinicians to determine the clinical best practice when facing specific clinical circumstances. Nevertheless, these rules can be also integrated into organizational processes that combine complex activities such as the management of flexible clinical workflows.

  In that respect, since guideline rules trigger single actions, the workflow engine must coordinate all events fired by the rule engine to determine the transition to the coming healthcare activity to be addressed in the clinical process. Thus, at this stage of the proceeding, the workflow model must specify the healthcare activities to be addressed, and the roles allocated to carry them out when the conditions specified in the previous step are fulfilled.
- Context: Any implementation of clinical guidelines in practical scenarios must be adapted to specific context parameters. Thus, considering context information regarding patients, clinical staff, resources, and location, in addition to the information strictly related to the clinical process would improve the management of priorities among guideline rules within complex workflows. In this way, when various care procedures are valid for a patient, the context will determine the optimum pathway for the patient depending on the characteristics of service available in each time. For example, a workflow including different healthcare facilities with different characteristics must exploit the capabilities of the personnel and the equipment available in each one of them to address a specific healthcare activity from the clinical process.
- Roles: In this sense, considering that the service proposed is aimed at supporting clinical decisions, clinicians will have the last say about the decisions affecting patients. Thus,

different permissions must be defined within the workflow model, according to the roles associated to each clinical activity and decision involved in the clinical process. Consequently, the workflow would be distributed among personnel with specific capabilities and skills toward best clinical practice.

Modelling UI forms (step C.5)

The design of UI forms will normalize how the information modelled within archetypes and templates is displayed to clinicians. Nevertheless, UI forms are in the early stages of development; hence, their implementations are still prototypes. Thus, this concept has to be discussed extensively before arriving at a de facto standard.

Thus, considering that UI form specifications may vary depending on the implementation, five generic steps were identified to model any UI upon a content model based on archetypes:

- Concept mapping: Every data field to be displayed within the UI form must be connected to the corresponding data elements defined inside archetypes or templates. Thus, the UI definition would be built upon a list of paths pointing the concepts defined on the content model (archetypes and templates). In this way, on the one hand the form could automatically inherit properties and constraints necessary to validate each data element according to the specifications set out on the content model. And, on the other hand, the data submitted through the UI form will be automatically allocated to the corresponding data elements, thus generating a valid contribution of a medical record.
- Design of the form layout: Next, the whole display area must be divided in zones that would be used to distribute the data elements referenced in the UI definition along the screen. This would enable clinicians to shape the UI form according to their specific needs.
- Description of UI views: specialisations applied to elements from the UI form would be specified along this step. For example, languages supported, form style settings (text alignment, font, size, colour, etc.), or support elements such as explanatory text labels, titles, etc.
- Allocation of UI controllers according to data types: The way the information is displayed and handled on the screen is defined by the UI controllers. Thus, depending on the output technology chosen, a different set of controllers would be available to generate the UI views for the front-end application. So, each data element, including any connection to external terminology services if available, must be mapped with a specific UI controller according to the data type they contain, i.e., a number, a date, or plain text must be handled differently within the form. In this way, a specific data-type would generate a known piece of programming code, which, in turn, would be compiled as a data field in the screen of the visualization device.
- Definition of output views: At least, three different views must be created for each UI form defined. These would correspond to the basic transactions of medical records: creation, visualization, and update of clinical information.

3.2 ARCHITECTURE PROPOSAL FOR IMPLEMENTING A MODEL-DRIVEN E-HEALTH PLATFORM

In this section a health computing architecture is proposed, for setting up the e-health environment necessary to manage the electronic models resulting from the methodology depicted in section 3.1. Such architecture coordinates distributed but interoperable information systems toward an efficient management of patient-centred clinical processes. To that end, all information systems involved in the management of a specific clinical process are coordinated through an Enterprise Service Bus (ESB) built on a Service-Oriented Architecture (SOA) approach.

It should be noted that the structure of this computing platform is seamless for end-users; the requests to specific services are tunnelled through a centralized gateway by the underlying infrastructure of the ESB. Indeed, the major part of the implementation – repositories of information, business logic and definition of services – takes place at the back-end of the platform. And meanwhile, end-users perceive the services offered by the ESB through a set of interfaces implemented at the front-end.

These front-end applications are lightweight and flexible compared to the design of the back-end. In fact, front-end applications rely on services offered by the back-end, so their functionalities can be customized depending on the interfaces they implement to the ESB. Thus, the complexity of the front-end would be determined by the functionalities provided upon the services called through the ESB.

Likewise, end-users would use diverse electronic workstations to get access to the services from the ESB. In other words, the same front-end can be built indiscriminately as web, desktop or mobile application, but nevertheless interoperability with the ESB must be guaranteed regardless the technology used. For that reason, communication between the ESB and every front-end must be designed in compliance with standardized web service protocols, e.g., SOAP, JavaScript Object Notation (JSON) or Representational State Transfer (REST) compliant web services (see Figure 10). With consideration of all the above, front-end applications are expected to arise to cover the specific requirements of each healthcare scenario.

At the back-end, this architecture implements communication interfaces to aggregate vendor-independent information systems to the platform. Then, the ESB implements services that correspond to the functionalities provided by every information system connected to the platform. In this way, the service requests initiated at front-end applications are redirected seamlessly to the corresponding system that offers the requested service. Likewise, all operation concerning connectivity, data transformation and routing for these services is managed through the ESB.

Different modules have been made available for managing the access to the services in the ESB. Each of these are responsible for providing a specific range of functionalities to the platform according to the types of information systems they connect. Given that the scope of some services is transversal to a single information system, these modules can also coordinate the capabilities of multiple systems into complex services. Each of these modules specifies a set of standards that the information systems must comply with before connecting to the ESB. In this way, the information systems would be interchangeable with other systems that implement equivalent services whenever they adhere to the conformance points of the module. With regard to the architecture proposed, the modules identified in Figure 10, are further described along this section.

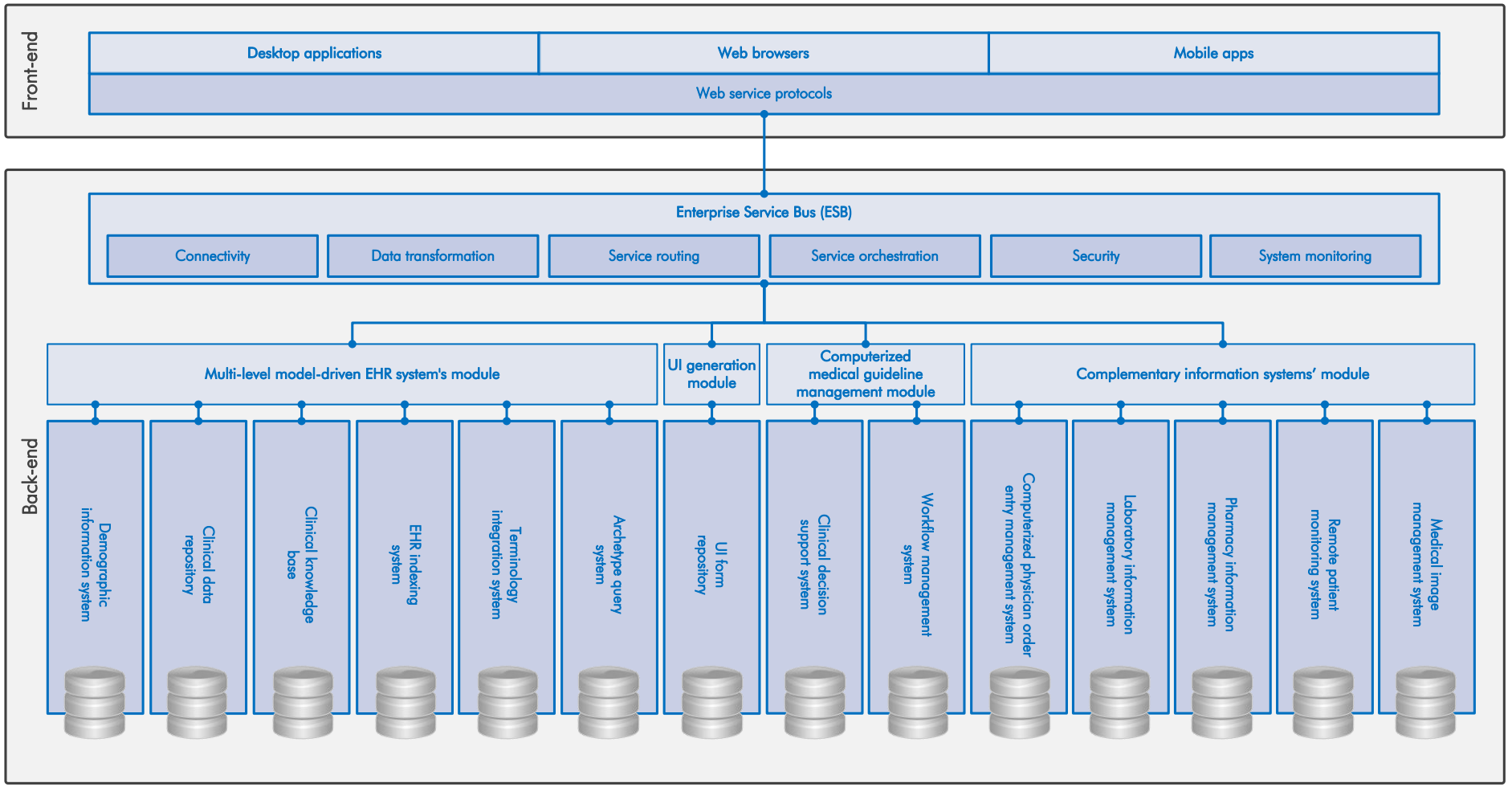

Figure 10: *Distributed architecture for the services comprised in the health computing platform proposed.*

3.2.1 THE ENTERPRISE SERVICE BUS (ESB)

The ESB is an integration platform that enables aggregation of heterogeneous information systems, to provide standard interfaces to the services they offer. It must provide a gateway between those services and any front-end applications too. Considering the requirements of the health computing platform proposed, and reviewing similar design patterns in section 2.4, the functionalities described below were considered for the ESB (see Figure 10):

- Connectivity: It must provide connectivity between the ESB and the different endpoints. Thus, it must support a variety of communication protocols.
- Data transformation: It must harmonize all data resulting from different communication standards, to allow interoperability between the information systems connected to the ESB. This transformation of data and protocols would enable a seamless integration of the information systems involved in a service. Thus, the service consumers would access to all information they need through interfaces compliant to pervasive web service protocols (SOAP, JSON, REST-compliant web services, etc.). Meanwhile, the ESB would deal with the middleware necessary, for example, to connect not-standardized interfaces, legacy systems, or proprietary solutions to the platform.
- Service routing: For each service request, the ESB must provide interfaces toward the appropriate system which provides that service. Nevertheless, the functionalities available in the back-end are hidden to users, so that users are not allowed to call the services directly to the source repositories. The ESB provides a normalized showcase of interfaces to those services instead. In this way, different versions of the same service can coexist, seamlessly to the service consumer. Indeed, when more than one service is available to fulfil a service request, the ESB can apply a content based routing to provide the service most suitable for the requesting user.
- Service orchestration: It must be able to coordinate elementary services of various information systems and provide composite services to the users.
- Security: Although the information systems may implement their own security, all services are centralized at ESB, so it is appropriate to apply an additional security layer at this point (encryption, data validation, antivirus, etc.). Unique authentication and authorization services including Single Sign-on such as OpenID Connect should be implemented to get access to any service provided by the ESB. In that respect, an authorization server could deliver fine-grained permissions to access specific resources from systems integrated in the ESB. To that end, a Role-Based Access Control services could be used to manage the access permissions according to the user's credentials and the scope of the service requested. For instance, an authorization framework such as OAuth2 would facilitate identity validation, and hence define the permissions issued to the end-users of the platform [158].
- System monitoring: It would provide functionalities associated to the overall usage of the platform. For example, the workload on specific systems, the use of specific services, or the status of information systems can be useful for determine the further steps to be taken on next developments. In addition, the authentication logs can be used to determine audits-trails based on the access of specific users to each service.

3.2.2 MULTI-LEVEL MODEL-DRIVEN EHR SYSTEM'S MODULE

This module is the cornerstone of the health computing platform architecture proposed, as it manages the clinical information resulting from the healthcare episodes registered for each patient. It distinguishes internal components which contribute together to a faithful registry of the clinical and administrative information registered on the system. As the EHR centralizes all healthcare events regarding the care history of patients, it provides further communication interfaces to feed the services from the rest of modules. Specifically, the EHR system's module integrates a demographic information

system, a CDR, an EHR indexing system, a CKB, a terminology integration system and a query system for data mining within a showcase of coordinated services in common (Figure 11). With regard to the resulting diverse knowledge artefacts – archetypes, templates, terminology subsets and queries–, they are handled by separated and standalone systems, and thus their use is combined solely at runtime [159].

Moreover, the architecture proposed enables managing data from distributed information repositories into a loosely centralized platform. Thus, although registered in different sources of information, the complete healthcare information of a patient will be accessible ubiquitously as a unique EHR. In this way, if innovative information systems are connected to the platform, they will coexist with older technologies, and hence their information will be appended to the existing EHR records.

In this sense, as this architecture encloses many vendor-neutral systems, each one must provide normalized interfaces to enable interoperability when information is exchanged among them with the aim of coordinating the logic concerning the implementation of final services. The diverse information systems involved in that architecture, the services they provide, and their connections are detailed in Figure 11.

Demographic information system

It provides unambiguous identification of patients handled by any service connected to the ESB. To that end, the demographic service can be implemented either as standalone system, or a "wrapper" service for existing systems such as a PMI or clinical repositories with demographic information embedded. Considering healthcare environments in which distributed systems contain demographic data scattered around different organizations, the demographic information system must be capable to update and merge consistently all that information requested on the fly. In this regard, requests to other demographic services are handled by the Patient Identifier Cross-reference (PIX) and Patient Demographics Query (PDQ) profiles provided by the organization Integrating the Healthcare Enterprise (IHE). The former is used to ensure that all systems employing demographic resources will associate the personal health data they handle with the right patient. However, when the use of a patient identity cross-reference manager may not be required or appropriate, the PDQ profile is likely to be most appropriate. This one lets applications to query by patient demographics against demographic information systems, obtaining a list where those patients that match the specifications of the request are identified [160]. Finally, the information gathered is offered through a demographic information model compliant to the openEHR standard, since the flexibility and complexity of structures it covers make it possible to manage the information of other demographic solutions such as EN/ISO 13606 demographic model [161, 162].

This setting up enables the rest of the systems to access demographic data as a service integrated in the ESB (Figure 11). Thus, patients' data privacy is managed individually according to the access permissions established for each user. Moreover, the synchronization of demographic information will reduce problems resulting from wrong identification of patients, duplicated patient files, and outdated or incorrectly registered data.

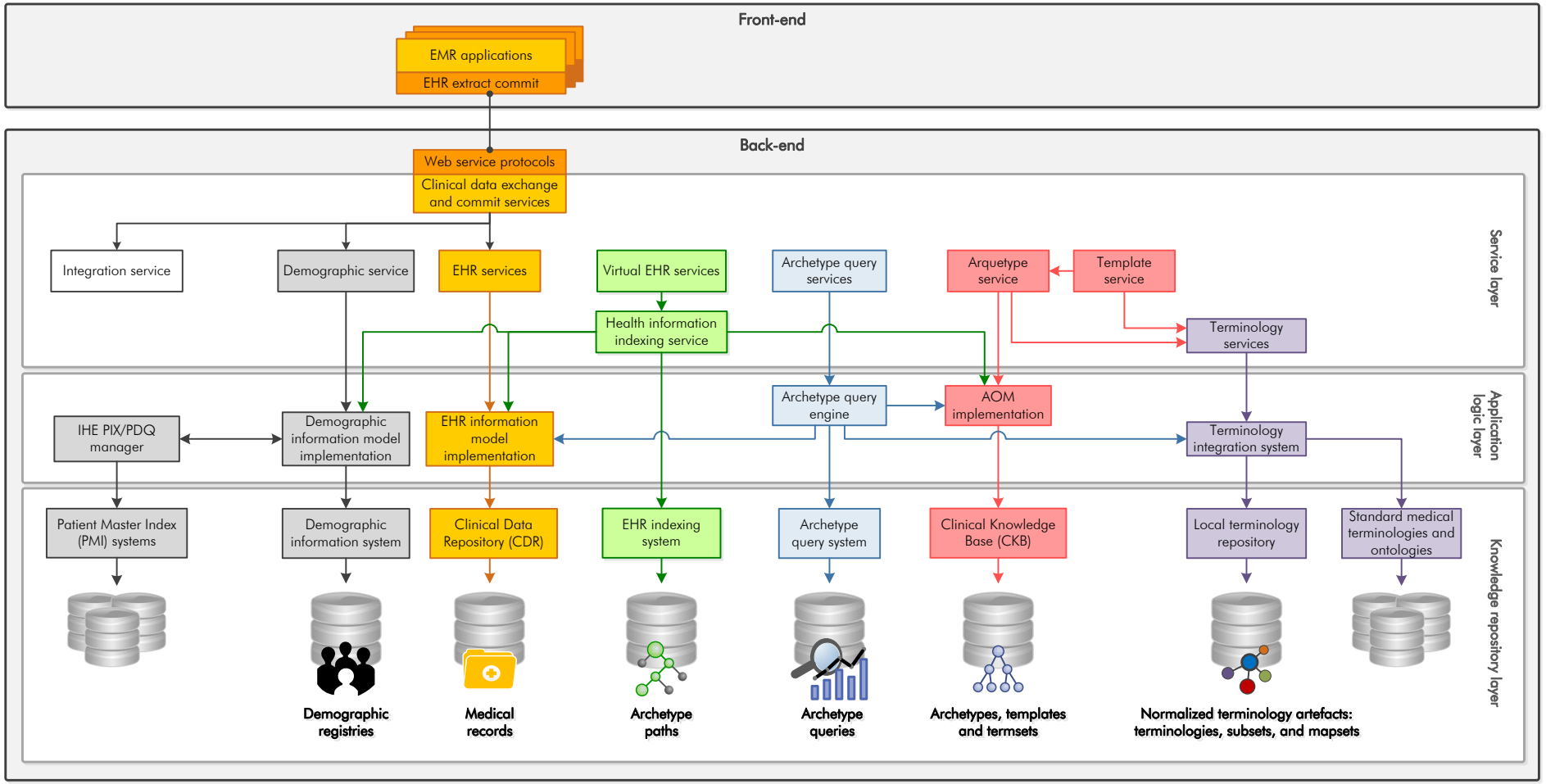

Figure 11: *SOA proposed for the multi-level model-driven EHR system's module.*

Clinical Data Repository (CDR)

The patients' clinical data can be scattered in distributed clinical information systems built in compliance with different standards. In addition, the clinicians would use different EMR systems as front-end which use web services to dispatch the clinical information registered during their clinical practice to the ESB.

Therefore, the EHR architecture includes a primary clinical data repository to centrally manage the overall information of the healthcare service, and it also enables the exchange of "EHR extracts" among other repositories of clinical data compliant to different standards. Furthermore, the central CDR will be the repository in which the medical records are continuously updated according to the information periodically dispatched by every EMR station involved within the healthcare service (Figure **11**).

Considering those requirements, the information model chosen for the EHR implementation is based on the openEHR standard. Although, this standard implements "EHR extracts" to exchange medical records with EHR systems built in compliance with the same standard, it also provides an integration module to harmonize, – by using "integration archetypes" – the information modelled in compliance with reference models built on other standards such as EN/ISO 13606, HL7 CDA, or HL7 FHIR [163, 164].

Clinical Knowledge Base (CKB)

As it has already been explained in the introduction, the EHR system architecture provided registers medical records using standards based on two-level modelling (also known as multi-level modelling). In that regard, the CKB is a standalone system responsible for the management of the knowledge artefacts corresponding to the AM, in compliance with the requirements of the two-level modelling approach. This system would be dedicated to host the archetypes and templates that specify the clinical concepts to be registered into the CDR.

The CKB system would implement the Archetype Object Model (AOM) to transform the knowledge artefacts into computer-processable objects. And, in turn, those objects would be used by the final services accessible through the ESB to structure the information registered into the CDR.

To that end, archetype and template services have been made available to include new knowledge artefacts into the CKB or to modify the existing ones in accordance with the latest clinical procedures for best practice care.

EHR indexing system

While access to the services from the primary CDR is direct, in some cases, when several healthcare facilities participate in the same clinical process, the management of medical records can get complicated. Therefore, given a distributed environment where medical records from a given patient may be located in multiple information systems, the corresponding EHRs must converge into a unique "virtual EHR". Hence, the EHR indexing system will mediate the synchronization of those distributed information systems so as to return up-to-date medical records relating to a specific clinical study. In other words, whenever clinical information is distributed among several CDR or demographic information systems, the indexing system will provide the services inherent in a virtual EHR. Consequently, the requests for clinical information addressed to the overall EHR architecture would be automatically redirected to the corresponding information systems. And likewise, for each of those requests, all responses sent back from different information systems would be checked jointly into the virtual EHR, thereby providing comprehensive and consistent results [164].

Terminology integration system

The purpose of terminology services is to provide for computerized systems an unambiguous identification strategy for semantically equivalent concepts when information is exchanged among different information systems. Indeed, the classification of the concepts according to normalized semantics increases the processing capabilities toward interoperability and harnessing of information registered in the EHR.

To that end, standardized medical terminologies provide codes, classifications, terminologies and nomenclatures to be used by concepts defined in the EHR [122]. Furthermore, archetypes, templates and computerized guideline rules, can include correspondences to resources from terminology services within their definitions of clinical knowledge.

Considering that the standardized terminology services are provided externally to the ESB, the architecture proposed must include an integration system dedicated to manage all terminology-related services used by the EHR. Therefore, it would manage the terminology artefacts defined locally, but it also would provide a centralized access to all resources available remotely in standard medical terminologies.

In this sense, the AM provide two approaches to handle terminologies: "term bindings" and "constraint bindings". The former, formalizes direct correspondences to concepts or terms from standard medical terminologies and ontologies for the data elements defined within archetypes, templates, or computerized guideline rules. Thus, the terminology integration system must provide a query service to different standardized terminology providers. The latter, defines "terminology subsets" or "ref sets" modelled on the basis of standard terminologies to constraint the occurrences of entire archetype branches. Therefore, pervasive archetypes can be specialised to healthcare scenarios applicable in multiple clinical domains by the attachment of different terminology subsets. As those subsets are locally modelled to fulfill the requirements of clinicians within a specific clinical procedure, the reusability of archetypes increases accordingly [159].

To that end, the integration system must include a standalone repository for terminology subsets and locally agreed terminology artefacts defined for the healthcare scenarios covered by the EHR system. In addition, this repository would be connected to the query service which populates the elements in the archetypes with the information retrieved from standard medical terminologies and ontologies such as LOINC, SNOMED-CT, or ICD-x (see section 2.2.1). Likewise, custom terminologies, subsets and mapsets (mappings between different terminologies) would be defined to adapt the standardized medical terminologies and ontologies to localized healthcare environments (Figure 11).

Archetype query system

The archetypes were originally devised to formally define the content of medical records registered using the multi-level model-driven architecture of the EHR system proposed. Nonetheless, they can likewise be applied in the opposite direction, i.e. to build the data queries used to retrieve structured information from the EHR. These queries modelled upon archetypes, would be equally applicable to all EHR systems using the same CKB to register the medical records, regardless of whether the clinical information is scattered along distributed CDRs.

Accordingly, the model-driven EHR architecture requires a dedicated system to manage the query and data mining services for every information systems connected to the health computing platform. In this way, it would be possible to make use of the massive data also known as "big data" available in distributed CDR-s. To that end, the system proposed must include an archetype query engine, specialized in processing data queries built in compliance with multi-level modelling standards, e.g. the Archetype Query Language in the case of openEHR.

As introduced above, the information in the EHR was registered in accordance with the tree-structure defined by the archetypes. Thus, the syntax of queries would rely on the use of "archetype paths". Therefore, first, the archetype query system would list the set of paths for each archetype (known as "path maps") contained in the clinical knowledge repository, and it would apply terminology services to them, so as to present an archetype query builder in a human readable format. In this way, clinicians would design complex queries without need of programming skills, since archetype paths are connected to the meaning of the concepts they refer to. Therefore, archetype query building would consist in identifying specific concepts within archetypes and choosing the appropriate filters to narrow the search.

Not all queries merit being treated as designed entities, in which case they can be directly executed on the archetype query engine. However, many queries will be reused, particularly those designed for use in research studies and also decision support systems. Thus, the archetype query system incorporates a repository connected to the archetype query engine, engaged to host the most commonly used queries, ready to be launched whenever necessary.

In which case, the query engine analyzes all links provided by the health information indexing service that refer to the medical records in the CDR, and filters the results according to the search parameters specified in the query. Those links are retrieved at runtime, so the archetype query engine would retrieve real-time updated results each time the query is processed (Figure 11).

3.2.3 UI GENERATION MODULE

Even the minor changes on the content model from the EHR will be reflected in the UI views of front-end applications. Thus, the continuous evolution of knowledge on the clinical domain will entail regular maintenance for those applications.

Furthermore, the design of diverse forms of front-end applications is expected to make the most of the information registered into EHR systems compliant to multi-level modelling standards. That will constitute a healthcare environment comprised of autonomous applications, built on diverse technologies and software platforms, whereby each one implements specific functionalities. Thus, considering that the UI views must fit the day-to-day work of each user, the maintenance of those applications will become a challenge unless automation is established to generate the UI views [10]. Nevertheless, a fully automatic UI view generation based solely on the representation of content model does not reach the usability required by end-users. Thus, custom requirements from end-users must be included somehow in the computerized generation of UI views.

In this regard, the module illustrated in Figure 12 proposes a model-driven information system to computerize the generation of the programming code necessary to establish the presentation layer into front-end applications. This module implements a service that delivers UI views for different front-end applications in conformance with a set of specifications defined within each UI request addressed to such service. Likewise, the aforementioned specifications can be formalized into UI forms. Such forms specify the arrangement of the elements contained into a specific UI view. Furthermore, there is no need of programming skills to build those forms, since the UI generation engine generates the code automatically from the specifications of the end-users. So, end-users supported with proper software tools should be able to model the UI from front-end applications according to their specific requirements.

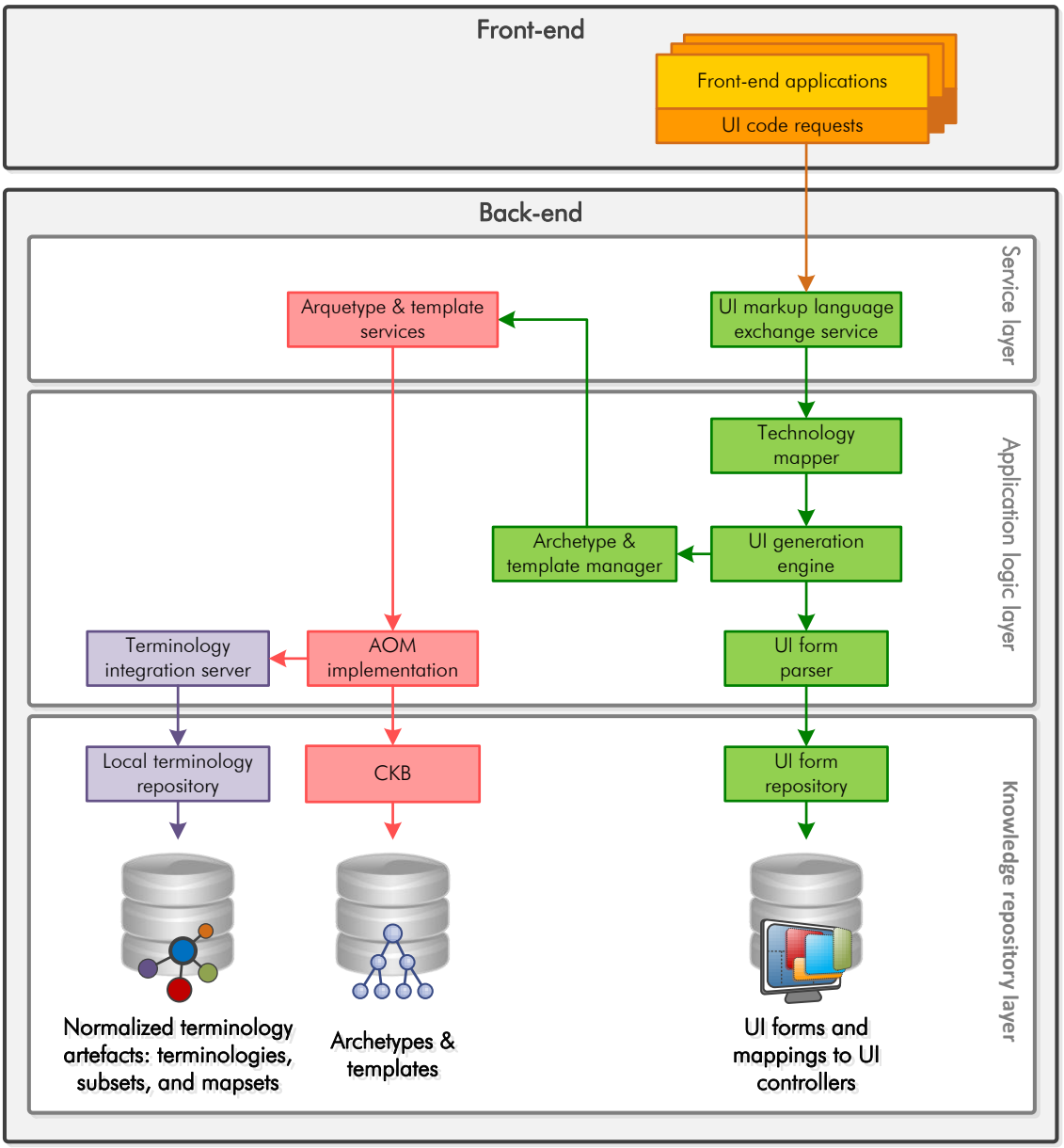

Figure 12: *Detail of UI view generation system dependencies.*

UI form repository

Once defined, UI forms will be accessible from a dedicated repository, to be reused whenever necessary. Therefore, UI requests will refer to specific UI forms available in the repository, to avoid having to redesign the UI specifications each time.

In this way, the UI generation engine will parse the UI forms instantiated in each request and it will process the UI definitions they contain. Normalized UI views are then automatically generated to cover the operations of creation, visualization, and edition of medical records. The UI form definitions, in turn, will instantiate the archetypes and templates that constitute the content model to be displayed on screen. In this way, the UI generation engine also features an archetype and template manager to integrate AOM objects into the UI views.

Once all the elements to be displayed on the screen have been identified, the UI generation engine will build the programming code to be integrated into the application that initiated the request. However, such application has to be capable to interpret correctly the code provided by this service so as to generate the respective UI view. To that end, a mapping service will transcribe the UI specifications into the corresponding classes and controllers provided by a UI markup language compatible with the application receiving the UI code. In this way, whenever the UI generation engine processes a specific UI form, equivalent UI views are produced regardless the front-end application used, since the resulting code will be adapted depending on the output technology set as target.

Finally, the UI delivery service uses web service protocols to send the resulting code addressed to the application where such UI views will be deployed (Figure 12).

3.2.4 COMPUTERIZED MEDICAL GUIDELINE MANAGEMENT MODULE

The systems of this module are responsible for processing the information registered during clinical practice to provide the clinicians with the necessary tools to make decisions based on the information registered on the EHR. So, first of all, computerized medical guideline management systems must implement interfaces to query and retrieve data as it is recorded in the EHR. To that end, the aforementioned systems must implement a service continuously listening to the events in the services of the EHR concerning clinical data exchange and commit.

Therefore, whenever a front-end application uses the commit service to submit new contributions to the EHR, a guideline rule inference engine would analyze the incoming EHR extracts and process them proactively according to the guideline rules contained in the rule repository. Those rules will determine a set of conditions which instantiate elements described in specific archetypes or templates. Moreover, the elements contained within those archetypes could use terminology services to provide semantics to their possible occurrences. So, unlike unstructured medical records, the information retrieved through archetypes would be unambiguously analyzed by the rule engine.

Whenever one of those rules is executed, different events are triggered depending on whether the conditions specified within rules are fulfilled or not in the instances analyzed. In this way, the events determined by guideline rules will be applied dynamically in accordance with best clinical practices, whatever the healthcare scenario found.

At this point, some of those rules may require additional information from the EHR to access all instantiated elements. In such case, the computerized guideline rule engine would leverage the query services provided by the EHR to obtain retrospective information.

In summary, the computerized guideline rule engine will be the core for any computerized medical guideline system, but different services are provided depending on the use given to the rules when triggered. In this regard, according to the architecture proposed in this PhD dissertation, two main groups of systems were differentiated: CDS system and Workflow Management System (WfMS). Although the Computerized Physician Order Entry (CPOE) management system acts as a standalone

management system and belongs to the "complementary information systems' module", occasionally it will be used to coordinate the CDS and WfMS. Especially when the workflow being processed depends on actions occurring on complementary information systems (Figure 13).

Clinical decision support system (CDS)

Digitalization of clinical practice provided a huge amount of heterogeneous data to be evaluated by each clinician. The more context data are handled, the more accurate diagnoses should result from clinical practice. However, rather than improve diagnosis, clinicians are more prone to committing errors due to the difficulty to consider every clinical guideline applicable to such a complex context.

In that respect, CDS services define computerized guideline rules based on medical evidence or by consensus from domain experts and provide notification services to support clinicians toward best healthcare practices. Each CDS service implemented would entail a specific set of rules managed by the computerized guideline rule engine.

Thus, whenever any of those rules is triggered, the CDS services referenced to that rule will activate the corresponding events within that service. Then, the CDS services process the information contained in those rules and notifies clinicians about the best care procedure in the form of reminders, alerts, and recommendations (Figure 13). For example, a CDS service could be designed to alert about possible incompatibilities among medications during the treatment of a patient. To that end, computerized guideline rules identifying the medication actions carried out throughout the study would be checked and then verified against a table of incompatible compounds. Then, before every new prescription of medicament, the CDS service would warn clinicians about incompatibilities due to previous dispenses.

Workflow Management System (WfMS)

Unlike CDS services which implement stateless decisions, the WfMS must determine dynamically the pathway for each patient enrolled in a clinical process depending on the context of care at a given time.

To that end, the guideline rule inference engine is used to execute the rules concerning management of decision points of the clinical process. Nevertheless, most rules processed by this engine belong to CDS services, and those that correspond to the workflow management services are decisive only as long as patients are situated in specific decision points of the clinical process.

For this reason, additional components are required to handle the appropriate guideline rules at any given time. In this regard, a process engine will transcribe the workflow models into decision points, roles, activities, and rules toward a patient-centred care plan. Then, a process event listener would detect any event in the computerized guideline rule engine, whenever it concerns the workflow of clinical processes being executed on the process engine. This listener will supply the information required to move forward on decision points, so it would manage priorities among rules and execution order for conflicting events accordingly (see Figure 13).

Bearing the above in mind, a patient choreographer service would manage the instances corresponding to a specific patient enrolled in the clinical process. In this way, the workflow model deployed by the process engine is applied to single patients.

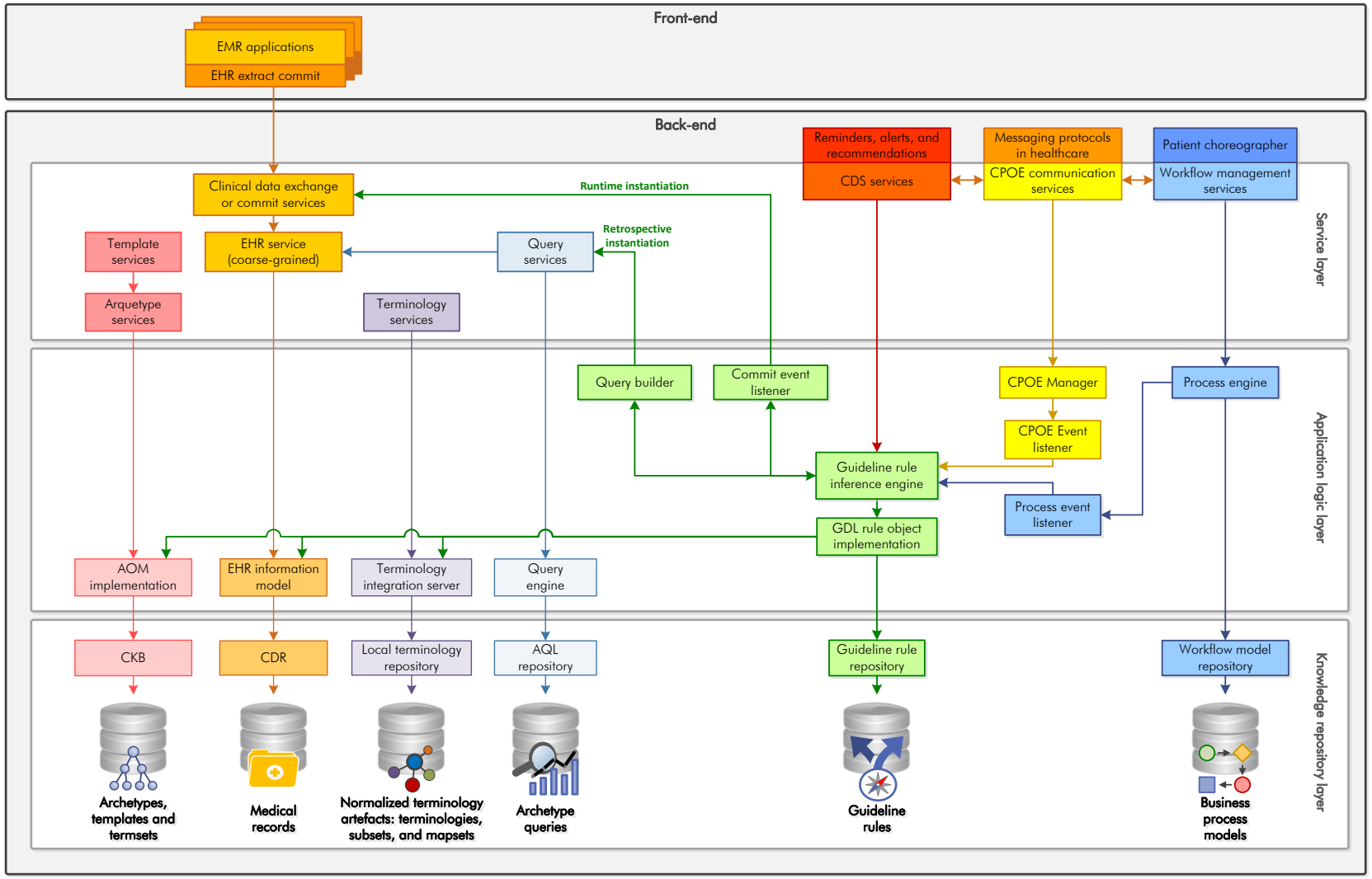

Figure 13: *Architecture and dependencies among information systems toward the implementation of CDS and workflow services.*

3.2.5 COMPLEMENTARY INFORMATION SYSTEM'S MODULE

As the EHR is a longitudinal electronic record of patients' health information [21], every information system that can contribute with significant information about patients' healthcare must be included in the SOA approach proposed.

The information systems described along this section comprise medical image management, RPM, clinical laboratory automation and pharmacy administration. Anyway, other systems can be incorporated as well to the architecture, as long they provide interfaces compliant to the standards implemented within the ESB. These systems work independently from the EHR, and each of them deals with very specific requirements which cannot be covered by a unique information system (Figure 14). For instance, the medical image management system requires large volumes of storage and high bandwidth to send the imaging studies through network, whereas the laboratory automation system will require less volume of data on the network, but greater number of simultaneous transactions.

Given that each of these information systems has been optimized to govern clinical information in very specific areas, only clinically significant information would be transferred to the EHR. Nonetheless, ubiquitous access to all data records must be guaranteed for the cases in which the medical records in the EHR are not conclusive, and hence an in-depth analysis is needed. Thus, the architecture proposed must implement interfaces to access the information registered on every complementary information system connected to the ESB. With the aim of getting a standard-oriented solution to implement the communication scenarios mentioned above, the services offered by the information systems connected to the ESB must include messaging interfaces compliant to pervasive communication protocols in healthcare (TCP, MLLP, HTTP, and SOAP) for the exchange of messages structured in compliance with different normalized syntaxes such as ER7, XML, JSON, HL7 CDA.

Once each information system connected to the platform uses normalized communication profiles, the ESB must administer the corresponding profiles to enable data exchange with each of the complementary information systems integrated into the framework. Considering the wide choice of standards available to achieve coordination among the diverse information systems involved in the healthcare environment, the IHE integration profiles were considered. As IHE promotes the coordinated use of established standards, the profiles it provides offer a clear implementation path toward a truly efficient interoperability for specific clinical scenarios that involve diverse information systems [165]. In this regard, the CPOE management system has been conceived to coordinate the different information systems toward the same care plan (see Figure 14).

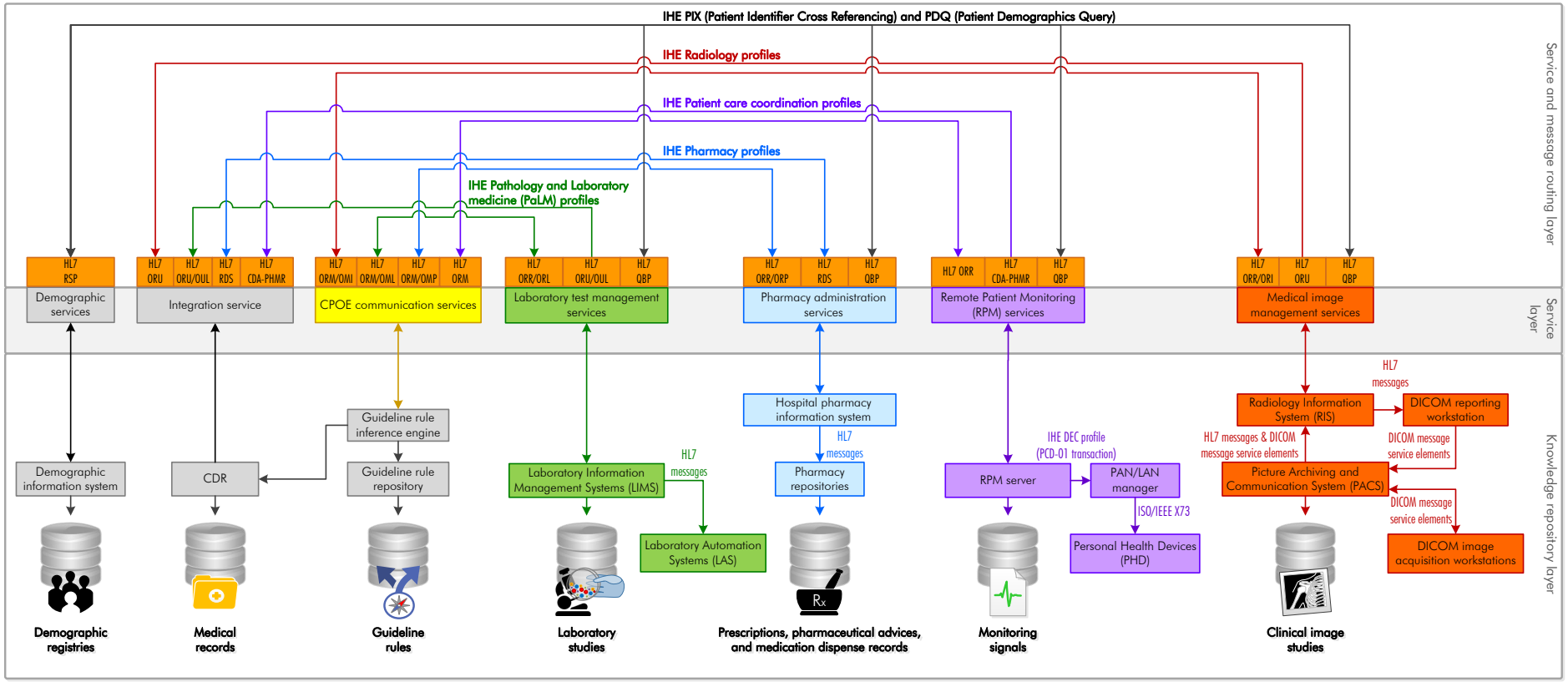

Figure 14: *Message exchange required for aggregation of complementary tests to the EHR architecture.*

Computerized Physician Order Entry (CPOE) management system

The CPOE management systems provide messaging services aimed at handling the overall lifecycle of computerized orders/instructions defined by clinicians to request any service external to the EHR. Traditionally, the notification of physicians' orders is conducted using referral notes in paper, whereas the system described along this section provides equivalent services but using pervasive standards on ICTs in healthcare to that end. Therefore, the electronic message exchange from the time a physician submits a computerized order, until all activities specified by such order are completed according to the standard Instruction State Machine (ISM) will be administered within this module.

Considering that all communication in the CPOE management system is initiated by electronic referral notes, instruction-type archetypes will be used to originate the CPOE messages addressed to remote information systems. Accordingly, computerized guideline rules with instances to those archetypes must be specified into the CDS system. In this way, those rules will be triggered by the guideline rule inference engine whenever a clinician defines a new referral note built on the aforementioned instruction-type archetypes.

For its part, the CPOE management system implements an event listener which focuses on identifying those events triggered only by rules associated with referral notes. Thus, every new CPOE request recorded into the EHR is processed by this system, which consequently instructs the CPOE manager to initiate the computerized orders specified in the referral note.

As a result, the CPOE manager generates the corresponding messages addressed to remote information systems based on the instructions specified in the archetype that activated the rule. To that end, the specifications inside a computerized order will be accessed by using the same archetype that triggered the CPOE instruction to query the EHR. Consequently, the CPOE manager is responsible for classifying the incoming orders depending on the services requested, and then generate the messages specifying the activities to be undertaken (see Figure 13).

Accordingly, the CPOE management system must implement diverse communication profiles depending on the specific services that clinicians could require from remote information systems. In addition, in the event that a number of complementary information systems must work together, the workload of those systems will also be coordinated through the diverse communication profiles implemented at the CPOE management system. In these terms, the CPOE communication services will be used to deliver the resulting messages to the target information system in compliance with the IHE profiles it corresponds for each integration scenario. For instance, the imaging related archetype "openEHR-EHR-INSTRUCTION.request-imaging_exam.v1" from the openEHR's CKM [113], would generate a HL7 ORM/OMI message requesting imaging study to the RIS in compliance with the radiology profiles provided by IHE [166] (see Figure 14).

The CPOE management system also must handle any result or progression upon the activities requested, reported by the remote information systems receiving the CPOE instructions. Specific action-type archetypes are used at this point to transcribe the incoming messages into the EHR system. Although the management of some clinical reports is traditionally allocated to specific information systems, the EHR must be ready also to receive reports built in compliance with different reference models. Thus, to maintain the autonomy among information systems, the integration service of the EHR is used to distinguish different types of reports received in the service. Then, the information contained inside those reports is mapped according to the archetype model formalized in the EHR (Figure 14).

At this point, it should be noted that the CPOE management system must handle in parallel the communication profiles involved to complete every activity planned within a specific computerized order. Thus, considering that completing those activities will extend in time, the CPOE manager will put them in queue as long as the requesting order is still active. In this way, the notification delivery

addressed to remote information systems will be administered according to the progress and priority of queued activities.

In that respect, the CPOE management system uses a standard ISM which defines normalized states and transitions for each one of those activities specified in the instruction. Given that a single computerized order produces several activities which can be undertaken in parallel, an aggregate state determined as a combination of the states reported by all those activities is used to manage the overall lifecycle of single instructions. Thus, according to all possible combination of activities, the state for instructions has been simplified into four steps (pre-active, active, inactive, terminated) [149].

Monitoring the states of activities related to active instructions or actions can also be used to determine the transitions among workflow stages and move forward through decision points defined within clinical processes. In fact, the same instruction and action-type archetypes analyzed by the CPOE manager can be included in clinical processes handled by the WfMS (Figure 13).

Laboratory Information Management System (LIMS)

Basically, the LIMS would implement the ordering, scheduling, processing, and result reporting activities proposed in the Laboratory Testing Workflow (LTW) integration profile provided by IHE [165].

According to this, the LIMS will receive CPOE requests in the form of HL7 ORM/OML messages dispatched from the EHR. Those messages would specify the orders to conduct specific laboratory studies. Based on the orders received, the LIMS must schedule the patients whose samples would be extracted for analysis. At this point, IHE PIX and PDQ profiles are used to retrieve demographic information to link unambiguously the extracted samples with the patient they belong.

Then, the laboratory automation system would proceed with the analytics requested, and would send results obtained to the LIMS.

Finally, clinically significant observations about the analytics registered into the LIMS would be sent back to the EHR using HL7 Unsolicited transmission of an Observation or Result (ORU) or Unsolicited Laboratory Observation (OUL) messages.

Pharmacy information management system

According to the pharmacy interoperability model defined in the Hospital Medication Workflow (HMW) from the IHE pharmacy profiles, all pharmaceutical prescriptions are notified to the pharmacy information system of the hospital using HL7 Pharmacy/Treatment Order (OMP) messages. Such information system is engaged to administer those prescriptions. To that end, all pharmaceutical advices (allergies, equivalent drugs, etc.) and medication dispense (stock, resupply, preparation, etc.) must be checked from pharmacy repositories before validating the new dispense [167].

When the prescription is confirmed and prepared for the corresponding patient, the information system would identify them unambiguously (using IHE PIX, PDQ profiles) and provide them personalized information about which medications have to receive in each case.

Whenever a prescription of medication has been addressed, the pharmacy information system would send back HL7 Pharmacy/Treatment Dispense Messages (RDS) informing to the EHR system about details concerning the medication dispense carried out.

Remote Patient Monitoring (RPM) system

The implementation of RPM services was determined according to interoperability design guidelines for personal health systems proposed by Continua Health Alliance [168]. According to those recommendations, the service monitoring a patient begins with an ORM order message sent from the EHR system. This would provide the parameters required to set up a monitoring scenario aimed at registering specific parameters concerning a patient for a period of time.

A monitoring service can involve more than one personal health device, each one of which periodically registers heterogeneous diagnostic parameters about a patient. Thus, all data contributed by each one of those devices would be received, using specialisations of the ISO/IEEE 11073 communication standard depending on the health device used, into a monitoring manager system.

That manager in turn would transfer periodically any clinically significant signals and measurements from all health devices it handles, to a RPM server for data analysis. In this regard, IHE PCD-01 transactions of the IHE Device to the Enterprise Communication (DEC) profile in the IHE patient care devices technical framework would be used to guarantee a reliable arrival of the information (Figure **14**).

The monitoring server would register all data received from health devices, and then filter – either automatically or as a result of analysis of clinicians – the huge amount of data generated over time to recognize clinically significant patterns and findings. In that respect, demographic services would be checked (using IHE PIX and PDQ profiles), to identify unambiguously all contributions that correspond to the monitoring studies of a patient in particular. In this way, services aimed at data visualization would provide to clinicians a framework to analyse jointly all data comprised in specific studies. And thereby, the information considered relevant for diagnosis would be registered as reports along with corresponding observations of clinicians.

Finally, according to the IHE Cross-enterprise Document Reliable interchange (XDR) profile, the RPM server would send back HL7 CDA compliant Personal Healthcare Monitoring Reports (PHMR) to the EHR system which initially requested the monitoring service [160, 168].

Medical image management system

These systems provide a standard-based solution to manage clinical studies that involve medical imaging. In this regard, DICOM is the most extended standard for medical image management. Therefore, the communication among imaging systems is addressed in compliance with this standard. According to this, the architecture of medical image management distinguishes the three components below:

- Imaging modalities: Any device that acquire diagnostic images in compliance with DICOM standard is categorized by an imaging modality. Those use DICOM Message Service Elements (DIMSE) built upon TCP communication protocol to exchange information with the PACS. According to those services, the imaging modalities are able to process worklists corresponding to the patients scheduled to conduct imaging studies in that device. In addition, once the studies described in the worklist have been acquired, the resulting images are sent to the corresponding PACS.
- Picture Archiving and Communication System (PACS): Basically it is a server allocated to store, organize and share the imaging studies provided by all imaging modalities which administers. The PACS are moreover connected to the RIS, so they receive orders for scheduled imaging studies and demographic information retrieved from information systems distributed along the ESB. That information which is then distributed as worklists among the corresponding imaging modalities. On the other hand, PACS are also responsible of supplying the imaging studies displayed into the DICOM viewers used by the image-reporting workstations. The resulting reports, however are managed by the RIS. The PACS implements DIMSE upon TCP communication protocol, to coordinate the services it provides with regard to the aforementioned components contained in a DICOM network (RIS, DICOM viewer, image modalities).
- Radiology Information System (RIS): It provides services regarding medical imaging studies to other information systems connected to the ESB. At this point, IHE SWF (Scheduled Workflow) profile can be used to define the communication from when imaging studies are requested to when the report is returned to the requestor. In this regard, the RIS is able to handle the requests for imaging studies coming from other information systems (HL7 ORM/OMI messages), and redirect them to the PACS as DICOM worklists [166]. Once those studies have been acquired using the imaging modalities, they are loaded from the PACS to be reviewed and reported according to the clinically significant findings observed on the images. Then, the reports resulting from the imaging studies are handled by the RIS, so they can be sent to the EHR as unsolicited observation messages in compliance with HL7 standard (HL7 ORU).

Chapter 4:

Contributions to clinical process modeling in ophthalmology

This chapter gathers some modelling experiences carried out in the SNS-O in compliance with the guidelines presented in the last chapter. Specifically, three healthcare scenarios in the SNS-O were formalized into electronic models: a remote screening for DR, a high resolution consultation to monitor the treatment in AMD, and a follow-up service for patients diagnosed with CG.

In light of the continuous evolution of the clinical knowledge, it is expected that future revisions will lead the aforementioned electronic models to evolve accordingly. For this reason, it should be noted that the knowledge artefacts mentioned along this Thesis were last verified in July 2016.

4.1 MODELLING A REMOTE SCREENING SERVICE FOR DR

4.1.1 DEFINITION OF THE PROJECT

Previous experiences have proved that specifically trained GPs can screen patients for DR using NMR [50, 169]. Specifically trained nurses and imaging technicians also can perform the diagnostic tests required in this healthcare process [170]. Whereas traditional consultation considers that the expert ophthalmologist is responsible for handling the entire process, this new framework distinguishes different active roles in the process of detecting DR [47]:

- The "test acquisition" role involves the use of medical devices to obtain images and data of sufficient quality for diagnosis. Nurses or technicians can reliably perform this task.
- The "DR screening" role includes observation of diagnostic tests to identify signs of DR and determine if the patient being examined has treatable DR. GPs can reliably perform this task.
- The "medical care supervision" role is that in which retina specialists assume the ultimate responsibility in this process by interpreting the signs of DR to classify the disease and choose the appropriate treatment. Occasionally, they also supervise the work of other clinicians to verify correct functioning of the service.

A primary consequence of this new assignment of different tasks to specialized personnel based on fundus photography is that it is more cost effective compared to traditional methods of DR assessment [55, 171-173].

However, the implementation of new healthcare proposals is hindered by the intense modelling efforts required to update the knowledge base, already registered into static and vendor-specific electronic health information systems [10]. This is due to several factors. First, there is an important interdisciplinary gap between clinicians and software developers when it comes to define the specific healthcare scenarios; and, second, the continuous evolution of medical knowledge. The consequent developmental costs resulting from this endless redesign become unaffordable for any healthcare service [10]. Further, specifically in ophthalmology, EHRs have special requirements regarding other clinical specialties that are not considered by traditional information systems [22].

In the light of the above, although this DR screening strategy was successfully implemented into the SNS-O [30, 35], the lack of normalization of the information inside the service makes it difficult to manage this service in the long term. This setting for the DR screening service is restricted to the specific healthcare scenario in the SNS-O to which it was designed for. Thus, any change upon the clinical procedure and extending this experience to new healthcare scenarios were not supported.

Considering the effort invested in the design and coordination of the healthcare resources available, the need arises to formalize this screening service so as to make the clinical process independent to the setting of local implementations. The methodology proposed in the previous chapter of this Thesis was used to that end. Therefore, different healthcare organizations sharing the same model could coordinate the clinical activities focused on a specific patient, toward a care plan in common.

With the aim of developing a model-driven e-health system for the SNS-O that can automatically manage the information generated during follow-up of retinopathy for diabetic patients, a study of the state of art was performed regarding this evidence-based medicine process. Experts in that clinical domain (ophthalmologists, GPs and nurses), as well as statisticians of the SNS-O, in collaboration with engineers of the UPNA specialized in ICTs participated in a multidisciplinary discussion committee. Once the roles within the work team were established, different knowledge sources were reviewed (literature, evidence based experience in SNS-O, healthcare standards/guidelines) to establish an up-to-date clinical process to handle a DR screening service [47, 57, 58].

Before implementing that clinical process, the work team interconnected every device involved to share the information registered during medical practice, for which the essential tasks were organizing and standardizing the ICTs to be used during the service.

4.1.2 DESIGN OF THE CLINICAL PROCESS

B.1 Definition of the Clinical Process

The process regarding DR screening was defined according to the different stages a patient goes through in the healthcare service. First, patients in a population at risk for DR are evaluated before they begin the follow-up. Then, if convenient, those patients are scheduled for periodic necessary diagnostic tests to detect existing DR, ensuring the quality of acquisitions for diagnostic purposes. GPs trained to detect symptoms of DR then remotely review images and information acquired during evaluations. Retina specialists reassess the cases positive for DR. Depending on disease severity, the specialists reach a therapeutic decision and schedule a clinical procedure accordingly. Finally, the corresponding treatment is administered depending on each patient's specific diagnosis (see Figure **15**).

Once the work team identified those different stages, they were analyzed in detail:

- STAGE 1 (Patient admission): A patient can be referred for follow-up of DR since diabetes was diagnosed by an endocrinologist or if there is suspicion of DR due to symptoms detected while evaluating another eye disease during an ophthalmologic consultation or a routine primary care examination. In that sense, the admission stage is used to gather relevant patient clinical information. That preliminary information will be useful during follow-up and to determine the convenience of including or not including the patient in the screening service.

- STAGE 2 (Follow-up schedule): In the event that the DR screening is considered appropriate, the follow-up service can initiate. Therefore, the diagnostic tests to detect and classify the disease are scheduled.

- STAGE 3 (Diagnostic tests): The diagnostic tests of SNS-O consist of NMR and the measurement of IOP. Most healthcare organizations recommend repeating these tests at least once annually for patients with diabetes even in those without signs of DR. This prevents clinicians from overlooking serious symptoms of disease progression during the intermediary period between revisions [57].
  The development of digital and interoperable diagnostic devices implemented in the SNS-O provides ubiquitous access from remote workstations to the results of the diagnostic tests. So, the results of these tests can be evaluated remotely [174]. This allows nurses or imaging technicians (referred to as "imagers") to use those devices to perform diagnostic tests, whereas traditionally the presence of ophthalmologists was required during consultations [175]. At this point, the imagers must guarantee the quality of the acquisitions, so that the ophthalmologists can make reliable evaluations of those acquisitions.
  The measurement of corrected IOP involves tonometry and pachymetry. However, the results of those tests include a single IOP value, and registering this measurement is sufficient for later diagnostic purposes. Initially, the IOP measurement was not a component in the screening procedure for DR, but it later was included due to the epidemiologic interest in identifying early symptoms of other ophthalmic diseases associated with diabetes. In fact, measuring the IOP identifies patients with dangerous IOP levels (≥22 mmHg), the point at which patients must be referred directly to the corresponding ophthalmologist, even if other tests do not show evidence of disease.

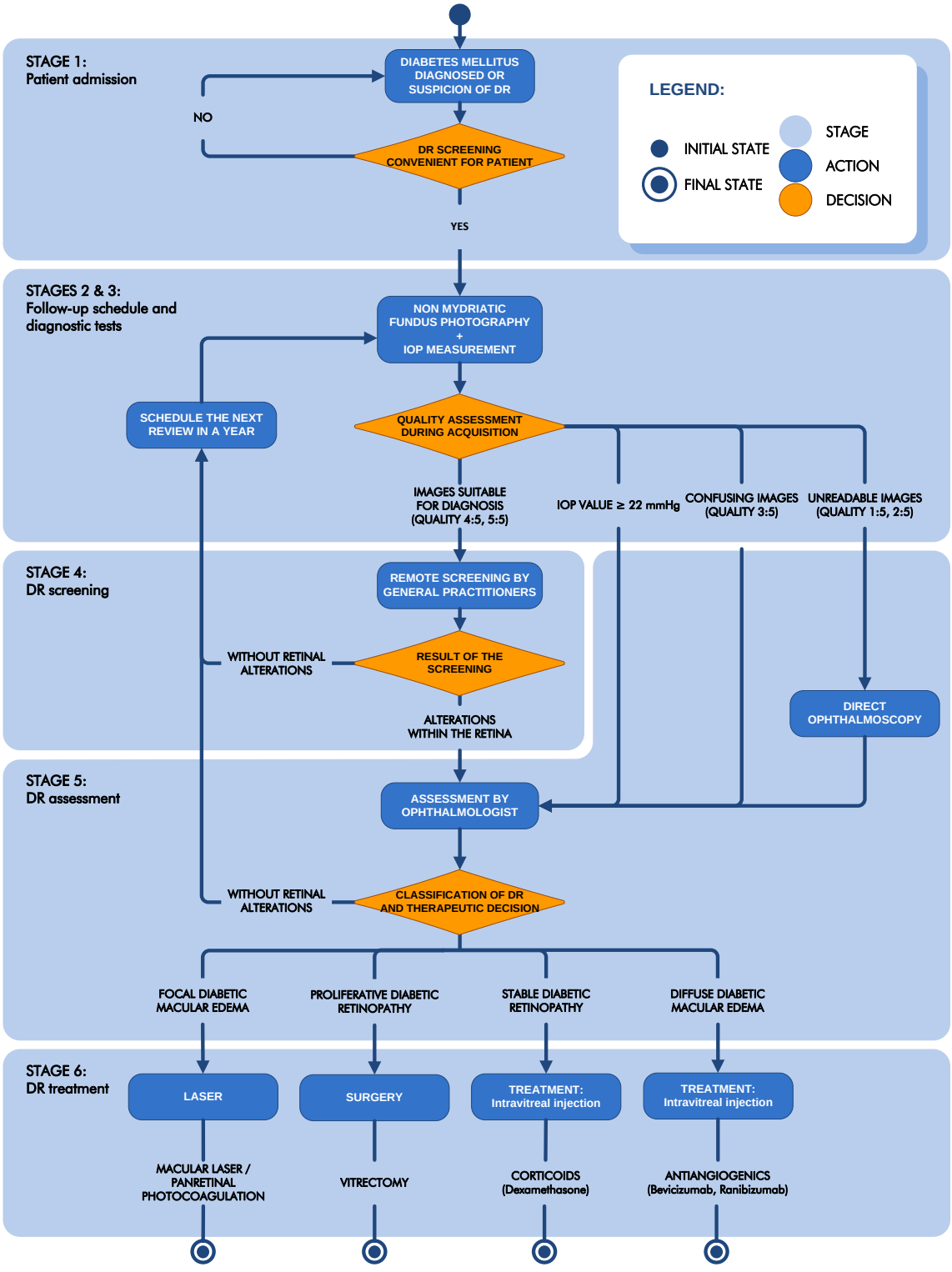

Figure 15: *Activity diagram showing the workflow DR screening service in the SNS-O.*

However, validation of the funduscopic photographs is more complex since imagers must review the quality of each acquisition at the capture stage before referring them for assessment. The procedure chosen for that purpose involves classifying fundus images according to the overall photographic quality using a scale based on objective findings [172, 176, 177]. Different proposals have been reported when choosing a scale to measure quality; we used a scale ranging from 1–5, in which 1 indicates the worst and 5 indicates the best as Lamirel et al. proposed in the FOTO-ED study [176]. For diagnostic purposes, images of level 3 or lower that can confuse imagers are discarded. With unreadable images (≤2), the patient is referred immediately for a face-to-face ophthalmic consultation.

When images of the ocular fundus are obtained, the numbers of retinal fields photographed vary depending on the purpose of the study. Considering the seven fields defined by the ETDRS [56, 58], Vujosevic et al. suggested [178] that a central 45-degree color image is sufficient to determine the absence or presence of DR and DME; however, a minimum of three fields is needed to classify the disease according to the international classification of DR proposed by the AAO [45, 46]. Nevertheless, according to clinical criteria, within the specific scenario of the SNS-O, two fields were considered adequate to manage the DR screening: one focused on the papilla and one focused on the macula.

During acquisition, some artefacts can appear due to small pupils, cataracts, or other complications resulting from the capture. Therefore, acquisition is repeated when the image is inadequate for diagnostic purposes. To avoid extending this procedure unnecessarily, the test is limited to three attempts unless a technical issue is identified. From the fourth attempt on, the probability of obtaining a high-quality photograph is 20% at most [176].

In patients with a small pupil, the imager can request a mydriatic agent to obtain suitable retinal images; an ophthalmologist must supervise the drug instillation to reduce the risk of angle-closure glaucoma. For this reason, these patients must be referred directly for a face-to-face ophthalmic consultation.

Once the necessary images for DR assessment are acquired and validated (quality level 4 or 5), they are sent to a PACS accessible to image reviewers. These acquisitions are labelled with the same study identification number, making it possible for a reviewer to retrieve every image corresponding to that specific diagnostic study.

- **STAGE 4 (DR screening):** Image studies suitable for diagnosis are loaded from the PACS to remote workstations where image reviewers search for symptoms of DR.

  Retinopathy can be classified with different levels of precision, although for screening purposes it is sufficient to classify patients into two categories: those presenting signs of DR and those without signs of DR, to wit, ETDRS severity level ≤20 (seen in section 2.1.1) [47, 56]. There is a third option in case of uncertain images: the patient is referred to a specialist for review. To support this classification, it is recommended that the findings identified during the examination of the posterior chamber and the criteria chosen to reach a diagnostic decision be described. Given that most patients with diabetes do not present with symptoms of DR, this screening will markedly reduce the workload of ophthalmologists, since only retinopathies and uncertain studies need more specific assessment [31].

- **STAGE 5 (DR assessment):** The images in this stage must show signs of DR except for: false positives generated during screening, images that created uncertainty for GPs, or diagnostic test acquisitions without sufficient quality for remote screening [31].

  Thus, ophthalmologists must assess the diagnostic tests available and, where necessary, schedule an office assessment to thoroughly study each case and determine the best procedure to avoid disease progression.

By reviewing the findings and diagnostic criteria registered during screening, the assessment can be accelerated. Even so, the final classification of DR must be based on the criteria and findings of the ophthalmologists. Before reaching a therapeutic decision, the studies are classified using the "International Clinical Diabetic Retinopathy and Macular Edema Disease Severity Scale" proposed at the AAO [45, 46]. Therefore, according to the DR types, the studies can show proliferative or non-proliferative disease; the latter, depending on symptom severity, is classified as mild, moderate, or severe. ME, if present, also can be classified as mild, moderate, or severe. Thereafter, different therapies will be chosen according to the severity and specific symptoms of DR (Figure 15).

- STAGE 6 (DR treatment): Once the most suitable treatment is determined, the special features of the procedure being performed are documented. Intraocular injections, laser therapy, and surgery are the procedures considered in this model. Diffuse DME is treated either by intravitreal corticoids (e.g. dexamethasone) and/or anti-VEGF agents (ranibizumab, aflibercept, or bevacizumab); focal DME is treated by macular laser. In contrast, PDR requires PRP or vitrectomy [57].

B.2 Study of Clinical Concepts

As a result of studying the healthcare scenario described in step B.1, a set of clinical concepts were identified for structuring the electronic model that would manage the remote screening service for DR.

Given that archetypes are formal definitions of concepts from a clinical domain, these would be used to model the clinical concepts listed at this point in a standardized and reusable manner [26]. Therefore, rather than modelling every concept from scratch, first the work team reviewed the archetypes available in the openEHR CKM repository [113]. Consequently, equivalent archetypes were found for some of the clinical concepts involved in the healthcare scenario. Other archetypes found were close to the concepts sought, but they would need to be adapted to meet the requirements of the healthcare scenario. Lastly, the rest of clinical concepts for which no equivalent archetypes were found would be modelled from scratch.

All concepts considered relevant for the management of the DR screening have been listed in Table 5. These concepts will constitute the basis upon which to further develop the electronic model that would manage DR screening service.

B.3 Hierarchical Organization of Knowledge Artefacts

The design of archetypes for the healthcare scenario of DR screening did not begin until the work team agreed to the overall screening service.

First of all, the clinical concepts listed in Table 5 were structured according to their occurrence into the clinical stages described for that clinical process. Then, based on the hierarchy described in section 3.1.2, relationships were drawn from each of these concepts toward the rest of knowledge artefacts involved in the DR screening service (see Figure 9).

During this process, the work team used collaborative diagramming and mind-mapping tools to facilitate organizing the knowledge from domain experts, resulting into the diagram shown in Figure 16 [146, 147].

Table 5: *Clinical concepts to be modelled as a result of study of each stage in the service of DR screening.*

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
1.	Reason for encounter	- Found on CKM - Usable as is	Evaluation	Stage 1
2.	Clinical synopsis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4 Stage 5
3.	Problem/diagnosis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4 Stage 5
4.	Diagnostic criteria DR	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 1 Stage 4 Stage 5
5.	Story/history	- Found on CKM - Usable as is	Observation	Stage 1
6.	Symptom/Sign	- Found on CKM - Usable as is	Cluster	Stage 1
7.	DR screening convenient	- No equivalences found - Archetype has to be modelled from scratch	Evaluation	Stage 1
8.	Care plan (request)	- Found on CKM - Usable as is	Instruction	Stage 2
9.	Care plan	- Found on CKM - Usable as is	Action	Stage 2
10.	Referral request	- Found on CKM - Usable as is	Instruction	Stage 2
11.	Imaging examination request	- Found on CKM - Usable as is	Instruction	Stage 2
12.	Acquisition details on eye fundus images	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 2 Stage 3
13.	Procedure	- Found on CKM - Usable as is	Action	Stage 3 Stage 6
14.	Intraocular pressure measurement	- Found on CKM - It has to be adapted	Observation	Stage 3
15.	Central corneal thickness details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 3
16.	Medical device	- Found on CKM - Usable as is	Cluster	Stage 3
17.	Medical device details	- Found on CKM - Usable as is	Cluster	Stage 3
18.	Imaging examination	- Found on CKM - Usable as is	Action	Stage 3
19.	Anatomic location	- Found on CKM - Usable as is	Cluster	Stage 3
20.	Mydriasis application	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 3
21.	Medication amount	- Found on CKM - Usable as is	Cluster	Stage 3

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
22.	Funduscopic examination of eyes	- Found on CKM - It has to be adapted	Observation	Stage 3 Stage 4 Stage 5
23.	Diagnostic report request	- No equivalences found - Archetype has to be modelled from scratch	Instruction	Stage 3 Stage 4
24.	Classification of Diabetic Retinopathy	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 4 Stage 5
25.	Exclusion of a problem/diagnosis	- Found on CKM - Usable as is	Evaluation	Stage 4 Stage 5
26.	Service request	- Found on CKM - Usable as is	Instruction	Stage 4 Stage 5
27.	Recommendation	- Found on CKM - Usable as is	Evaluation	Stage 5
28.	Medication order	- Found on CKM - Usable as is	Instruction	Stage 6
29.	Medication action	- Found on CKM - Usable as is	Action	Stage 6
30.	Intravitreal injection details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 6
31.	Adverse reaction	- Found on CKM - Usable as is	Evaluation	Stage 6
32.	Procedure request	- Found on CKM - Usable as is	Instruction	Stage 6
33.	Ophthalmic laser procedure details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 6
34.	Ophthalmic surgery details for posterior segment of eye	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 6

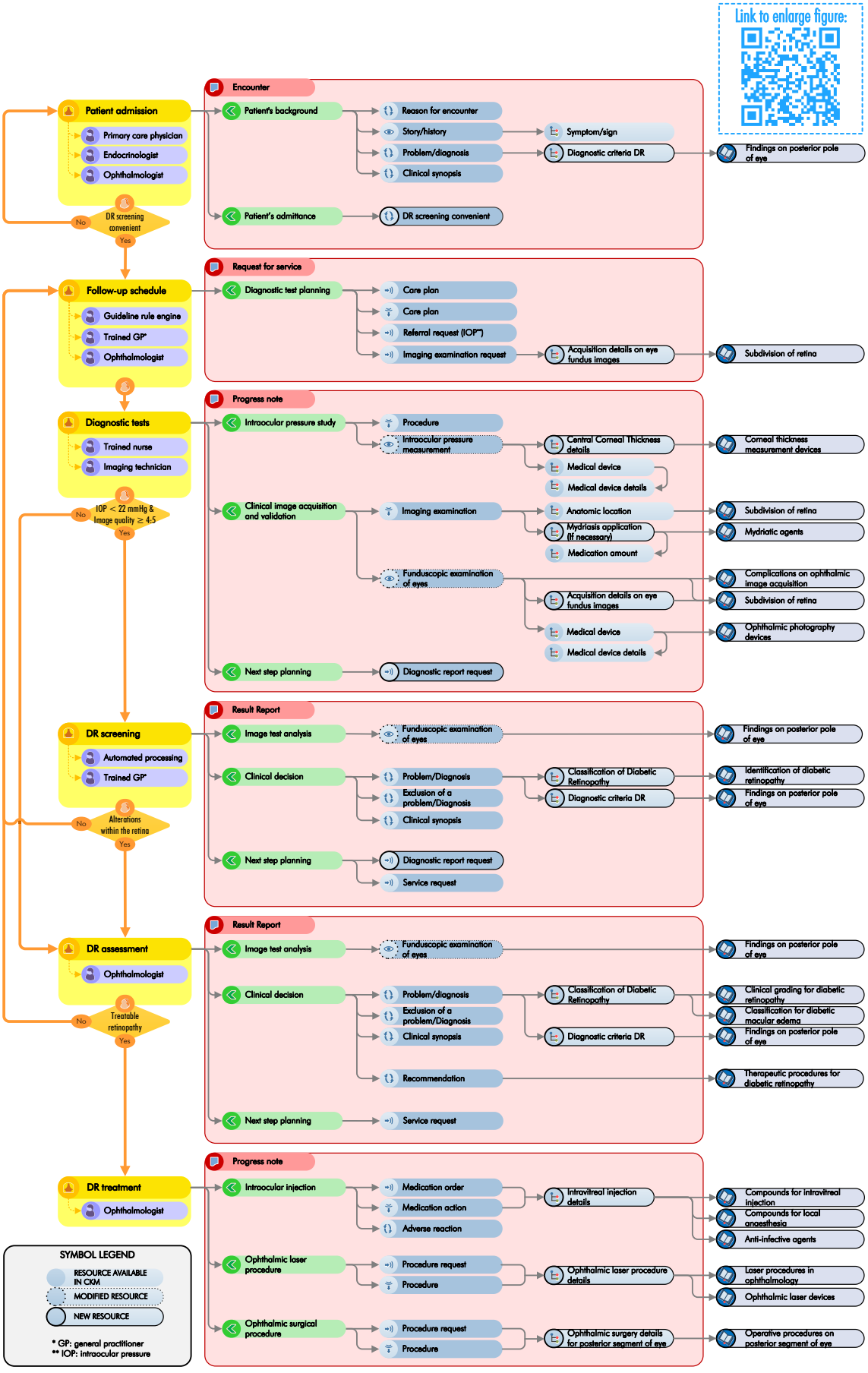

Figure 16: *Hierarchy among the knowledge artefacts involved in the remote screening service for DR.*

4.1.3 BUILDING THE ELECTRONIC MODEL

Once the DR screening service had been discussed at a theoretical level, the same work team that defined this clinical process was convened to transcribe the resulting knowledge into electronic models interpretable by health information systems.

To that end, first, the concepts identified during the design of the clinical process would be integrated into archetypes that could be used in any clinical scenario; then, those concepts in the archetypes would be linked to standard terminologies. Once the archetypes had been defined, they were enclosed and constrained into templates. Indeed, each template must be designed according to the specifications of the clinical scenario in which it will be used. Then, the guideline rules aimed at managing the service workflow were defined. Finally, UI forms were designed to organize all these artefacts into end-users' front-end applications.

Furthermore, given all the knowledge artefacts involved in this procedure, a model-driven health computing platform must be launched to manage them all and test the electronic model into a real use case scenario.

C.1 Creation and Update of Archetypes

Theoretically, archetypes must be designed to be independent of the usage context. Nevertheless, our efforts focused on development of elements responding to the needs of the remote screening service for DR. In that respect, diverse archetypes were made available to formalize each of the clinical concepts listed in Table 5. Therefore, excluding organizational classes (section and composition), 34 different archetypes were necessary to cover the clinical concepts involved in the DR screening service launched in the SNS-O: 10 archetypes were created from scratch, and 24 were downloaded from the openEHR CKM, two of which had to be adapted.

At this moment the authoring process continues on the CKM. In this regard, our work team was convened to actively collaborate in an archetype incubator in which ophthalmologists and healthcare modellers distributed around the world contribute with their expertise to continuously improve the archetypes from the clinical domain of ophthalmology. Consequently, the proposed new archetypes as well as those resulting from modifying the existing ones were uploaded to this repository with the purpose of make them available to be reviewed by experts from all over the world.

Therefore, it is expected for this model to be in constant evolution depending on the progress of the methodology for the follow-up of DR. Consequently, extending this clinical process to other healthcare facilities and periodic updating of that model will be immediate. And each healthcare organization adopting these archetypes also will be interoperable worldwide.

C.2 Definition of Semantic links to Clinical Terminologies

Once the clinical concepts had been modelled, terminology definitions were determined for those data elements contained in each one of the archetypes. First, considering that most archetypes obtained from the CKM were originally defined in English, the new archetypes we proposed were also modelled using that language. Once modelled, we translated the archetypes into additional languages so as to use them into the SNS-O. In this way, we expect to reach greater participation on the part of the modellers during the authoring process which takes place in the CKM.

Secondly, as many data elements as possible were linked to standard terminology services such as SNOMED-CT or ICD-10; even some references to equivalent concepts from technical standards like DICOM were included. In this way, these terms maintain the semantic meaning independently from the translation, since selected terminology services support multiple languages.

Some of the data elements identified can adopt different values depending on the context they are used. So, instead of modifying the source archetypes, the occurrences of those elements were

determined by mapping them to normalized lists of terms at template level. In this regard, some normalized lists of terms – known as termsets – were specially designed for the DR screening service.

Specifically, 16 new termsets were created to bind selectable data elements to standard terminology services. Some of them were used to specialize generic archetypes with lists of terms specific to the healthcare scenario proposed. Other termsets were reused in different archetypes, making it possible to work with the same list of terms in different archetypes (e.g. "Findings on posterior pole of eye" or "Subdivision of retina") (see Table 6).

C.3 Building Templates

The archetypes modelled in previous steps were structured into templates, according to the hierarchy defined along the design of the clinical process (Figure 16). These templates, therefore, specify which data elements must be registered for each clinical stage defined in the DR screening service. Because the archetypes contain generic elements to support every use case, their data elements must be constrained to the specialized healthcare scenario where they will be used. Therefore, most elements were disabled at the template level to register only those data elements required for the DR screening service proposed. Any template designer compliant to openEHR ADL could be used to that end [155, 179]. In our case, ADL 1.4 was chosen to build templates and archetypes, since development tools available so far are more mature.

Templates are very changeable knowledge elements, so larger ones should be adapted to more manageable proportions. In this sense, composition-level templates were built from grouping section-level templates, which embedded the archetypes assigned to section-type archetypes into self-contained templates. These section-level templates can be reused within different compositions, hence in the event of modifying or updating a specific section, the respective compositions would be automatically updated instead of repeating the modifications repeatedly.

As a result of that modelling, 18 new templates were built; 12 of them corresponded to the section-type templates devised to organize the archetypes involved in each clinical stage. With the goal of not duplicating templates, 2 of these templates were reused along the clinical process: on the one hand, the template "Image test analysis for DR" was equally applicable to DR screening and assessment stages. On the other hand, in the case of "Next step in DR screening service" the same goes for requesting a remote screening or an office assessment when the results of IOP and NMR study tests are available, to schedule next review in a year, or to plan the appropriate treatment for the patient. Therefore, although it first appears on the stage for diagnostic tests in the DR screening service, this template was also needed in DR screening and assessment stages.

The remaining 6 templates were created to manage the compositions containing the aforementioned sections. Therefore, clinicians can use the latter to register information about clinical evaluations (see Figure 17).

Although the resulting templates were originally built for the use case scenario presented along this section, these were made available on the CKM under a Creative Commons licence. Thus, any healthcare modeller can obtain our templates and adapt them to the requirements of specific healthcare organizations.

Table 6: *Termsets modelled to support the archetypes modelled for the DR screening service.*

	Termset name	Description of termset	Process stages in which it is applicable
1.	Findings on posterior pole of eye	Clinical findings identifiable in posterior pole of eye.	Stage 1 Stage 4 Stage 5
2.	Subdivision of retina	List of zones in eye retina for ophthalmic image positioning.	Stage 2 Stage 3
3.	Corneal thickness measurement devices	List of methods to obtain the corneal thickness measurement.	Stage 3
4.	Mydriatic agents	List of mydriatic agents and their corresponding doses validated for ophthalmologic use.	Stage 3
5.	Complications on ophthalmic image acquisition	List of possible complications during ophthalmic imaging studies that may affect the quality of acquisitions (based on Table CID 4222 of DICOM standard).	Stage 3
6.	Ophthalmic photography devices	Lists the ophthalmic photography acquisition devices (based on Table CID 4202 of DICOM standard).	Stage 3
7.	Identification of diabetic retinopathy	Identification of presence or absence of DR for screening purposes.	Stage 4
8.	Clinical grading for diabetic retinopathy	International Clinical Diabetic Retinopathy Disease Severity Scale.	Stage 5
9.	Classification for diabetic macular edema	Classification levels for the presence of ME as defined by the international scale for DR grading.	Stage 5
10.	Therapeutic procedures for diabetic retinopathy	List of therapies available to treat different stages of DR.	Stage 5
11.	Compounds for intravitreal injection	Compounds administered in ophthalmology in the form of intraocular injection.	Stage 6
12.	Compounds for local anaesthesia	Compounds available to apply local anaesthesia.	Stage 6
13.	Anti-infective agents	List of anti-infective agents available.	Stage 6
14.	Laser procedures in ophthalmology	List of laser procedures available for ophthalmic purposes.	Stage 6
15.	Ophthalmic laser devices	List of laser devices for ophthalmic use.	Stage 6
16.	Operative procedures on posterior segment of eye	List of operative procedures on the posterior segment of eye.	Stage 6

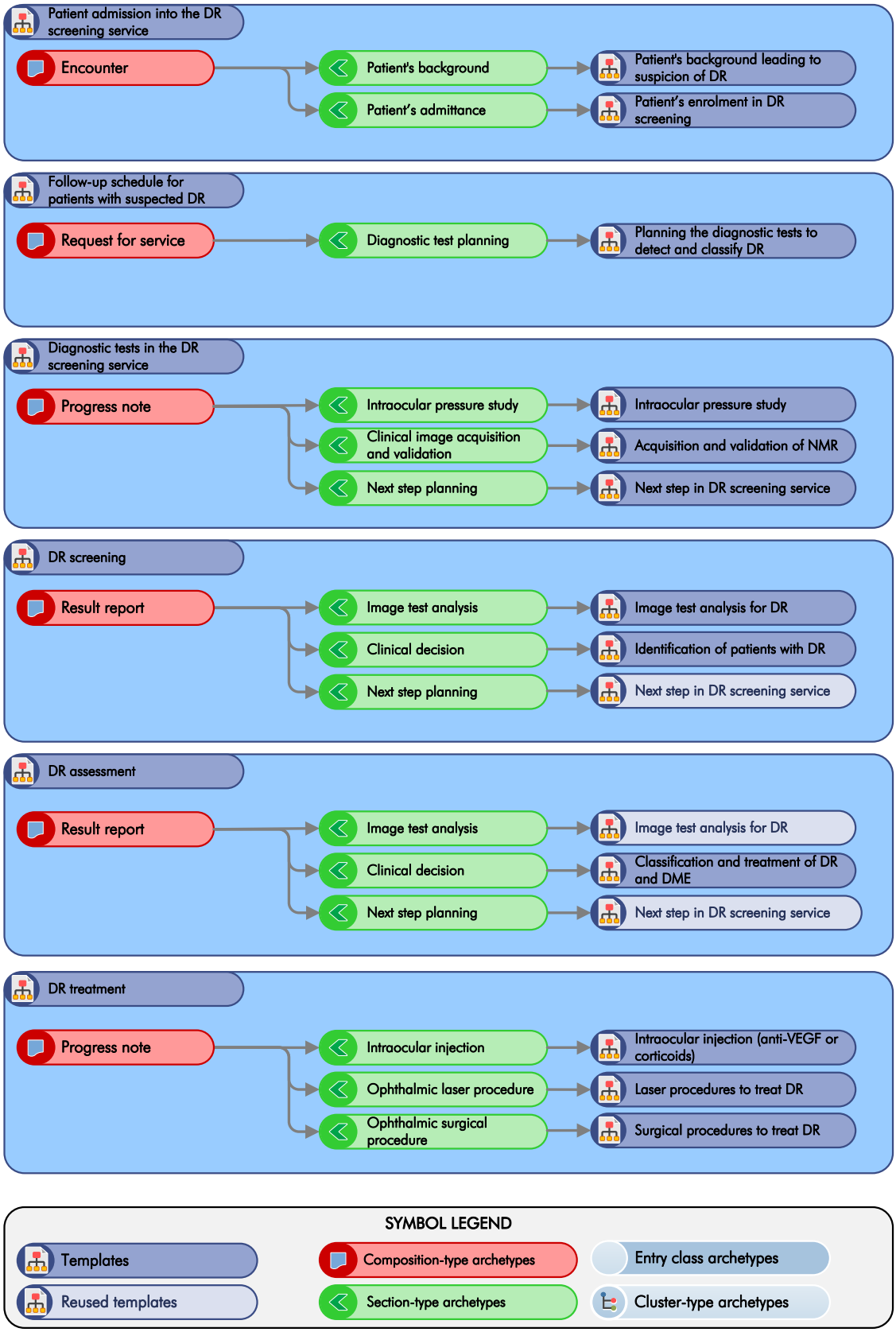

Figure 17: *The structure of templates envisaged to register clinical encounters resulting from the remote screening service for DR.*

C.4 Modelling Guideline Rules and Workflow

Seven rules were configured to handle the decisions about workflow. To define these rules, the GDL editor developed by Cambio Healthcare Systems was used because it makes use of the reference and archetype models from openEHR [180].

The GDL language queries to EHRs the information registered by means of archetypes or templates and it applies conditions and consequent actions accordingly, making it possible to trigger automatically real-time alerts or events for CDS when data are registered in the EHR.

In this sense and based on the clinical guidelines defining the workflow for the DR screening service proposed, different events were configured such that clinicians receive specific instructions about how to refer patients through clinical stages. In any case, clinicians will make the final decision, and they are free to handle the service manually if required. The guideline rules identified in Figure 16 to manage the workflow of the DR screening service are first described in general terms and then are further detailed in Table 7:

- **DR screening convenient:** The first encounter is used to check if the patient meets the criteria for inclusion in the screening process. This rule activates (or not) the archetypes involved in requesting the diagnostic tests necessary to start the follow-up.
- **Diagnostic tests valid for screening:** This rule validates the diagnostic tests once acquired, and discards any unusual value before proceeding with the screening stage. Then, if everything is correct, this rule requests a DR screening report to the corresponding GPs.
- **Office examination required:** Conversely, this rule identifies patients with dangerously high IOP values (≥22 mmHg) or low-quality fundus images (<4 of 5 levels of quality), and therefore arranges directly the patient's assessment at the ophthalmologist's office.
- **Altered retina:** Any alteration identified during screening is reported to the corresponding ophthalmologist (based on the *"Classification of Diabetic Retinopathy"* archetype). Consequently, this rule requests an assessment report to an ophthalmologist. Likewise, the studies that require a second opinion due to the evaluator's uncertainty are referred to ophthalmologist's office.
- **Apparently not altered retina:** In contrast, patients without DR are referred to the next evaluation defined by the follow-up process. Thus, this rule must schedule the diagnostic tests defined for the DR screening service.
- **DR treatment required:** It is triggered whenever the ophthalmologist recommend a therapeutic procedure to avoid disease progression. Consequently, this rule will schedule the procedures and medication prescriptions determined by such recommendation.
- **DR treatment not required:** In case the ophthalmologist, after the office assessment, does not consider it necessary to treat the patient, this rule will refer the patient to the next review irrespective of whether or not there are alterations of retina.

Table 7: *Description of the guideline rules modelled for the remote screening service for DR.*

	Rule name	Conditions	Actions
1.	DR screening convenient	Archetype *"DR screening convenient"*: • Admittance in screening: "Screening compliant"	Archetype instantiated *"Care plan (request)"*: • Care plan name: "Remote screening service for DR" Archetype instantiated *"Referral request"*: • Service requested: IOP measurement Archetype instantiated *"Imaging examination request"*: • Service requested: NMR
2.	Diagnostic tests valid for assessment	The preconditions for this rule are a "Pressure" value below 22mmHg for the archetype *"Intraocular pressure measurement", and levels 4 or 5 for the* "Quality of acquisition" proposed for the archetype *"Funduscopic examination of eyes"*. Archetype *"Care plan"*: • Care plan name: "Remote screening service for DR" • Pathway: "Care plan completed"	Both diagnostic tests must be completed to run the corresponding actions. Archetype instantiated *"Diagnostic report request"*: • Service requested: "Remote screening of DR" • Reason for request: "Completed the diagnostic tests necessary for assessment"
3.	Office examination required	Archetype *"Intraocular pressure measurement"*: • Pressure ≥22 mmHg (Dangerously high intraocular pressure) Archetype *"Funduscopic examination of eyes"*: • Quality of acquisition: Level 1, level 2, or level 3 (Low eye fundus image quality)	When any of the two conditions ("Dangerously high intraocular pressure" or "Low eye fundus image quality") are met, the request for assessment on the ophthalmologist's office would be triggered. Archetype instantiated *"Diagnostic report request"*: • Service requested: "DR assessment at ophthalmologist's office" • Reason for request: "Patient presenting dangerously high intraocular pressure" or "Quality of eye fundus images inadequate for remote diagnosis" depending on the case.

	Rule name	Conditions	Actions
4.	Altered retina	Archetype *"Classification of Diabetic Retinopathy"*: • DR identification: "DR identified" or "Ungradable"	Archetype instantiated *"Diagnostic report request"*: • Service requested: "DR assessment at ophthalmologist's office" • Reason for request: "Clinically relevant ophthalmological disorders identified" or "Second opinion needed" depending on the case.
5.	Apparently not altered retina	Archetype *"Classification of diabetic retinopathy"*: • DR identification: "No apparent DR"	Archetype instantiated *"Service request"*: • Service name: "Follow-up schedule for patients with suspected DR" • Description: "Follow-up comprised by NMR study and IOP measurement" • Service due: 12 months
6.	DR treatment required	The conditions established within the rule "Altered retina" comprise the precondition for this rule. Archetype *"Service request"*: • Service name: "DR treatment" Archetype *"Recommendation"*: • Recommendation: "Scatter PRP laser therapy", "Focal and/or grid laser photocoagulation", "Intravitreal injection of corticosteroids", "Intravitreal injection of antiangiogenics", or "Vitrectomy surgery"	Archetype instantiated *"Medication order"*: • Medication item: "Corticoids" or "Antiangiogenics" depending on the values defined in the archetype "*Recommendation*". • Route: "Intravitreal injection" • Clinical indication: Determined by the values defined in the archetype "Classification of Diabetic Retinopathy" for "DR classification" and "Macular edema classification". Archetype instantiated *"Procedure request"*: • Procedure name = "Scatter PRP laser", "Laser photocoagulation" or "Vitrectomy" depending on the values in the archetype "*Recommendation*". • Objective: "DR treatment" • Indication: Determined by the values defined in the archetype *"Classification of Diabetic Retinopathy"* for "DR classification" and "Macular edema classification".
7.	DR treatment not required	Archetype *"Recommendation"*: • Recommendation: "Do not treat" The ophthalmologist has the last word, hence can determine that there is no need for treatment and instantiate the next review, as in the rule "Apparently not altered retina".	Archetype instantiated "Service request": • Service name: "Follow-up schedule for patients with suspected DR" • Description: "Follow-up comprised by NMR study and IOP measurement" • Service due: 12 months

C.5 Modelling UI Forms

When we considered designing UI forms for the DR screening service, we identified different solutions to the same end. However, each of the form definitions studied was exclusive to specific e-health implementations. The lack of agreement on UI specifications nowadays hinders the development of pervasive software tools for UI form modelling, which are in fact essential to implement this strategy. Therefore, for as long as no consensus is reached on this matter, we must stick with the UI form modelling tools available today.

On the one hand, the template designer of Ocean Informatics includes a form designer feature, which leverages the openEHR templates modelled to build customized UI forms. As an outcome, the template designer generates the C# code necessary to compile the resulting UI forms. However, the fact that the resulting code is provided in a given programming language limits the potential implementations on which these UI forms could be applied. Nonetheless standards-based open health computing platforms must interoperate with front-end applications functioning on heterogeneous electronic terminals, regardless if they are built upon diverse technologies.

Alternatively, the open source software tools provided by Cabolabs should be considered in this regard. Indeed, such tools have recently incorporated a library which parses the openEHR Operational Template (OPT) files and automatically generates the corresponding UI forms built upon HTML code. This avoided to define one by one the specific data fields necessary for representing the archetype paths defined within the openEHR templates. Moreover, although by default such library generates HTML code, given that the UI generation tool is provided in open source, it can be adapted to generate the UI views in other programming codes. However, the fully automated generation of views lacks of tools for customization of the UI to the needs of final user.

In this regard, the Marand EhrExplorer provides an excellent form builder which includes a dedicated web interface to model UI forms in an agile way. Once modelled, the resulting forms are saved into the EhrScape server as three complementary form resources: the form-layout, which arranges the information and data fields on the screen. The form-description, which defines how the content of the form would be shown (language, data validation, data-types, etc.). And the form-dependencies, which determine GDL rules among the data elements within the form. The EhrScape server provides these form definition components in JSON format through REST interfaces. Thus, any front-end application connected to the EhrScape server can retrieve the form specifications modelled in a language-independent data format. Then, these form definitions would be transformed by each application into UI views on the programming language it corresponds.

Given the flexibility of this approach, the Marand EhrExplorer was chosen to build the UI forms for the DR screening service at issue. Consequently, 6 different UI forms were created to represent each one of the stages that comprise the clinical process. To build the UI form definitions, first of all, the section-type templates were assigned to different blocks of the layout. Then, separate rows were used to arrange the different entry-type archetypes contained in the same block. This provided a basic structure to arrange the elements on the templates. Otherwise, the resulting clinical forms would be too large and unwieldy to register medical records. On this basis, clinicians applied the modifications considered necessary to adapt the UI forms to the needs of the daily clinical practice.

However, this approach requires access to a valid EhrScape domain. In our case, we used a demo domain from "ehrscape.com" as temporary solution to build the UI forms. Even so, the scenario for this Thesis ought ideally to be provided with open access. For this reason, looking ahead, we prefer the implementation proposed by Cabolabs, as despite the UI form generation tools are still under development, includes open source EHR and EMR applications which have unrestricted access in the cloud, and, if necessary, can also be implemented in our own servers for research purposes.

4.1.4 IMPLEMENTATION OF THE SERVICE

To integrate the use of the electronic models defined along this chapter into the DR screening service from the SNS-O, every information system, diagnostic device, and workstation involved in the clinical process must be adapted beforehand so as to guarantee ubiquitous and instant access to the information registered. To that end, an analysis of the technical environment was conducted, and a standards-based implementation was devised accordingly.

As mentioned in the definition of the project, this clinical process involves three types of workspaces: one for diagnostic test acquisition, one for DR screening, and, one for DR assessment. The first contains the tonometry plus pachymetry instruments for IOP measurement, a non-mydriatic retinal camera, and a PC workstation to register findings identified during acquisitions. The second workspace is located in the workplace of the GPs; there, a PC workstation has access to the PACS and EHR to remotely visualize clinical images and register the consequent clinical reports. The third workspace is similar to the screening workstation but is in the consulting room of the ophthalmologist in the same building where diagnostic tests are performed. Thus, if a patient needs more extensive analysis, immediate face-to-face consultations are possible with retina specialists.

To interconnect those workplaces, two independent but complementary standards were chosen to coordinate the information among different devices and locations: on the one hand, the openEHR standard would be used to manage the medical records resulting from clinical encounters that occur in the DR screening service. On the other hand, DICOM would arrange the acquisition and exchange of diagnostic tests involving medical imaging.

First of all, the non-mydriatic fundus cameras involved in the DR screening service were connected in compliance with DICOM standard to the PACS server that manages clinical images from the entire health service. This server, in turn, is accessible through the corporative network of the health service to the remote workstations where DICOM image viewing tools were installed for assessment purposes (Figure 18).

Concurrently, the openEHR-compliant EHR system should be connected to the PACS server. In this way, the CPOE management system from the EHR would schedule the diagnostic tests through the PACS, and then, the healthcare provider responsible for each workspace could complement the test results with information originated as a result of the healthcare encounter. However, most information systems available within current healthcare services do not yet support the openEHR standard.

Thus, while the diagnostic tests are scheduled through the main EHR server of the healthcare service, which actually is already connected to the PACS, an additional EHR would be dedicated to manage the DR screening service in compliance with openEHR specifications. When necessary, this server will send EHR extracts with relevant healthcare results to the main information system, making that information reusable for other clinical processes. These extracts must be compliant to healthcare messaging standards, according to the different EHRs involved in the health service (Figure 18).

As mentioned above, the openEHR-compliant EHR would be specifically tailored to manage the information generated during clinical encounters corresponding to the DR screening service. To this end, it would implement the archetypes, templates, guideline rules, and UI form specifications modelled along this section. Likewise, the workstations allocated at each workspace would include customized EMR applications that would report the medical records it corresponds to the EHR system.

A primary advantage of the EHR based on archetypes is its flexibility, because it can load a model to manage the DR screening service and apply changes to it as necessary. There is no need to introduce any changes in the main EHR system of the service, even if there are modifications in the clinical process.

As proof of concept, the EHRServer provided by Cabolabs was designated as EHR system for openEHR clinical data storage, whereas the EHRCommitter would serve as front-end to commit the medical records to the EHR. Both applications are provided in open source, they are compliant to openEHR specifications, and provide secure REST API for data exchange. These features fit the modular architecture of open health computing platforms; they establish the knowledge model by loading openEHR-compliant OPTs, hence although different front-ends can be appended in the future, the health service will always retain control of the data recorded [181, 182]. This implementation does not leverage the UI form specifications defined through the Marand EhrExplorer tool, but it was sufficient to get started using the electronic models built. Anyway, these UI form definitions could be used to build a specific front-end interoperable with the EHRServer of Cabolabs when it comes to exchange medical records.

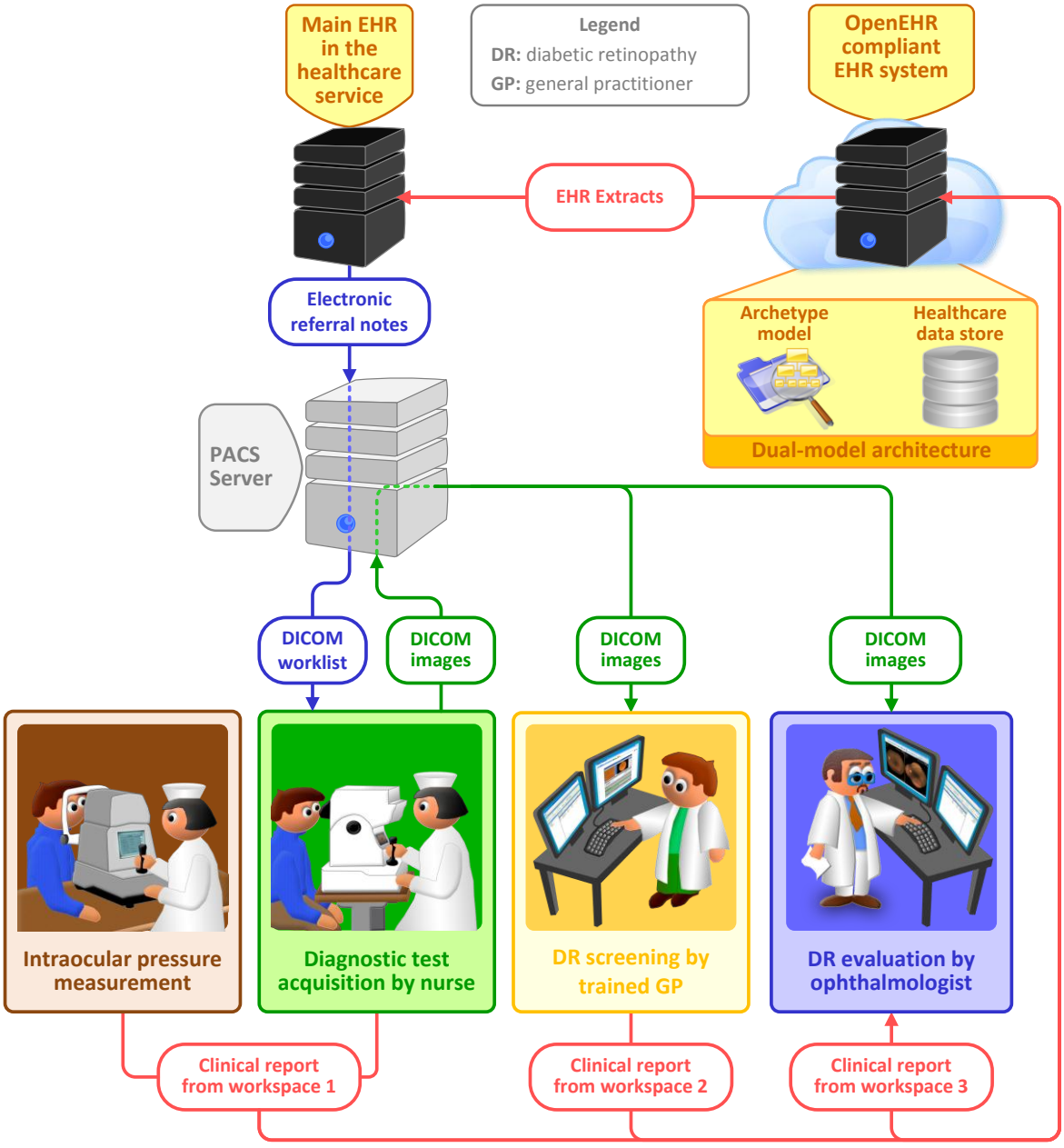

Figure 18: *Flow of information through the service for DR screening.*

4.2 HIGH RESOLUTION CONSULTATION TO MONITOR THE TREATMENT OF WET AMD

As seen in section 2.1, the treatment of wet AMD is particularly critical regarding the management of chronic conditions in ophthalmology. In fact, this condition may present visual loss from 28 days from the time of last assessment [64]. Thus, the consultation required to manage this clinical process must coordinate tightly the assessment of progression of the disease, with an immediate provision of the most suitable therapeutic interventions to minimize the risk of visual loss in each case.

In that respect, the integration of ICTs with interoperable diagnostic tests provides a new framework toward modelling patient-centred efficient and accurate healthcare processes. To that end, this chapter of the PhD dissertation proposes a service designed for periodic and long-term monitoring of the treatment of patients diagnosed with wet AMD.

4.2.1 DEFINITION OF THE PROJECT

On the basis of the above, patients diagnosed with wet AMD must follow a strict treatment of intraocular injections to avoid irreversible progression of the disease (see section 2.1.2). Likewise, in view of optimizing the effectiveness of this clinical procedure, the response of the patient to each treatment can be analysed so as to adjust the next therapeutic intervention accordingly.

In the case of the ophthalmology department of the SNS-O, patients included within the treatment circuit are regularly examined out for any signs of progression within AMD. Namely, they are convened monthly for a monitoring of the treatment that includes the periodic measurement of VA, and the examination of the macula using slit lamp biomicroscopy and a non-contact fundus lens, combined with OCT. However, due to the complexity of the aforementioned procedure for monitoring each response to therapy, as the volume of patients requiring treatment for wet AMD increases the healthcare resources available to carry out this clinical process may become insufficient to treat all patients within recommended intervals [183].

Consequently, a multidisciplinary group comprised of ophthalmologists expert in retina (belonging to the CHN and the HUB), and specialists in ICT engineering (from the Department of Electrical and Electronic Engineering of the UPNA) was convened to work toward efficiency in devising a clinical process aimed at providing the appropriate therapy to patients diagnosed with wet AMD. In that respect, the work team proposed a high resolution consultation –also known as 'one-stop outpatient consultation'– geared to manage the treatment of wet AMD.

This approach would optimize the waiting time and cost-effectiveness of the clinical process by conducting all examinations, diagnostic decisions and consequent therapies along a single outpatient visit. Thus, the work team determined the following changes upon traditional proceedings to integrate the high resolution consultation strategy into the monitoring of the treatment of wet AMD:

- Rethink of the treatment: Considering that the clinical knowledge evolves continuously, the modelling must consider the emerging new therapeutic strategies: as seen in section 2.1.2, traditionally, the treatment by repeated injections of antiangiogenic agents into the vitreous cavity was systematically applied to all patients diagnosed with wet AMD. Conversely, the guidelines in the ophthalmology department of the SNS-O includes, after each treatment, a stage for monitoring the progression of the disease so as to adjust the therapy accordingly. Thereby, the number of treatments per patient is limited to the cases in which such treatment is effective, hence the suppression of unnecessary interventions leads to alleviate the waiting lists.

  With regard to intravitreal injections of VEGF inhibitors, the alternative use of bevacizumab is considered since its effectiveness is similar to ranibizumab, or aflibercept but at lower cost (see section 2.1.2). This makes the treatment accessible to more patients, considering a

limited health budget to meet the demand of a treatment administered regularly and restricted by the recommended periods.

The location of the treatment itself has been reconsidered. Whereas traditionally intraocular injections were carried out within an operating room, by setting up a dedicated procedure room compliant to guidelines for best practice that guarantee the safety of patients, this intervention can take place in the same office where ophthalmologists assess the patients [78]. This will accelerate considerably the workflow regarding the time elapsed from the examination of patients until their treatment. In addition the waiting list of the operating rooms reserved to intravitreal anti-VEGF injections will be alleviated, and thus, those would be allocated to other interventions.

- Redistribution of the workload: The integration of ICTs in healthcare provides to clinicians ubiquitous access to the clinical information registered within a clinical process. This new scenario facilitates the redistribution of the workload of traditional healthcare processes toward services that use the human and technical resources more efficiently. This will facilitate dealing with the scarcity of highly qualified professionals in healthcare services. The workload can be divided in simpler modules but requiring very specific skills, and then the clinical staff available can be trained accordingly so as to cover diverse roles specifically defined to manage the clinical process. In that respect, it is noteworthy that similarly to the DR screening service modelled, the management of the treatment of wet AMD is limited by the scarcity of specialists in retina. Thus, routine tasks that require less specialization such as the acquisition of diagnostic tests can be delegated to specifically trained nurses. In this way, the workload of ophthalmologists would be alleviated, so they can concentrate their efforts on specialized tasks such as analysis of clinical data, determine therapeutic decisions or conduct surgery.
- Allocation of specialized workspaces: According to the high resolution consultation, every clinical encounter (diagnostic tests, assessment and treatment) must be completed along a single outpatient visit. To that end, differentiated points of care would be specifically equipped with the technical and human resources necessary to carry out each of the clinical encounters concerned. In this way, instead of making successive reservations at a non-earmarked ophthalmologist's office, disease-specific workspaces would be allocated, for some hours a day, to manage the complete workflow.

The integration of all these proposals into the process of monitoring the treatment of patients diagnosed with wet AMD should accelerate the flow of patients through the clinical process, and hence alleviate the waiting lists in that service. It is estimated that whereas an ordinary consultation of ophthalmology in the SNS-O attends approximately 24 encounters per day including patients presenting different eye diseases, the high resolution consultation proposed would alleviate a patient every 10 minutes exclusively from the waiting lists of wet AMD (about 30 patients dispatched in 5 hours of operation).

4.2.2 DESIGN OF THE CLINICAL PROCESS

B.1 Definition of the Clinical Process

The high resolution consultation designed by the work team manages patients from different clinical processes which, after specific diagnostic tests and assessments, have been diagnosed with wet AMD. Therefore, the clinical process actually begins when, based on clinical information gathered during diagnosis, a retinologist determines whether the therapy of anti-VEGF intravitreal injections is suitable or not for a patient being assessed.

If so, the patients selected receive the first cycle of treatments directly on the ophthalmologist's office, which entails one monthly intravitreal injection for three months. Thereafter, the progression of AMD must be monitored periodically, so patients are convened once a month and the corresponding diagnostic tests are performed and electronically registered.

Finally, a retinologist from a remote workstation examines the results of those clinical tests, and determines, depending on the response of the patient to the last treatment, whether to repeat or not the anti-VEGF intravitreal injections. The treatment takes place directly in the office of the ophthalmologist expert in retina, and whether treated or not, a patient's review is scheduled for next month.

Therefore, as shown in Figure 19, the management of the treatment for wet AMD was defined into four clinical stages, plus an additional stage to contextualize new patients diagnosed with wet AMD. Each one of these stages is analysed in detail along this section:

- BACKGROUND (Diagnosis of wet AMD): Patients, who during routine clinical encounters such as primary care services, eye emergency services, or general ophthalmology presented signs of possible AMD, are immediately referred for further examination to specialized consultation of a retinologist. During that consultation, the diagnostic tests of VA, eye fundus examination using slit lamp biomicroscopy and a non-contact fundus lens, OCT and angiography are undertaken. Besides, depending on each case, the retinologist can consider appropriate carrying out additional tests, such as direct eye fundus examination. Then, the retinologist examines those tests as a whole, and determines a diagnosis for the clinical findings that initially raised the suspicion of AMD. Once diagnosed, only patients presenting wet/exudative AMD are included in the healthcare process proposed, and thus receive treatment of intravitreal anti-VEGF injections. Nevertheless, patients with dry AMD could develop wet AMD in the future. Therefore, their condition is periodically reviewed (within periods of 1-2 years) to detect any sign of disease's progression leading to wet AMD. Finally, some of the patients examined could be affected any other condition beyond AMD, so an appropriate therapeutic strategy should be determined according to each case. This last scenario is out of the scope of the model proposed.
  Actually, the high resolution consultation does not begin until next stage, in which patients are enrolled for the treatment of wet AMD. For this reason, the process to establish the diagnosis of wet AMD was not included from the electronic model. Nevertheless, to avoid duplication of diagnostic tests, the decision on admission for the first cycle of treatments is mainly based on retrospective information from this stage. Therefore, the diagnostic tests resulting from the diagnosis of wet AMD are analysed in the admission stage, to provide a context to each candidate for the intravitreal anti-VEGF therapy (Figure 19).

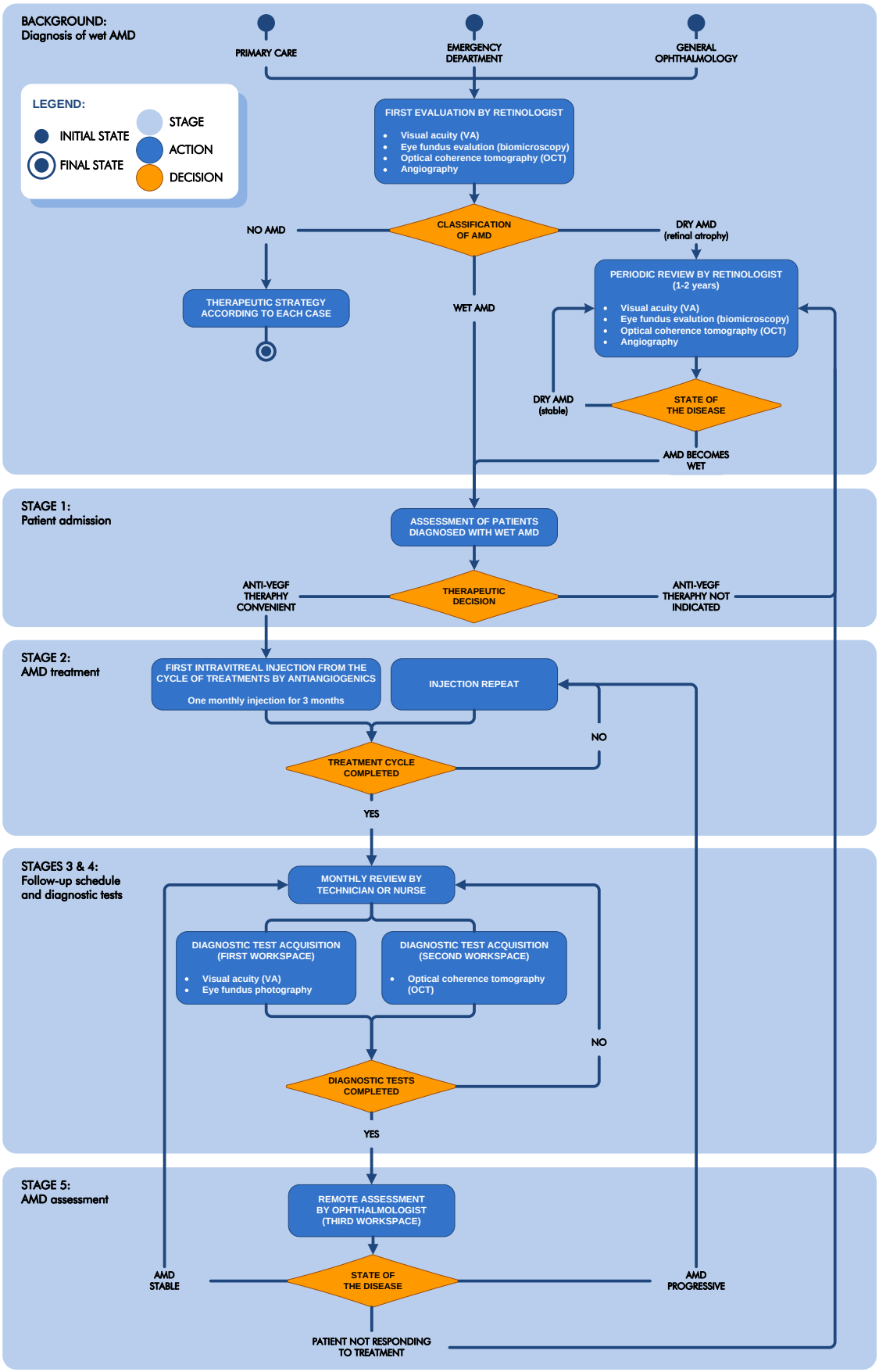

Figure 19: *Activity diagram describing the workflow proposed for a high resolution consultation to monitor the treatment for wet AMD.*

- **STAGE 1 (Patient admission):** The same ophthalmologist expert in retina entrusted of determining the diagnosis of AMD, evaluates each patient to decide whether will be or not enrolled into the long-term treatment for wet AMD. To that end, the retinologist must address two decisions before admit a patient within the cycle of treatments proposed for wet AMD:

    - Diagnosis of wet AMD: As seen above, only patients assessed with wet/exudative AMD are included into the first cycle of treatments of intravitreal anti-VEGF injections. Thus, evaluation of new candidates for such treatment is triggered whenever the retinologist confirms the diagnosis of wet AMD during the review of a patient.
    - No contraindications for anti-VEGF therapy: Then, the ophthalmologist must determine the best therapy for each case, thus verifies whether patients fulfil the minimum requirements to receive the anti-VEGF injections. Thereby, patients presenting contraindications such as very low VA (values below 0.1 in decimal scale) or healed lesions resulting from previous treatments are excluded from the treatment.

  Those patients chosen in accordance with those conditions are enrolled into the high resolution consultation service, and thus scheduled to receive the first cycle of intravitreal anti-VEGF injections described below.

- **STAGE 2 (AMD treatment):** The first cycle of treatments consists of monthly administration of an intravitreal antiangiogenic injection for three months. Once those treatments have been completed, an ophthalmologist must evaluate the response of patients to previous treatments right before determining each new retreatment. In this way, ophthalmologists are able to adjust the frequency of injections administered, or even interrupt the treatment according to the needs of each patient.

  Whenever an ophthalmologist, as a result of the therapeutic assessment described along the last stage, determines the retreatment for a patient with wet AMD, the patient is called urgently to his office. There, the patient is informed about the procedure, then the ophthalmologist examines its eye fundus to prepare the intervention, and finally the intravitreal anti-VEGF injections are administered in-situ. However, there is an ongoing debate on the safest procedure for administering the intravitreal injections [78, 184]. In that respect, the following guidelines were established for the healthcare scenario of the SNS-O so as to ensure the safety of the intervention:

    - Clinical setting for injection: Intravitreal injections may be safely performed in an office setting, with the added advantages of greater agility and flexibility compared to booking an operating room. Hence, most patients will receive by default, the injections directly at the same office used by the ophthalmologist for assessment.
    - Prevention of infection: Both the clinicians responsible for the injection and the patient himself must wear surgical masks to avoid the microbe spread coming from their upper respiratory tract. The clinical personnel involved in the procedure must wear sterile gloves before any patient contact. The use of topical antibiotics is not considered necessary due to insufficient evidence in literature supporting this routine. To prevent contact between the needle/injection site and the eyelashes and eyelids, a speculum is used, or alternately, a nurse conducts a manual eyelid retraction while the ophthalmologist administers the injection.
    - Topical anesthetics: Topical anesthetic drops are applied to reduce patient discomfort during the intervention.

- Antiseptic usage: Povidone-iodine (5-10%) is applied to the conjunctival surface at the intended injection site, avoiding eyelid contact on this area. This must be the last agent applied before injection so as to reduce the incidence of endophthalmitis. In addition, according to the guidelines in force at the ophthalmology department of the SNS-O, the application of povidone-iodine is also contemplated on eyelids, including the eyelashes and eyelid margins. In that respect, eyelid scrubbing or eyelid pressure should be avoided since, this routine increases the risk of liberating bacteria from the meibomian glands.
- Anti-VEGF agents administered: Ranibizumab, aflibercept and bevacizumab are injected indistinctly, as they present equivalent outcomes in the treatment of wet AMD (see section 2.1.2).

– STAGE 3 (Follow-up schedule): The diagnostic tests aimed at the assessment of the response of patients to the treatment are then scheduled for the month following the last injection from the current treatment cycle. In this way, the ophthalmologists will have at their disposal the results of these tests just before proceeding with next treatment.

– STAGE 4 (Diagnostic tests): As seen in section 2.1.2, the ophthalmologist must combine the assessment of patient's latest measurements of VA, eye fundus photographies, and OCT studies so as to review the treatment of wet AMD. The measurement of VA must be conducted in the first place, in order to subsequently administer mydriatic agents to the patient. This is because, although mydriasis is recommended to conduct the OCT test, and it is beneficial for the acquisition of eye fundus images, it is contraindicated for the measurement of VA. Then, once the mydriatic effect is active, NMR and OCT tests could be carried out.
Based on these guidelines, three differentiated workspaces were proposed to distribute the patient flow due to the diagnostic tests involved on the high resolution consultation (see Figure 19):

  - The first workspace: Point of care managed by a nurse specialized on VA testing and acquisition of non-mydriatic retinal photographs. It is worth mentioning that, at this workspace, the eye fundus evaluation using slit lamp biomicroscopy undertaken in traditional consultation of ophthalmology has been substituted by digital retinography. In this way, the eye fundus photographs will be ubiquitously available for their remote assessment. Therefore, the workspace must be equipped with a non-mydriatic fundus camera, and a Snellen chart for VA testing. Likewise, the illumination and dimensions of the room must be appropriate for such diagnostic tests. First of all, the nurse obtains the VA test in decimal scale. Then converts the results into a logarithm of the Minimum Angle of Resolution (logMAR) for easier comparison of values along subsequent consultations. Next, the nurse induces mydriasis to the eye or eyes affected by AMD so as to prepare the patient for the clinical imaging tests. Once pupils are dilated, the nurse acquires in-situ the non-mydriatic retinographies corresponding to the study of AMD, and orders a study of the macula for the OCT situated in the second workspace (described below).
    Regarding the fundus photography, the same guidelines used for DR screening were considered adequate for the study of AMD. Thus, two funduscopic images are obtained, one centred from the papilla and the other from on the macula. Thereby, although the assessment of AMD is focused on the examination of the macula, the additional picture of papilla will be available for future studies, e.g. concerning DR. Finally, those images are uploaded to the PACS, whereas the results of VA are registered into the EHR. In this way, diagnostic tests will remain remotely accessible for the ophthalmologist responsible for their assessment.

- The second workspace: This point of care is equipped by an OCT device. Therefore, a nurse or imaging technician specifically trained on the use of the OCT is in charge. The studies of AMD scheduled in the OCT consist of cross-sectional images of the retina nearby to the macula. Thus, in terms of the protocol used in the healthcare service of the SNS-O in that respect, a scan containing ten OCT sections in parallel which covers the whole macula, plus an extra scan comprised of a high-resolution section centred on the macula are acquired. For the same reason as in the case of fundus photographs, all resulting OCT sections are uploaded to the PACS.
- The third workspace: It corresponds to the office of the retinologist in which the AMD monitoring was managed along with other eye diseases. Nevertheless, it is also the office from which the high resolution consultation is coordinated and monitored. Therefore, during the time slots reserved for the high resolution consultation, this workspace is dedicated exclusively to manage patients diagnosed with wet AMD. To that end, the office has been equipped with a workstation from which, the retinologist requests and assesses the diagnostic tests necessary for monitoring the progression of wet AMD. Those tests are acquired in the other two workspaces mentioned above, whereas the retinologist uses this office to evaluate the acquisitions remotely as it is described in next stage. Nonetheless, besides the treatment and the remote assessment, this workspace was prepared as well to host diagnostic examinations whenever required. Thus, patients presenting any adverse drug reaction such as the mydriatic agent, or other problems that require the specific expertise of a retinologist are called to this office for further examination. Likewise, if the retinologist, having assessed the results of all diagnostic tests available remotely, still requires additional information to make the adequate therapeutic decision, the corresponding patients are referred to his office for a face-to-face consultation. In light of this, the office was equipped with a slit-lamp with a non-contact lens given that the retinologist could consider necessary the direct examination of eye fundus.

– **STAGE 5 (AMD assessment):** Once the diagnostic tests contemplated in the high resolution consultation are completed, the ophthalmologist in charge of AMD assessment has remote access to all clinical information it requires to determine the most suitable therapeutic decision for the patient. First of all, the ophthalmologist must determine whether the condition is progressive, or on the contrary it has been stabilized due to previous treatments. In that respect, the progression of AMD is identified by the occurrence of at least one of the following criteria:

  - Loss of at least one line of VA, in comparison to the previous revision, associated with the presence of macular fluid indicative of activity on AMD. The macular fluid indicative of activity or progression on AMD is detected using the OCT, and can be either intraretinal or subretinal.
  - Persistence of macular fluid indicative of activity identified through the OCT.
  - Emerging new macular haemorrhage detected by digital retinography or fundus examination of the patient.

If the condition turns out to be stable, the retreatment is postponed and the next review of the patient is scheduled within a month. Nevertheless, if AMD is unstable, the effectiveness of anti-VEGF therapy must be guaranteed prior to decide the retreatment. In fact, patients not responding to the treatment may require a different therapy, hence the anti-VEGF treatment is permanently discontinued for the following cases:

- There is established or suspicion of hypersensitivity to the anti-VEGF agents used on the therapy (Ranibizumab, Aflibercept and Bevacizumab).
- VA decreased for three consecutive reviews below 0.1 in decimal scale.
- Progressive deterioration of the morphology of the lesion, detected either by fundus examination or by OCT.

Finally, those patients with signs of progression but responding to previous treatments receive immediately a new intravitreal injection and next review is scheduled within a month.

B.2 Study of Clinical Concepts

At this point, the stages of the clinical process defined above were reviewed so as to identify the clinical concepts to be included in the electronic model. Nevertheless, the high resolution consultation proposed for monitoring patients receiving treatment for wet AMD is still in a pilot stage. This means that this healthcare approach will coexist with the traditional face-to-face consultation whilst the high resolution consultation is validated for the healthcare scenario of ophthalmology in the SNS-O. Hence, the EHR system must be prepared to handle indistinctly the information resulting from both strategies of consultation. In this sense, given that the high resolution consultation must cover the same procedures comprehended in traditional consultations held in an office of specialized care, the clinical concepts considered at this point should be valid for both models (Table 8). Nonetheless, the implementation of the new model has to be supported by objective parameters of efficiency and reliability with respect to the face-to-face consultation which to date is regarded as gold standard.

In consequence, besides the clinical concepts identified in the clinical process above, administrative and sociodemographic concepts for benchmarking both approaches were also considered. The inclusion of those non-clinical concepts in the modelling would enable the analysis of sociodemographic information (current age, sex, age at diagnosis, VA when the study began), the study of comparative administrative variables (time spent during each consultation, compliance with established time limits between revisions, need to repeat treatment, record of problems such endophthalmitis stemming from the treatment), and the consequent data mining of the studies from each of the two approaches (number of treatments received along the year of monitoring, patients with VA below 0.1, cases with no treatable damage). The outcomes of these parameters would be useful to take further steps toward validation of the high resolution consultation.

With consideration of all the above, the concepts listed in Table 8 were chosen to model a service that would gradually integrate in the SNS-O a high resolution consultation, into the current service monitoring the treatment of wet AMD. As seen in Table 8, the concepts identified at this point were reused, whenever possible, from those available either in the CKM or described in the preceding model presented for DR screening.

B.3 Hierarchical Organization of Knowledge Artefacts

As in the modelling of the DR screening service, the clinical concepts identified in previous step were structured according to their occurrences into the clinical stages described along step B.1. Although this time, most concepts were reused from the archetypes modelled for the DR screening service. Thus, the organization of the concepts gained relevance with respect to the effort put into modelling.

In that respect, the work team designed the diagram shown in Figure 20 according to the specifications for establishing the hierarchy between knowledge artefacts proposed in Figure 9.

Table 8: *Clinical concepts identified as a result of studying each stage in the service proposed to monitor the treatment of AMD.*

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
1.	Reason for encounter	- Found on CKM - Usable as is	Evaluation	Stage 1
2.	Story/history	- Found on CKM - Usable as is	Observation	Stage 1
3.	Symptom/Sign	- Found on CKM - Usable as is	Cluster	Stage 1
4.	Visual acuity	- Found on CKM - It has to be adapted	Observation	Stage 1 Stage 4
5.	Funduscopic examination of eyes	- Concept reused from DR screening service	Observation	Stage 1 Stage 4 Stage 5
6.	Ophthalmic tomography examination	- No equivalences found - Archetype has to be modelled from scratch	Observation	Stage 1 Stage 4 Stage 5
7.	Clinical synopsis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 5
8.	Problem/diagnosis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 5
9.	Classification of age-related macular degeneration	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 1 Stage 5
10.	Contraindication	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 5
11.	Recommendation	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 5
12.	Enrolment in a long-term healthcare process	- No equivalences found - Archetype has to be modelled from scratch	Evaluation	Stage 1 Stage 5
13.	Medication order	- Found on CKM - Usable as is	Instruction	Stage 2
14.	Medication action	- Found on CKM - Usable as is	Action	Stage 2
15.	Intravitreal injection details	- Concept reused from DR screening service	Cluster	Stage 2
16.	Adverse reaction	- Found on CKM - Usable as is	Evaluation	Stage 2
17.	Care plan (request)	- Found on CKM - Usable as is	Instruction	Stage 3
18.	Care plan	- Found on CKM - Usable as is	Action	Stage 3
19.	Referral request	- Found on CKM - Usable as is	Instruction	Stage 3
20.	Imaging examination request	- Found on CKM - Usable as is	Instruction	Stage 3
21.	Acquisition details on eye fundus images	- Concept reused from DR screening service	Cluster	Stage 3 Stage 4

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
22.	Acquisition details on ophthalmic tomography	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 3 Stage 4
23.	Procedure	- Found on CKM - Usable as is	Action	Stage 4
24.	Medical device	- Found on CKM - Usable as is	Cluster	Stage 4
25.	Medical device details	- Found on CKM - Usable as is	Cluster	Stage 4
26.	Imaging examination	- Found on CKM - Usable as is	Action	Stage 4
27.	Anatomic location	- Found on CKM - Usable as is	Cluster	Stage 4
28.	Mydriasis application	- Concept reused from DR screening service	Cluster	Stage 4
29.	Medication amount	- Found on CKM - Usable as is	Cluster	Stage 4
30.	Diagnostic report request	- Concept reused from DR screening service	Instruction	Stage 4 Stage 5
31.	Service request	- Found on CKM - Usable as is	Instruction	Stage 4 Stage 5
32.	Healthcare procedure efficiency	- No equivalences found - Archetype has to be modelled from scratch	Admin entry	Stage 5

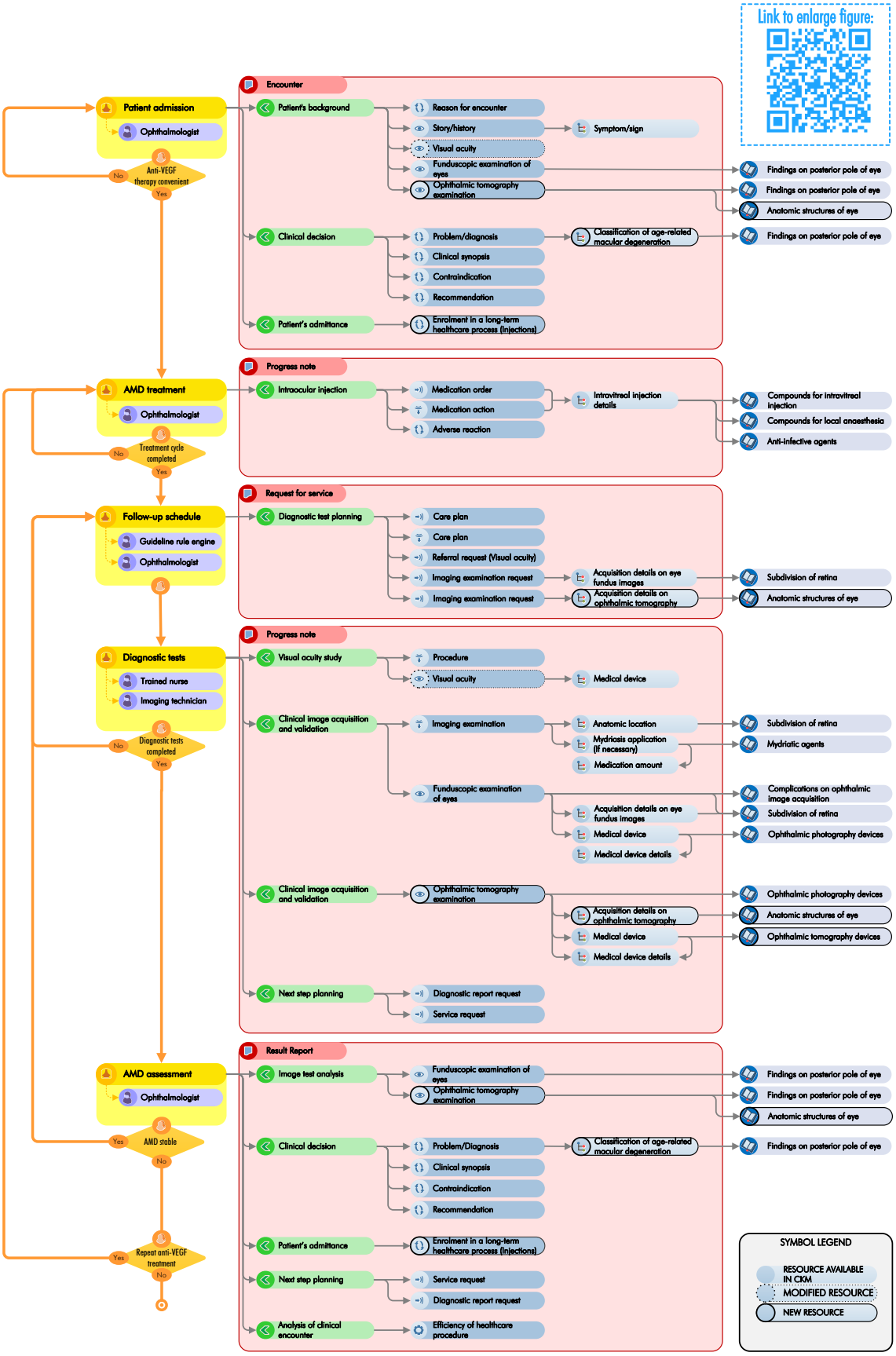

Figure 20: *Hierarchy among the knowledge artefacts involved in the treatment of wet AMD.*

4.2.3 BUILDING THE ELECTRONIC MODEL

C.1 Creation and Update of Archetypes

The high resolution consultation proposed to monitor the treatment for wet AMD consists of 32 different archetypes (excluding organizational section and composition type archetypes).

From those, 21 were obtained from the openEHR CKM and directly used on the model. Besides, the "Visual acuity" archetype was also included, in whose development we were actively engaged so as to meet the requirements of our electronic models. With regard to the remaining 10 archetypes not provided by CKM, only half were completely new, whereas the rest were reused from those previously modelled for the DR screening service (see Table 8).

From the new archetypes proposed, *"Healthcare procedure efficiency"* is noteworthy. It introduces the admin entry class into the electronic model: a new type of entry-type archetype besides the care entry archetypes (observation, evaluation, instruction and action) seen up to now. This new type of archetype is used to capture administrative information in parallel to the clinical activity recorded by care entry archetypes.

In this regard, the *"Healthcare procedure efficiency"* archetype was designed to register objective parameters regarding the evaluation of efficiency for a specific healthcare activity, namely the encounter type, duration, healthcare resources expended, success of the encounter and so on.

Thereby, it constitutes a powerful tool to evaluate the efficiency for a specific healthcare activity, and hence a means of improving the management of healthcare resources. As proof of concept, this archetype proved to be useful regarding the treatment of wet AMD, in terms of comparing the high resolution consultation with the traditional face-to-face approach.

C.2 Definition of Semantic links to Clinical Terminologies

A total of 10 different termsets were used to extend the terminology of archetypes involved in the electronic model. Nevertheless, according to reusability of the knowledge artefacts, eight of the termsets initially designed for the DR screening service proved to be applicable too in the clinical process monitoring the treatment for wet AMD. Furthermore, some of the termsets were reused along the clinical process corresponding to wet AMD (see Figure 20).

Consequently, only two new termsets had to be specifically created to adjust the electronic model to the new healthcare scenario proposed. Those new termsets were built on the basis of tables normalized in the DICOM standard, so as to increase their use in future healthcare scenarios.

All the aforementioned termsets and their use along the stages in the clinical process are described in Table 9.

Table 9: *Termsets modelled to support the archetypes in the service proposed to monitor the treatment of AMD.*

	Termset name	Description of termset	Availability	Process stages in which it is applicable
1.	Findings on posterior pole of eye	Clinical findings identifiable in posterior pole of eye.	Reused from DR screening	Stage 1 Stage 5
2.	Anatomic structures of eye	List of regions of interest in the study of eye (based on DICOM Tables: CID 4209, CID 4211 and CID 4266).	Newly created	Stage 1 Stage 3 Stage 4 Stage 5
3.	Compounds for intravitreal injection	Compounds administered in ophthalmology in the form of intraocular injection.	Reused from DR screening	Stage 2
4.	Compounds for local anaesthesia	Compounds available to apply local anaesthesia.	Reused from DR screening	Stage 2
5.	Anti-infective agents	List of anti-infective agents available.	Reused from DR screening	Stage 2
6.	Subdivision of retina	List of zones in eye retina for ophthalmic image positioning.	Reused from DR screening	Stage 3 Stage 4
7.	Mydriatic agents	List of mydriatic agents and their corresponding doses validated for ophthalmologic use.	Reused from DR screening	Stage 4
8.	Complications on ophthalmic image acquisition	List of possible complications during ophthalmic imaging studies that may affect the quality of acquisitions (based on Table CID 4222 of DICOM standard).	Reused from DR screening	Stage 4
9.	Ophthalmic photography devices	Lists the ophthalmic photography acquisition devices (based on Table CID 4202 of DICOM standard).	Reused from DR screening	Stage 4
10.	Ophthalmic tomography devices	List of acquisition devices (based on Table CID 4210 of DICOM standard).	Newly created	Stage 4

C.3 Building Templates

The archetypes modelled in previous steps were structured into templates in the same way as described for the remote screening service for DR. As a result of that modelling, 16 different templates were built: among those, 11 corresponded to templates designed to adapt the archetypes contained in each section identified in Figure 20 to the requirements of the service for monitoring the treatment of AMD. The remaining 5 templates were designed to manage the information corresponding to each one of the stages in which the healthcare was divided along the clinical process seen in Figure 20.

Among those templates corresponding to sections, 3 were reused along the clinical process: considering that there is some common ground between the first encounter for patient admission and the subsequent AMD assessments, the templates *"Classification and treatment of AMD"* and *"Patient's enrolment in anti-VEGF therapy"* were reused along the first and last stage. Likewise, the *archetype "Next step in AMD monitoring service"* was devised to manage the pathway among stages, so it was first used at the fourth stage to refer patients toward the office assessment once all diagnostic tests were acquired, but besides, turned out to be useful at the fifth stage to schedule the next review in a month, and then, arrange or postpone the anti-VEGF treatment.

In addition, the DR screening service modelled beforehand provided interesting patterns with regard to the current proposal for AMD. In this sense, 2 templates initially modelled for the DR screening were reused with the consequent time saving for modellers:

- Intraocular injection: Although originally used by the DR screening service, its template had to be enhanced since the intraocular injection is a critical activity on the treatment of wet AMD. Therefore, the corresponding template was redesigned in light of the service monitoring the treatment of AMD, and then, the model that describes the DR screening was retrospectively updated. Thus, at this point both models share the same template *"Intraocular injection"*.
- Funduscopic test: This diagnostic test is required on both clinical processes, so its corresponding template *"Acquisition and validation of NMR"* resulted equally applicable in both models.

Many other templates used in the AMD monitoring service were slightly adapted from those originally built for the DR screening. For example, the templates *"Patient's background leading to the diagnosis of AMD"* and *"Classification and treatment of AMD"* enclose practically the same archetypes used in *"Patient's background leading to suspicion of DR"*, but including some additional archetypes specific to the diagnosis of wet AMD.

Finally, the *"Diagnostic tests in the DR screening service"* and *"Diagnostic tests for monitoring the treatment of wet AMD"* share the same structure although the archetypes included must cover different diagnostic tests (see Figure 21).

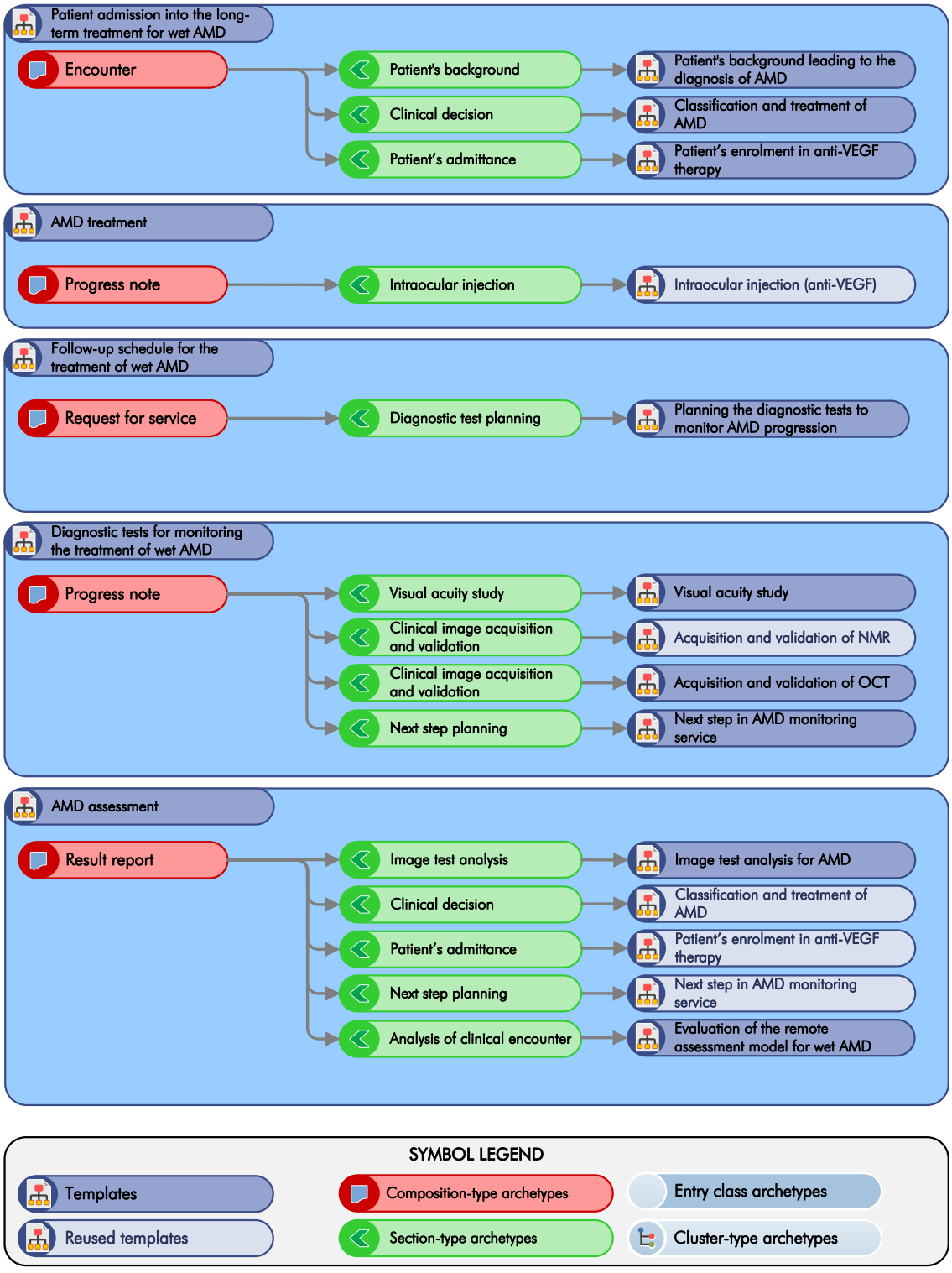

Figure 21: *The structure of templates envisaged to register clinical encounters resulting from the high resolution consultation devised to monitor the treatment of wet AMD.*

C.4 Modelling Guideline Rules and Workflow

Six rules were designed to govern patients' flow through the clinical process. The archetypes participating in these rules can be found in Appendix A:

- **Anti-VEGF therapy convenient:** From every patient diagnosed with wet AMD, only those which comply with this rule will access to the long-term treatment of wet AMD by intravitreal injections. Thus, this rule is activated when, after a consultation on specialized care, a retinologist determines whether the anti-VEGF therapy is convenient or not for the current patient. The archetype named *"Enrolment in a long-term healthcare process"* is used to register such decision.
  This rule checks the value chosen in the data element "admittance" of that archetype, and if the patient is inscribed in the therapy, activates the medication order to initiate the first cycle of anti-VEGF treatments comprised of three monthly intraocular injections.
- **Treatment cycle completed:** This rule verifies if every anti-VEGF injection ordered for a specific patient have been carried out, and, if true, automatically schedules the next consultation for patient review. Basically, it checks for every new contribution submitted to the EHR, if the pathway of the archetype *"Medication action"* has been registered as completed. If so, the rule queries the CPOE manager for all open orders for intravitreal injections related to a specific patient, and then tags as closed the corresponding one. At this point, in case of treatment discontinuation for whatever reason, the retinologist must intervene in consequence either by ordering again the missing interventions or by suspending definitively the treatment. Once all medication orders for intravitreal injection have been closed, this rule determines that the cycle of treatments is completed. As a result, the archetype "Care plan (request)" is instantiated, in which the diagnostic tests involved on reviewing the outcomes of the treatment for wet AMD are specified.
- **Diagnostic tests completed:** Similarly to the preceding one, this rule must guarantee the completion of every diagnostic test ordered for a specific patient before proceeding with the remote assessment. Except instead of medication orders for intravitreal injection, this rule must coordinate the lifecycle of every diagnostic test scheduled to review the effectiveness of the treatment of wet AMD (i.e. VA, NMR and OCT).
  To that end, every new contribution of the archetype "Care plan" submitted to the EHR that corresponds to the "Service for monitoring the treatment of wet AMD" is reviewed. When the pathway of this archetype is set to "Care plan completed", it means that every diagnostic tests scheduled within the follow-up have been acquired. Consequently, the rule uses the archetype *"Diagnostic report request"* to request the remote assessment for the set of diagnostic tests acquired.
- **AMD stable:** Provided that the retinologist does not identifies signs of activity or progression on AMD since the last review (neither new haemorrhages nor worsening of VA), a new anti-VEGF injection would not be effective to treat such disease. In light of the above, this rule checks the therapeutic decision in the archetype *"Recommendation"*, and if the therapeutic recommendation corresponds to "Do not treat", the rule will schedule the respective diagnostic tests to review the patient in a month. In this way, the progression of the disease is periodically monitored, whereas the treatment is postponed until applying the injections is really effective. At this point, the archetype *"Service request"* is instantiated to schedule the follow-up service for the treatment of wet AMD, where the diagnostic tests included in the monthly revision of wet AMD are planned (VA, NMR and OCT).
- **Repeat anti-VEGF treatment:** This rule orders a new intravitreal injection if the retinologist, as a result of the assessment of diagnostic tests, determines that the patient presents signs activity or progression on AMD. The criteria to repeat the treatment is the worsening of VA associated to macular fluid, identifying macular fluid, and emerging new haemorrhages

within the macula. If any of these criteria are identified during the remote assessment of a patient, the retinologist would set the "Intravitreal anti-VEGF injection" as therapeutic recommendation for the archetype *"Recommendation"*. Likewise, the rationale of the same archetype would be used to register the criteria used to reach that therapeutic decision. Finally, the retinologist must reconsider patient's enrolment in the intravitreal anti-VEGF therapy. Thus, the positive value of admittance registered in the archetype *"Enrolment in a long-term healthcare process"* for the healthcare process "Long-term therapy of anti-VEGF intravitreal injections" will trigger this rule. And whenever this rule is triggered, it will instantiate the *"Medication order"* archetype so as to schedule the anti-VEGF injection corresponding to the current month.

- Discontinuation of anti-VEGF therapy: Finally, if the minimum conditions of "Admittance" for the long-term therapy of anti-VEGF intravitreal injections are not fulfilled, directly the patient would not be included into the cycle of treatments (stage 1: anti-VEGF therapy not indicated). Moreover, if the patient is already included in the cycle of anti-VEGF injections, but the retinologist identifies contraindications to continue with the therapy during any of the periodic assessments, the patient's enrolment in the long-term treatment for wet AMD will be revoked (stage 4: patient not responding to treatment). Both scenarios above will trigger this rule, which in consequence excludes the patient from the treatment and then schedules the next consultation for AMD review at the retinologist's office. Thereby, these patients fall beyond the scope of our model, given that they have been excluded from the long-term therapy of anti-VEGF injections.

  With consideration of the above, first of all, the rule verifies the latest contribution in the EHR of the archetype *"Classification of age-related macular degeneration"*. In fact, only patients with the classification of "Exudative or wet AMD" are covered by the long-term therapy proposed, so other diagnoses will trigger this rule.

  Conversely, if the diagnosis of AMD corresponds to the abovementioned classification, then the rule must verify if there is any contraindication that could jeopardize effectiveness of intravitreal injections:

  - Exclusion criteria for new patients: During the admission stage of the anti-VEGF therapy, those patients who show very low VA (below 0.1), healed lesions due to previous treatments (PDT, laser photocoagulation scars, or any vitreoretinal operative procedure), multimorbidity (coexistence of AMD with other alterations on the retina causative of visual impairment), or any known adverse reaction to anti-VEGF agents used in intravitreal injections will definitely trigger this rule.
  - Exclusion criteria for permanent discontinuation of therapy: From the patients already receiving intravitreal anti-VEGF injections, those who at some point have presented hypersensitivity to the anti-VEGF agents used in the injections, those not responding to treatment (VA decreased for three consecutive reviews below 0.1 in decimal scale), and cases affected by a progressive deterioration of the morphology of the lesion will definitely trigger this rule.

  In this regard, any contribution to the archetype *"Contraindication"* referring to intravitreal anti-VEGF injections will lead to withdraw the patient from therapy.

  Thus, if any of the conditions above triggers the rule, it would be necessary to place on record the exclusion of the patient from the "Long-term therapy of anti-VEGF intravitreal injections". So that, the value of "Admittance" in the archetype *"Enrolment in a long-term healthcare process"* is set to false, and "Criteria" is established according to the value of "Evidence/Rationale" registered within the archetype *"Contraindication"*. Finally, the *"Service request"* archetype is instantiated so as to schedule next patient's review at the retinologist's office.

Table 10: *Description of the guideline rules designed for the high resolution consultation proposed to monitor the treatment for wet AMD.*

	Rule name	Conditions	Actions
1.	Anti-VEGF therapy convenient	The precondition for this rule is the therapeutic recommendation of "Intravitreal anti-VEGF injection" for the archetype "*Recommendation*". Archetype *"Enrolment in a long-term healthcare process"*: • Healthcare process: "Long-term therapy of anti-VEGF intravitreal injections" • Admittance: "True"	Archetype instantiated *"Medication order"*: • Dose directions description: "Intravitreal anti-VEGF injections for wet AMD" • Dose timing description: "Three monthly intraocular injections" Other details about the intravitreal injection will depend on each clinical setting.
2.	Treatment cycle completed	Archetype *"Medication action"*: • Reason: "Treatment of wet AMD" • Pathway: "Complete medication" All orders active in the CPOE for a specific patient, which belong to the treatment of wet AMD must be completed.	Archetype instantiated *"Care plan (request)"*: • Care plan name: "Service for monitoring the treatment of wet AMD" Archetype instantiated *"Referral request"*: • Service requested: VA test Archetype instantiated *"Imaging examination request"*: • Service requested: NMR • Service requested: OCT study
3.	Diagnostic tests completed	Archetype *"Care plan"*: • Care plan name: "Service for monitoring the treatment of wet AMD" • Pathway: "Care plan completed"	Archetype instantiated *"Diagnostic report request"*: • Service requested: "Remote assessment of wet AMD" • Reason for request: "Completed the diagnostic tests necessary for assessment"

	Rule name	Conditions	Actions
4.	AMD stable	Archetype *"Recommendation"*: • Therapeutic recommendation: "Do not treat"	Archetype instantiated: *"Service request"* • Service name: "Follow-up schedule for the treatment of wet AMD" • Description: "Follow-up comprised by VA, NMR, OCT tests" • Service due: 1 month
5.	Repeat anti-VEGF treatment	Similarly to the first rule, the precondition for this rule is the therapeutic recommendation of "Intravitreal anti-VEGF injection" for the archetype "*Recommendation*". Then, patient's enrolment in the intravitreal anti-VEGF therapy is reviewed. Archetype *"Enrolment in a long-term healthcare process"*: • Healthcare process: "Long-term therapy of anti-VEGF intravitreal injections" • Admittance: "True"	Archetype instantiated: *"Service request"* • Service name: "Repeat anti-VEGF injection to treat wet AMD" Archetype instantiated *"Medication order"*: • Dose directions description: "Intravitreal anti-VEGF injections for wet AMD" • Dose timing description: "A monthly intraocular injection" Other details about the intravitreal injection will depend on each clinical setting.
6.	Discontinuation of anti-VEGF therapy	Archetype *"Classification of age-related macular degeneration"*: • AMD classification != "Exudative or wet AMD" In addition, any new contribution of the archetype *"Contraindication"* referring to intravitreal anti-VEGF injections will definitely trigger this rule.	Archetype instantiated *"Enrolment in a long-term healthcare process"*: • Healthcare process: "Long-term therapy of anti-VEGF intravitreal injections" • Admittance: "False" • Criteria = Evidence/Rationale (in archetype "Contraindication") Archetype instantiated *"Diagnostic report request"*: • Service name: "Review of AMD state at the retinologist's office" • Reason for request: "Patient not responding to treatment"

C.5 Modelling UI Forms

Following the same guidelines described for the DR screening service, 5 UI forms were created using the Marand EhrExplorer. These UI forms represent each one of the stages that comprise the AMD monitoring service proposed. This will enable to automatically generate the UI views to be displayed on front-end applications, based on the UI specifications detailed on the form-description files resulting from the UI modelling. However, given the lack of consensus on the definition of UI form specifications, the parsers available which transform the form specifications resulting from the Marand EhrExplorer into HTML views, will only work for front-end applications devised for the Marand EhrScape server. Therefore, specific UI generators must be implemented in order to reuse our UI form definitions into front-end applications compliant to other openEHR-compliant EHR implementations. For example, in the case of the open source applications proposed by Cabolabs, the UI generator from the openEHR-OPT project can be adapted to parse the UI form-description files instead of the OPTs used to define these UI forms. In this way, anyone could build their own HTML front-end applications based on the UI form definitions modelled in this Thesis.

4.2.4 IMPLEMENTATION OF THE SERVICE

Currently, both the high resolution consultation and traditional approach coexist in the SNS-O toward monitoring patients receiving anti-VEGF therapy for wet AMD. This stems from the fact that the high resolution consultation proposed is still in a pilot stage. As such, before proceeding with an extensive implementation, it must prove its efficiency and reliability against traditional consultation.

As regards the traditional consultation model, except for the OCT acquisitions provided in printed form, the diagnostic tests involved in the study of AMD require the presence of the patient at the ophthalmologist's office (measurement of VA and eye fundus examination using slit lamp biomicroscopy). This facilitates the face-to-face assessment, in contrast to the high resolution consultation approach, which redistributes those diagnostic tests among specialized workspaces. Thus, in case of the latter approach, the evaluation of the acquisitions resulting of all those workspaces must be managed remotely. At this point, the need arises to share through the corporate network of the SNS-O, the studies acquired concerning the diagnosis and follow-up of AMD. Therefore, the proposal of a remote assessment service entails reconsidering the technical requirements of the current healthcare service, initially designed to accommodate the traditional consultation.

In that respect, the ICT infrastructure arranged in the SNS-O for the DR screening service described along section 4.1 was reused to cover some of the technical requirements of the high resolution consultation. On the one hand, the workspace allocated for diagnostic test acquisition in DR screening was adapted to receive also patients affected by wet AMD. As seen in section 4.1.4, this workspace already included tonometry and pachymetry devices for IOP measurement, a non-mydriatic retinal camera, and a PC workstation to register findings identified during acquisitions. Thus, by installing a Snellen chart for VA measurement, this space covered every diagnostic test specified for the first workspace of the high resolution consultation.

On the other hand, given that in principle, the OCT test is not considered for the DR screening, a new workspace was allocated in the SNS-O to host that test according to the specifications of the high resolution consultation. There, to connect such diagnostic device to the PACS server available in the healthcare service, the workstation and the server side were configured in compliance with DICOM specifications for both ends.

Moreover, the workspace allocated for remote assessment whether in the case of DR or AMD, it was established into the office of an ophthalmologist expert in retina. In that office, the ophthalmologist uses a PC workstation, connected to the PACS and EHR servers, to evaluate remotely the diagnostic tests and then register the diagnostic reports. Furthermore, given that some diagnostic tests are

overlapped in the study of both DR and AMD, the whole set of tests contained in the PACS would be accessible regardless the process for which they were originally intended.

As proof of concept for the healthcare scenario modelled along this chapter, the archetypes and templates built were loaded into an openEHR-compliant EHR. The same information systems used in the DR screening service were chosen to that end, namely the EHRServer and the EHRCommitter, both developed by Cabolabs [181, 182]. In this way, clinicians involved in both clinical processes can use the same EHR system to register clinical information specific to each healthcare scenario.

For the time being, the openEHR-compliant EHR is only used for research purposes, hence medical records must be recorded into the main EHR in the SNS-O as well. And once it is proved that the openEHR-compliant EHR is reliable enough to be connected to the main EHR, both information systems will be able to exchange EHR extracts. Consequently, the information among systems will be coordinated automatically.

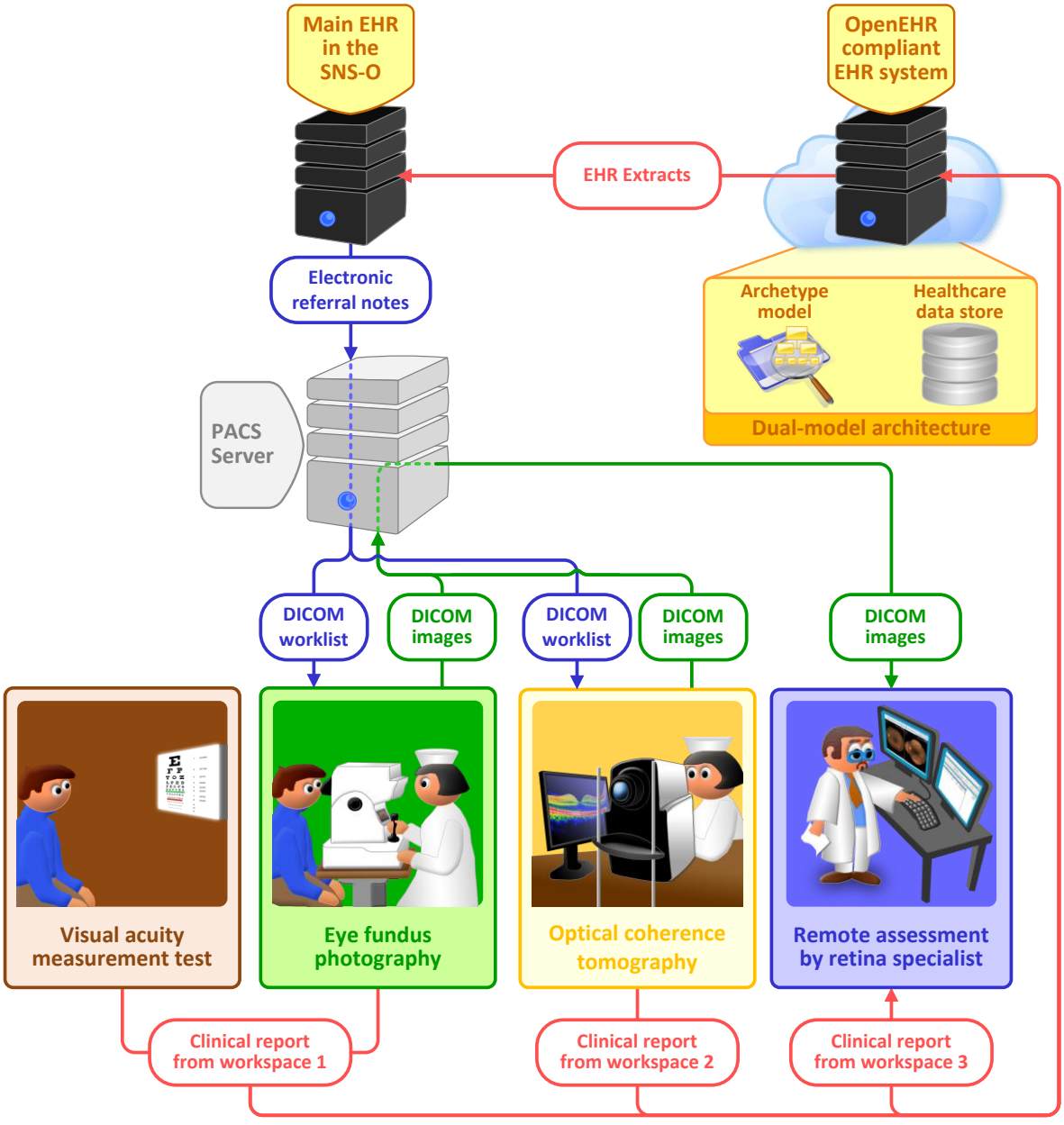

Figure 22: *Flux of information through the service monitoring the treatment of wet AMD.*

Building on the electronic model described for the service monitoring the treatment of wet AMD, a solution was considered in order to standardize the information recorded through the web platform launched at the SNS-O to evaluate the telemedicine model for wet AMD follow-up [38]. Originally this platform was not compliant to the openEHR specifications, but given the clinical domain in common, it could be easily standardized using the knowledge artefacts modelled along this section.

Standardization of the platform would enable to exchange medical records with other systems compliant to openEHR, hence extending the applicability of the information registered beyond the walls of an institution. Likewise, fine-grained data-mining functionalities would be enabled thanks to the semantically computable EHR data. This could be a proof of concept toward integration of many software tools and information systems found in health services, which being designed for very specific healthcare scenarios, usually end up being an information silo.

The challenge on this approach was to model, ex post, the use case scenario presented in the web platform. Therefore, instead of generating the UI views from the knowledge models, the modelling was reversed to avoid having to modify the UI views defined on the non-standardized web platform. In this case, an OPT was specifically designed to conform to the clinical concepts originally registered through the web platform as described in Appendix B. Most of the clinical concepts defined in the OPT have direct correspondence with the data fields represented on the UI forms. Conversely, other concepts defined in the OPT are not shown on the view. These must be inferred from the context, since the clinical practice is well-known for this healthcare scenario.

The aforementioned template was modelled in compliance with the ADL 1.4 specifications, using the template designer developed by Ocean Informatics. Once finished, it was uploaded to the CKM under the name of *"Consultation for AMD assessment"*, thus allowing the OPT to be available for everyone to download (steps 1 and 2 in Figure 23).

Next, the methods provided by the project openEHR-OPT of Cabolabs were used to extract the paths pointing to every data element specified within the OPT [185](step 3 in Figure 23). Each one of those paths was then assigned to equivalent data fields identified in the HTML file that depicts the UI form at the web platform. The data types (according to the openEHR reference model), default values, and other data constraints were also included into the HTML elements where necessary (step 4 in Figure **23**).

Furthermore, the resulting HTML view was integrated with a controller as explained in the openEHR-skeleton example of how to create e-health apps [186]. This controller is responsible for validating the data entered in the form, creating EHR instances from these data, and committing them to the EHR. In this regard, the openEHR-OPT was used to validate the clinical data, and compose new EHR instances in conformance with the openEHR EHR information model [185]. Indeed, the openEHR compositions generated whenever the HTML form is submitted, may be considered equivalent to a signed clinical document. In this way, although the resulting HTML form apparently presents no changes for end users, it would be prepared to exchange medical records with openEHR-compliant EHR systems (step 5 in Figure 23). To that end, the project EHRCommitter developed by Cabolabs was adapted to send the resulting versioned compositions to the EHRServer [182] (last step in Figure **23**).

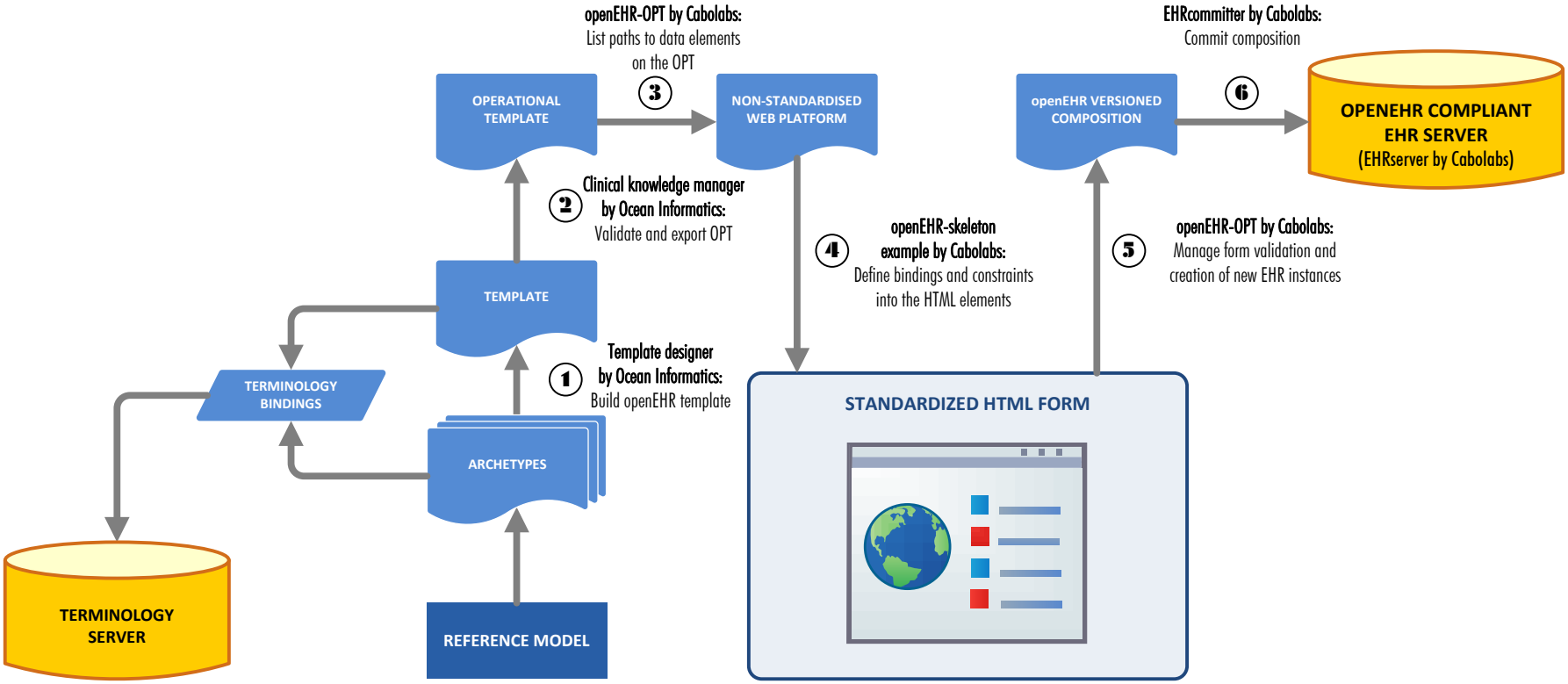

Figure 23: *Adaptation of data registered through the non-standardized web platform into openEHR-compliant medical records.*

4.3 MODELLING AN E-HEALTH BASED FOLLOW-UP PROCEDURE FOR CG

As seen in section 2.1, individuals affected with CG are asymptomatic until late in the disease process, while even mild VF loss decreases health-related quality of life. Furthermore, once patients with CG have been diagnosed, they would require lifelong ophthalmic care. Consequently, although the clinical course of CG is usually slow, periodic examinations are necessary to detect the slightest hint of disease progression.

In this regard, a follow-up service for patients undergoing therapy of CG would make it possible for ophthalmologists to adapt the treatment whenever considered necessary to slow or prevent the VF loss before it becomes significant. This section of the PhD dissertation defines a proposal to that effect that leverages ICTs and model-driven information systems in healthcare to manage efficiently the follow up of any sign of progression in patients diagnosed with CG.

4.3.1 DEFINITION OF THE PROJECT

Considering the complexity of the overall health management in glaucoma, the modelling proposed was focused on the follow-up of patients already diagnosed with CG who are medically stable. Regarding those patients, with the treatments available nowadays, many of them do not exhibit signs of progression or worsening over the long term. Therefore, the healthcare process concerned comes down to check periodically if the disease shows signs of progression. And, if so, to adapt the treatment accordingly.

As seen in section 2.1.3, the follow-up of patients receiving treatment for CG relies on observation of the optic disc, examination of the VF, measurement of IOP and the VA. Thus, the traditional model to monitor the progression of the disease requires numerous consultations with ophthalmologists to address the clinical tests and decide accordingly the suitable treatment. However, after analysing individually the diagnostic tests concerned in the follow-up of glaucoma, none of them require the presence of an ophthalmologist during acquisition.

The use of a tonometer and a pachymeter for IOP measurement as well as the VA test are reasonable processes for specifically trained personnel. Additionally, digital retinography can reliably substitute the direct examination, hence specifically trained nurses and imaging technicians can reliably photograph the optic disc with sufficient quality for diagnosis [170]. Finally, the OCT to observe the thickness of fiber layers surrounding the optic disc, and the perimetry to register the VFs are usually carried out by auxiliary personnel.

Consequently, it is feasible to establish an e-ophthalmology-based model that distinguishes the stage of acquisition for the diagnostic tests, from the later examination and assessment of clinical data. In this way, the clinical encounters aimed to diagnostic acquisitions are handled in parallel in workspaces assigned for that purpose. Meanwhile, ophthalmologists expert in glaucoma can access to the results of the whole set of tests concerned in the follow-up and hence decide if the current treatment is the most suitable for each case.

Unlike the model proposed for DR screening, due to the complexity of identifying the progression of the glaucoma, ophthalmologists are the only ones responsible of the examination and assessment of diagnostic tests. However, improving the patient flow on clinical encounters aimed to acquisition and validation of diagnostic tests brings key advantages to the management of CG:

- A more agile workflow: Patients affected with CG require periodic examinations to assess the progression of the disease. However, none of the diagnostic tests involved in those examinations requires the presence of an ophthalmologist. Therefore, an e-health approach would enable a redistribution of the workload into differentiated workspaces managed by specifically trained personnel. Consequently, the waiting lists would be alleviated compared to standard clinical procedure which present a bottleneck in the office of ophthalmology [33].

- Broader diagnostic perspective: All measurements and diagnostic images implied in the follow-up are accessible ubiquitously. Thus, once those have been acquired in distributed workspaces, the ophthalmologists would examine remotely the resulting diagnostic tests using a single workstation. Thereby, all diagnostic information required to determine an accurate diagnosis is displayed in a single screenshot, whereas the traditional approach requires numerous consultations. As a result, the therapeutic decisions made using the e-health approach are supported by a comprehensive study of the disease.
- Less time-consuming for specialists: From a clinical standpoint, e-health models are less time-consuming for specialists than standard clinical evaluations. Furthermore, as the assessment is not limited to the timing of patients during clinical encounters, ophthalmologists can multitask, and thereby organize more efficiently their work time. Thus, in view of the fact that the scarcity of ophthalmologists with expertise in glaucoma limits the capacity of the service, an efficient use of the time of specialists would foster the assistance of a greater number of patients.
- Comparison of studies retrospectively: The comparison of clinical information corresponding to the same patient, but registered along different consultations successive in time provide interesting information about disease progression. In that respect, the follow-up service proposed has a clear advantage with regard to the medical records in paper. Indeed, in case of the e-health model, a single workstation provides ubiquitous access to all clinical information registered longitudinally along the healthcare process of each patient.
- Clinical data mining: The digitized diagnostic tests, and normalized clinical records enable the development of powerful tools for data mining. These tools, in turn, foster the design of clinical and epidemiological studies based on the clinical information registered during the follow-up of CG. The outcomes of these studies will provide objective and real-time information to support on decisions made toward improving the management of the follow-up service.

Considering these premises, a multidisciplinary work team including ophthalmologists and nurses from the SNS-O, and engineers with expertise in implementation of ICTs in healthcare were convened to redesign the follow-up service in the SNS-O for CG.

4.3.2 DESIGN OF THE CLINICAL PROCESS

B.1 Definition of the Clinical Process

With consideration of the signs of evolution in CG such as morphologic changes on parapapillary region or VF loss can be very subtle but still progressive over the long term, the work team devised a follow-up service to review patients undergoing treatment of CG in the SNS-O.

As seen in Figure 24, first and foremost patients have to go through three consultations on specialized care to determine the diagnosis and a stable treatment for CG: suspicion of glaucoma, diagnosis of glaucoma and establishment of long-term therapy. Originally, these consultations fall outside the scope of the follow-up service. Nevertheless, the information registered up to this point will provide a baseline to identify the slightest sign of glaucomatous progression with regard to the disease trajectory envisioned for every new patient enrolled in the follow-up service.

Once patients are medically stable, they are included in the circuit monitoring the evolution of CG. Then, as seen in Figure 25, the specialist arranges the next review specifying the diagnostic tests necessary for the follow-up of each case of CG. That review begins with the acquisition and digitization of the diagnostic tests requested by the specialist. Specialised workspaces managed by nurses and imaging technicians are allocated to that end. Once all scheduled diagnostic tests have been completed, their results are recorded into the respective information systems (EHR and PACS).

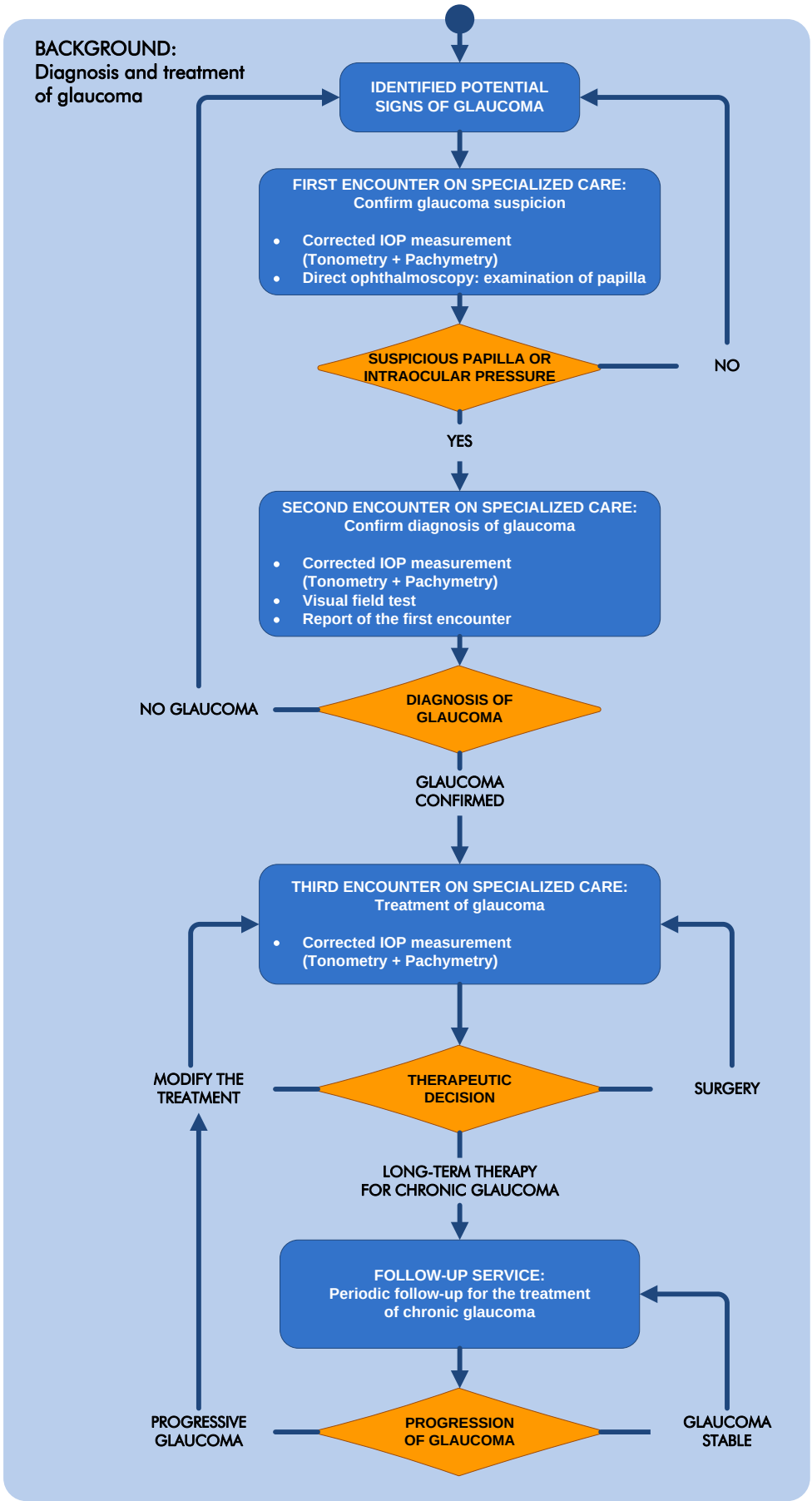

Figure 24: *Activity diagram describing the overall management of CG in the SNS-O.*

Thereafter, the specialist would assess from a remote workstation all acquisitions comprised on the follow-up of a patient, so as to identify any sign of glaucomatous progression. Stable patients are therefore scheduled for next review, whereas patients presenting progressive glaucoma are called for further examination at the office of specialised care. During the office examination, the glaucoma specialist would conduct the additional examinations considered necessary to determine the appropriate therapy that would curb the progression of glaucoma into a medically stable state.

At this point, the follow-up service proposed for CG was organized into the background described in Figure 24, which consists of the consultations in specialised care preceding the diagnosis of glaucoma, plus the subsequent four clinical stages identified in Figure 25. Each one of these stages is analysed in detail along this section:

- BACKGROUND (Diagnosis and treatment of CG): Patients who presented potential signs of glaucoma during routine eye consultations, or on the review of a specific eye condition, and patients with family history of glaucoma are referred to the office of an ophthalmologist specialized on glaucoma for further examination. For example, the IOP measurement included in the DR screening service, inter alia, could be useful to identify asymptomatic patients presenting early stages of glaucoma.

  Along the first consultation on specialized care, first of all, tonometry and pachimetry tests are scheduled to obtain patient's corrected IOP measurement. Then, the ophthalmologist examines the papilla through direct ophthalmoscopy and confirms (or not) the suspicion of glaucoma.

  Accordingly, patients presenting elevated IOP or suspicious papilla are therefore scheduled to perform perimetry. With the results of VF test, the patient is convened at the ophthalmologist's office for a thorough analysis that would help to confirm the diagnosis of glaucoma. Once there, a new measurement of corrected IOP is carried out to reveal any progression with regard to the last encounter. This second consultation on specialized care entails the joint analysis of patient's visual field, the progression of IOP since the previous encounter, and the clinical findings reported as a result of the examination of the papilla conducted in the first consultation (see Figure 24). In consequence, the ophthalmologist confirms (or not) the diagnosis of glaucoma and classifies the type and severity for such condition.

  The IOP can be lowered by medical treatment, laser therapy, or incisional glaucoma surgery. Thus, the ophthalmologist must determine, according to the state of the disease they present, the appropriate treatment for each one of patients on which glaucoma has been confirmed. In that regard, the objective of the third consultation on specialized care is to adjust the treatment toward stabilizing the disease evolution. To that end, regardless the treatment chosen, a target IOP is estimated for each patient. Below this value, further optic nerve damage is unlikely to occur or the worsening of glaucoma will be slow enough that the risk of additional intervention is not justified.

  For that reason, the following clinical encounters include patient's corrected IOP measurement. Indeed the ophthalmologist use that value to adapt the treatment by successive approximations until patient's IOP is stabilized below the aforementioned target value. Therefore, the third consultation comprises as many encounters as the ophthalmologist considers necessary so as to find the adequate treatment for a specific patient.

  Finally, the third consultation on specialized care is closed once the ophthalmologist determines that a patient has been stabilized. At which point such patient should be included into the follow-up service of CG as it is described in next stage (Figure 25).

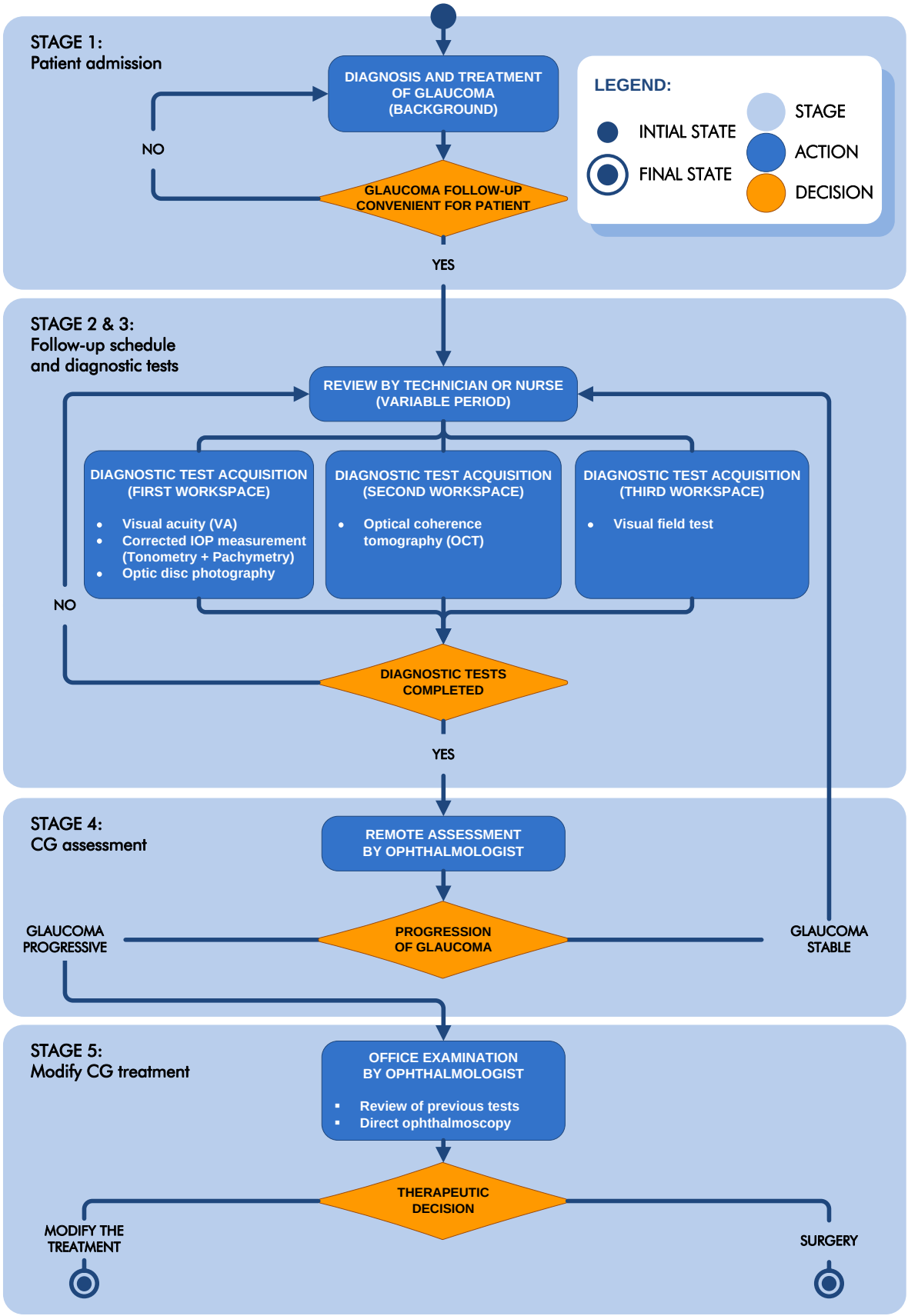

Figure 25: *Activity diagram detailing the follow-up service proposed for CG.*

- **STAGE 1 (Patient admission):** The patient admission stage would correspond to the encounter on specialized care on which the adaptation of treatment for a specific patient concludes. As such, patients affected with CG are included into the follow-up service when the IOP is stabilized under a target value, and hereby the ophthalmologist considers the therapy chosen as appropriate for a long-term treatment.
  To make such a decision, the ophthalmologist must review the set of diagnostic tests registered during the background stage so as to determine whether the disease trajectory has stabilized. The first examination of papilla, the VF test that confirmed the diagnosis of glaucoma and the progression of IOP values obtained so far are available in this regard (see Figure 24).
  At the end of this stage, the responsible ophthalmologist establishes the long-term treatment and schedules the next consultation for patient's review.

- **STAGE 2 (Follow-up schedule):** Once the long-term therapy has been established, next appointment is requested through a referral note in which the period for patient's review and the diagnostic tests indicated on that review are specified.

- **STAGE 3 (Diagnostic tests):** The advance of CG may be manifested in different ways, and the slightest sign of progression could lead to reconsider the therapeutic strategy. Consequently, toward the completeness of the review, the study of CG in the SNS-O covers the examination of various fronts simultaneously: the evolution of IOP, observation of the optic disc, and examination of the VF.
  In that respect, the patient goes through different workspaces managed by specifically trained nurses and imaging technicians, where the corresponding diagnostic tests are carried out. Those workspaces were devised in the spirit of maximizing the infrastructure sharing with the other e-health developments described along this chapter. Specifically, the diagnostic tests involved in the follow-up of CG were distributed into three differentiated workspaces (see Figure 25):

  - The first workspace: This workspace is equipped with a non-mydriatic fundus camera, a non-contact tonometer, a pachymeter and a Snellen chart. First of all, the nurse in charge of the workspace conducts the VA test to patients as they arrive to this point of care. As well as in monitoring of patients with wet AMD, VA is obtained in decimal scale and then converted into logMAR. This way, the overall visual loss caused by the current stage of glaucoma is appreciated before proceeding with the following tests.
    Next, the nurse obtains patient's IOP measurements using a non-contact tonometer. Since this procedure does not requires direct contact with the eye, there is no need of topical anesthesia either. Then, pachymetry is used to adjust the IOP values obtained by tonometry according to the corneal thickness measured for each patient. In this way, the resulting corrected IOP provides key information about the disease trajectory, especially concerning the fulfillment of target IOP value.
    Then, the corresponding nurse uses a non-mydriatic fundus camera to acquire photographs of patient's optic disc, as an alternative to the direct examination of the optic disc carried out by ophthalmologists in face-to-face consultations. The resulting acquisitions are uploaded to the PACS server of the health service. Likewise, the VA and IOP values are registered into the EHR system. In this way, all diagnostic information is accessible for remote assessment.

- The second workspace: This workspace is specialized on acquisition of OCT studies. Concerning the follow-up of CG, the OCT test provides the analysis of three parameter groups for classification and detection of disease progression: optic nerve head, RNFL and ganglion cell complex. From those, trend analyses of the RNFL thickness measurements around the optic disc are especially useful to quantify the glaucomatous progression in terms of the loss of visual fibers.
  Therefore, a nurse or imaging technician conducts a study of the thickness of the RNFL to every patient with CG, as they arrive to the OCT workstation.
  That OCT study consists of a radial scan acquired around the optic disc of the eye or eyes affected by glaucoma. As such, this scan will provide the current thickness of the RNFL, so once the study is sent to the PACS server, it could be compared with previous studies. Thereby, the aforementioned OCT study will be crucial in next stage for identifying signs of thickness reduction over time.
- The third workspace: Whereas the workspaces above were adapted from other clinical processes presented along this Thesis, the third workspace is exclusive of the CG follow-up service.
  This workspace was set in an office reserved to host the VF test. Consequently, the office is managed by a nurse especially assigned to operate with the Humphrey perimeter available in the service.
  As patients scheduled arrive to the office, first of all, the nurse in charge evaluates the refraction parameters obtained during the VA test conducted in the "first workspace" seen above. That result is then applied in the calculation of the offset needed to correct the refractive error given during the VF test.
  Thereafter, the nurse configures the perimetry test in view of studying the progression of CG: given that threshold perimetry is the recommended standard in glaucoma, SITA-Standard or SITA-Fast test strategies are used indistinctly in the SNS-O. These strategies are governed by the Swedish Interactive Thresholding Algorithm (SITA), which optimizes the sequence of the stimuli presented and estimates the expected threshold values for each point measured all over the VF. Those are continuously estimated based on the patient's age and the thresholds established in neighbouring points. Although the ophthalmologist who requested the review can specify other test patterns whenever considers necessary, the Humphrey 24-2 testing algorithm is chosen by default in the SNS-O. In fact, the 54 individual points tested all over patient's VF, save in exceptional cases, provide a sufficient resolution for studying progression in CG [89, 187].
  Traditionally the report resulting from the VF testing is printed and then examined by an expert ophthalmologist. Thus, despite the fact that most of the information provided by perimetry is comprised of numeric and statistical data, at this stage of the proceeding, the report is uploaded to the PACS server as an image.

– **STAGE 4 (CG assessment):** Once all the diagnostic tests necessary for the assessment of a specific patient have been completed, the ophthalmologist who requested those tests must assess the resulting clinical data and diagnostic images. In that respect, a workstation equipped with a DICOM image viewer and an EMR front-end connected to the EHR system is provided to make the remote assessment possible at the office of specialized care.
  There, the ophthalmologist begins the revision by loading into the DICOM viewer all diagnostic images considered relevant, including those from previous consultations, and related to the patient under study. This should provide an overall view of glaucoma on which to base the assessment.

At this point, the ophthalmologist analyzes the VA measurements and especially the IOP values recorded in the EHR to date. In fact, an upward trend, or values exceeding the target IOP can lead into irreversible glaucomatous damage still not identifiable by the rest of diagnostic tests. Given that perimetry depicts pretty graphic representation of glaucomatous functional deterioration, the VFs resulting from consecutive studies of a specific patient are then compared so as to determine whether there are signs of progressive visual loss. Nevertheless, it should be noted that, although in some cases progression may be detected before, the analysis of CG requires a long enough time span (two years approximately), and at least five consecutive tests before presenting evident signs of progression [89].

Next, the ophthalmologist focuses the assessment on reviewing the funduscopic and OCT studies archived. Whereas perimetry provided information about functional deterioration of the optic nerve, these tests are analyzed for structural findings that could reveal glaucomatous activity. Regarding the assessment of funduscopic photographs, the ophthalmologist pays special attention to the enlargement of the optic disc cupping, changes in RNFL appearance, evolution of parapapillary atrophy, positional changes of the vessels at the optic disc, and emerging new haemorrhages on or bordering the optic disc. Whilst the OCT studies provide excellent tools for identifying signs of thickness reduction in the RNFL.

Provided that perimetry reveals progressive visual loss, the assessment of funduscopic and OCT acquisitions could explain the cause of such deterioration on the VF. Conversely, if perimetry does not indicate a clear disease progression, the aforementioned tests are reviewed anyway so as to identify any glaucomatous activity that could lead to visual loss in the future.

As a result of the overall analysis of the aforementioned test results, at this point, the ophthalmologist must determine whether the CG remains stable, or on the contrary there is any sign of disease progression. Regardless of the diagnostic decision, how to proceed in each case is described in the next stage.

- STAGE 5 (Modify CG treatment): Provided that after consulting the examination results, the ophthalmologist determined that a specific patient is well controlled, a new examination is scheduled within a given period, and the necessary tests are ordered accordingly.

  If, conversely, the specialist considers that treatment modification is warranted but the change is simple, the patient will be kept informed about any adjustment on medication by telephone or e-mail.

  However, whenever the problem is more complex or if surgery is required, the patient is temporally excluded from the follow-up service, and a new hospital visit is scheduled. That visit would correspond to the third encounter on specialized care intended to adjust the treatment and stabilize the disease evolution, which indeed is further described along the "background stage" above. Thus, in light of the above, the clinical process would continue from that point on.

B.2 Study of Clinical Concepts

As a result of the analysis of the clinical process described in the previous step, the clinical concepts listed in Table 11 were chosen to register the clinical information generated during the follow-up service for CG. Every concept was then associated with the clinical stages they belonged to.

Excluding the concepts inherent to the assessment of glaucoma, or those related to the VF test, most of the clinical concepts identified on this healthcare scenario were reused, either from the electronic models presented along this Thesis, or the CKM. On the basis of the modelling work carried out beforehand, defining the follow-up service for CG turned out to be more agile than the previous use cases presented along this Thesis.

Table 11: *Clinical concepts identified as a result of studying each stage in the follow-up service proposed for CG.*

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
1.	Reason for encounter	- Found on CKM - Usable as is	Evaluation	Stage 1
2.	Story/history	- Found on CKM - Usable as is	Observation	Stage 1
3.	Risk factors in glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 1
4.	Intraocular pressure measurement	- Concept reused from DR screening service	Observation	Stage 1 Stage 3
5.	Visual acuity	- Concept reused from AMD monitoring service	Observation	Stage 1 Stage 3
6.	Funduscopic examination of eyes	- Concept reused from the two preceding models	Observation	Stage 1 Stage 3 Stage 4
7.	Ophthalmic tomography examination	- Concept reused from AMD monitoring service	Observation	Stage 1 Stage 3 Stage 4
8.	Visual field measurement	- Found on CKM - It has to be adapted	Observation	Stage 1 Stage 3 Stage 4
9.	Problem/diagnosis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4
10.	Classification of glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 1 Stage 4
11.	Findings in glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 1 Stage 4
12.	Clinical synopsis	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4
13.	Contraindication	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4
14.	Recommendation	- Found on CKM - Usable as is	Evaluation	Stage 1 Stage 4
15.	Enrolment in a long-term healthcare process	- Concept reused from AMD monitoring service	Evaluation	Stage 1
16.	Care plan (request)	- Found on CKM - Usable as is	Instruction	Stage 2
17.	Care plan	- Found on CKM - Usable as is	Action	Stage 2
18.	Referral request	- Found on CKM - Usable as is	Instruction	Stage 2
19.	Imaging examination request	- Found on CKM - Usable as is	Instruction	Stage 2
20.	Acquisition details on eye fundus images	- Concept reused from the two preceding models	Cluster	Stage 2 Stage 3
21.	Acquisition details on ophthalmic tomography	- Concept reused from AMD monitoring service	Cluster	Stage 2 Stage 3

	Identified concept name	Equivalent archetype	Archetype class	Process stages in which it is applicable
22.	Acquisition details on visual field test	- No equivalences found - Archetype has to be modelled from scratch	Cluster	Stage 2 Stage 3
23.	Procedure	- Found on CKM - Usable as is	Action	Stage 3 Stage 5
24.	Medical device	- Found on CKM - Usable as is	Cluster	Stage 3
25.	Medical device details	- Found on CKM - Usable as is	Cluster	Stage 3
26.	Central corneal thickness details	- Concept reused from DR screening service	Cluster	Stage 3
27.	Imaging examination	- Found on CKM - Usable as is	Action	Stage 3
28.	Anatomic location	- Found on CKM - Usable as is	Cluster	Stage 3
29.	Mydriasis application	- Concept reused from the two preceding models	Cluster	Stage 3
30.	Medication amount	- Found on CKM - Usable as is	Cluster	Stage 3
31.	Diagnostic report request	- Concept reused from the two preceding models	Instruction	Stage 3 Stage 4
32.	Service request	- Found on CKM - Usable as is	Instruction	Stage 3 Stage 4
33.	Medication order	- Found on CKM - Usable as is	Instruction	Stage 5
34.	Medication action	- Found on CKM - Usable as is	Action	Stage 5
35.	Adverse reaction	- Found on CKM - Usable as is	Evaluation	Stage 5
36.	Procedure request	- Found on CKM - Usable as is	Instruction	Stage 5
37.	Ophthalmic laser procedure details	- Concept reused from DR screening service	Cluster	Stage 5

B.3 Hierarchical Organization of Knowledge Artefacts

The clinical concepts identified in the previous step were structured according to their appearance in the follow-up service detailed for CG. During the organization of that service, many similarities were found with regard to the models proposed in previous sections.

For example, patient admission and follow-up schedule are essentially the same for the study of CG and the service monitoring wet AMD, except for the additional diagnostic tests involved on the former. However, both services differ in the way the treatment is managed: when monitoring wet AMD, the treatment is applied immediately after a patient is enrolled on the therapy. And thereafter, the retreatment must be confirmed after each assessment. Conversely, every patient admitted for the CG follow-up service should remain stable due to the medical treatment they are receiving. In fact, the office examination and therapeutic decision is reserved for exceptional cases in which the specialist considers that treatment modification is warranted. Thus, the stage for modifying the treatment of glaucoma was mainly based on the stage defined for the treatment in the DR screening service.

Regarding the acquisition and validation of diagnostic tests, they were configured as a combination of the analogous clinical stages provided within the DR screening and wet AMD monitoring services. That was possible because the follow-up of CG covers all diagnostic tests used in the preceding models, and besides, introduces the VF test. Finally, the clinical stage for the remote assessment of these tests was designed in line with the AMD assessment seen in Figure 20.

Considering all the above, the work team captured the hierarchy among knowledge artefacts involved within the follow-up of CG into the Figure 26. As in the other healthcare scenarios modelled so far, the resulting diagram was built according to the hierarchy among knowledge artefacts described in Figure 9.

4.3.3 BUILDING THE ELECTRONIC MODEL

C.1 Creation and Update of Archetypes

The model proposed to follow-up patients diagnosed with CG consists of 37 entry-type archetypes. Of these, 22 archetypes were obtained from the openEHR CKM: 21 were directly used on the model, and a new version of the *"Visual field measurement"* was provided to fulfil the requirements of our model. For further information, a list of all the archetypes modelled along this Thesis can be found in Appendix A.

Then, the work team was engaged in the creation of the other 15 archetypes not available in the CKM. Given the clinical processes modelled along this Thesis, the follow-up of CG is the one that presents the greatest complexity in terms of diversity of archetypes. However, given the high rate of archetypes that were reused from previous electronic models, only 4 archetypes were specifically built for this use case: *"Risk factors in glaucoma"*, *"Classification of glaucoma"*, *"Findings in glaucoma"*, and *"Acquisition details on visual field test"*.

Therefore, excluding the aforementioned, the 11 ones left were obtained from previous models: 3 archetypes were reused from the DR screening service, another 4 from the service monitoring the treatment of wet AMD, and the remaining 4 were common in all three models described along this Thesis (see Table 11).

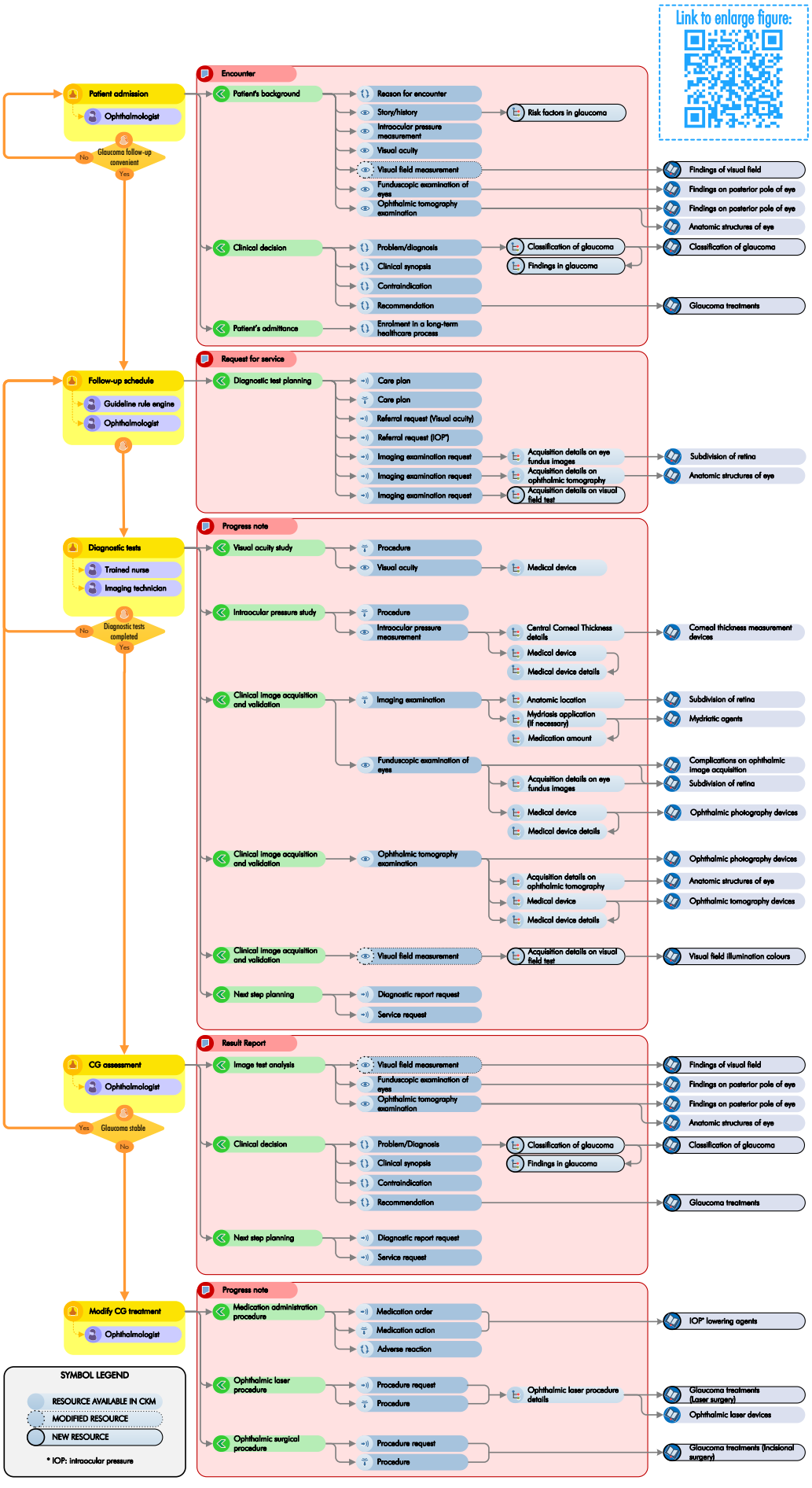

Figure 26: *Hierarchy among the knowledge artefacts involved in the follow-up of CG.*

C.2 Definition of Semantic links to Clinical Terminologies

A total of 14 termsets were used to model the follow-up of patients diagnosed with CG. Of these, 5 were specifically created for this use case, 7 were reused from the DR screening service modelled beforehand, whereas the remaining two were initially created for the monitoring of wet AMD. All the aforementioned termsets and their use along the stages in the clinical process are described in Table **12**.

C.3 Building Templates

The model comprises 19 different templates: 14 of those organize the archetypes contained inside sections, whereas the remaining templates compose each one of the 5 stages of the clinical process that contain the aforementioned sections (Figure 26).

From the aforementioned, 2 templates were reused along the clinical process: on the one hand, the treatment established before patient's admittance, must be periodically reviewed along the CG follow-up service. For this reason, the template *"Classification and treatment of CG"* was replicated for the first and third stages (admission and assessment). On the other hand, the template *"Next step in CG follow-up service"* was first used at third stage, to refer patients toward the CG assessment once all diagnostic tests were acquired, but also at the fourth stage, either to schedule next review or to ask for modifying the treatment.

Furthermore, taking advantage of the common clinical domain among the models proposed along this Thesis, some templates used on this healthcare scenario were directly reused from our previous modelling experiences. Of the total number of templates used, 2 came from the DR screening service, and another 2 were obtained from the service proposed to monitor the treatment of AMD. This is because some of diagnostic tests required to follow-up CG were also contemplated in the aforementioned services. In this way, templates that describe the *"Intraocular pressure study"* and the *"Acquisition and validation of NMR"* proposed in the DR screening clinical process were used with no need of modifications to follow-up CG. Likewise, the *"Visual acuity study"* and the *"Acquisition and validation of OCT"* were obtained, as is, from the model proposed to monitor the treatment of wet AMD.

Therefore, 15 templates were specifically created for this healthcare model, and yet most of them share similarities to analogous templates used in the healthcare services modelled beforehand. For instance, the template corresponding to the section "Patient's admittance", originally built for the service monitoring the treatment of AMD was adapted to enrol patients in the follow-up for CG. Furthermore, the template *"Laser procedures to treat CG"* is practically the same as *"Laser procedures to treat DR"* used in the DR screening service. It only differs on the use of a different termset adapted to each healthcare scenario, since the choice of laser surgery differs depending on the condition to be treated (Figure 27). This is because most of knowledge artefacts required to model the follow-up of CG were already available, hence more than modelling a new healthcare process, the templates available were reorganized and adapted to conform this use case.

Table 12: *Termsets that support the archetypes within the follow-up service proposed for CG.*

	Termset name	Description of termset	Availability	Process stages in which it is applicable
1.	Findings of visual field	List of findings distinguishable on the visual field test.	Newly created	Stage 1 Stage 4
2.	Findings on posterior pole of eye	Clinical findings identifiable in posterior pole of eye.	Reused from DR screening	Stage 1 Stage 4
3.	Anatomic structures of eye	List of regions of interest in the study of eye (based on DICOM Tables: CID 4209, CID 4211 and CID 4266).	Reused from the AMD monitoring	Stage 1, Stage 2 Stage 3, Stage 4
4.	Classification of glaucoma	List of disorders distinguishable on the diagnosis of glaucoma.	Newly created	Stage 1 Stage 4
5.	Glaucoma treatments	List of therapeutic options to treat different types and stages of glaucoma.	Newly created	Stage 1 Stage 4 Stage 5
6.	Subdivision of retina	List of zones in eye retina for ophthalmic image positioning.	Reused from DR screening	Stage 2 Stage 3
7.	Corneal thickness measurement devices	List of methods to obtain the corneal thickness measurement.	Reused from DR screening	Stage 3
8.	Mydriatic agents	List of mydriatic agents and their corresponding doses validated for ophthalmologic use.	Reused from DR screening	Stage 3
9.	Complications on ophthalmic image acquisition	List of possible complications during ophthalmic imaging studies that may affect the quality of acquisitions (based on Table CID 4222 of DICOM standard).	Reused from DR screening	Stage 3
10.	Ophthalmic photography devices	Lists the ophthalmic photography acquisition devices (based on Table CID 4202 of DICOM standard).	Reused from DR screening	Stage 3
11.	Ophthalmic tomography devices	List of acquisition devices (based on Table CID 4210 of DICOM standard).	Reused from the AMD monitoring	Stage 3
12.	Visual field illumination colours	List of illumination colours used as visual stimuli on visual field test (based on Table CID 4255 of DICOM standard).	Newly created	Stage 3
13.	IOP lowering agents	List of agents used in ophthalmology for IOP lowering.	Newly created	Stage 5
14.	Ophthalmic laser devices	List of laser devices for ophthalmic use.	Reused from DR screening	Stage 5

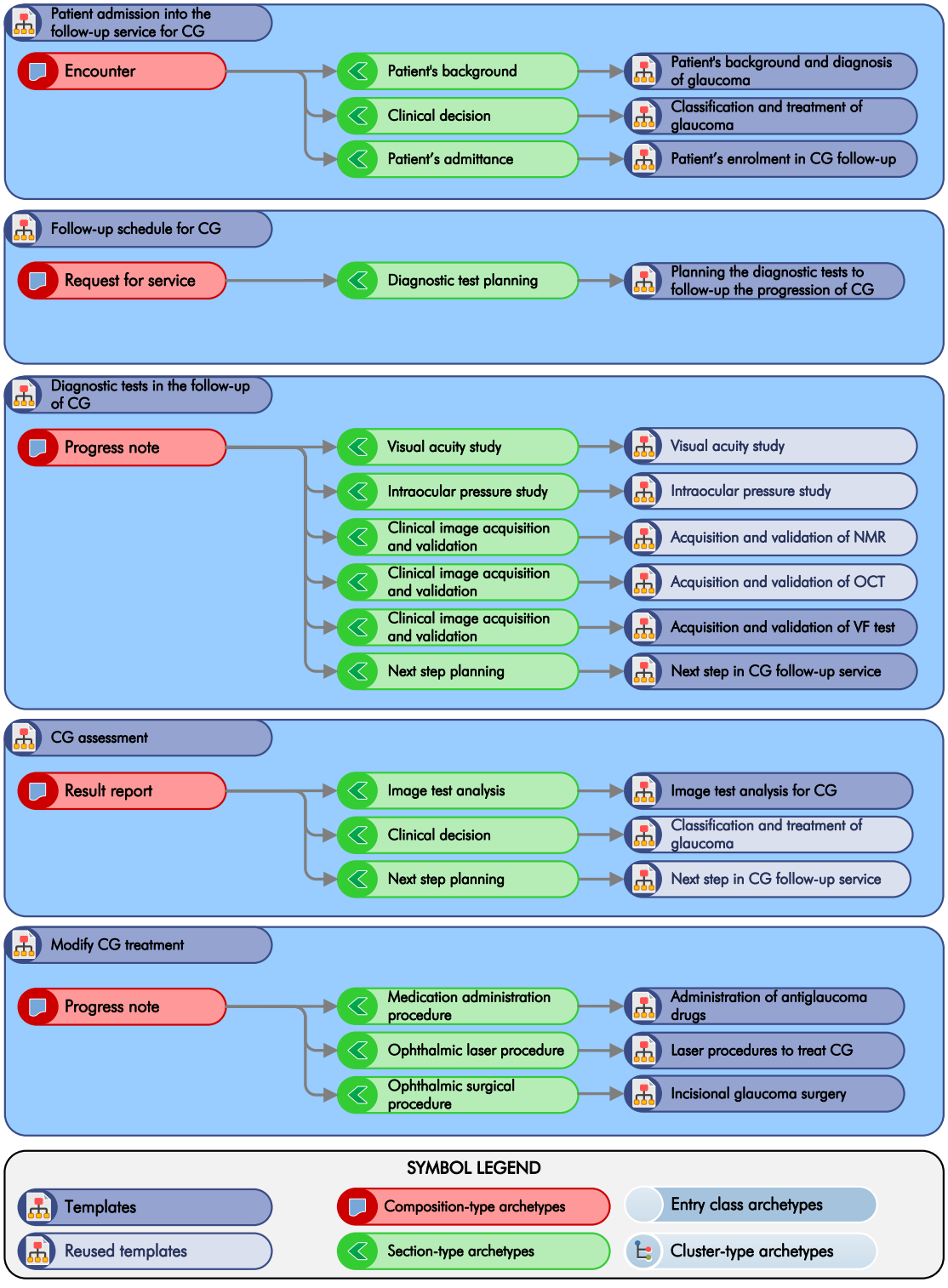

Figure 27: *The structure of templates envisaged to register clinical encounters resulting from the follow-up of CG.*

C.4 Modelling Guideline Rules and Workflow

A total of 6 rules were designed to govern patients' flow through the clinical stages defined for the clinical process. The archetypes participating in these rules can be found in Appendix A:

- **Glaucoma follow-up convenient:** Patients diagnosed with CG would be enrolled into the follow-up service, when the ophthalmologist responsible of their therapy establishes a medical treatment that achieves the target IOP and curbs the progression of the disease into a medically stable state.

  Consequently, the follow-up begins the instant that the ophthalmologist registers a patient into the medical treatment for CG by submitting the archetype *"Enrolment in a long-term healthcare process"* to the EHR.

  In light of this, this rule checks all contributions for that archetype, so as to detect the admittance of every new patient to the glaucoma follow-up service. Thus, if the healthcare process corresponds to the "Follow-up service for chronic glaucoma" and patient's admittance is set to "true", this rule automatically will define a care plan where the diagnostic tests necessary for monitoring the progression of chronic glaucoma would be scheduled.

  At this point, the *"Referral request"* and *"Imaging examination request"* archetypes are used to manage the reservation of the diagnostic tests of VA, IOP, NMR, OCT, and VF measurement. Besides the aforementioned, if necessary, the ophthalmologist can also include additional tests into the care plan, according to the severity presented by each patient.
- **Diagnostic tests completed:** Similarly to the homonymous rule defined for the monitoring of wet AMD, this rule must guarantee the completion of every diagnostic test ordered for a specific patient before proceeding with the remote assessment. Except in this case, the diagnostic tests to be managed include VA, IOP, NMR, OCT, and VF measurement, plus the complementary tests considered necessary by the ophthalmologist.

  In the same way as in the case of monitoring wet AMD, as diagnostic tests are carried out, every new contribution for the archetype *"Care plan"* submitted to the EHR would be checked until the pathway is set to "Care plan completed". This would mean that all diagnostic tests defined in the care plan are available for assessment.

  Finally, when all diagnostic tests required for the follow-up of CG are completed, the rule instantiates the archetype *"Diagnostic report request"* to schedule a consultation for remote assessment of chronic glaucoma.
- **Glaucoma stable:** If, as a result of an overall assessment of glaucoma, the ophthalmologist does not identify clear signs of disease progression, it means that the patient is well controlled, so the treatment applied so far is appropriate. Thus, with the aim of identify which patients present a medically stable state of glaucoma, this rule verifies every contribution upon the archetype *"Classification of glaucoma"* submitted as a result of the assessment of progression in CG. Hence, this rule only considers patients with a confirmed diagnosis of glaucoma (glaucoma suspects are excluded), in which the data element about disease progression has been set to false. If so, provided that patients presenting a stable state of glaucoma should maintain the medical treatment they are receiving, the rule is triggered whenever the therapeutic recommendation registered within the archetype *"Recommendation"* is set to "Maintain medical therapy".

  Then, as there is no need of therapeutic adjustments, the next consultation for glaucoma review is automatically scheduled using the *"Service request"* archetype. At this point, the follow-up scheduled for chronic glaucoma will specify the same diagnostic tests considered in the first rule, to wit, VA, IOP, NMR, OCT, and VF measurement.

- **Glaucoma progressive:** In contrast to the previous rule, this one identifies patients diagnosed with glaucoma that present any sign of disease progression that could lead to visual loss in the future. Thus, the rule is triggered whenever the ophthalmologist responsible of the remote assessment of CG records as true the parameter "Progressive disease" from the archetype *"Classification of glaucoma"*.

  For such cases, the follow-up service envisages an office examination where the same ophthalmologist responsible of the remote assessment would determine the appropriate therapeutic decision for each patient. Therefore, this guideline rule organizes such encounter by instantiating the archetype *"Diagnostic report request"* similarly to the request made for the remote assessment, except this time the service is scheduled at the ophthalmologist's office.
- **Modify the medical treatment:** This rule covers the scenario in which, as a result of the office assessment, the ophthalmologist considers that treatment modification is warranted, but the disease could be easily stabilized by adjusting the medication regimen.

  Thus, the rule is triggered whenever the ophthalmologist records the therapeutic recommendation of "Medical treatment" into the archetype *"Recommendation"*. Hereby, this rule creates an instance of *"Medication order"*, in which the ophthalmologist must establish the details of the new medical treatment. Subsequently, the archetype *"Service request"* is used to plan the follow-up for chronic glaucoma in order to review if the condition returns to a medically stable state after the new treatment.

  Therefore, the patient is informed about the new instructions for the administration of the medication, and then, the diagnostic tests corresponding to the next consultation for glaucoma review are scheduled (VA, IOP, NMR, OCT, and VF measurement).
- **Surgery required:** When clear signs of CG progression are identified in the office assessment, and the target IOP is not reached through medical treatment, the ophthalmologist must consider surgical procedures for lowering IOP. In this regard, the archetype *"Recommendation"* predefines the therapeutic procedures involving surgery on the treatment of progressive glaucoma. Therefore, from all therapeutic recommendations that the ophthalmologist recorded on that archetype, this rule is activated when one of the following are chosen: "Laser therapy", "Incisional glaucoma surgery", "Cyclodestructive surgery" or "Other glaucoma surgeries". If it is the case, this rule will automatically instantiate the *"Procedure request"* archetype, and request the surgical procedure specified as therapeutic recommendation. Likewise, the "Indication description" for that procedure will be determined by the rationale submitted to support the therapeutic recommendation.

  Finally, given that the surgical procedures fall outside the scope of the follow-up service, the patient must be temporally excluded from glaucoma monitoring. Indeed, before resume the follow-up, the ophthalmologist must reassess the validity of the medical treatment and must readjust the target pressure in accordance with the outcomes of the surgery. Thus, in light of the above, the archetype *"Enrolment in a long-term healthcare process"* is instantiated to temporally deregister the patient from the "Follow-up service for chronic glaucoma".

Table 13: *Description of the guideline rules designed for the follow-up service proposed for CG.*

	Rule name	Conditions	Actions
1.	Glaucoma follow-up convenient	Archetype *"Enrolment in a long-term healthcare process"*: • Healthcare process: "Follow-up service for chronic glaucoma" • Admittance: "True"	Archetype instantiated *"Care plan (request)"*: • Care plan name: "Follow-up service for chronic glaucoma" Archetype instantiated *"Referral request"*: • Service requested: VA test • Service requested: IOP measurement Archetype instantiated *"Imaging examination request"*: • Service requested: NMR • Service requested: OCT study • Service requested: VF measurement
2.	Diagnostic tests completed	Archetype *"Care plan"*: • Care plan name: "Follow-up service for chronic glaucoma" • Pathway: "Care plan completed"	Archetype instantiated *"Diagnostic report request"*: • Service requested: "Remote assessment of chronic glaucoma" • Reason for request: "Completed the diagnostic tests necessary for assessment"
3.	Glaucoma stable	The preconditions for this rule, are the *"Classification of glaucoma"* to be different to "No glaucoma" (Concept ID in SNOMED-CT: 310596004) and "Glaucoma suspect" (Concept ID in SNOMED-CT: 232079008), and besides, the parameter "Progressive disease" to be set as false. Archetype *"Recommendation"*: • Therapeutic recommendation: "Maintain medical therapy" • Rationale: "Glaucoma stable"	Archetype instantiated *"Service request"*: • Service name: "Follow-up schedule for chronic glaucoma" • Description: "Follow-up comprised by IOP measurement, VA, NMR, OCT and VF tests"

	Rule name	Conditions	Actions
4.	Glaucoma progressive	Archetype *"Classification of glaucoma"*: • Classification: Exists and it is different to "No glaucoma" and "Glaucoma suspect" • Progressive disease: "True"	Archetype instantiated *"Diagnostic report request"*: • Service requested: "Office assessment of glaucoma" • Reason for request: "Determine therapy for progressive glaucoma"
5.	Modify the medical treatment	The conditions established within the rule "Glaucoma progressive" comprise the precondition for this rule. Archetype *"Recommendation"*: • Therapeutic recommendation: "Medical treatment"	Archetype instantiated *"Medication order"* (modify the medical regimen). Then, the follow-up service for chronic glaucoma is requested to review if the condition returns to a medically stable state after the new treatment. Archetype instantiated *"Service request"*: • Service name: "Follow-up schedule for chronic glaucoma" • Description: "Follow-up comprised by IOP measurement, VA, NMR, OCT and VF tests"
6.	Surgery required	The conditions established within the rule "Glaucoma progressive" comprise the precondition for this rule. Archetype *"Recommendation"*: • Therapeutic recommendation: "Laser therapy", "Incisional glaucoma surgery", "Cyclodestructive surgery" or "Other glaucoma surgeries"	Archetype instantiated *"Procedure request"* • Procedure name = Therapeutic recommendation (in "Recommended treatment for glaucoma") • Objective: "Curb the progression of glaucoma into a medically stable state" • Indication description = Rationale (in "Recommended treatment for glaucoma") Archetype instantiated *"Enrolment in a long-term healthcare process"*: • Admittance: "False" • Healthcare process: "Follow-up service for chronic glaucoma"

C.5 Modelling UI Forms

As in previous electronic models, the Marand EhrExplorer was used to model UI forms for each of the 5 stages that comprise the CG follow-up service. Given that the final users must interact with the resulting UI views, their modelling was closely supervised by ophthalmologists. Because the framework chosen for modelling the UI forms is restricted to test purposes, the resulting form-description files were downloaded for further study. Consequently, we can deploy the UI forms defined in our own servers.

4.3.4 IMPLEMENTATION OF THE SERVICE

Given the background on management of clinical information in the SNS-O and the common ground of the CG follow-up service with regard to the previous implementations presented along this Thesis, this service would be built upon the ICT infrastructure and information systems deployed so far.

Returning to the workspaces established for this clinical process, the electronic devices allocated to each of them must be interconnected so as to exchange data with the corresponding information systems. In this regard, the first workspace includes tonometry and pachymetry devices for IOP measurement, a non-mydriatic retinal camera, and a PC workstation in compliance with the DR screening service. In addition, a Snellen chart for VA measurement was incorporated afterwards, as stated in the technical requirements of the wet AMD monitoring. The second workspace corresponds to the office originally set up for acquisition of the OCT studies carried out in the service monitoring the treatment of wet AMD. Because of previous implementations, no action was necessary on these workspaces.

In fact, the main contribution of the follow-up service for CG was the establishment of the third workspace. This one was specifically conceived for VF measurement, as this test was not covered by the previous implementations. Therefore, a Humphrey perimeter was installed in the healthcare service, and then, it was connected into the DICOM network of the SNS-O. In this way, the nurse responsible of operating with the perimeter can consult the worklist of patients scheduled into the device, and upload the resulting VF measurements to the PACS server.

Finally, the workspace dedicated to the assessment, was established in the office of the ophthalmologist specialized on glaucoma. There, besides complementary diagnostic tests available for further examination of patients, in line with analogous workspaces in the preceding models, a PC workstation was included to ensure access for the ophthalmologist to PACS and EHR servers. This will enable the ophthalmologist to evaluate patients presenting CG remotely.

At this point, similarly to the previous implementations proposed along this Thesis, the archetypes and templates modelled for the CG follow-up service were loaded into an openEHR-compliant EHR. On the one hand, the EHRServer originally launched for DR screening service (and reused on the AMD monitoring service) was chosen to register the medical records. On the other hand, the openEHR-OPT developed by Cabolabs would be used to generate UI forms from the OPT files. And then, the EHRCommitter would be used as front-end to send toward the EHR the clinical reports produced at the different workspaces. In this way, clinicians would be able to register clinical information specific to the follow-up of CG, using the UI forms dedicated to each stage of the clinical process, and with no need of introducing changes on the main EHR system of specialized care in the SNS-O. Meanwhile, the main EHR system would be used to coordinate the services provided by the complementary information systems involved in the clinical process: medical imaging management through PACS, arrange appointments on specialized care on the HIS, handle the electronic referrals using the CPOE management system, or keep track of electronic prescriptions on the pharmacy information management system.

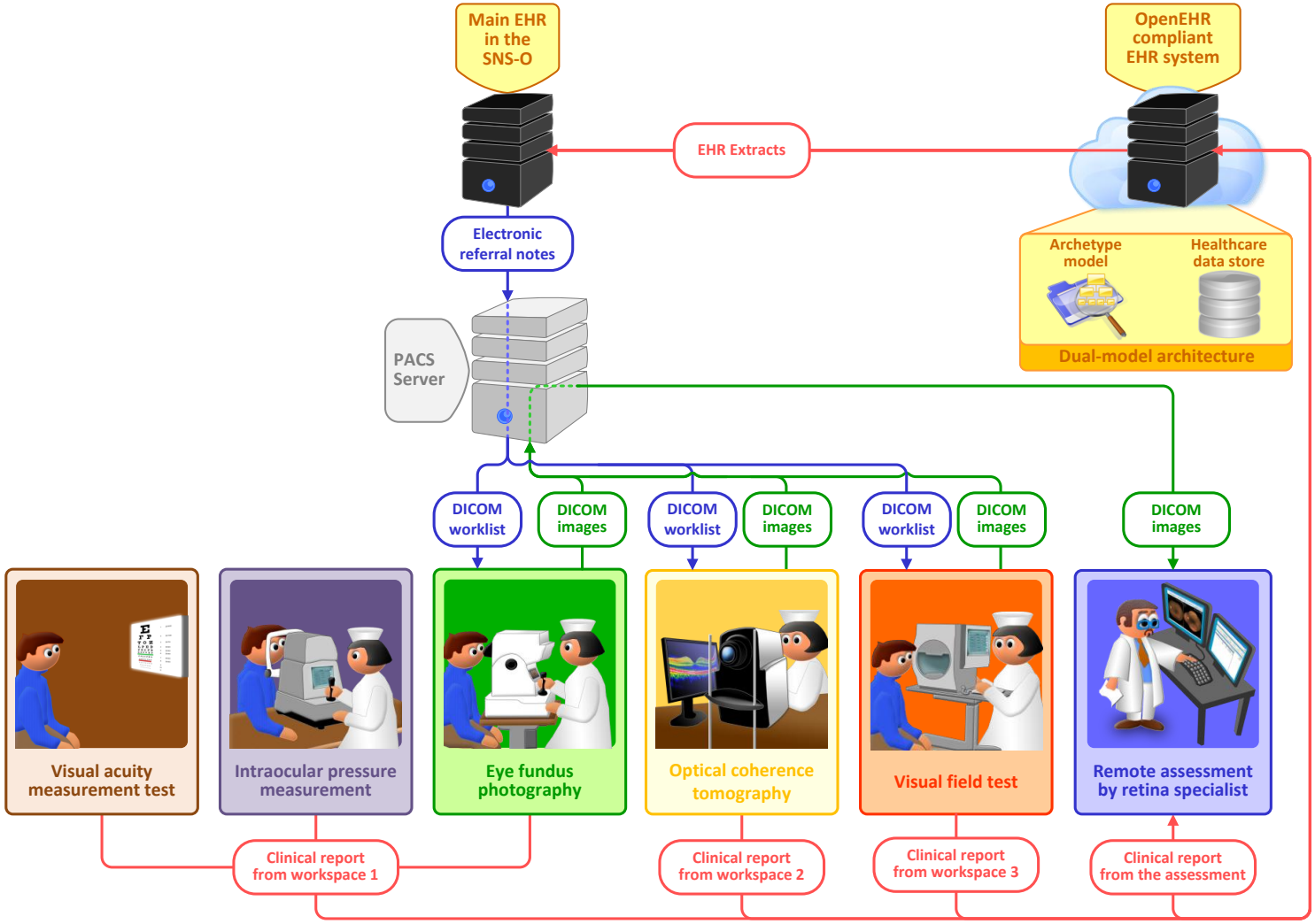

Figure 28: *Flux of information through the service monitoring the treatment of CG.*

Chapter 5:

Discussion

This Chapter discusses the topics covered along the Thesis. First of all, the implications of applying the methodology proposed for modelling healthcare into model-driven information systems are outlined. Then, how the health computing platform proposed could change the strategy for management of clinical information is discussed. Finally, the conclusions reached after modelling three clinical processes in ophthalmology are described.

5.1 DISCUSSION ABOUT THE METHODOLOGY PROPOSED TO FORMALIZE CLINICAL PRACTICE

As seen in Chapter 2.3, the advent of model-driven information systems enabled clinicians to participate actively in building their own electronic models. However, building such models is an intricate, laborious process. Moreover, it requires tight collaboration among multidisciplinary professionals (domain experts, physicians, technical developers, terminologists, etc.). This is a complex situation which requires high levels of coordination for harmonizing the different schedules. But nevertheless, to make the most of this technology, we need to attract experts in the clinical domain to contribute to the knowledge base available today. To that end, as a result of a thorough study of the different approaches for modelling clinical knowledge found in scientific literature, a comprehensive methodology was proposed in Chapter 3.1, to formalize the clinical practice into model-driven information systems.

One of the limitations of this methodology is that it should be adapted to the extent that model-driven information systems evolve and integrate new knowledge artefacts. Additionally, open modelling tools must be provided so that any workgroup can contribute to the knowledge base without restrictions. However, the software tools found, especially open-access ones, still have to improve their user-friendliness to encourage domain experts and terminologists to develop electronic models with no need of additional training. Many of these tools are technified, i.e. require advanced understanding of e-health standards, present bugs or they are still in development due to the ongoing discussion on the specifications of the e-health standards involved.

For example, there is a modelling tool for building archetypes and templates in compliance with openEHR ADL 2 specifications [179]. However, given the recent development of ADL 2, although such application is going to be essential for modellers in the near future, it would not be widely used until the modelling tools and information systems necessary to implement the model-driven approach incorporate these specifications. Until then, applications based on ADL 1.4 specifications will prevail with regards to building electronic models using openEHR archetypes and templates. In the case of modelling UI forms, there is no even a consensus on their specifications. Hence each company must create its own proprietary solutions. It would be therefore interesting to work toward filling this gap by providing open specifications and modelling tools for UI form building.

Another issue which may discourage modellers is the difficulty of setting up the workspace to start on the modelling. In this regard, diverse software tools must be configured, besides organizing local and remote knowledge repositories depending on the knowledge artefacts handled. In this sense, there are initiatives such as the CKM platform, or the aforementioned ADL-designer that provide open-access to a web platform in which the modelling tools have been configured beforehand. In this way, once registered on the platform, modellers can immediately start modelling healthcare without worrying about technical matters. In addition, as virtual workspaces are used to model knowledge artefacts located into remote repositories, this approach would foster collaborative, peer-reviewed modelling strategies, thus facilitating coordination among multidisciplinary modellers. It is therefore expected that the trend in modelling tools should follow these examples and be integrated into open-access web platforms.

In any case, all the limitations described above, such as the need of user-friendlier software tools, are common among the other proposals of methodologies cited in the literature. However, the approach proposed in this Thesis solves some of the limitations that discourage clinicians to engage in modelling the clinical practice. For example, the guidelines found in literature do not cover all aspects of clinical processes pursued by this work. Conversely, the methodology proposed covers the whole process to build electronic models from the clinical concept to the presentation layer. Moreover, within this methodology, the guidelines covering specific stages of the overall modelling were unified following a common thread: the layers of interoperability presented in section 2.2. This is a two-fold advantage. First, the modellers would be able to use only part of the methodology proposed, which

will depend on the scope of their projects, with the certainty that the rest of the layers could be added in a straightforward manner in the future. Second, the methodology proposed has been defined to guide domain experts in building high-quality electronic models, independently of their knowledge on technologies and e-health standards, which have little to do with their expertise.

5.2 DISCUSSION ABOUT THE ARCHITECTURE PROPOSAL FOR AN OPEN HEALTH COMPUTING PLATFORM

Given the state of the art on the different open health computing platform, described in section 2.4, and together with the current management of clinical information in the SNS-O, described in section 2.5, an overall architecture for implementation of a model-driven e-health platform was proposed in section 3.2.

As regard to the limitations, this proposal includes the most commonly used modules in the health care environment. However, being as comprehensive as it is, additional modules could be considered depending on the requirements of each specific implementation of the platform. This may imply a slight modification of the architecture proposed. Moreover, the proposal provides some examples of architectures and technologies that could be used for implementing the platform (such as SOA, REST, JSON, etc.). However, these are mere recommendations in order to facilitate the practical implementation of the platform. Obviously, a software architect is free to choose other technologies for specific implementations. Also, the selected technologies could be changed in the future. Nevertheless, although the specific implementations could differ one from another, the general architecture proposal would be still valid, as long as all the components that comprise the platform share the same reference model.

Additionally, with the advent of connectable e-health devices in healthcare, today, diverse diagnostic tests can be combined to reach a valid diagnosis. Therefore, the clinical guidelines applied in each healthcare scenario should be adapted depending on the diagnostic equipment available, even if they respond to the same care plan. This would lead to a patient-centered health environment in which clinicians must choose between different clinical procedures, all valid to solve a specific healthcare problem. On top of this, each health service must deal with an installed base of legacy information systems developed by different manufacturers which probably use proprietary formats to register clinical information. In this regard, unlike other existing proposals in the literature, the modular and standards-based architecture described in section 3.2 would enable to progressively structure the clinical information of such legacy systems into a semantically computable format. The advantages of the normalization of clinical information are two-fold. First, since the content of the medical records is arranged depending on the archetype model, clinicians could use the paths pointing to specific clinical concepts of the archetype model to build queries for precise exploitation of data without the need of programming skills. Second, the normalization of data could lead to establishing conformance points among manufacturers toward a platform-based economic ecosystem. In other words, unifying all clinical information into a vendor-independent health computing platform would enable scalable and tailor-made solutions for health services.

Rather than building applications from scratch to cover the needs of specific healthcare scenarios, the proposed platform approach aims at building customized plugins with the interfaces necessary to interact with the health computing platform. Moreover, as in the example shown in section 4.2.4, by adding the appropriate data mapping and communication interfaces, even the existing legacy applications could be integrated into the platform of the health service. Alternatively, as Marco-Ruiz et al. proposed [136], relevant clinical information contained in databases of non-standardized information systems could be directly mapped to archetype-based EHR standards.

To sum up, in this new scenario, in which all the modules integrated in this platform are normalized with respect to the same reference model, the control and ownership of the data at the health

computing platform are guaranteed. This prevents the technical lock-in when incorporating departmental software tools and information systems to support clinical practices ongoing into the health service. Consequently, on the basis of the architecture proposed in section 3.2, the health computing platforms implemented would be unique for each health service, as they would progressively integrate heterogeneous modules and applications developed by diverse manufacturers according to the local needs of the service at the time of procurement.

5.3 DISCUSSION ABOUT THE ELECTRONIC MODELS BUILT FOR OPHTHALMOLOGY

The advent of model-driven information systems plus the methodology for modelling clinical knowledge proposed in Chapter 3.1 provided a direct way for clinical experts to be involved in the specification of their own clinical models.

Nevertheless, the novelty of this approach still requires modelling different healthcare scenarios to compete with specialised software tools used so far in healthcare. This is because the knowledge artefacts available for download are scarce, and there are even fewer peer-reviewed artefacts. In fact, healthcare modellers worldwide tend to define clinical concepts widely used in medicine, whereas more specific concepts are also necessary with regards to building electronic models for real healthcare scenarios. It is assumed that the more specific the clinical concepts are to a clinical specialty, the higher the likeliness that the corresponding knowledge artefacts either have not been modelled yet, or, at best, they are only available as draft proposals, i.e. they have not yet overcome the peer review procedure. This limits the use of the open-access clinical knowledge base available so far to very specific use cases, such as the case of ophthalmology.

Consequently, seeing no short-term prospects for leveraging the effort made in modelling healthcare, many clinicians will get discouraged from contributing with their expertise to open-access clinical knowledge repositories. In order to address this issue, the electronic models proposed along Chapter 4 of this Thesis covered three real healthcare scenarios in ophthalmology. However, the task of modelling every possibility into each archetype involved in a complex clinical process (constraints, translations, terminology bindings, and maintenance regarding updates in the model) turned out to be a huge workload for a single research group. Therefore, each knowledge artefact proposed can be further improved if we analyse them separately. Nonetheless, the resulting electronic models were intended to provide comprehensive turn-key solutions for the three healthcare scenarios, i.e. any user interested in implementing our models can download and directly start using them. This should encourage clinicians interested in these specific implementations to contribute toward improving the specific components of these models. Therefore, it is expected the critical mass of clinicians involved in modelling the clinical knowledge to increase, and thus the quality of knowledge artefacts defined for ophthalmology. In subsequent revisions, the clinical processes proposed can be modelled even in more detail. For example, the electronic models proposed in this Thesis were focused on assessment more than therapy. Thus, the stages corresponding to treatment can be extended in the future.

Finally, although in principle these models were built for the SNS-O, this Thesis pursues the reusability of electronic resources that comprise these models, so they have been made available in the CKM. Consequently, any healthcare institution managing DR screening services, AMD monitoring services, or CG follow-up services can download these resources (archetypes, templates, termsets, and CDS rules) and adapt them to meet the needs of specific healthcare scenarios.

Chapter 6:

Conclusions and future lines

This last Chapter highlights the final conclusions and the main outcomes of the work presented up to this point, based on the hypotheses and objectives established at the outset of this Thesis. To conclude, this chapter envisions lines of prospective further research that could be strategic to move forward based on the contributions made along this work.

6.1 OVERALL CONCLUSIONS

Seven overall objectives were raised in the first chapter of this Thesis. Below is an overview of how these have been addressed along the different chapters of this PhD dissertation:

> **First objective:** "To deeply study the ecosystem of standards and specifications pervasive in e-health, remarking initiatives focused on interoperability among EHR systems, e.g. openEHR, EN/ISO 13606, DICOM, Health Level 7 (HL7v2, HL7v3, HL7 Clinical Document Architecture or CDA, and more recently HL7 FHIR), and standard medical terminologies (Logical Observation Identifiers Names and Codes – LOINC, Systematic Nomenclature of Medicine - Clinical Terms – SNOMED-CT, International Statistical Classification of Diseases and Related Health Problems – ICD-x or International Classification of Primary Care – ICPC)."

According to the first of those objectives, main standards and specifications involved in the electronic management of information in healthcare were studied. Such study provided the background presented in Chapter 2 with regard to the different layers of interoperability considered along the Thesis.

Further on, along Chapter 3, second and third overall objectives were approached in sections 3.1 and 3.2 respectively:

> **Second objective:** "To design a methodology that would guide domain experts to actively engage in modelling their own electronic models compliant to model-driven e-health standards."

On the one hand, section 3.1 guides domain experts in creating high-quality electronic models for specific clinical processes. Given that health computing platforms involve multitudinous e-health standards and entail different layers of interoperability, modelling healthcare domain must be carefully planned to facilitate an active participation of domain experts. Otherwise, the information systems not receiving continuous contributions from domain experts would be likely to fall into obsolescence. In consequence, a methodology was proposed to model patient-centred clinical processes with the goals of interoperability and reusability of all knowledge components necessary to ensure continuity of patient care. This methodology enables experts of the clinical domain to actively engage in content definition of EHRs, without recourse to software developers. Additionally, the information registered through the health information standards entailed in the methodology fosters the exchange of knowledge artefacts with information systems worldwide, the scalability and extensibility of the resulting models, and the data mining – with no need of programming skills – of the information registered during clinical encounters.

> **Third objective:** "To propose an open architecture for building health computing platforms based on the e-health standards mentioned above, so as to coordinate heterogeneous information systems toward a comprehensive management of patient-centred clinical processes and guaranteeing the continuity of care of patients."

On the other hand, in section 3.2, a health computing platform was proposed toward integration and harmonization of e-health standards into patient-centred clinical processes. Although other proposals equally valid can be found in literature, it is projected that computerized management of healthcare will progress in the direction of a health computing ecosystem based on the open platform architecture in which different e-health standards coexist. Thus, software developers would build applications for multiple competing platforms, whereas health services retain control and ownership of the data regardless of manufacturers.

All remaining overall objectives were approached throughout Chapter 4, where a DR screening service, a high resolution consultation to monitor the treatment of wet AMD, and a follow-up service for CG were considered strategic to alleviate the main bottlenecks in waiting lists for the chronic

conditions with greatest burden in ophthalmology. Thus, each section from Chapter 4 (4.1, 4.2 and 4.3) was focused on modelling each of the aforementioned services, considering the specific requirements of the healthcare scenario found in the SNS-O:

> **Fourth objective:** "To contribute to the design of new e-health services in the SNS-O that would optimize clinical practice in chronic diseases threatening to overload the waiting lists of the ophthalmology department (DR, wet AMD, and CG)."

First of all, the design and development of efficient e-health services was addressed as proposed in the fourth objective. To that end, the clinical practices applied to manage the above mentioned ophthalmic conditions were studied within the SNS-O, and new clinical processes were proposed accordingly to address the shortcomings found in the health service. In this regard, pervasive clinical guidelines were adapted to the resources available in the health service. As a result, the consequent e-health services were depicted using diagrams and tables, which were made available to health domain modellers interested on reproducing such services into other health services.

> **Fifth objective:** "To formalize into electronic models the clinical processes devised in the previous point, i.e. a DR screening service, a service monitoring the intravitreal antivascular endothelial growth factor (anti-VEGF) therapy used to treat wet AMD, and a follow-up service for CG."

Secondly, once the e-health services were well defined, the knowledge artefacts required to build the corresponding electronic models were modelled as proposed in the fifth objective. During the definition of the domain knowledge for the electronic models provided along this Thesis, a total of 103 archetypes were used, excluding organizational classes (section and composition). Of these, 46 were different from the others, which means that the reusability accounted for more than half of the archetypes used among the three models. Regarding non-repeated archetypes, 23 were used as is from the openEHR CKM, 4 were adapted to the needs of the healthcare scenario, and the remaining 19 were specially created from scratch for this Thesis. These archetypes conformed to structure-specific clinical encounters within 47 different templates, of which 31 were devised to structure the aforementioned archetypes inside the sections in order to ease clinician readability. The remaining 16 templates were created to manage the compositions containing these section-type templates. Among all the clinical processes modelled, 19 guideline rules were designed to manage the navigation of patients through the healthcare service. Furthermore, 23 termsets were created to bind selectable data elements from the archetypes and templates to standard terminology services. Once modelled, these standardized representations for clinical knowledge were published in open-access repositories so that any healthcare service interested on implementing the same e-health services could download and adapt these resources to meet the needs of specific health services. In this way, although the clinical processes proposed were initially modelled for the SNS-O, these can be reproduced in a variety of healthcare scenarios, facilitating collaboration among healthcare facilities. Consequently, clinical information resulting from these e-health services would be managed electronically using model-driven health computing platforms. All these knowledge artefacts have been listed in Appendix A.

Besides the aforementioned elements, 16 UI forms were also defined; one for each composition-type template built. Nevertheless, these UI forms were not published given that their applicability was limited to the specific healthcare scenarios proposed for the SNS-O.

> **Sixth overall objective:** "To collaborate closely with standard-setting institutions and to use open platforms to share the experience gained during this Thesis."

Thirdly, and according to the sixth overall objective, modelling of clinical domain was carried out in close collaboration with standard-setting institutions, especially with the openEHR community members. In fact, the electronic models designed along this work were devised with a view to endeavour to maximise their usability in miscellaneous healthcare scenarios worldwide.

Seventh objective: "To prepare the ophthalmology department to implement e-health proposals: standardization of the diagnostic tests and information systems involved in the clinical processes proposed above."

Fourthly, as proposed in the last overall objective, specialised workspaces were set up in the ophthalmology department of the SNS-O, equipped with the technical and human resources necessary to implement the aforementioned e-health services. In the case of the high resolution consultation to monitor the treatment of wet AMD, additionally, a web platform was launched in compliance with openEHR specifications, to validate the therapeutic decisions made in the e-health service proposed.

As a general conclusion, this Thesis proves that a definition of a comprehensive methodology for formalizing clinical practice into information systems, the design of a model-driven, standard-based, open e-health platform and the creation semantically enabled electronic models improves the management of electronic information in healthcare, the interoperability as well as the reutilization of the resources.

6.2 FUTURE LINES

The normalization of clinical knowledge in electronic information systems, in the way it has been proposed in this Thesis, provides interesting opportunities for objective evaluation of the parameters regarding the quality and efficiency of clinical practice:

- The day-to-day functioning of services can be monitored, to identify bottlenecks and points for improvement on the current clinical practice.
- The working services can be compared to new healthcare strategies resulting from research, before their widespread implementation.
- New possibilities arise in medical research, such as objective assessment and comparison between therapies or drugs available.

Therefore, besides facilitating the worldwide spread of more efficient care models, the model-driven e-health approach should facilitate research toward modelling new clinical services.

Furthermore, building electronic models is an intricate, laborious process which requires tight collaboration among multidisciplinary professionals (domain experts, physicians, technical developers, terminologists, etc.). For instance, the task of modelling every possibility into each archetype involved within a complex clinical process (constraints, translations, terminology bindings, and maintenance regarding updates in the model) represents a huge workload for just one research group. Consequently, most knowledge artefacts proposed so far were published as drafts. Nevertheless, it is envisaged that the peer-review process in openEHR's CKM repository would fill the gaps of that first version of the electronic models proposed:

- Considering that the electronic models proposed in this Thesis were focused on assessment more than therapy, the stages corresponding to treatment could be extended in subsequent revisions.
- The electronic models presented should be adapted to the extent that clinical practice evolves and integrates new concepts and healthcare strategies.
- Future versions of the knowledge artefacts should adhere to the openEHR ADL 2 specifications.
- The methodology proposed for modelling healthcare into model-driven information systems could be applied to new healthcare scenarios.

Moreover, the applications available to build standardised electronic models still have to become user-friendly to encourage domain experts and terminologists to develop their own knowledge artefacts with no need of additional training:

- There is work to be done in development of stable releases of modelling tools, and integrate them into fully-functional, open-access web platforms.
- In the case of UI forms, there is not even a consensus on how to build them. It would be therefore interesting to provide open specifications and modelling tools to normalize the UI form building.

Provided that open source knowledge modelling tools are along these lines, the expectation is that the electronic models will evolve over time as the number of users interested in adopting and testing them in real healthcare scenarios increases. And accordingly, the more healthcare scenarios these archetypes are used in, the more healthcare facilities will be able to share semantically enabled clinical information.

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Appendix A:

Knowledge artefacts proposed along this Thesis

This appendix lists all archetypes, templates, termsets and guideline rules defined for the different electronic models presented along this Thesis.

Table 14: *List of archetypes used on the proposed electronic models.*

	Archetype name	Archetype source	Archetype class	Process stages in which it is applicable
1.	Reason for encounter	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 1 AMD monitoring service: stage 1 CG follow-up service: stage 1
2.	Clinical synopsis	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 1, stage 4, and stage 5 AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1 and stage 4
3.	Problem/diagnosis	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 1, stage 4, and stage 5 AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1 and stage 4
4.	Diagnostic criteria DR	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 1, stage 4, and stage 5
5.	Story/history	- Found on CKM - Usable as is	Observation	DR screening service: stage 1 AMD monitoring service: stage 1 CG follow-up service: stage 1
6.	Symptom/Sign	- Found on CKM - Usable as is	Cluster	DR screening service: stage 1 AMD monitoring service: stage 1
7.	DR screening convenient	- No equivalences found - Archetype has to be modelled from scratch	Evaluation	DR screening service: stage 1
8.	Care plan (request)	- Found on CKM - Usable as is	Instruction	DR screening service: stage 2 AMD monitoring service: stage 3 CG follow-up service: stage 2
9.	Care plan	- Found on CKM - Usable as is	Action	DR screening service: stage 2 AMD monitoring service: stage 3 CG follow-up service: stage 2
10.	Referral request	- Found on CKM - Usable as is	Instruction	DR screening service: stage 2 AMD monitoring service: stage 3 CG follow-up service: stage 2
11.	Imaging examination request	- Found on CKM - Usable as is	Instruction	DR screening service: stage 2 AMD monitoring service: stage 3 CG follow-up service: stage 2

	Archetype name	Archetype source	Archetype class	Process stages in which it is applicable
12.	Acquisition details on eye fundus images	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 2 and stage 3 AMD monitoring service: stage 3 and stage 4 CG follow-up service: stage 2 and stage 3
13.	Procedure	- Found on CKM - Usable as is	Action	DR screening service: stage 3 and stage 6 AMD monitoring service: stage 4 CG follow-up service: stage 3 and stage 5
14.	Intraocular pressure measurement	- Found on CKM - It has to be adapted	Observation	DR screening service: stage 3 CG follow-up service: stage 1 and stage 3
15.	Central corneal thickness details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 3 CG follow-up service: stage 3
16.	Medical device	- Found on CKM - Usable as is	Cluster	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
17.	Medical device details	- Found on CKM - Usable as is	Cluster	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
18.	Imaging examination	- Found on CKM - Usable as is	Action	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
19.	Anatomic location	- Found on CKM - Usable as is	Cluster	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
20.	Mydriasis application	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
21.	Medication amount	- Found on CKM - Usable as is	Cluster	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
22.	Funduscopic examination of eyes	- Found on CKM - It has to be adapted	Observation	DR screening service: stage 3, stage 4, and stage 5 AMD monitoring service: stage 1, stage 4, and stage 5 CG follow-up service: stage 1, stage 3, and stage 4

	Archetype name	Archetype source	Archetype class	Process stages in which it is applicable
23.	Diagnostic report request	- No equivalences found - Archetype has to be modelled from scratch	Instruction	DR screening service: stage 3 and stage 4 AMD monitoring service: stage 4 and stage 5 CG follow-up service: stage 3 and stage 4
24.	Classification of Diabetic Retinopathy	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 4 and stage 5
25.	Exclusion of a problem/diagnosis	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 4 and stage 5
26.	Service request	- Found on CKM - Usable as is	Instruction	DR screening service: stage 4, stage 5 AMD monitoring service: stage 4 and stage 5 CG follow-up service: stage 3 and stage 4
27.	Recommendation	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 5 AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1 and stage 4
28.	Medication order	- Found on CKM - Usable as is	Instruction	DR screening service: stage 6 AMD monitoring service: stage 2 CG follow-up service: stage 5
29.	Medication action	- Found on CKM - Usable as is	Action	DR screening service: stage 6 AMD monitoring service: stage 2 CG follow-up service: stage 5
30.	Intravitreal injection details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 6 AMD monitoring service: stage 2
31.	Adverse reaction	- Found on CKM - Usable as is	Evaluation	DR screening service: stage 6 AMD monitoring service: stage 2 CG follow-up service: stage 5
32.	Procedure request	- Found on CKM - Usable as is	Instruction	DR screening service: stage 6 CG follow-up service: stage 5
33.	Ophthalmic laser procedure details	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 6 CG follow-up service: stage 5
34.	Ophthalmic surgery details for posterior segment of eye	- No equivalences found - Archetype has to be modelled from scratch	Cluster	DR screening service: stage 6

	Archetype name	Archetype source	Archetype class	Process stages in which it is applicable
35.	Visual acuity	- Found on CKM - It has to be adapted	Observation	AMD monitoring service: stage 1, and stage 4 CG follow-up service: stage 1 and stage 3
36.	Ophthalmic tomography examination	- No equivalences found - Archetype has to be modelled from scratch	Observation	AMD monitoring service: stage 1, stage 4, and stage 5 CG follow-up service: stage 1, stage 3, and stage 4
37.	Classification of age-related macular degeneration	- No equivalences found - Archetype has to be modelled from scratch	Cluster	AMD monitoring service: stage 1 and stage 5
38.	Contraindication	- Found on CKM - Usable as is	Evaluation	AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1 and stage 4
39.	Enrolment in a long-term healthcare process	- No equivalences found - Archetype has to be modelled from scratch	Evaluation	AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1
40.	Acquisition details on ophthalmic tomography	- No equivalences found - Archetype has to be modelled from scratch	Cluster	AMD monitoring service: stage 3 and stage 4 CG follow-up service: stage 2 and stage 3
41.	Healthcare procedure efficiency	- No equivalences found - Archetype has to be modelled from scratch	Admin entry	AMD monitoring service: stage 5
42.	Risk factors in glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	CG follow-up service: stage 1
43.	Visual field measurement	- Found on CKM - It has to be adapted	Observation	CG follow-up service: stage 1, stage 3, and stage 4
44.	Classification of glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	CG follow-up service: stage 1 and stage 4
45.	Findings in glaucoma	- No equivalences found - Archetype has to be modelled from scratch	Cluster	CG follow-up service: stage 1 and stage 4
46.	Acquisition details on visual field test	- No equivalences found - Archetype has to be modelled from scratch	Cluster	CG follow-up service: stage 2 and stage 3

Total of different archetypes used: 46

Archetypes in DR screening service: 34

Archetypes in AMD monitoring service: 32

Archetypes in CG follow-up service: 37

Archetypes built from scratch: 19

Archetypes directly used from the CKM: 23

Archetypes adapted from CKM: 4

Table 15: *List of templates designed for the proposed electronic models.*

	Template name	Template class	Process stages in which it is applicable
1.	Patient admission into the DR screening service	Composition	DR screening service: stage 1
2.	Patient's background leading to suspicion of DR	Section	DR screening service: stage 1
3.	Patient's enrolment in DR screening	Section	DR screening service: stage 1
4.	Follow-up schedule for patients with suspected DR	Composition	DR screening service: stage 2
5.	Planning the diagnostic tests to detect and classify DR	Section	DR screening service: stage 2
6.	Diagnostic tests in the DR screening service	Composition	DR screening service: stage 3
7.	Intraocular pressure study	Section	DR screening service: stage 3 CG follow-up service: stage 3
8.	Acquisition and validation of NMR	Section	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
9.	Next step in DR screening service	Section	DR screening service: stage 3, stage 4 and stage 5
10.	DR screening	Composition	DR screening service: stage 4
11.	Image test analysis for DR	Section	DR screening service: stage 4 and stage 5
12.	Identification of patients with DR	Section	DR screening service: stage 4
13.	DR assessment	Composition	DR screening service: stage 5
14.	Classification and treatment of DR and DME	Section	DR screening service: stage 5
15.	DR treatment	Composition	DR screening service: stage 6
16.	Intraocular injection (anti-VEGF or corticoids)	Section	DR screening service: stage 6 AMD monitoring service: stage 2
17.	Laser procedures to treat DR	Section	DR screening service: stage 6
18.	Surgical procedures to treat DR	Section	DR screening service: stage 6

	Template name	Template class	Process stages in which it is applicable
19.	Patient admission into the long-term treatment for wet AMD	Composition	AMD monitoring service: stage 1
20.	Patient's background leading to the diagnosis of AMD	Section	AMD monitoring service: stage 1
21.	Classification and treatment of AMD	Section	AMD monitoring service: stage 1 and stage 5
22.	Patient's enrolment in anti-VEGF therapy	Section	AMD monitoring service: stage 1 and stage 5
23.	AMD treatment	Composition	AMD monitoring service: stage 2
24.	Follow-up schedule for the treatment of wet AMD	Composition	AMD monitoring service: stage 3
25.	Planning the diagnostic tests to monitor AMD progression	Section	AMD monitoring service: stage 3
26.	Diagnostic tests for monitoring the treatment of wet AMD	Composition	AMD monitoring service: stage 4
27.	Visual acuity study	Section	AMD monitoring service: stage 4 CG follow-up service: stage 3
28.	Acquisition and validation of OCT	Section	AMD monitoring service: stage 4 CG follow-up service: stage 3
29.	Next step in AMD monitoring service	Section	AMD monitoring service: stage 4 and stage 5
30.	AMD assessment	Composition	AMD monitoring service: stage 5
31.	Image test analysis for AMD	Section	AMD monitoring service: stage 5
32.	Evaluation of the remote assessment model for wet AMD	Section	AMD monitoring service: stage 5

	Template name	Template class	Process stages in which it is applicable
33.	Patient admission into the follow-up service for CG	Composition	CG follow-up service: stage 1
34.	Patient's background and diagnosis of glaucoma	Section	CG follow-up service: stage 1
35.	Classification and treatment of glaucoma	Section	CG follow-up service: stage 1 and stage 4
36.	Patient's enrolment in CG follow-up	Section	CG follow-up service: stage 1
37.	Follow-up schedule for CG	Composition	CG follow-up service: stage 2
38.	Planning the diagnostic tests to follow-up the progression of CG	Section	CG follow-up service: stage 2
39.	Diagnostic tests in the follow-up of CG	Composition	CG follow-up service: stage 3
40.	Acquisition and validation of VF test	Section	CG follow-up service: stage 3
41.	Next step in CG follow-up service	Section	CG follow-up service: stage 3 and stage 4
42.	CG assessment	Composition	CG follow-up service: stage 4
43.	Image test analysis for CG	Section	CG follow-up service: stage 4
44.	Modify CG treatment	Composition	CG follow-up service: stage 5
45.	Administration of antiglaucoma drugs	Section	CG follow-up service: stage 5
46.	Laser procedures to treat CG	Section	CG follow-up service: stage 5
47.	Incisional glaucoma surgery	Section	CG follow-up service: stage 5

Total of different templates used: 47

Templates used in DR screening service: 18 **Templates used in AMD monitoring service:** 16 **Templates used in CG follow-up service:** 19

Total of templates reused: 12 **Templates reused in different processes:** 5 **Templates reused within a process:** 7

Table 16: *List of termsets built for the proposed electronic models.*

	Termset name	Description of termset	Process stages in which it is applicable
1.	Findings on posterior pole of eye	Clinical findings identifiable in posterior pole of eye.	DR screening service: stage 1, stage 4, and stage 5 AMD monitoring service: stage 1 and stage 5 CG follow-up service: stage 1 and stage 4
2.	Subdivision of retina	List of zones in eye retina for ophthalmic image positioning.	DR screening service: stage 2 and stage 3 AMD monitoring service: stage 3 and stage 4 CG follow-up service: stage 2 and stage 3
3.	Corneal thickness measurement devices	List of methods to obtain the corneal thickness measurement.	DR screening service: stage 3 CG follow-up service: stage 3
4.	Mydriatic agents	List of mydriatic agents and their corresponding doses validated for ophthalmologic use.	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
5.	Complications on ophthalmic image acquisition	List of possible complications during ophthalmic imaging studies that may affect the quality of acquisitions (based on Table CID 4222 of DICOM standard).	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
6.	Ophthalmic photography devices	Lists the ophthalmic photography acquisition devices (based on Table CID 4202 of DICOM standard).	DR screening service: stage 3 AMD monitoring service: stage 4 CG follow-up service: stage 3
7.	Identification of diabetic retinopathy	Identification of presence or absence of DR for screening purposes.	DR screening service: stage 4
8.	Clinical grading for diabetic retinopathy	International Clinical Diabetic Retinopathy Disease Severity Scale.	DR screening service: stage 5
9.	Classification for diabetic macular edema	Classification levels for the presence of ME as defined by the international scale for DR grading.	DR screening service: stage 5
10.	Therapeutic procedures for diabetic retinopathy	List of therapies available to treat different stages of DR.	DR screening service: stage 5
11.	Compounds for intravitreal injection	Compounds administered in ophthalmology in the form of intraocular injection.	DR screening service: stage 6 AMD monitoring service: stage 2
12.	Compounds for local anaesthesia	Compounds available to apply local anaesthesia.	DR screening service: stage 6 AMD monitoring service: stage 2
13.	Anti-infective agents	List of anti-infective agents available.	DR screening service: stage 6 AMD monitoring service: stage 2

	Termset name	Description of termset	Process stages in which it is applicable
14.	Laser procedures in ophthalmology	List of laser procedures available for ophthalmic purposes.	DR screening service: stage 6
15.	Ophthalmic laser devices	List of laser devices for ophthalmic use.	DR screening service: stage 6 CG follow-up service: stage 5
16.	Operative procedures on posterior segment of eye	List of operative procedures on the posterior segment of eye.	DR screening service: stage 6
17.	Anatomic structures of eye	List of regions of interest in the study of eye (based on DICOM Tables: CID 4209, CID 4211 and CID 4266).	AMD monitoring service: stage 1, stage 3, stage 4, and stage 5 CG follow-up service: stage 1, stage 2, stage 3 and stage 4
18.	Ophthalmic tomography devices	List of acquisition devices (based on Table CID 4210 of DICOM standard).	AMD monitoring service: stage 4 CG follow-up service: stage 3
19.	Finding of visual field	List of findings distinguishable on the visual field test.	CG follow-up service: stage 1 and stage 4
20.	Classification of glaucoma	List of disorders distinguishable on the diagnosis of glaucoma.	CG follow-up service: stage 1 and stage 4
21.	Glaucoma treatments	List of therapeutic options to treat different types and stages of glaucoma.	CG follow-up service: stage 4 and stage 5
22.	Visual field illumination colours	List of illumination colours used as visual stimuli on visual field test (based on Table CID 4255 of DICOM standard).	CG follow-up service: stage 3
23.	IOP lowering agents	List of agents used in ophthalmology for IOP lowering.	CG follow-up service: stage 5

Total of different termsets built: 23

Termsets in DR screening service: 16 **Termsets in AMD monitoring service:** 10 (2 new) **Termsets in CG follow-up service:** 14 (5 new)

Table 17: *List of guideline rules designed to direct the patients through the proposed clinical processes.*

	Rule name	Description of the rule	Process stages in which it is applicable
1.	DR screening convenient	This rule checks if the patient meets the criteria for inclusion in the screening process, and, if so, schedules the corresponding diagnostic tests.	DR screening service: transition from stage 1 to stage 3
2.	Diagnostic tests valid for screening	This rule validates the diagnostic tests once acquired, and discards any unusual value before proceeding with the screening stage.	DR screening service: transition from stage 3 to stage 4
3.	Office examination required	This rule identifies patients with dangerously high IOP values (≥22 mmHg) or low-quality fundus images (<4 of 5 levels of quality), and therefore arranges directly the patient's assessment at the ophthalmologist's office.	DR screening service: transition from stage 3 to stage 4
4.	Altered retina	This rule requests an assessment report to an ophthalmologist, if any alteration on the retina is identified during the screening.	DR screening service: transition from stage 4 to stage 5
5.	Apparently not altered retina	Provided that the patient does not present signs of DR, this rule must schedule the diagnostic tests to conduct the next review defined by the follow-up process.	DR screening service: transition from stage 4 to stage 2
6.	DR treatment required	This rule schedules the corresponding procedure or administration of medication to carry out treatment of DR.	DR screening service: transition from stage 5 to stage 6
7.	DR treatment not required	If the ophthalmologist does not consider necessary to treat the patient on this point, this rule refers the patient to the next review defined by the follow-up process.	DR screening service: transition from stage 5 to stage 2

	Rule name	Description of the rule	Process stages in which it is applicable
8.	Anti-VEGF therapy convenient	After a consultation on specialized care, this rule determines whether the patient will access or not to the long-term treatment of wet AMD by intravitreal injections.	AMD monitoring service: transition from stage 1 to stage 2
9.	Treatment cycle completed	This rule verifies if every anti-VEGF injection ordered for a specific patient have been carried out, and, if true, automatically schedules the next consultation for patient review.	AMD monitoring service: transition from stage 2 to stage 4
10.	Diagnostic tests completed (AMD)	This rule must guarantee the completion of every diagnostic test ordered for a specific patient before proceeding with the remote assessment.	AMD monitoring service: transition from stage 4 to stage 5
11.	AMD stable	This rule postpones the treatment provided that the retinologist does not identifies signs of activity or progression on AMD, and therefore a new anti-VEGF injection would not be effective to treat such disease.	AMD monitoring service: transition from stage 5 to stage 3
12.	Repeat anti-VEGF treatment	This rule orders a new intravitreal injection if the retinologist, as a result of the assessment of diagnostic tests, determines that the patient presents signs activity or progression on AMD.	AMD monitoring service: transition from stage 5 to stage 2
13.	Discontinuation of anti-VEGF therapy	This rule revokes the patient's enrolment in the long-term treatment for wet AMD, if the retinologist identifies contraindications to continue with the therapy during any of the periodic assessments.	AMD monitoring service: terminate the clinical process from stage 1 or stage 5
14.	Glaucoma follow-up convenient	This rule checks if the patient meets the criteria for admittance to the glaucoma follow-up service, and, if so, schedules the corresponding diagnostic tests.	CG follow-up service: transition from stage 1 to stage 3

	Rule name	Description of the rule	Process stages in which it is applicable
15.	Diagnostic tests completed (CG)	This rule must guarantee the completion of every diagnostic test ordered for a specific patient before proceeding with the remote assessment. What differentiates this one from the homonymous rule defined for the monitoring of wet AMD are the diagnostic tests to be completed in each case.	CG follow-up service: transition from stage 3 to stage 4
16.	Glaucoma stable	This rule schedules the diagnostic tests involved in the follow-up process, whenever as a result of an overall assessment of glaucoma, the ophthalmologist does not identifies clear signs of disease progression, and hence, the patient is well controlled.	CG follow-up service: transition from stage 4 to stage 2
17.	Glaucoma progressive	This rule is triggered by patients diagnosed with glaucoma that present any sign of disease progression that could lead to visual loss in the future. For such cases, the rule arranges an office examination where the same ophthalmologist responsible of the remote assessment would determine the appropriate therapeutic decision for each patient.	CG follow-up service: transition from stage 4 to stage 5
18.	Modify the medical treatment	This rule covers the scenario in which, as a result of the office assessment, the ophthalmologist considers that treatment modification is warranted, but the disease could be easily stabilized by adjusting the medication regimen.	CG follow-up service: terminate the clinical process from stage 5
19.	Surgery required	This rule arranges a surgical procedure for lowering IOP, when an ophthalmologists identifies clear signs of glaucoma progression, and the target IOP is not reached through medical treatment.	CG follow-up service: terminate the clinical process from stage 5

Appendix B:

Web platform for evaluation of the high resolution consultation to manage the treatment of wet AMD

This appendix presents the web platform used at the SNS-O for validating the high resolution consultation approach in comparison to the traditional strategy for the treatment of wet AMD. To that end, first, the procedure used for the validation is presented. Second, an OPT was modelled to enable objective comparisons between traditional and high resolution consultations in compliance with openEHR specifications. Third, the preliminary results of the study that established the validity of therapeutic decisions made in a remote setting are presented.

B.1 EVALUATION OF THE HIGH RESOLUTION CONSULTATION

The high resolution consultation is still in pilot stage. Therefore, it would not be sensible to implement the whole model built for monitoring of the treatment of patients diagnosed with wet AMD before proving the feasibility of the new consultation with regard to the traditional approach.

In that respect, firstly, a web platform was launched to facilitate the integration of the high resolution consultation into the SNS-O. Considering the traditional consultation as the gold standard, this website would validate the therapeutic decisions made in remote workstations as suggested in the high resolution consultation approach. To that end, patients with exudative AMD treated with at least three intravitreal injections were evaluated through the office examination, and the corresponding diagnostic reports were registered into the web platform. At this point, a waiting period of four weeks was considered sufficient for the specialists not to recognize test acquisitions already assessed. Then, the same patients were reassessed but this time the evaluation was addressed remotely, i.e. based on diagnostic tests examined through an electronic workstation. Therefore, the web platform compared the records corresponding to both models of consultation to determine the agreement at the time of deciding for each patient whether an additional intravitreal treatment was necessary. Other parameters such as sociodemographic variables, or information concerning the efficiency of each consultation approach were analyzed by the platform.

Originally, the web platform was launched to manage a study on the local scenario of the SNS-O, without regard for the interoperability and reusability of information. Nevertheless, eventually different healthcare facilities joined the platform, and new parameters were considered for analysis. In consequence, the exploitation of the information became more complex to the extent that the study evolved toward more ambitious projects. Thus, to avoid the ungovernability of information, the medical forms defined in the web platform were modelled in compliance with openEHR specifications. The resulting electronic models should provide backward compatible medical records, even if different users work with custom-made medical forms, or the study incorporates new concepts on the future.

B.2 MODELLING AN OPENEHR OPT TO EVALUATE THE HIGH RESOLUTION CONSULTATION APPROACH

In light of the entire clinical process modelled for monitoring patients receiving anti-VEGF therapy for wet AMD, this study would cover the fifth clinical stage established in the AMD monitoring service (see Figure 20). Therefore, some of the clinical concepts identified for that clinical stage were combined to build a template analogous to the medical forms provided by the web platform. It is possible to review this template since it was uploaded to the CKM under the name of *"Consultation for AMD assessment"*.

On the one hand, the template proposed consists of some sociodemographic variables considered useful for later epidemiologic purposes (patient's identifier, age, and sex). Information about the reporting healthcare professional is also included to facilitate the development of interobserver and intraobserver studies. The *"Individual's personal demographics"* and *"Healthcare professional"* archetypes from CKM were included in the template to that end.

On the other hand, as seen along the design of the clinical process, the office examination includes VA, fundus exam and OCT. Considering that eye fundus evaluation can be reliably substituted by digital retinography, a non-mydriatic fundus camera is used during office examination in addition to the direct ophthalmoscopy. Therefore, the resulting retinographies are converted to DICOM and then submitted to the PACS server along with the OCT acquisitions, so that they can be remotely reviewed in the high resolution consultation. However, the clinical findings identified from the examination of these tests must be registered using the web platform. Thus, the template includes the archetypes *"Funduscopic examination of eyes"* and *"Ophthalmic tomography examination"* to that end. In case of

the VA measurement, the archetype *"Visual acuity"* is provided twice into the template: one to register the VA value at the study onset, and one for the latest measurement obtained. In this way, it is possible to identify any progression on visual loss.

The template also comprises the *"Healthcare procedure efficiency"* archetype. It was included to record the time spent to complete the remote assessment, and thus compare the measured value with the duration of an office examination which is estimated at 10 minutes per patient.

Finally, the archetype *"Recommendation"* was added toward the end of the template. This stems from the need of registering into the web platform, the therapeutic decision of whether treat or not the patient with anti-VEGF injections as well as the criteria used to arrive at this conclusion whatever the type of consultation.

Therefore, based on the same sociodemographic variables and VA measurements, the imaging studies were first examined directly in the ophthalmologist's office and later reviewed remotely by means of a DICOM visualizer. Accordingly, a study of agreement was carried out, by comparing the therapeutic decisions, and criteria registered in the web platform for both models of consultation. Likewise, the time spent by retina specialists was compared for the office and remote models of assessment (see Figure 29).

B.3 STATISTICS RESULTING FROM THE STUDY

According to the last analysis of results carried out on the web platform, 201 patients were included in the study at 31th August 2016. 88 were male (44%) and 113 female (56%). Mean age was 81 years. During office examination in 87 cases (43%) the decision was to repeat the injection while in 114 cases (57%) it was decided not to repeat treatment. With respect to the comparison among office and remote evaluation, in 181 (90%) cases the results were the same. Among the 20 remaining patients and considering office examination as the gold standard, 17 correspond to false positives (office examination indicates not to repeat treatment but remote examination indicates to repeat treatment) and 3 to false negatives (office examination indicates to repeat treatment but remote examination indicates not to repeat treatment). With these data the sensitivity and specificity of remote evaluation are 96 and 87% respectively. The average amount of time spent in remote evaluation is 1 minute 22 seconds compared with 10 minutes spent in office examination.

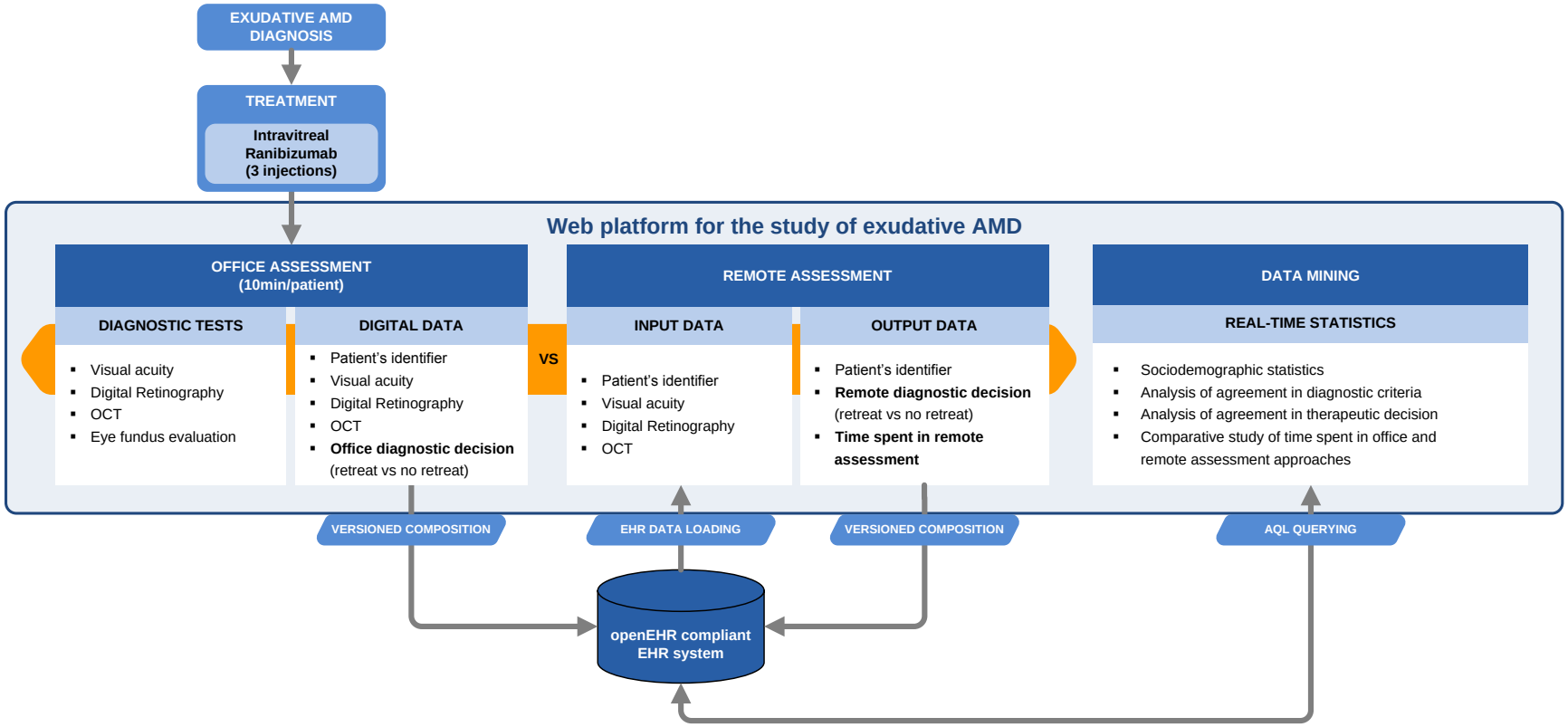

Figure 29: *Comparative study between office examination and remote evaluation with regard to determine the treatment of exudative AMD.*