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ORIGINAL PAPER

A collaborative RESTful cloud-based tool for management of chromatic pupillometry in a clinical trial

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Abstract
Chromatic Pupillometry represents a novel approach for the assessment of Inherited Retinal Diseases. A multi-centric pilot study with a sample of 40 paediatric patients has been designed, involving physicians and engineers. In this paper, the Electronic Medical Record, named ORÁO and specifically developed to collect ophthalmologic and pupillometric data, is presented. The platform is a cloud- based application, with a RESTful and three-tier architecture. These features make it available via web for the ophthalmologists involved in the project and working in two different University centres. The platform has been designed by the whole team and developed by the Department of Information Engineering of the University of Florence. The interfaces of the medical record have been evaluated in term of Usability, according to standards. An Heuristic Evaluation has been performed in the first stage of the design of the platform and the main severe usability issues have been addressed. The outcome of the project is a customized software solution. Moreover, the physicians have an excellent attitude toward the use of ORÁO and they perceive it as a useful tool to gather the data they collect with the aim of evaluating the overall progression of the pilot study.

Keywords Chromatic pupillometry · IRDs · EMR · Web-based · Cloud-based · 3-tier · RESTful · REST API · Usability · Heuristic evaluation

1 Introduction

Inherited Retinal Diseases (IRDs) are a wide set of ocular diseases, which lead to photoreceptor death or dysfunction and blindness. They are genetically complex and are characterised by a significant clinical overlap between the different types. Retinitis Pigmentosa (RP) is the most common IRD.

It primarily affects the rod photoreceptors, with mutations in over 100 genes. One of the earliest symptoms of RP is night blindness, then it brings to the reduction in the peripheral visual field, [1].

The *gold standard* for the diagnosis of these diseases consists of an instrumental and biomolecular investigation, with subsequent genotyping, [2]. The widely adopted instruments for IRDs diagnosis, such as Ophthalmic Computerised Tomography (OCT), Electro-Retinography (ERG) and Electro-Oculography (EOG), can be too invasive for investigating IRDs in children. For these reasons, an alternative and cutting-edge approach to IRDs diagnosis can be the Chromatic Pupillometry (CP). It represents a pioneering method for the objective and quantitative evaluation of IRDs in paediatric population, [3] and [4]. CP consists in stimulating the patient's eyes with different wavelengths and light intensities. The various stimulations generate a different pupil response, and physicians can evaluate the status of rods and cones by measuring the variation of the pupil diameter.

The Italian Ministry of Education, Research and University funded the project *Toward new methods for early diagnosis and screening of genetic ocular diseases in childhood* (PRIN 2015). The purpose of the project is to consider if CP is an efficient approach for IRDs diagnosis in paediatric patients. A pilot study has been designed by the physicians involved in the study, who belong to the University centres of Naples and Milan. It establishes the recruitment of 40 children, with an age-range from 8 to 16 years. 20 of those patients are IRDs-affected subjects (cases). The remaining 20 ones are healthy and they are included in the study as controls. Each participant

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in the pilot study must undergo a baseline visit, during which his/her personal data are collected and a classical ophthalmologic clinical and instrumental examination and pupillometry is performed. After the baseline visit, the patient is asked to undergo a follow-up visit after 28 ± 7 days, [5].

Pupillometry is performed according to the pupillometric protocol. It establishes the type of stimulations that must be performed on the subject: the colour and intensity of light stimulus and the background colour. Initially, the patient undergoes a 10-min period of adaptation to dark. After this period, the patient's eyes are stimulated under three different conditions:

1. Low intensity with dark background stimulation
2. High intensity with dark background stimulation
3. High intensity with blue background stimulation

The last stimulation is performed after a 3-min period of adaptation to the blue background. Each stimulus is repeated three times both for the red and blue coloured lights (See Table 1). The different types of stimulation cause a different response by rods and cones. Indeed, cones detect fine details and colours and require high brightness of light, while rods detect a grayscale of black and white and have a lower threshold of activation than cones. The physicians study the velocity of variation of the pupil diameter and the amplitude of the variation itself. These parameters allow them to evaluate the functionality of the photoreceptors of the subject's eyes.

As described above, the pilot study involves physicians and patients of different parts of Italy. Thus, the necessity of an Information Technology (IT) platform, reachable via web, has arisen, to gather data collected from scholars. One of the roles of the Department of Information Engineering, University of Florence (DINFO) in the project is to realise the above-mentioned platform. In this paper ORÁO,[1] the Electronic Medical Record (EMR) for chromatic pupillometry, is presented. It has been designed to match with the workflow of the examinations expected by the pilot study, and it is based on the specifications given by the physicians involved in the project.

2 Materials and methods

2.1 The pupillometer: Hardware and software

The pupillometry is performed by a specified instrument: the multi-chromatic binocular Pupillometer DP-2000 by NeurOptics. It is an optical scanner which captures and analyses a digital video of a subject's pupil responding to light stimulation.

Table 1 Pupillometric protocol

Stimuli index		Light intensity	Background color
Red stimuli	Blue stimuli		
0–2	3–5	Low	Dark
6–8	9–11	High	Dark
12		Blue background adaptation	
13–15	16–18	High	Blue
19		No stimulus for technical reasons	

The DP-2000 Human Laboratory Pupillometer is a multichromatic binocular/dual camera system that tracks both pupils and stimulates both eyes. It is specifically designed for measuring the pupils of human subjects. The video stream is captured at 30 Hz. The video frame is digitised into 640 × 480 pixels with 8-bit grey level resolution. The profile of the light stimulation can be customised using a Graphic User Interface (GUI). Pupil variables are automatically analysed, reported graphically in a special window and saved into a results file, with. DAT extension.

Light stimulation has four different chromatic options: Red (622 nm), Green (528 nm), Blue (463 nm) and White. Light is emitted through a diffusing screen (approx. 50° × 35° of visual angle). Camera height can be adjusted by pressing the button on the arm and lifting the arm to the desired position. Pupillary distance can be adjusted to fit the subject's eyes by turning the knob located below the cameras, see Figs. 1 and 2.

2.2 ORÁO: development of the platform

The necessity of an EMR reachable via web to gather data collected by the two clinical centres involved in the project has arisen with the design of the pilot study itself, as previously stated. This task has been assigned to the DINFO because of its previous experience in the development of RESTful web applications [6–8] (Tables 1, 2, 3, 4 and 5).

2.2.1 A cloud-based solution

ORÁO has been designed as a cloud-based application, to meet the need of a common platform for the physicians to collect the data of the subjects involved in the study. A Virtual Machine (VM) has been created on the DINFO server farm, see [9] and Fig. 3, to host the web server and the database engine of ORÁO. The VM is running Windows Server 2012 Datacenter, by Microsoft. It is provided with two Intel Xeon E5–4620 processors, 2,20 GHz CPU, 4,00 GB RAM and with a 64 bit operative system.

In this way, the EMR is remotely reachable via web and accessible by authentication with username and password, after the administrator's agreement.

[1] From the ancient Greek verb ὁράω. It means *I see*. Here, ORÁO is used as the acronym for **O**phthalmologic Medical **R**ecord for Chrom**A**tic Pupill**O**metry

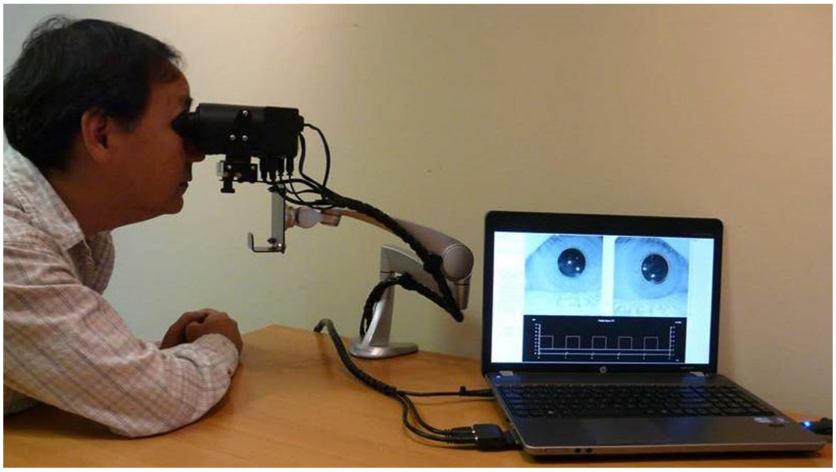


Fig. 1 This figure shows the whole system of acquisition of chromatic pupillometry. It is possible to see the patient and the binocular camera of the pupillometer, connected to the computer where the software to control the instrument is running

2.2.2 RESTful application

The EMR has been developed with the REST architecture (see Fig. 4), to reach a better data exchange between server and client and to permit an easy integration of third-party applications, [10].

The Representational State Transfer (REST) architectural style was introduced by T. Fielding in his PhD Dissertation *Architectural Styles and the Design of Network-based Software Architectures*, [11]. The REST architecture's foundation is *resources*. REST architecture is based on four principles:

1. *Resource identification through URI*: resources are exposed by the Web Service through an URI (Uniform Resource Identifier);
2. *Uniform interface*: the operations that can be executed on the resources are a fixed set of four. They are expressed by the HTTP methods PUT, GET, POST and DELETE;
3. *Self-descriptive messages*: each message contains the information required for its management. Each resource is different from its representation given to client. In this way, the content of the resources is available in a lot of different formats;
4. *Stateless interactions*: the interaction with resources is stateless. The session status is kept only by the client: no client data are stored in the server. The server stores the status of the resources. There is no exchange of resource status between client and server.

The RESTful architecture is widely adopted because it is based on the well-known HTTP standard, [12].

2.2.3 Three-tier architecture

The EMR has been realised in MS Visual Studio 2017 using Visual Basic. NET (VB.NET) and ASP.NET framework 4.5.2. It has been created as a three-tier application, see Fig. 5. The presentation tier has been implemented using Twitter Bootstrap v.3.3.7 framework, an open source toolkit for web development with HTML 5.0, CSS 3, and JavaScript (JS). The JS library JQuery v.3.2.0 has been adopted for front-end coding. The JS libraries D3.js (Data-Driven Document) and Moment.js have been used too. The first one is employed for the creation of dynamic visualizations, while the second one is a library for the manipulation of dates formats and values in JS. The Business Logic Layer (BLL) is the application core: it controls and manages the functionalities and data elaborations. In the BLL, there are four modules for the main application sections: authentication, patient data management, ophthalmology and pupillometry. The Data Access Layer is realised with the Entity Framework (EF). This is a technology

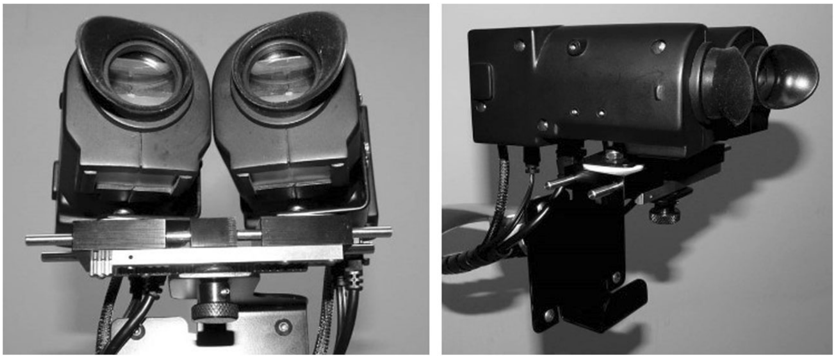


Fig. 2 The binocular camera of the DP-2000 multi-chromatic pupillometer by NeurOptics

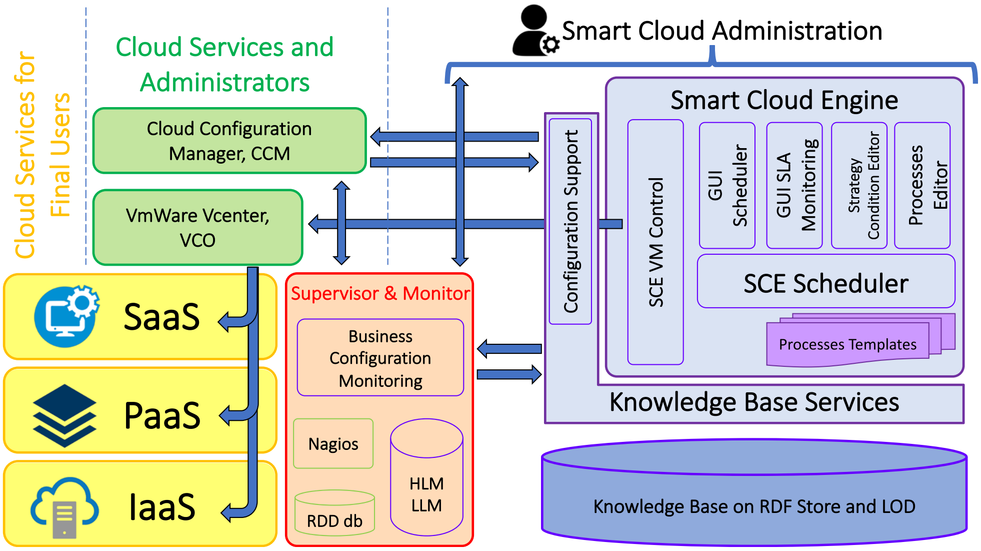


Fig. 3 The figure shows the architecture of the cloud farm provided by the DINFO, [9]

that allows the. NET application to work with data from relational DBs, using objects of the application domain without the need of a direct access to the DB. The EF creates the Entity Data Model (EDM), a conceptual model of the DB that the BLL can use to manage data from and to the DB. Moreover, the code has been organised according to the Model-View-Controller (MVC) pattern, [13]. The database has been realised using the Relational Database Management System (RDBMS) engine Microsoft SQL Server Express 2008 R2.

2.3 Usability evaluation

According to standards, ORÁO's interfaces have been designed giving high attention to their usability. Usability is the characteristic of the interface of a Medical Device (MD) that makes its use easier and safer for the end user. A MD must be designed with ergonomic characteristics, including its interface, that reduce the risk of error as much as possible. Usability is defined by the international standard ISO 924111:2018 as *"The extent to which a system, product or service can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use"*, [14]. In a medical software usability is strictly related to safety: an interface poorly designed can induce the user to commit errors. Moreover, the international standard IEC 62366–1:2015 (Application of usability engineering to medical devices) has been considered, [15]. It establishes a process for manufacturers to evaluate the usability of a MD. The study and the evaluation of a MD usability must be performed during its design. The results of this evaluation must be considered to introduce changes in the interface with the aim to address the safety issues related to the identified usability issues. The usability of a MD can enhance or reduce its safety. Moreover, usability is a critical parameter that must be assessed in order to evaluate the quality of a software product, [16]. The usability of the EMR developed in this project has been evaluated with the Heuristic Evaluation.

2.3.1 Heuristic evaluation

Heuristic evaluation is an informal method to study the usability of a device interface. It represents a widely adopted method because it requires few resources and it permits an early identification of usability issues. The heuristic evaluation consists in the inspection of the interface by one or more evaluators, comparing it with a set of empirical rules, called *heuristics*. The most known and widely adopted heuristics for evaluating the usability of software interfaces are the Nielsen's heuristics, [17]. For the heuristic evaluation of ORÁO interfaces, the Zhang's heuristics have been adopted. These consist of a set of 14 heuristics developed for the usability evaluation of MDs: consistency and standards, visibility of system state, match between system and world, minimalism, minimization of memory load, informative feedback, flexibility and efficiency,

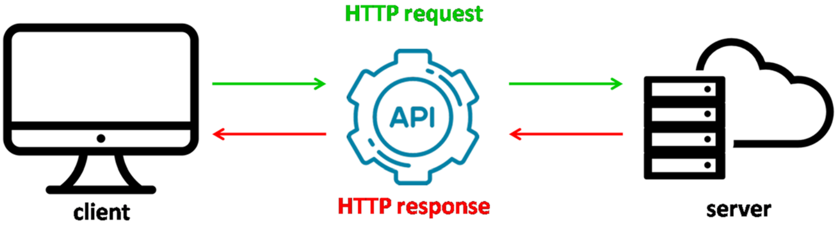


Fig. 4 The figure explains the REpresentational State Transfer Architecture of the platform ORÁO

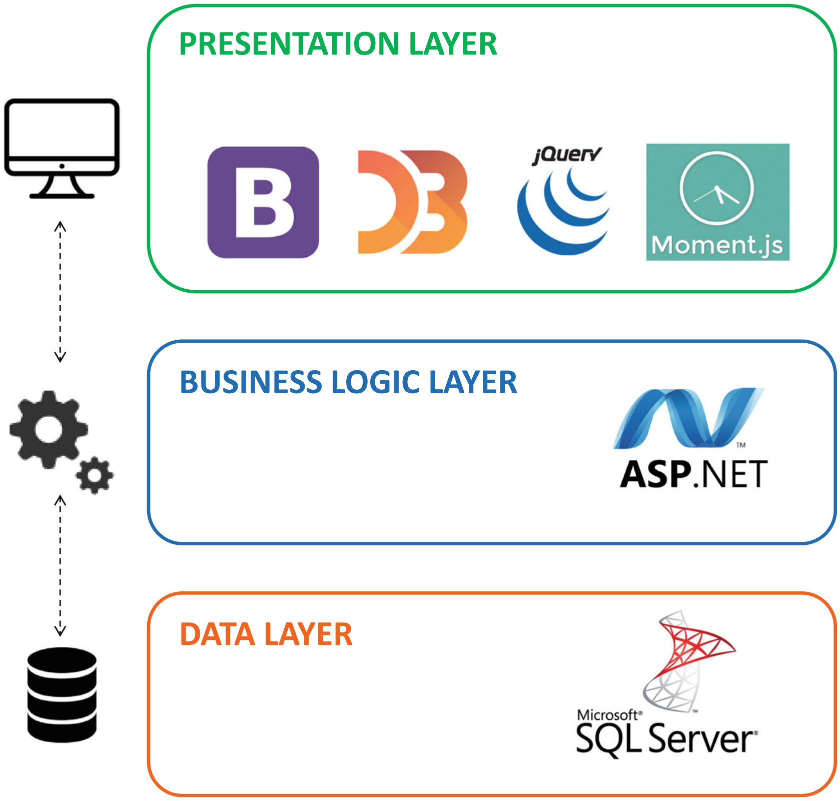


Fig. 5 Three-tier architecture of ORÁO. For each tier the employed software instruments are shown

good error messages, preventing errors, clear closure, reversible actions, use of understandable language, users in control and help and documentation, see Table 2.

During the inspection of the device interface, evaluators are expected to find all the violations to the heuristics and to consider, for each of them, the potential impact on the safe use of the MD. Each violation found by evaluators is associated to a severity index. This allows to evaluate where the priority of intervention is, in order to address the safety issues associated the use of the MD. If heuristic evaluation is performed during the design of the MD, it is possible to early address the potential safety issues. Thus, the solution is optimised versus safety standards and also versus the user expectations of the device outcome.

The product of an heuristic evaluation is a report, containing all the violations to heuristics, identified by the evaluators. A report of an heuristic evaluation must contain the following data:

1. **Where** the violation is
2. A description of the **problem** and of the **potential consequences** it could cause
3. The **heuristic** that has been violated
4. The **severity rate** associated to the issue

Once the evaluation has been carried out and the report has been created, the designer of the software interface is provided with a powerful instrument that makes him capable to modify the design in order to address the most dangerous violations for a safe use of the MD. This is why heuristic evaluation should be performed during the early phase of design of the MD interface.

As stated above, the heuristic evaluation is widely adopted for the study of the safety of the MDs interface. One of the main benefits is its scarce necessity of resources. It also makes the designer aware of the usability issues, since the first phases of the interface design process. On the other hand, the heuristic evaluation has also some limitations, due to the fact that it is an informal method of usability evaluation. All the usability issues the evaluator can find are strictly related, and thus limited, by the set of heuristics employed in the study of the interface. Moreover, the evaluation is performed with the tested device out of its context of use. This can prevent the detection of usability and safety issues that arise with the use of the MD in its proper context of use. Indeed, the effect of external factors influence is not considered in the evaluation. Despite these limitations, the heuristic evaluation represents an important and powerful instrument for the designer of the MD interface, with a very good cost-benefit ratio.

3 Results

In the following sections, the results of the development of ORÁO are presented. The DB *Pupil* for the application has

Table 2 The table lists and explains the 14 Heuristics for medical devices by Zhang, [18]

Heuristics	Explanation
1. Consistency and standards	Users should not have to wonder whether different words, situations, or actions mean the same thing. Standards and conventions in product design should be followed.
2. Visibility of system state	Users should be informed about what is going on with the system through appropriate feedback and display of information.
3. Match between system and world	The image of the system perceived by users should match the model the users have about the system.
4. Minimalist	Any extraneous information is a distraction and a slow-down.
5. Minimize memory load	Users should not be required to memorize a lot of information to carry out tasks.
	Memory load reduces users' capacity to carry out the main tasks.
6. Informative feedback	Users should be given prompt and informative feedback about their actions.
7. Flexibility and efficiency	Users always learn and users are always different. Give users the flexibility of creating customization and shortcuts to accelerate their performance.
8. Good error messages	The messages should be informative enough such that users can understand the nature of errors, learn from errors, and recover from errors.
9. Prevent errors	It is always better to design interfaces that prevent errors from happening in the first place.
10. Clear closure	Every task has a beginning and an end. Users should be clearly notified about the completion of a task.
11. Reversible actions	Users should be allowed to recover from errors. Reversible actions also encourage exploratory learning.
12. Use users' language	The language should be always presented in a form understandable by the intended users.
13. Users in control	Do not give users the impression that they are controlled by the systems.
14. Help and documentation	Always provide help when needed.

been deployed with the RDBMS engine Microsoft SQL Server Express, as stated above. The DB is organised in 26 tables, each of them dedicated to store data corresponding to a specific functionality or part of the EMR. There is a dedicated table to manage data relating to the authentication of the users, one for the personal data of the patients, one for each ophthalmologic examination (in particular there is a dedicated table for each instrumental monocular examination) and one for the pupillometry. The tables containing the data of ophthalmologic and pupillometric examinations are related to a specific follow up and in the DB they are identified by the follow up ID. This allows to gather all data recorded during the same examination, but saved in different tables in the DB, and to manage them through the application. Regarding the pupillometry table, each record of this table stores the name of the .dat file from the pupillometer as well as the follow up ID.

The EDM has been created with EF (that in our case represents the DAL) in Visual Studio, with a *Database first* approach (create the DB first and subsequently develop the model). The EDM is a map of the DB and of the data types each table must contain. The presence of the EDM avoids the direct interaction of the BLL with the DB.

The BLL is the core of the application. It manages the main functionalities of the EMR: authentication, management of patient data, ophthalmology and pupillometry, see Fig. 6.

3.1 Authentication

The first time each physician uses the EMR, he/she must register with an email address and a password. After the registration, the user access to the platform must be granted by the administrator (DINFO). Figure 7 shows the homepage of ORÁO, after the user login. The platform name and the partners' logos are shown in the middle of the page. The upper menu and buttons in the page provide user with a direct access to the functionalities related to the patients data management.

The authentication is managed by a dedicated RESTful Application Programming Interface (API). The input parameters of the API are the user email address and password encrypted with the Simple Triple Data Encryption Standard (Simple3DES), for the encryption and decryption of strings. The API searches for a correspondent record in the table of the DB dedicated to the authentication data storage (i.e. the TB_USERS table in the *Pupil* DB), through an HTTP GET request. If such correspondence is found and the authorization field of the record is set to *true*, then the API output is a structured data containing the following information: record ID, email address, user name and the associated token. The token is an alphanumeric string that gives the user access to the required resources for a limited time-period. Indeed, the

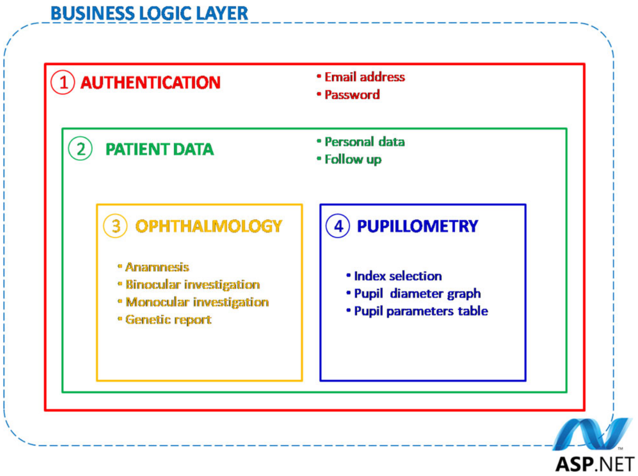


Fig. 6 The figure shows the structure of the BLL of ORÁO. It is possible to notice the *encapsulation* of the four functionalities provided by the EMR. All of them required the authentication of the user. Once the user is logged in, it is possible to access to all the patients data and, in particular, it is possible to reach the ophthalmologic and pupillometric functionalities, the actual core of the platform

token associated with the access expires when the user logs out the platform.

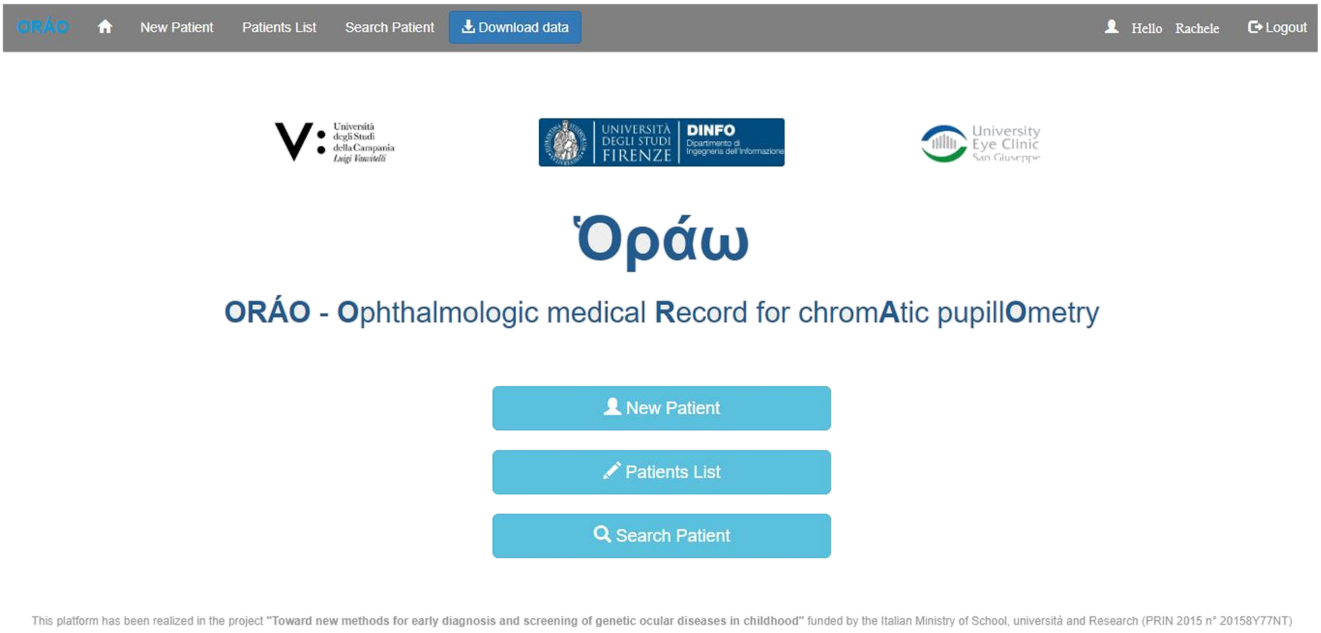
3.2 Patient data management

The patient management involves registration of new patient personal data, modification of pre-existing personal data and addition of new follow up examinations. The form for the registration of a new patient is composed by a list of fields regarding the patient personal data (name, last name, date and place of birth, gender, fiscal code), residence, date of the first visit and phone contacts. The user must also mark the patient as *Control* or *Case*, as stated by the design of the pilot study (see section??). The label for *Control* is blue while the one for *Case* is red. This association red-to-*Case* and blue-to-*Control* is used consistently throughout each page of the platform.

All the patients registered in the *Pupil* DB are included in the *Patients List*, see Fig. 8. Their personal details, as described above, are shown in this table. The user, after selecting a patient from the list, will press one of the two buttons *Edit patient data* or *Follow up* to access the corresponding functionalities. In both cases, a dedicated API manages the query and data exchange with the server DB. The API queries the specified table (i.e. HTTP GET request), searching for a record corresponding to the ID of the selected patient and follow up, which is the input data of the API. The data stored in this record are passed as API output to the presentation layer. The same API takes care of creating and updating records via HTTP POST. The API output is used by the presentation layer to provide an informative feedback to the user about the performed action.

3.3 Ophthalmology

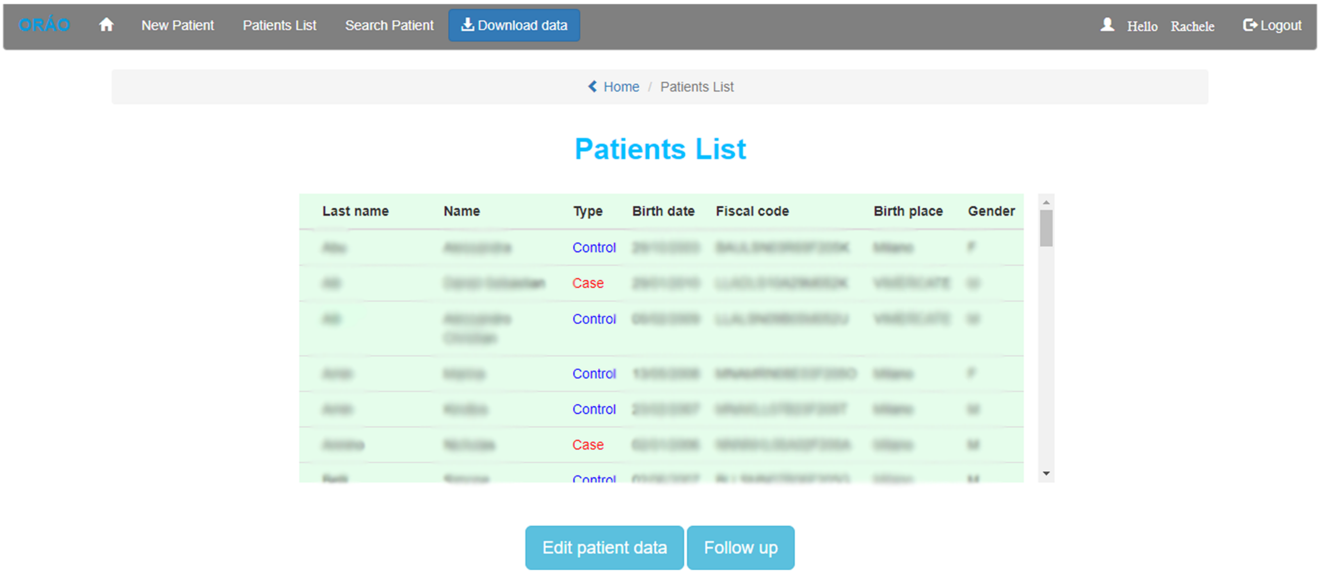
The Follow Up page, gives the possibility to register a new examination or to open an existing one, identified by its date. If the user clicks on the button *Show follow up*, a dropdown menu allows to choose the date of the follow up the physician wants to open. The dates in the menu have a white or green background colour. Green background indicates that the


ORÁO
New Patient
Patients List
Search Patient
Download data
Hello Rachele
Logout
V: Università degli Studi della Campania Luigi Vanvitelli
UNIVERSITÀ DEGLI STUDI FIRENZE
DINFO Dipartimento di Ingegneria dell'Informazione
University Eye Clinic San Giuseppe
Ὁράω
New Patient
Patients List
Search Patient

ORÁO - Ophthalmologic medical Record for chromAtic pupillOmetry

This platform has been realized in the project "Toward new methods for early diagnosis and screening of genetic ocular diseases in childhood" funded by the Italian Ministry of School, università and Research (PRIN 2015 n° 20158Y77NT)

Fig. 7 Homepage of ORÁO. At the top level of the page, it is possible to observe the main navigation menu, constantly shown in each page of the platform. This menu allows the user to rapidly change page, choosing one of the main sections: *New patient*, *Patients List*, *Search Patient* and *Download data*



Patients List

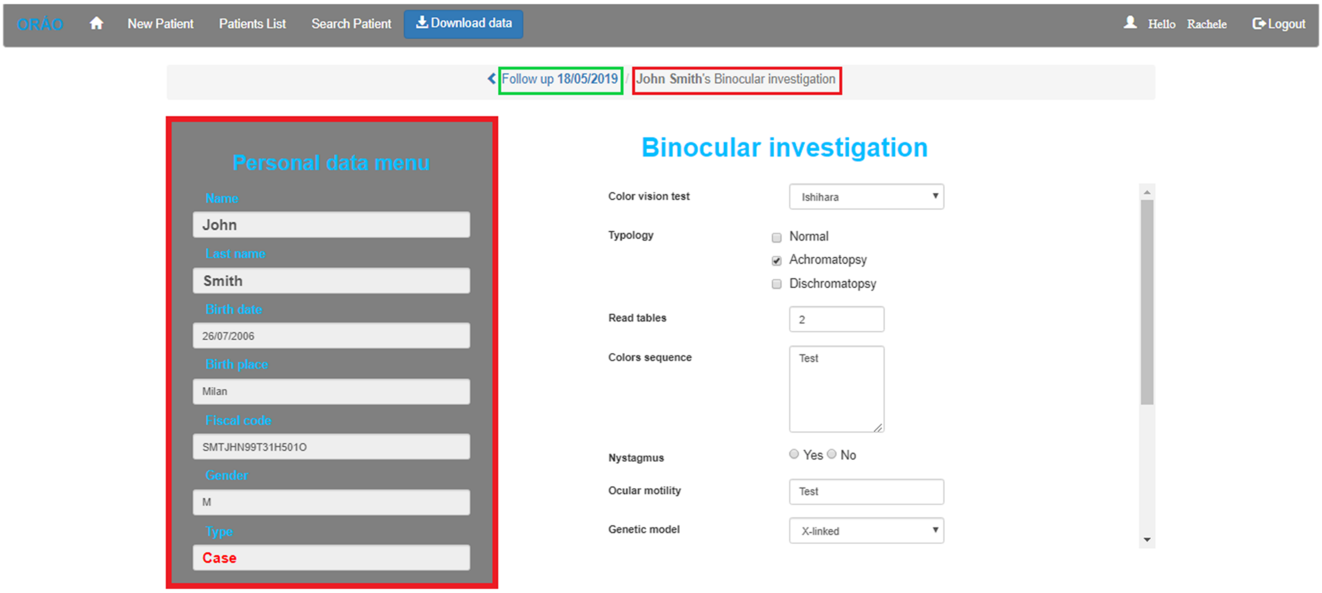
Last name	Name	Type	Birth date	Fiscal code	Birth place	Gender
[redacted]	[redacted]	Control	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Case	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Control	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Control	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Control	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Case	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Control	[redacted]	[redacted]	[redacted]	[redacted]

Fig. 8 The Patients List page. For each patient registered in the *Pupil* DB, the main personal data are shown. Also the *Type*, *Case* or *Control*, is shown to the end-user, associated with the proper colour, blue or red

follow up is consolidated: it is no more editable. In the page of the follow up, the ophthalmologic examination forms can be opened and compiled. The examinations belong to two different types: binocular and monocular. During a binocular examination, the physician analyses and gathers data about the two eyes together: the form of binocular examinations is organised in a one-column page. The binocular examinations are: anamnesis (medical history), binocular investigation and genetic report. The monocular examination regards the single eye. The examination form is divided in two columns. The right column in the form is intended to collect data about the left eye, the left column gathers data about the right eye. This represents a standard visualization, widely used by physicians. The monocular examination is clinical and instrumental.

Once the patient has been selected from the *Patients List*, in the subsequent pages (follow up and examination forms) a menu containing the data of the patient is always shown. It is placed on the left hand side of the page, see Fig. 9. It shows the name, last name and type of subject (*case* or *control*) in bold characters and other personal data: date of birth, fiscal code, gender and birthplace of the examined patient.

The navigation of the user throughout ORÁO is helped by two menus:



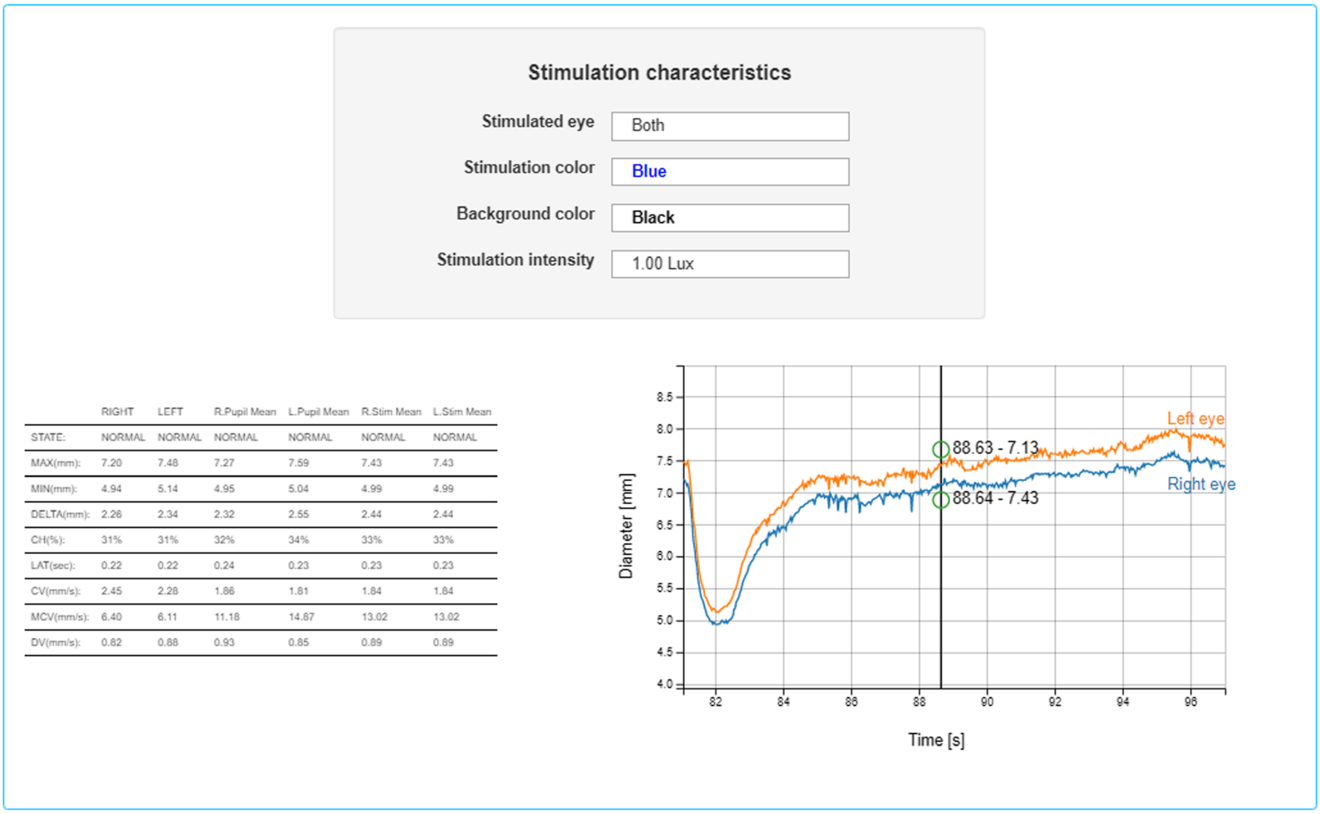
Personal data menu

Name: John
Last name: Smith
Birth date: 26/07/2006
Birth place: Milan
Fiscal code: SMTJHN99T31H501O
Gender: M
Type: **Case**

Binocular investigation

Color vision test: Ishihara
Typology: □ Normal ☑ Achromatopsy □ Dischromatopsy
Read tables: 2
Colors sequence: Test
Nystagmus: ○ Yes ○ No
Ocular motility: Test
Genetic model: X-linked

Fig. 9 The figure shows the patient personal data menu, highlighted in red color on the left hand of the page,the name of the patient which is repeated in the top menu, highlighted in red color too, and a label with the date of the chosen follow up. highlighted in green color



Stimulation characteristics

Stimulated eye	Both
Stimulation color	Blue
Background color	Black
Stimulation intensity	1.00 Lux

	RIGHT	LEFT	R.Pupil Mean	L.Pupil Mean	R.Stim Mean	L.Stim Mean
STATE:	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL
MAX(mm):	7.20	7.48	7.27	7.59	7.43	7.43
MIN(mm):	4.94	5.14	4.95	5.04	4.99	4.99
DELTA(mm):	2.26	2.34	2.32	2.55	2.44	2.44
CH(%):	31%	31%	32%	34%	33%	33%
LAT(sec):	0.22	0.22	0.24	0.23	0.23	0.23
CV(mm/s):	2.45	2.28	1.86	1.81	1.84	1.84
MCV(mm/s):	6.40	6.11	11.18	14.87	13.02	13.02
DV(mm/s):	0.82	0.88	0.93	0.85	0.89	0.89

Fig. 10 The graph of the pupil diameter trend over time and the two tables, one showing the technical characteristics of the selected stimulation and the other one summarising the parameters of the pupil measured during the pupillometric examination

1. A general navigation menu is positioned on top of each page. It gives the user the possibility to rapidly change page, accessing the main functionalities of the platform (*Homepage*, *New Patient* form, *Patients List*, *Search Patients*), and to download a file with the patient's data (*Download Data*).
2. A local menu of navigation: it provides a direct link to the previous page and the current position of the user in ORÁO. In particular, this menu repeats the name and last name of the patient and the date of the follow up examination the user has selected to study or to compile.

3.4 Pupillometry

In the follow up page, in addition to the previous-mentioned ophthalmologic examinations, the user can access the part of ORÁO dedicated to the pupillometric examination. This page has been specifically developed to match the workflow established by the protocol of the pilot study, [19].

After the performance of the pupillometric examination, the physician loads the .dat file coming from the pupillometer (as described in section 2.1). The file is then saved in a dedicated folder (*Upload*) on the VM and its file path is written in a DB record. Once the file is loaded and

Table 3 The table makes a list of the parameters measured during the pupillometry, with the meaning and the unit of measure of each of them

Parameter	Meaning	Unit of measure
MAX	Pupil diameter before the constriction	millimetres
MIN	Pupil diameter at the peak of the constriction, during the stimulation	millimetres
DELTA	Difference between MAX and MIN	millimetres
CH	(MAX-MIN)/MAX, given in percentage	
CLAT	Latency of the constriction	seconds
CV	Mean constriction velocity	millimetres/s
MCV	Maximum constriction velocity	millimetres/s
DV	Mean dilation velocity	millimetres/s

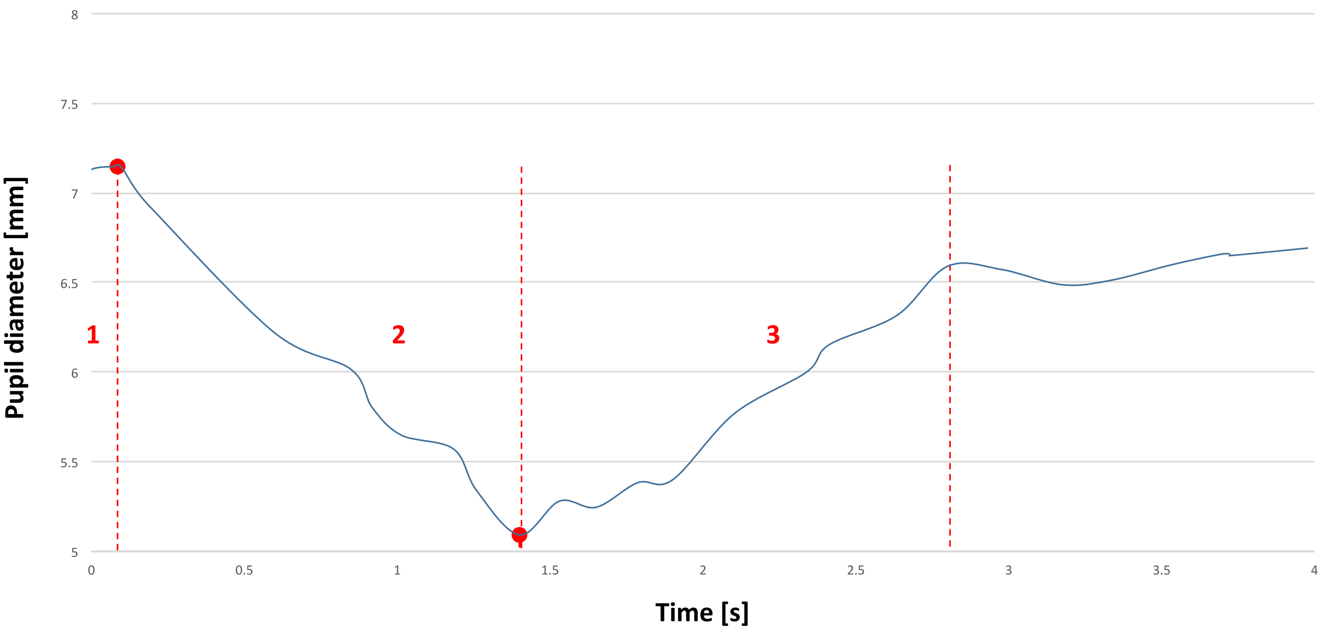


Fig. 11 The graph shows the response of the pupil to the light stimulation. The first red point highlights the maximum pupil diameter, before the contraction. On the other hand, the second red point identifies the minimum value at the peak of the contraction. Region 1 represents the latency between the stimulation and the pupil response. The slopes of the curve in region 2 and 3 correspond to the velocity of contraction and dilation of the pupil respectively

saved in the DB, the elaboration of the pupillometric data is performed.

The API developed for the pupillometry functionality of ORÁO queries the appropriate DB table an gets back the file path for the .dat file associated to the selected patient ID and the follow up ID. The API accesses and reads the content of the .dat file using the *System.IO* (i.e. Input Output) namespace of the. NET framework. This consists of IO related classes that can be used for reading and writing data to files and for file and directory support. In particular, the class *StreamReader* has been used to create a.

TextReader object that reads characters from the .dat file. The file is scanned up to the section starting with the line <MERGED-PUPIL-DATA>. This section contains the acquired samples of the pupil diameter during the pupillometric protocol. Each line of the section is stored in a list of strings in the API, until the line <\MERGED-PUPIL-DATA> is reached, indicating the end of the section. The total amount of these data is a list containing 21.290 strings, each made up of 14 parameters. Only three of these parameters are needed for the elaboration of the graph of the pupil diameter trend: time, right diameter and left diameter. They are extracted from the list and saved in a matrix for the following elaborations.

Also the section <RIGHT-PUPIL-ANALYSIS> must be read. It associates each index of stimulation (from 0 to 19) to the corresponding start/end samples of the pupil diameter trend. The data read from this section are stored in a matrix with 479 rows and 3 columns corresponding to index of stimulation, start/end sample.

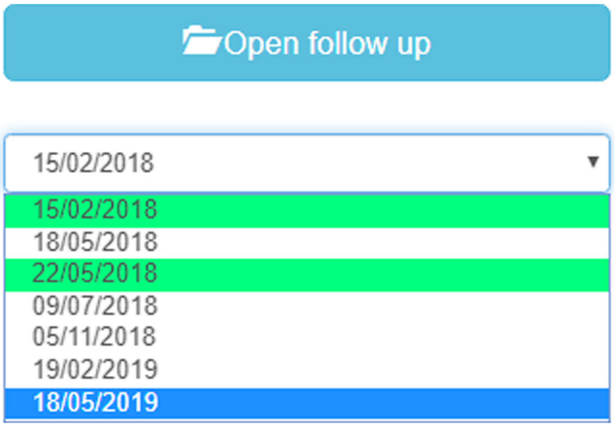
The physician must choose the index of the stimulation (from 1 to 20) he/she wants to analyse from a drop-down menu in the pupillometry page. The index is then used as an input for the API, together with the ID of the follow up. The elaborations described above are performed, and then the API sends to the presentation tier the values of time, right and left pupil diameter. These values feed the input of the JS function

Table 4 Severity Rating Scale adopted for the heuristic evaluation of ORÁO

Severity	Description
0	Low severity: not an usability problem at all. It could cause in the user a mild sense of frustration.
1	Medium severity: serious problem. It could cause a strong sense of frustration in the user and/or impede the correct and efficient completion of the tasks.
2	High severity: critical issue. It could be damaging for the user's ability to interact with the system and/or has potential for causing patient harm.

Table 5 The table lists the violations identified with the heuristic evaluation of ORÁO

Places of occurrence	Usability problem description	Potential consequences (if predictable)	Heuristics violated	Severity rating
Login page	Clicking on the top menu, the page loads but then it goes back to the Login page without a message for the user.	Time waste, mild sense of frustration in the user.	Informative feedback, Good error messages	0
New patient page	The user is asked to compile the fields regarding the patient's residence manually, without a menu from which to choose them.	Time waste, committing errors is more possible.	Prevent errors	0
New patient page	The user is asked to insert the patient fiscal code manually. There is no possibility to automatically generate it from the personal data of the patient.	Time waste, delay of the user work. Moreover, the patient can be searched in the platform also by his/her fiscal code. So, he/she could not be found later by the user.	Prevent errors, Minimize memory load	1
New patient page	Clicking on the button *Home* on the top menu, the user is immediately redirected to the homepage of ORÁO and the patient data inserted are lost.	Time waste, frustration in the user, higher likelihood of errors: the user must re-insert all the patient data.	Informative feedback, Prevent errors, Reversible actions	1
Follow up page	In the drop down menu *Show follow up*, it is impossible to distinguish editable follow ups from consolidated ones.	Great time waste, frustration in the user, chaos. The user is asked to open the follow up examinations one by one, to check their status. This could compromise his/her capability to complete the task.	Visibility of system state, Minimize memory load	2
Examinations page	From each examination page (i.e. Anamnesis, Genetic report, etc.), the user must always go back to the general examinations page to choose another one.	Time waste, frustration for a system expert user. The user could want to go directly from an examination form to another, to complete the task faster, without being forced to always go back to the general examination page.	Users in control, Flexibility and efficiency	0
Monocular clinical investigation	The unit measure of the fields *Tonometry* and *Corneal Thickness* are not shown.	Time waste.	Match between system and world	0
Examinations page	The user is not notified if an examination has been already compiled or not.	Time waste, error likelihood.	Informative feedback, Clear closure	1
Follow up page	Clicking on the button *Save*, the follow up is immediately created.	Irreversible action: the user could have selected the wrong date.	Reversible actions, Informative feedback	1
Monocular investigation pages (both Clinical and Instrumental)	These pages are not coherent with the design of the whole platform. Critical patient data are not visible, when the user scrolls down the page to compile it.	The user could register a monocular examination, attributing it to a wrong patient or putting it within a wrong follow up date.	Consistency and 2 standards, Prevent errors	2
Patients List	It is not immediately understandable for he user that the selection of a patient is made by clicking on the row of the table.	Time waste. If the user selects one of the buttons Edit patient data or Follow up, an error message is shown informing the user that it is necessary to select a patient from the list first, and then choosing one of the two actions.	Prevent errors	0
Pupillometry page	The page is slightly not coherent with the design of the rest of the platform.		Consistency and standards	0
Pupillometry page	The user is not notified if a pupillometric file has been loaded within the selected follow up.	Possibility to overwrite the pupillometry file, time waste.	Informative feedback	1



15/02/2018

15/02/2018
18/05/2018
22/05/2018
09/07/2018
05/11/2018
19/02/2019
18/05/2019

Fig. 12 This figure shows the follow up page modified after the heuristic evaluation. As it is possible to see, a green background has been added to the dates of the consolidated follow up. This change allows the immediate distinction between editable and consolidated follow up for the end user

responsible for the graph creation, through the D3 library. In the graph, time is expressed in seconds while the pupil diameter in millimetres. If the physician moves the mouse pointer over the graph, the x-value (time) and y-value (pupil diameter) are shown by two dynamic labels, to make the graph analysis as easy and immediate as possible (see Fig. 10).

A summary table of the technical characteristics of the stimulus is also presented. It contains the stimulated eye (right, left or both), the colour of light (red or blue), the intensity (in Lux) and the background colour (black or blue) for each stimulation. The physicians also need to study some more parameters of medical interest, measured during the pupillometric examination and contained in a section of the .dat file. The parameters are reported in Table 3. For a better understanding of these parameters, please refer to Fig. 11. These parameters are gathered in a table, from which physicians can clearly read them.

3.5 Usability evaluation

In the following sections the results of the usability evaluation of ORÁO are introduced. The method adopted to evaluate the interface is the heuristic evaluation, as stated in section 2.3.

3.5.1 Heuristic evaluation

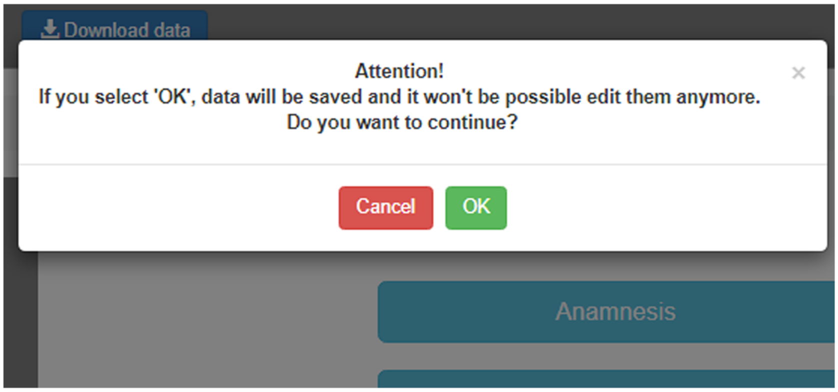
During the design of ORÁO, an heuristic evaluation has been performed to find out the usability issues of the interface and to address them. The evaluation has been carried out according to the method introduced in section 2.3.1. A three-level severity rating scale has been adopted, as reported in Table 4. The Task List has been composed considering all the possible application functionalities, giving high attention to those operations concerning the registration of the follow up examinations, considered the operations that introduce the major safety risk. A Reference Sheet (RS) has been prepared, containing the task list and the severity rating scale. Then the evaluator has been provided with the RS and a Data Collection Template.

The evaluation of ORÁO interface has identified thirteen usability problems. Among these, six have the lowest severity index (0), five have the mean severity index (1) and the remaining two have the highest severity index (2) (see Table 5). The latter have been addressed immediately. The first of these two more dangerous problems was related to the monocular examination forms (both clinical and instrumental). These pages resulted not coherent with the general design of the interfaces, violating the heuristic *Consistency and standards*, and in particular the *Spatial consistency*, [18].

They didn't have the data patient menu on the left side, moreover the fields to be filled where arranged over the whole page width. The second usability issue with the highest severity index was related to the follow up page. Once the patient is selected from the *Patient List*, the user can open and edit a follow up examination. This is selected from a drop down menu containing the follow up dates. Some follow ups are consolidated, while others are editable. These two different states of the follow up were not distinguished by anything in the drop down menu.

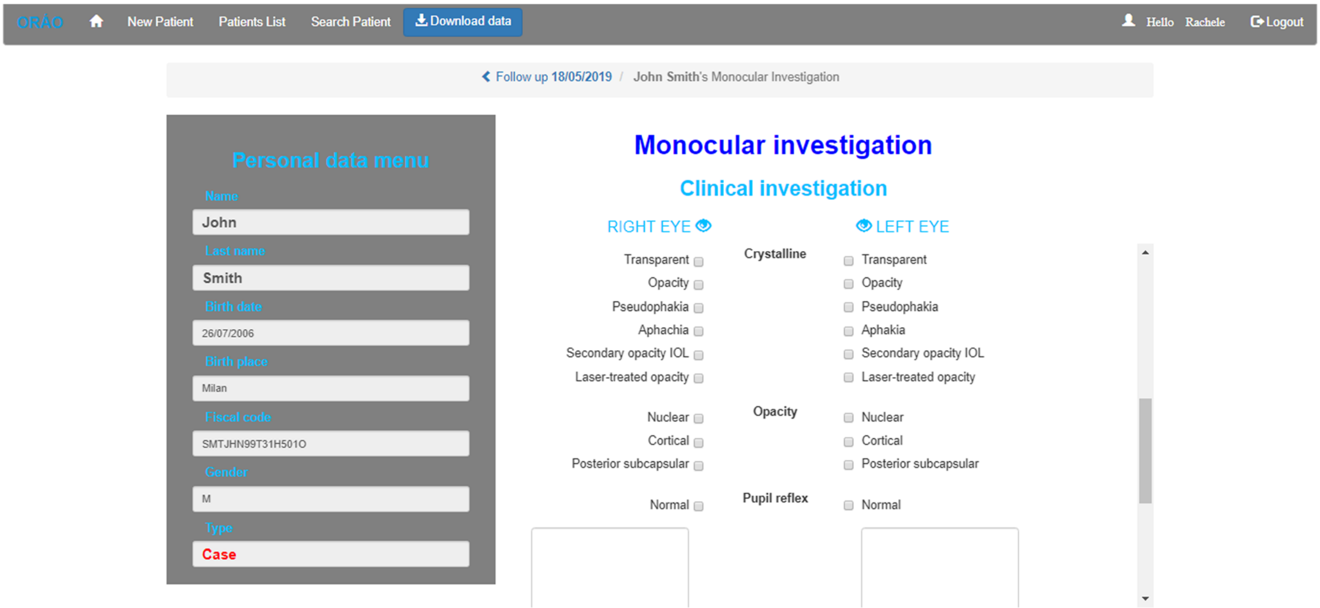
So, the user was expected to remember the state of each follow up of a patient or to open them one by one to verify if it was consolidated or not. This is a violation of the heuristic *Minimize memory load*.

Some of the middle severity usability issues concerned the error messages and feedback. For example, in the pupillometry



Attention!
If you select 'OK', data will be saved and it won't be possible edit them anymore.
Do you want to continue?

Fig. 13 In this figure, the message showed when the user press the button *Consolidate follow up* is presented. It gives the user the information about the consequences of the operation, asking for a further confirm of the will to consolidate the follow up



Personal data menu

Name	John
Last name	Smith
Birth date	26/07/2006
Birth place	Milan
Fiscal code	SMTJHN99T31H501O
Gender	M
Type	Case

Monocular investigation

Clinical investigation

RIGHT EYE		LEFT EYE
Transparent ☐	Crystalline	☐ Transparent
Opacity ☐		☐ Opacity
Pseudophakia ☐		☐ Pseudophakia
Aphachia ☐		☐ Aphakia
Secondary opacity IOL ☐		☐ Secondary opacity IOL
Laser-treated opacity ☐		☐ Laser-treated opacity
Nuclear ☐	Opacity	☐ Nuclear
Cortical ☐		☐ Cortical
Posterior subcapsular ☐		☐ Posterior subcapsular
Normal ☐	Pupil reflex	☐ Normal

Fig. 14 The monocular examination form after the heuristic evaluation. It is possible to notice the presence of the data patient menu on the left of the page and the distribution of the input fields, organized into two columns one for the left and one for the right eye. The examined eye is clearly indicated in the top of each column

page the user was not notified if the file of pupillometry (.dat file) had been loaded or not within that follow up examination. This represents a violation of the heuristic *Informative feedback*.

4 Discussion

The heuristic evaluation has constituted the basis for the final stage of the design of ORÁO. The identified usability issues have been addressed according to their severity, as stated in section 3.5.1. The first interventions have addressed the two issues with the highest severity index.

The design of the monocular examination pages has been redefined. The patient menu has been introduced on the left side of the page to reach a coherent structure with the rest of the examination pages. Moreover the input fields have been rearranged in a more compact appearance (see Fig. 14), making the monocular pages similar to the sheets used by the ophthalmologists for the manual registration of the examinations.

On the other hand, the issue concerning the follow up page has been addressed by introducing a green background for the dates of the consolidated follow up in the drop down menu, see Fig. 12. This intervention makes the user immediately aware of the status of the follow up examinations of the patient and avoids time-waste for checking the examinations one by one.

High attention has been given to the feedback and error messages. They have been made as clear as possible for the end user, in order to give a complete awareness of the consequences of the actions and to allow him/her to recover from errors, when possible. For example, in the follow up page the user can consolidate an examination, making it no more editable. When the button *Consolidate follow up* is pressed, a message asks the user to confirm the will to consolidate that follow up, see Fig. 13, reminding the irreversibility of the action.

Since ORÁO is available via web, the physicians involved in the project have constantly used it and they have expressed the need for a new functionality. The possibility to download a .csv file containing all the pupillometric parameters of all the patients registered in the *Pupil* DB was needed in order to evaluate the progression of the pilot study overall. The .csv file can be downloaded by pressing the button *Download data*, in the top menu of the platform (see Fig. 7). A dedicated query has been written in SQL. It creates a *view* which gathers data from different tables of the DB. Also for this functionality a specific API has been developed. It makes an HTTP GET request to the view and gets back all the required data for all patients, including patient data, data about the user who performed the input, follow up details as well as parameters measured during the pupillometric examination. These data are written in a .csv file, saved in the *Download* folder on the server, made accessible for download through an API.

A Clinical Decision Support System (CDSS) for pupillometry based on Machine Learning has been developed. CDSSs are introduced to improve the patient care as well as the hospitals' structure and organization, [20–22]. It is a classification system that gets some parameters from the .dat file of the pupillometer as input and gives back a label of *Affected by Retinitis Pigmentosa* or *Not affected by Retinitis Pigmentosa* as output for the selected patient. The CDSS is in the process of being integrated within ORÁO, thanks to the RESTful architecture. An additional VM, running the Apache Web Server, hosts the CDSS engine.

5 Conclusion

The design of ORÁO and all the phases of its development have been carried out in close collaboration with the whole project team. The platform matches with the needs they have expressed and with the workflow of the pupillometric protocol and of the ophthalmologic examinations. So, ORÁO turns out to be a customized IT solution for this project. Moreover, the high attention given to the usability of its interfaces made it very usable, according to all the subjects who have been using it for months.

This work shows how, given the growing complexity of healthcare systems and processes, the daily collaboration between biomedical engineers and physicians and the increasing demand for new tools and methods [23–25], there is a constant need for rigorous methodology in designing and realising collaboration tools that can facilitate these processes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study has been approved by the ethical committee of the clinical co-authors, who enrolled the patients.

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