ISEL – Instituto Superior de Engenharia de Lisboa
ADEETC – Área Departamental de Engenharia de Electrónica e Teleconumicações e de Computadores

MEIC
Mestrado em Eng. Informática e de Computadores
Tese

CASCIFFO - Software Capacitation in Hospital Fernando Fonseca Research Centre

Valdemar Antunes

Mentors

Engineer Miguel Gamboa

Engineer Pedro Vieira

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Chapter 1

This chapter consists of the introduction of the agencies involved in this application, as well as give a detailed view on the goals to be achieved in this thesis.

1.1 Introduction

The Hospital Professor Doutor Fernando Fonseca (HFF), is a first of the line hospital for the near 550.000 inhabitants of the municipalities of Amadora and Sintra. The Institution develops assistance and investigation activities as well as providing education, pre- and post-graduation training.

The Hospital's mission is to provide humanized and differentiated health care throughout a person's life cycle, in collaboration with primary and continuing health care, as well as other hospitals in the National Health Service's ("Serviço Nacional de Saúde") network.

The Clinical Investigation Unit ("Unidade de Investigação Clínica", UIC), created in March 2018, is an internal department within the Hospital that incorporated fundamental concepts of activities in line with the strategic objectives of the institution. The UIC is responsible for managing clinical investigations and is characterized by a multidisciplinary team responsible for ensuring accuracy in the scientific planning of the studies submitted, for the fulfillment of clinical best practices by researchers and for the negotiation of contracts for projects financed by external promoters.
UIC's mission is to promote quality clinical investigation in an organized and sustainable manner, following guidelines that value systematic knowledge through the management of interfaces associated with Investigation, Development, and Innovation, and complying with applicable ethical and legal provisions, for the benefit of the Hospital, the Community, the Patients, and the Families/Caregivers.
The goal is to become a reference of the promotion of best practices in hospital clinical research and to consolidate a transversal scientific culture within the institution.

Clinical investigations are very important to the world of medicine and health care. It's through them that new medicine and new ways of treatment are discovered and tested through strict adherence to scientific accuracy measurements and best practices before being administrated to the public.

There are two main types of clinical investigations, without intervention, which

includes observational trials ("Estudos Observacionais"), and with intervention, which includes clinical trials ("Ensaios Clínicos").
Observational Trials consist purely of observation, for example in the evaluation of a potential risk factor. On the other hand, Clinical Investigations with intervention can be characterized as any intervention that foresees any change, influence or programming of health care, behavior or knowledge of the participating patients or caretakers, with the end goal of discovering the effects it had on the participant's health.
Clinical trials consist of a scientific controlled investigation, done on humans (healthy or ill), with the end-goal of establishing or confirming the safety and efficiency of the experimental medicine.

Clinical trials have shown to be a vital tool in the development and testing of vaccinations and treatments for the safety of the entire world population, especially now during the present Covid19 pandemic. For this reason, the efficiency and simplicity in managing and monitoring the evolution of a clinical trial is essential. The current procedure of a clinical investigation relies on email exchanges with both external and internal parties involved, which adds a considerable amount of effort in the management and monitoring of clinical trials. Another concern is with the scheduling and monitoring of Clinical Trials patients, as there is currently no systematic way of distinguishing the types of appointments made for each patient. In this context, the application detailed in this document, CASCIFFO, aims to provide a solution in order to enhance the efficiency in the management and monitoring of clinical investigations.

1.2 CASCIFFO

CASCIFFO is a joint project between HFF and ISEL. It concerns the application to the clinical investigation Agency Award and Biomedical Innovation (AICIB). CASCIFFO is a web-app that aligns with the UIC's goals by promoting efficiency and quality in the management of clinical research. CASCIFFO strives to make the visualization, monitoring, and management of clinical Trials as simple and straightforward as possible. It will allow the UIC/HFF to be modernized, bringing a shift in how patients, researchers, and promoters view and value their institution.

The application aims to develop and provide innovative mechanisms for interoperability with internal and external information systems, allowing, when desired, data synchronization, index search, identification data management and even access to detailed clinical data. CASCIFFO consists of two core modules, the front-end and the back-end. The front-end supports interaction with users while the back-end connects to an internal database system to the HFF/UIC and which aggregates the total information of this ecosystem. The interaction with users will depend on their role within the platform, displaying the appropriate information to each one.

Chapter 2

This chapter consists of a detailed view over the inner workings and functional requirements of the platform CASCIFFO. It is structured with the following sections:

- Infrastruture: Description of technologies and frameworks used in the development of CASCIFFO.
- Access control: Identification and categorization of actors and their roles.
- Processes: Identification and detailing of the flow of processes.
- Functional Requirements: Description of functional requirements.

2.1 Infrastructure

The infrastructure of CASCIFFO, has mentioned previously, consists of two core modules, the front-end and the back-end. The front-end runs on a Node.js environment, using React with Typescript to build all front-end functionalities. The dependencies are managed using npm, npm was chosen over yarn due to its larger community and support. The back-end executes on a run-time Java environment, utilizing Spring-web as the server. CASCIFFO has its own database, utilizing the framework PostgreSQL. While CASCIFFO has its own databse, the patient and medical staff data will be imported from an internal database, "Admission", within the HFF/UIC. There are restrictions on the amount of queries made on the medical staff information, limiting this procedure to once per day.

2.2 Access control

Within the app CASCIFFO, in order for the management of clinical investigations to adhere to its natural progress, it needs to be reviewed by many entities, such as the Administrative Council ("Concelho administrativo", CA), the Finance and Juridical department. Given this nature of CASCIFFO, there needs to be a well-defined structure of access control, so that each entity can contribute to the management of clinical investigations within the scope of their responsibilities. Each involved entity must have a role and a set of permissions. The roles identified are as follows, the UIC role, given to the investigators who can create and edit clinical investigation proposals; the Team Member role, given to investigators belonging to the

team conducting the clinical investigation; the Management role, able to approve and reject clinical investigation proposals; the Finance and Juridical roles, given to collaborators who's function belongs within the Finance and Juridical departments, respectfully; and finally the Superuser role, who has complete access to every feature CASCIFFO has to offer.

2.3 Processes

This section details the types of processes occurring within the scope of the project. There are three identified processes consisting of the life-cycle of a clinical investigation proposal, the Clinical Trials and the addenda to the contract.

2.3.1 Clinical Investigation Proposals

From the moment a clinical investigation is proposed, it follows through a series of states and protocols that must be adhered to in order for it to be completely validated. There are two types of clinical investigations: Clinical Trials and Observational Trials. Each state, except the terminal one, has an entity responsible, 'owner', for advancing the state. The flow of states is as follows:

1. 'Submetido', 'owner=UIC'
2. 'Negociação de CF', 'owner=UIC'
3. 'Validação interna', 'owner=Finance,Juridical'
4. 'Validação externa', 'owner=UIC'
5. 'Submissão ao CA', 'owner=UIC'
6. 'Validação interna', 'owner=CA'
7. 'Validado'

The enumerated set of states corresponds to the life-cycle of a clinical trial Proposal. An Observational Trial Proposal consists of the enumerated states 1,4,5,6; it lacks a financial component and a promoter.

Taking the example of the submission of a clinical trial Proposal, an investigator starts by creating and submitting a proposal. Once it's submitted, the CA will be notified, via app and email. This state is described as 'Submetido'. When the negotiation of the financial contract begins, the principal Investigator, who belongs to the UIC role, will advance the state to its next step in the proposal's evolution, 'Negociação de CF'. When the financial negotiation reaches an agreement of the UIC and external promoter, the investigator advances the state to its next stage, 'Validação Interna'. Upon advancing, the users with the role of 'Finance' and 'Juridical', which represents the Financial and Juridical internal departments, respectfully, will be notified that a proposal is ready to be evaluated. The evaluation will consist of a simple 'Accept' or 'Refuse' with added justification for the choice. In the case of

either user with ‘Finance‘ or ‘Juridical‘ role reject the financial contract, the proposal’s will backtrack to ‘Negociação de CF‘, notifying the UIC of the occurrence. Once it’s accepted by both roles, the proposal will automatically advance into the next state, ‘Validação Externa‘. In this state the UIC will be notified of the change and asked to verify all the documents, including the final version of the financial contract. The UIC to the external promoter, requesting their signatures. When the reply is received via email, the UIC adds the received signatures and possible additional documents to the proposal in the CASCIFFO platform, advancing it to the next stage ‘Submissão ao CA‘. In the state ‘Submissão ao CA‘, the principal investigator will be notified both via the platform and email that a proposal requires their signature. Once the principal investigator submits their signature into the platform, he can advance the proposal’s state into ‘Validação interna‘. The progression to the mentioned state will notify users with the ‘CA‘ role stating that a proposal is ready for its final evaluation. Once a user with the role of ‘CA‘ checks the proposal it can validate or invalidate the proposal. In case it’s invalidated, the proposal will become ‘canceled‘ with its life-cycle ending there, however, if it is validated, the proposal can become fully validated once the termination of another process is ends successfully. This process, which can be considered a sub-process, is called the [validation] protocol. It starts in a parallel manner when the proposal is first submitted. The purpose of this protocol is to validate the clinical investigation’s ethical and safety values. It consists in the validation of the proposal by internal and external agencies, the clinical investigations Ethics Comity (”Comissão de Ética para Investigação Clínica”, CEIC) and INFARMED, I.P respectfully. The protocol ends when either of the mentioned agencies approves or rejects the proposal. Once it has successfully passed through the described validation protocol, the proposal becomes ‘Validated‘ and a Clinical or Observational Trial is automatically created, importing the core information from the proposal. If either process declares the proposal invalid, its state becomes ‘canceled‘, notifying the UIC and showing the root cause of cancellation.

Each proposal is distinguished by six main properties, the principal investigator, the type of investigation, the type of therapeutic service it’s integrated into (i.e Oncology), the ‘Sigla‘ which represents the name of the therapeutic or medicine, the partnerships involved in the investigation and the medical team participating in the investigation. Proposals with a financial component must also include the promoter of the investigation, in addition to the properties listed.

2.3.2 Clinical Trials

The life-cycle of a clinical trial is divided into three states: active, completed, and canceled. Starting with the active state, a clinical trial will become available for viewing and editing once its proposal has been accepted. Clinical trials as a process consist on the experimentation of new medicine or treatment on a set of participants. These participants can be added to the clinical trial directly from the application. The experimentation requires constant monitoring, through visits, on each partici-

pant. These visits can be scheduled either when a participant is added or created afterwards. In addition to monitoring participants, several studies can be made in the scope of the clinical trial, such as scientific articles, presentations, reports, etc.

2.3.3 Addenda to the contract

Throughout the life of a clinical trial, there can be made changes to the study's contract, be it changing the investigator team or other factors that impact the standard run of the study. These changes pass through two entities before being applied; the UIC and the CA. Addenda can only be made once a clinical trial is active, which means its proposal has already been approved. The addenda have five different states: submitted 'Submetido', internal validation by UIC 'Validação interna', internal validation by CA 'Validação interna', the terminal state validated 'Validado' and finally the terminal canceled state 'Indeferido'. The first four mentioned states are sequential, with the last one being an exception state. The sequential flow of states have an entity responsible for advancing their state, the 'owner'. Listed below, in similar fashion to the states presented in the proposal process, is the aforementioned sequence:

1. 'Submitido', 'owner=UIC'
2. 'Validação interna', 'owner=UIC'
3. 'Validação interna', 'owner=CA'
4. 'Validado'

2.4 Functional Requirements

This section details the functional requirements and presents a mock user interface (UI) that will satisfy the requirement. The main features of CASCIFFO can be separated into three groups, which are: general functionalities, clinical component and financial component.

1. General features
    - Visualization and management of Clinical Trials as a process;
    - Ability to edit and validate data (edit checks);
    - Access control based on different user profiles;
    - Access by computer, tablet or smartphone;
    - Ability to export information in numerical or graphical mode;
    - Ability to customize the form of visualization.
2. Clinical Component
    - View detailed characteristics and evolution of clinical Trials including the tested medicine or technique in question;

- Monitoring the set of patients included in clinical Trials and their characteristics;
- Insertion of patient data in face-to-face or tele-consultation;
- Characteristics of the treatment associated with the clinical trial and monitoring of the patient's behavior under trial and its attendance;
- Monitoring of physical and financial assets;
- Monitoring of visits & Recording of adverse events associated with patients due to the trial drug;

2.5 General Features

In this section, the general features mentioned in the document will be described and illustrated through mock-ups.

2.5.1 Visualization and management of Clinical Trials as a process

To view and manage a clinical trial as a process, a user needs only to view the general overview of Clinical Trials or clinical investigations Proposals. As shown in fig 2.1 and fig 2.2, the user has an overview of the all submitted proposals and clinical trials with their main characteristics, such as, the identification, current state, last alteration date, the principal investigator and whether it has partnerships or not.

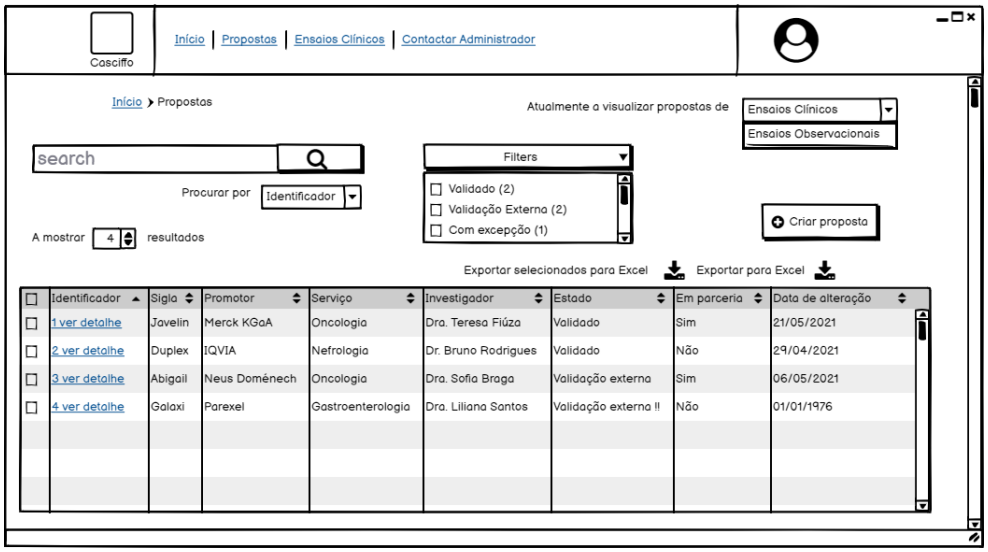

Figure 2.1: Mock overview of clinical investigations proposals

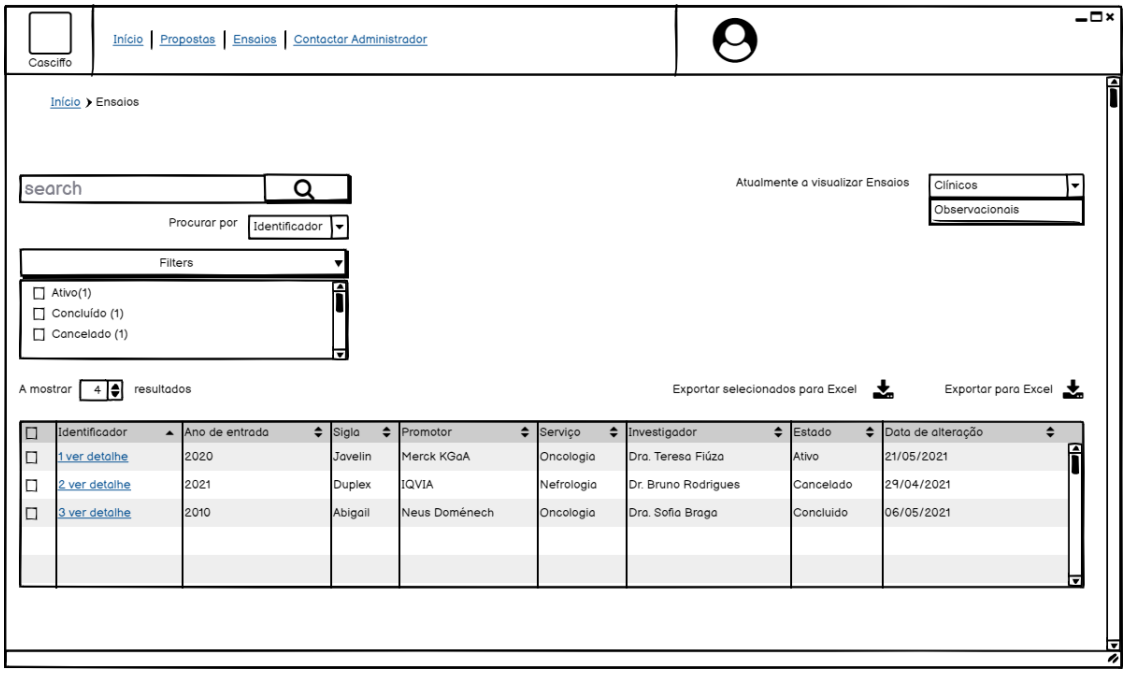

Figure 2.2: Mock overview of clinical trials

When a user clicks the link view details ("ver detalhe"), he will be redirected to a screen displaying the details of the target clinical investigation.

2.5.2 Ability to edit and validate data (edit checks)

Within the CASCIFFO platform, the UIC and internal departments can view the details of a certain clinical investigation proposal and edit or validate according to their roles. Users with 'UIC' role will be able to create and edit their own Investigations, whereas the internal departments, with roles of 'CA', 'Finance' and 'Juridical' will only be able to validate the proposals. The creation of a proposal starts in the overview of proposals screen, from there a user can click on "Criar proposta" and will be redirected to the screen illustrated in fig 2.3. Here an investigator can choose what type of investigation this proposal corresponds to, either an observational or clinical trial. In the case a clinical trial is selected, more options will be shown since clinical trials have a corresponding financial component. The data fields corresponding to the therapeutic area, the service and the pathology of an investigation are restricted to a set of possible inputs. In addition, the members of a medical team also belong to an already defined database, being validated at the time of creation of the medical team for the investigation. Certain fields cannot be altered once a proposal has been submitted, such as the promoter, the partnerships and the type of investigation can only be defined during the creation of a proposal.

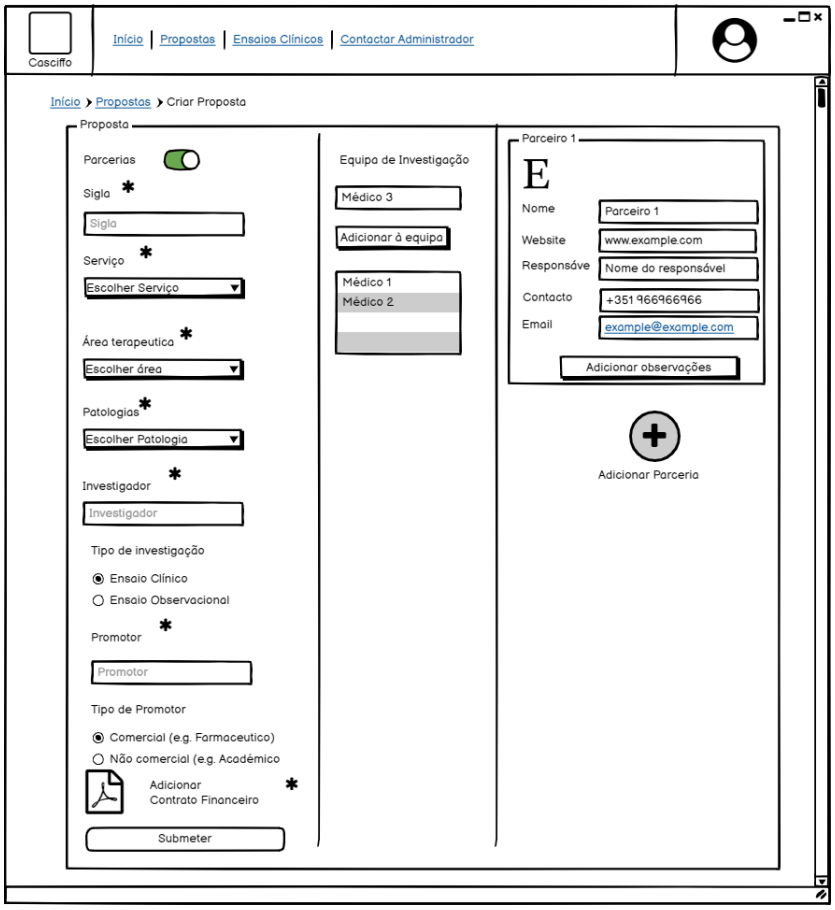

Figure 2.3: Mock creation of a clinical investigation proposal

2.5.3 Access control based on different user profiles

The access control within the CASCIFFO application is based on roles. As described in section 1, there are defined roles for each type of user. A user with the role ‘UIC‘ can manage their own clinical investigation, being able to edit and have a hand in advancing the state. In addition, it also has an overview over all ongoing investigations, not being able to edit those that weren't created by said user. Once this user logs in, a dashboard showing overall statistics of the platform, i.e. number of active clinical trials, number of submitted proposals, etc. The role ‘Financial‘ is responsible for validating and updating the financial components of the investigations, thus when a user with this role logs in, an appropriate financial management screen will be displayed, whereas the ‘Juridical‘ component validates the juridical component. The role ‘CA‘ is responsible for giving the final say in whether an investigation proposal can have the go-ahead to begin their clinical trials or observations. A user of role ‘CA‘ once logged in, will be shown a primary screen displaying the overview of clinical investigation proposals awaiting validation. Finally, we have the ‘Superuser‘ role, which besides having the ability to execute every mentioned action, it can also create new types of services, therapeutic areas and pathologies.

2.5.4 Access by computer, tablet or smartphone

CASCIFFO is a web-application which can be accessed via any device or browser. CASCIFFO offers extended functionality to browsers that support service workers, this is because it utilizes the Progressive Web Application (PWA) framework, allowing it to be installed and used as an application. Among the features a PWA allows, the framework was chosen by its ability to let an application run in offline-mode and versatility in that it can be installed via the browser, and used in similarity to a standalone mobile app.

2.5.5 Ability to export information in numerical or graphical mode

CASCIFFO offers the ability to export information via excel, and visualize graphic data within the app. There is a feature, shown in fig 2.4 that allows a user to export data, e.g a selected number of clinical investigation proposals. This feature is present in the screens showing listed data, e.g list of clinical investigation proposals, and the details of each clinical investigation, proposal or trial.

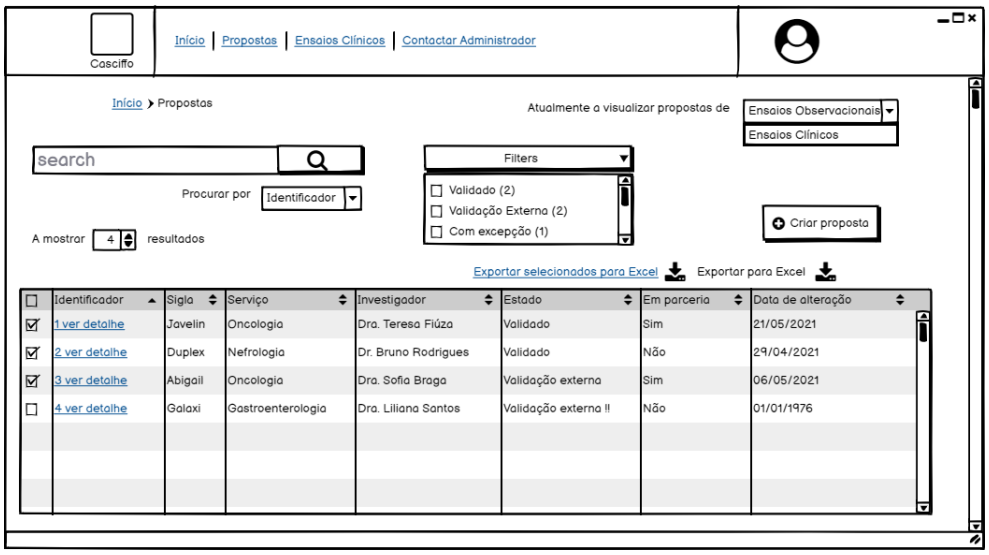

Figure 2.4: Mock screen selecting clinical proposals to export into excel

2.5.6 Ability to customize the form of visualization

The ability to customize the form of visualization will be available in the initial screen of the app, the Dashboard. Where the user will be able to view different types of graphs showing statistics based on the states of clinical investigations.

2.5.7 View detailed Characteristics and evolution of clinical Trials including the tested medicine or technique in question

To view detailed information about a clinical investigation, one needs to first overview the clinical investigations and then click on the details of a desired clinical investi-

gation. Doing this, the user will be redirected to a screen detailing the study. The evolution of any clinical investigation consists of its proposal followed the trial activity once the proposal has been fully validated. In fig 2.5, the details of a clinical trial proposal can be viewed. The flow of state of a proposal is shown in the form of a bar in a straight forward manner. Each state corresponds to a division, box, in the bar and has three properties: the name of the State; the date it was completed (if it hasn't been completed it will be shown as "——"); the deadline at which it should be completed and finally the entity responsible for advancing the state. It is possible to click in the box of a state to display information about the events that occurred during the time the proposal was in that state.

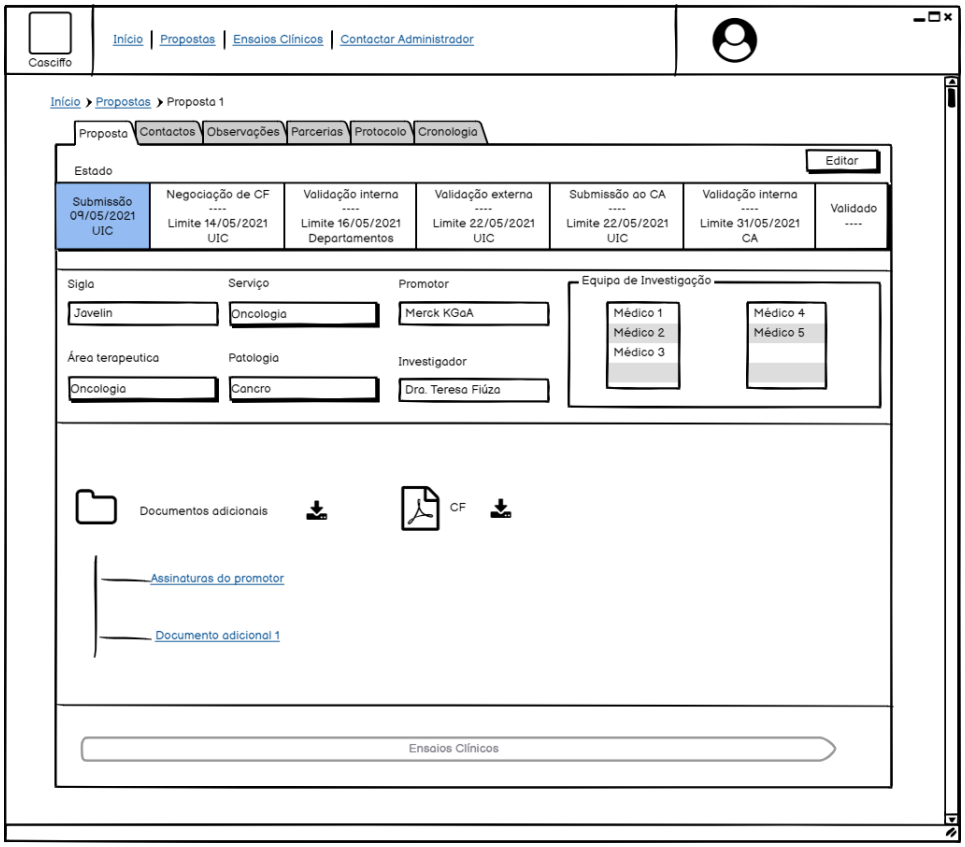

Figure 2.5: Mock overview of a clinical investigation proposal

A clinical trial proposal also another 5 components alongside its principal details displayed as tabs: the Contacts ("Contactos") which corresponds to comments related to external communications, viewed in fig 2.6; the Observations ("Observações") which contains comments made in regard to the proposal, viewed in fig 2.7; the Partnerships ("Parcerias"), where one can find the partnerships involved in the study proposal, viewed in fig 2.8; the validation Protocol ("Protocolo"), where it can be viewed the current state of affairs of the process described in section 2.5.1, viewed in fig 2.9; and finally the Chronology ("Cronologia") of events that also includes deadlines. This tab shows the timeline of events that have occurred, events can be considered changes of state as well as deadlines, the ability to view both deadlines and state transitions is given to the user as shown in fig 2.10. In all tabs except the one pertaining to the Protocol validation, the state of the proposal will

be shown.

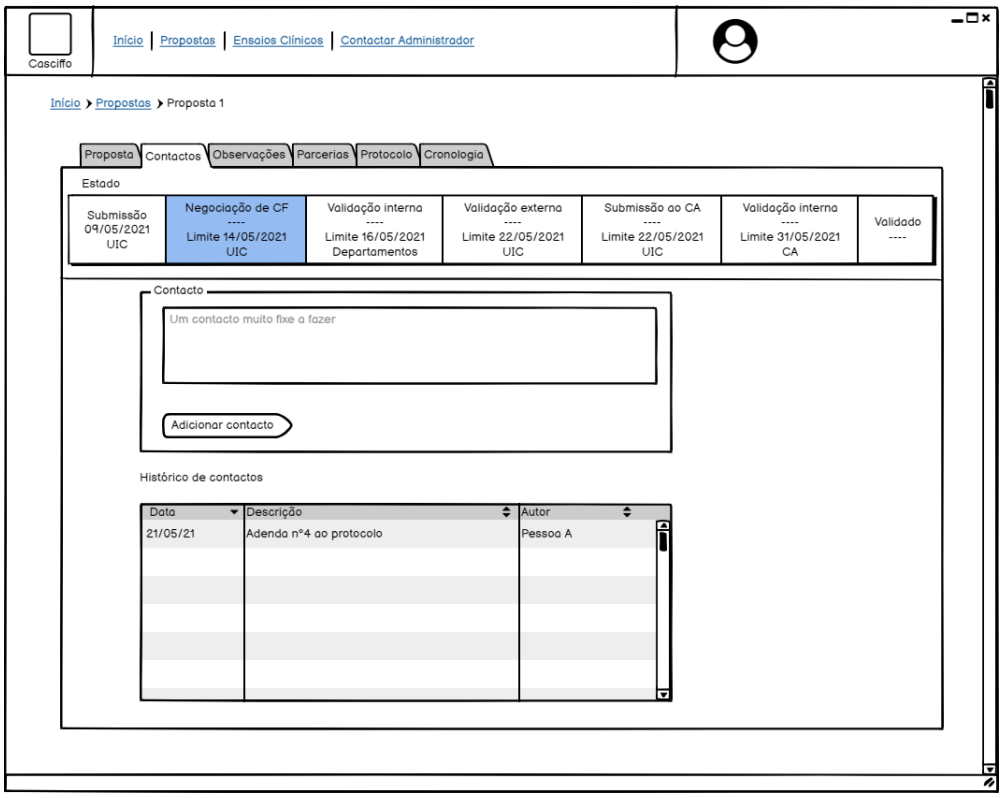

Figure 2.6: Mock overview of the contacts made within a proposal

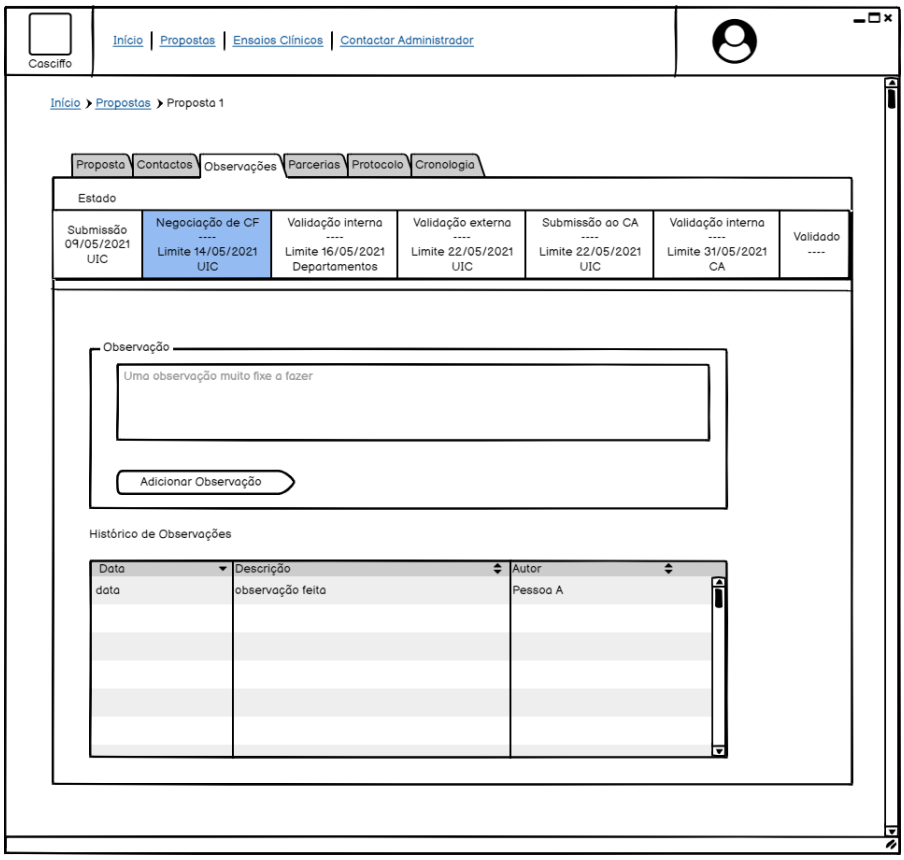

Figure 2.7: Mock

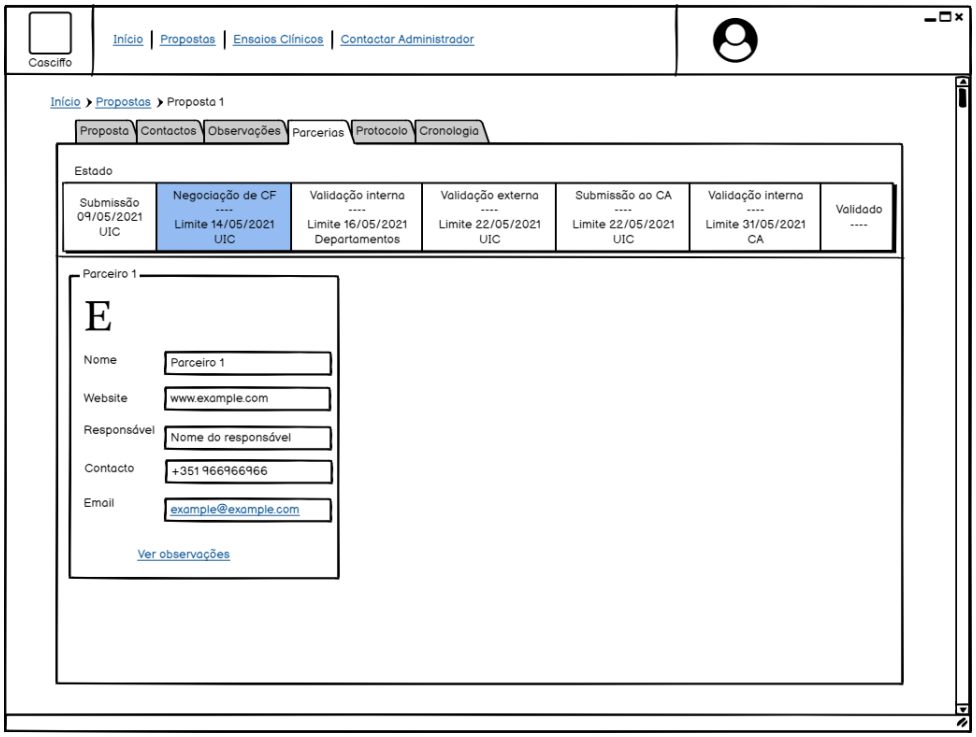

Figure 2.8: Mock

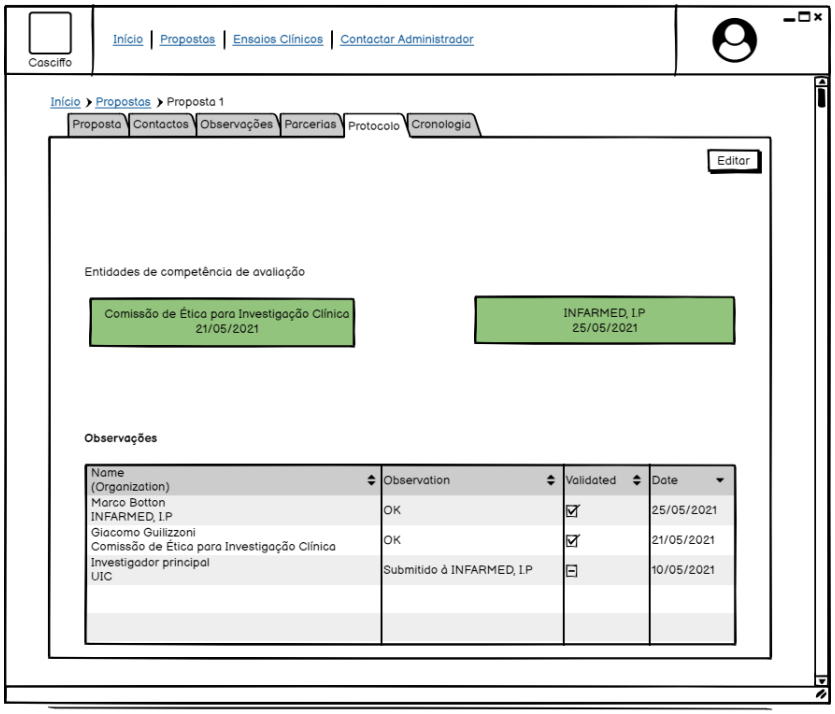

Figure 2.9: Mock

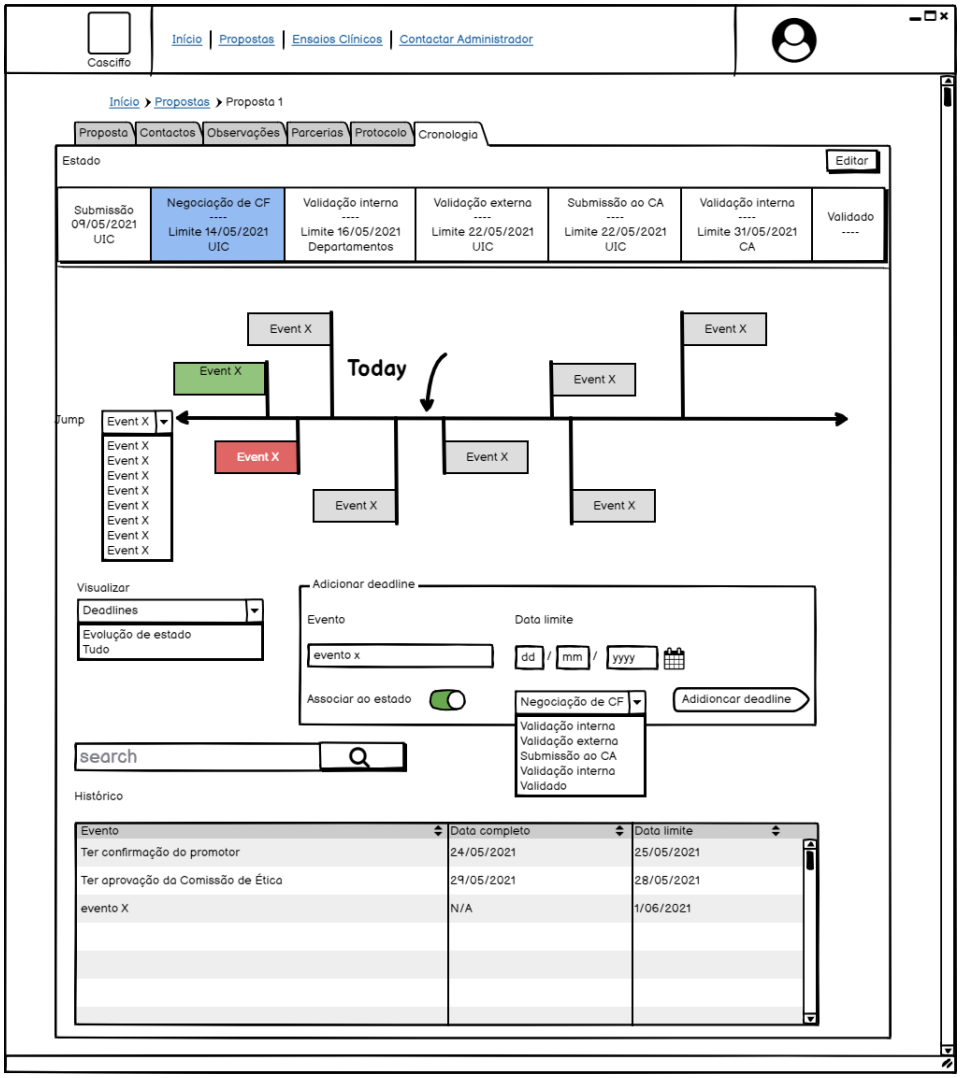

Figure 2.10: Mock

Once the proposal has reached its successful terminal state, as mentioned in section 3.1, a clinical trial will be created. To access the newly created trial, the user can either click the button "Ensaio Clínico" from the proposal details screen, as illustrated in fig 2.5, or from the overview of clinical trials click on the details of one. In the screen dedicated to the clinical trial, seen in fig 2.11, there are five different tabs: the clinical trial tab ("Ensaio Clínico") that displays the characteristics of the study; the scientific activities tab ("Atividades científicas"), viewed in fig 2.12, which includes scientific work in the scope of the study, such as articles, thesis, reports, etc.; the visits tab where the investigator team can have an overview of the history and scheduled visits; the patients tab ("Pacientes") with the purpose of showing an overview of the participants included in the trial; the partnerships tab ("Parcerias"), similar to the proposal's version of partnerships tab, displays the partnerships involved in the study; and finally the financial management ("Financiamento"), where one can view the flow of monetary gain from visits and the partition between the investigator team.

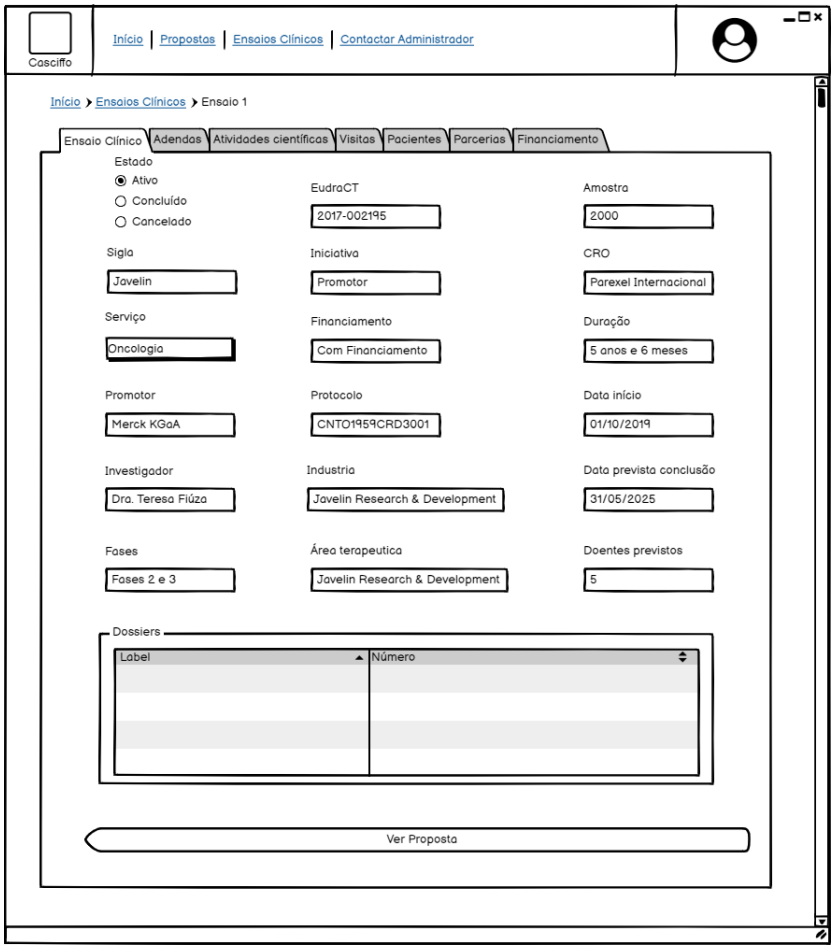

Figure 2.11: Mock overview of the details of a clinical trial

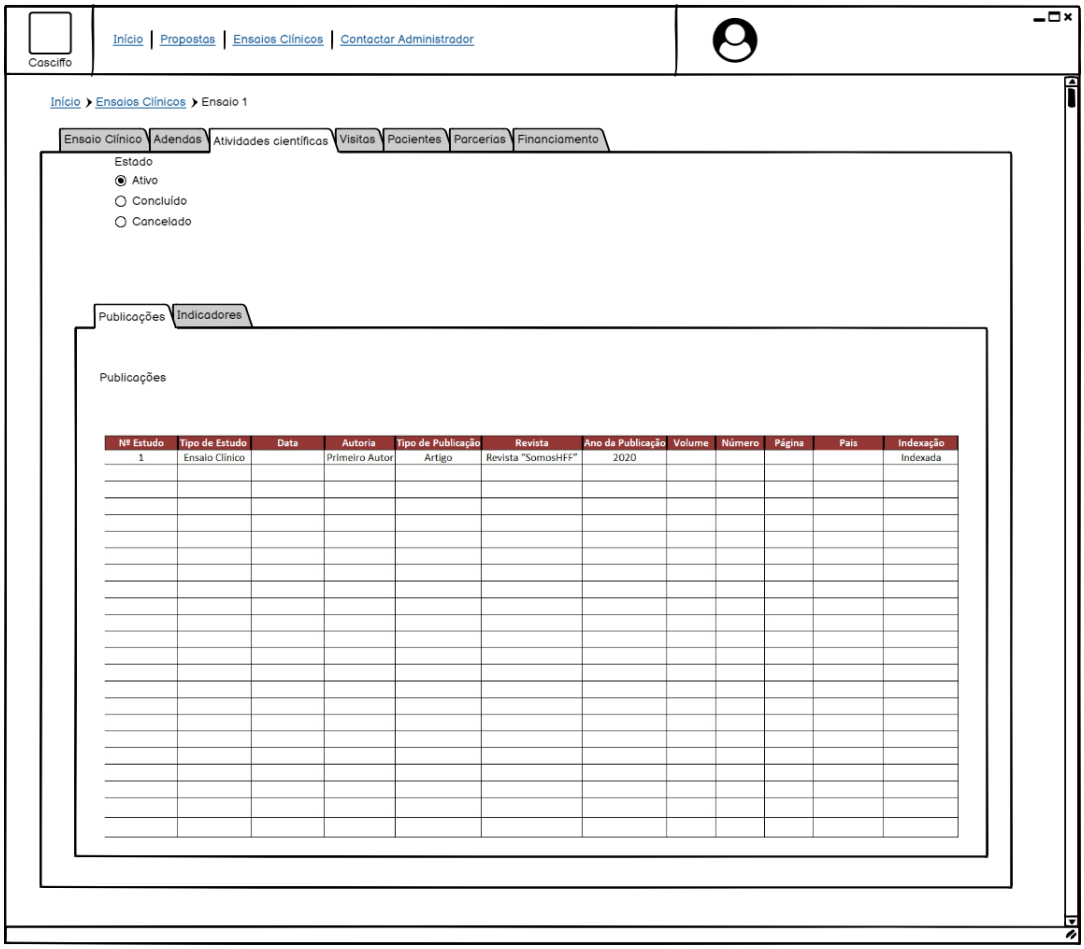

Figure 2.12: Mock overview of scientific activities made within the scope of the investigation

2.5.8 Monitoring the set of patients included in clinical Trials and their characteristics

The details of the set of patients involved in a clinical trial will be displayed when viewing the details of said clinical trial, under the tab "Pacientes", illustrated in fig 2.13. This tab displays the set of current participants undergoing the clinical trial and information such as the participant number, used to identify the participant throughout the study, the name of the participant, their age, the treatment branch they were assigned to within the scope of the study, their last and the closest upcoming visit. Included in this screen are the buttons Randomize ("Randomizar") and Add ("Adicionar"). The button randomize will randomly assign participants to treatment branches within the study, this one-time procedure is to be used once all the participants have been added to the clinical trial. The button add, will begin the procedure to add a patient. Upon clicking this button, the user will be shown a small box, as illustrated in fig 2.14, where he can input the name of the participant and then is also given the chance to immediately schedule several visits.

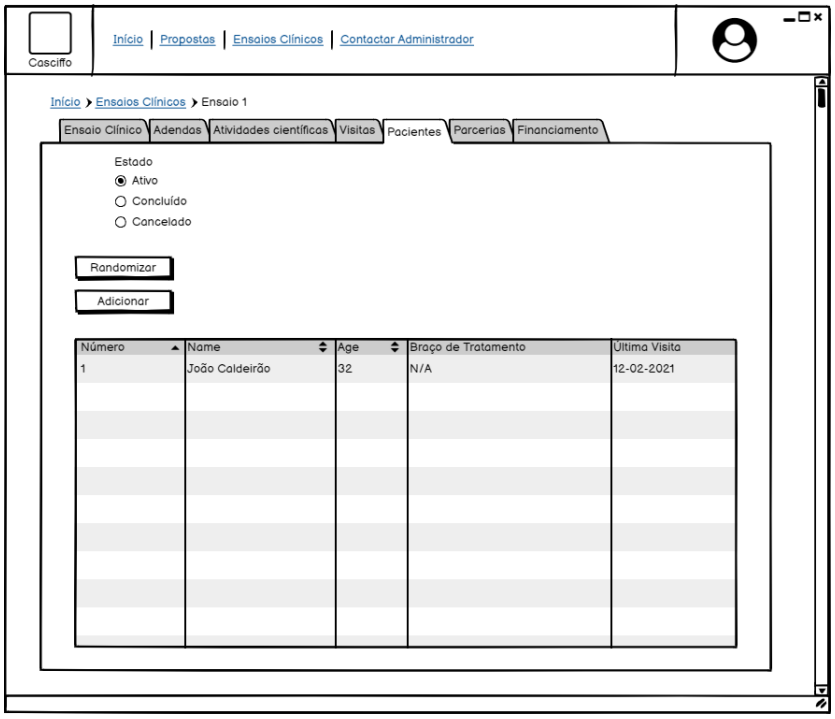

Figure 2.13: Mock overview of all participants included in the study

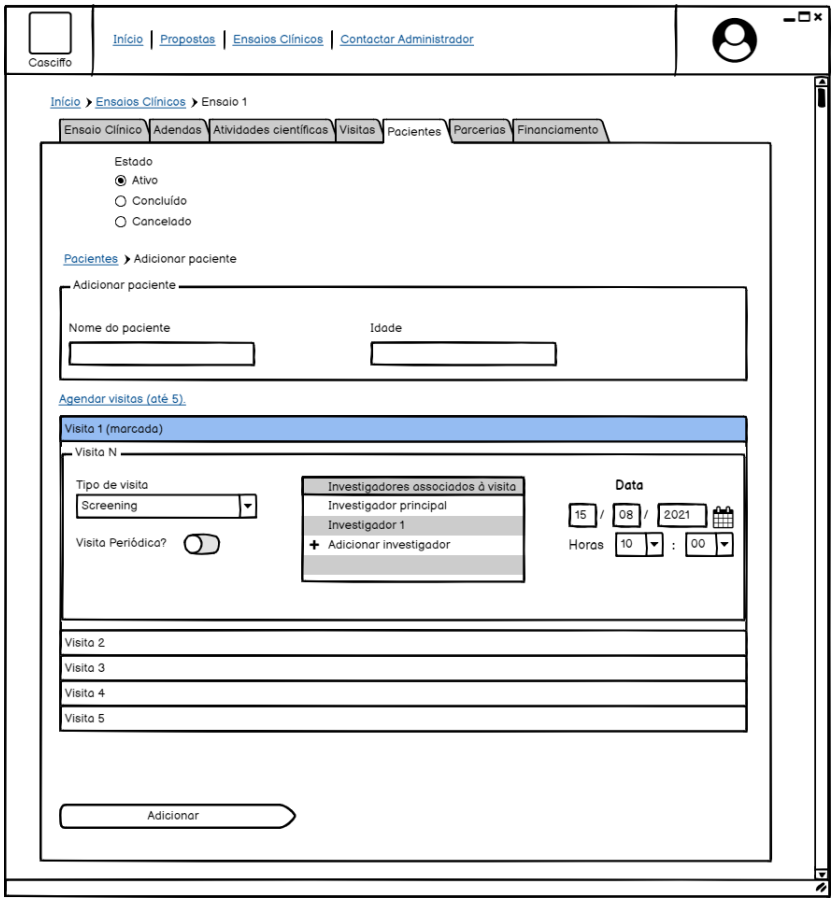

Figure 2.14: Mock screen of adding a new patient as a participant in the study

2.5.9 Insertion of patient data in face-to-face or tele-consultation

The insertion of patient data in the context of a visit is made by the investigator associated to said visit. In order to do this, the investigator has to navigate to the details of the visit, from the overview of clinical trials, to the details of the trial followed by the overview of visits and finally the details of the visit in question. Here the investigator can input observational data into the field "Observações" which will represent the observations made throughout the visit or tele-consultation. He is also asked to mark the attendance of the participant by clicking on a simple button "Marcar presença", as illustrated in fig 2.15.

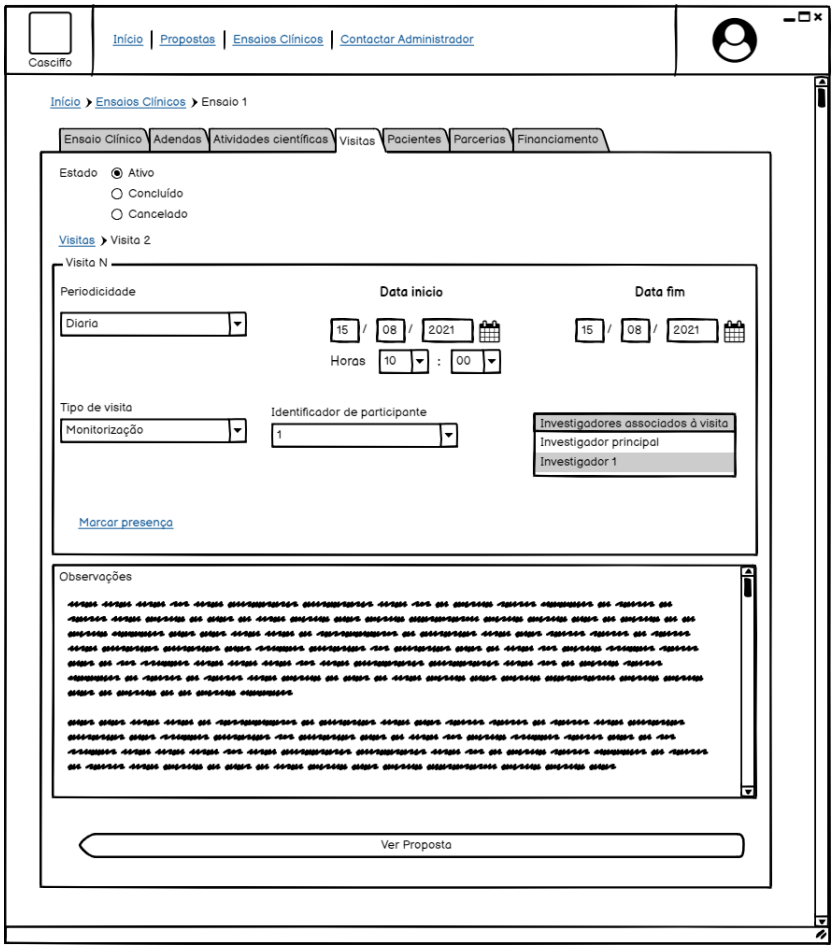

Figure 2.15: Mock overview of a visit's details

2.5.10 Characteristics of the treatment associated with the clinical trial and monitoring of the patient's behavior under trial and its attendance

The characteristics of the treatment associated with clinical trials consists of three main factors, the service area it's under, the therapeutic field and the pathology the clinical trial aims to investigate/treat. These details can all be found in the detailed view of a clinical trial under the tab "Ensaio Clínico". The monitoring of the patient's behavior and its attendance, can be tracked via the visits and viewed in two different ways. The first is to filter the visits, under the visits tab, to show only

the visits related to the participant in question. The second is to view the details of this participant in particular, from the overview of total participants in the study, clicking on the details of the participant and then checking the tab "Attendance", as illustrated in fig 2.16.

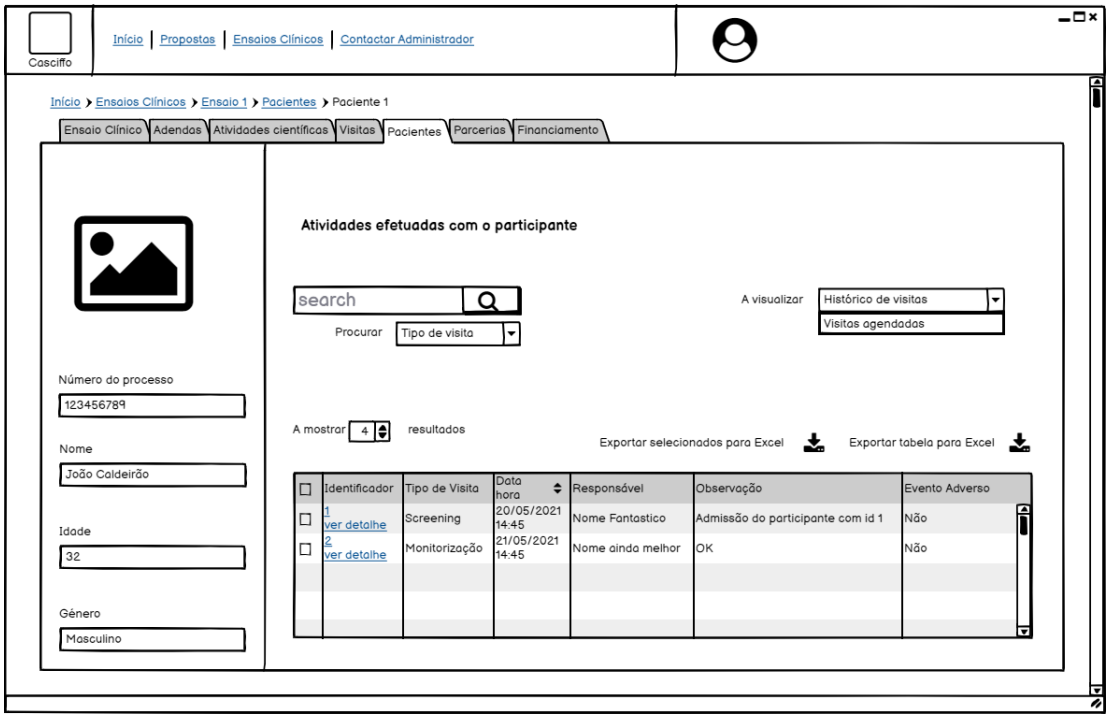

Figure 2.16: Mock overview of patient details

2.5.11 Monitoring of physical and financial assets

In regard to the monitoring of physical assets, these can be viewed under the tab "Ensaio Clínico" while in the detail page of the clinical trial in question. The assets to be monitored are documentation archives, consisting of three fields, the Volume, a Label and the total Number. CASCIFFO also offers another type of monitoring, the monetary flow. As described in section 4.2.1, each clinical trial has a financial management section that discriminates the earnings made by visit and the partitions of each team member involved in the study. Under the tab "Financiamento", the general monetary information, such as, total balance ("saldo"), amount per participant, etc., is displayed on a top section of the page. Below this section there can be observed another two tabs, differentiating the income made from the investigation team and the clinical trial itself. The first tab "EC", shown in fig 2.17, shows the income made according to the visits done, whereas the second tab "Equipa", illustrated in fig 2.18, shows the income by team member.

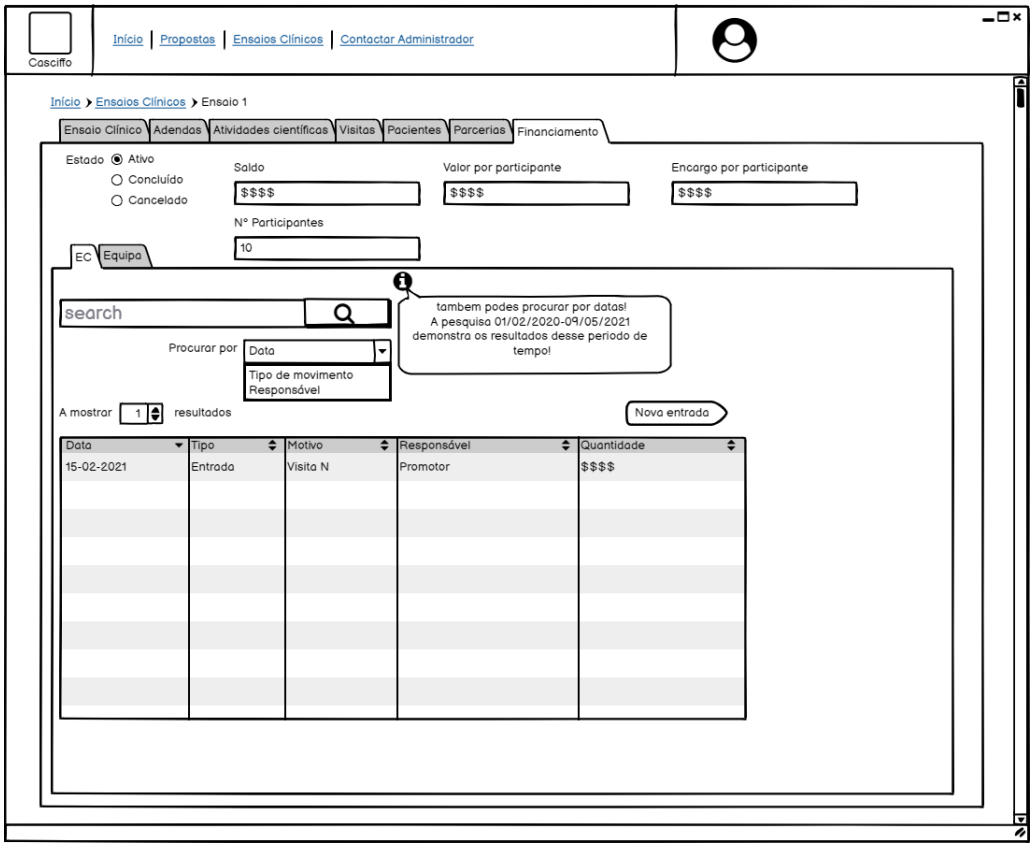

Figure 2.17: Mock detailed view of the income flow made in the investigation

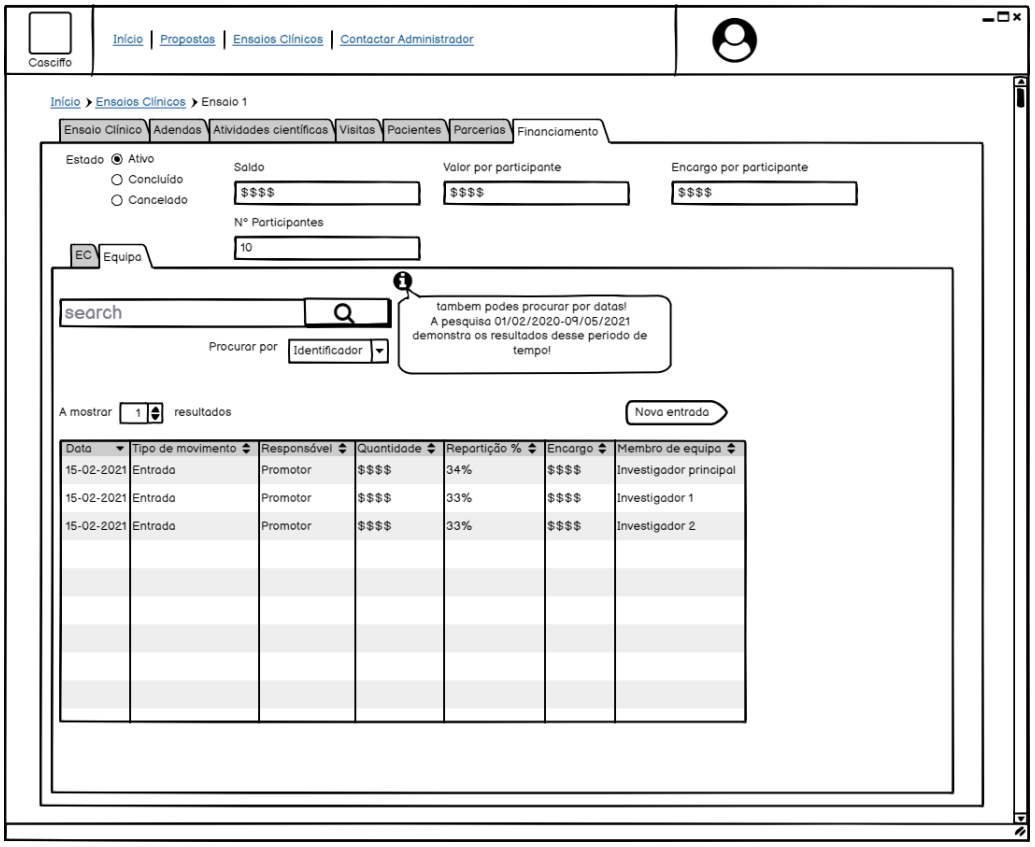

Figure 2.18: Mock detailed view of income flow divided by the investigator team

2.5.12 Monitoring of visits & Recording of adverse events associated with patients due to the trial drug.

The monitoring of visits during a clinical trial can be tracked and viewed under the tab "Visitas" existing in the detailed screen of a clinical trial. In this setting, any investigator associated to the clinical trial is able to view and track the past and scheduled visits made by the team. However, only the investigators associated to a visit are able to manipulate them. When creating a visit, that visit will automatically be associated to its creator, giving also the option to associate other investigators to the same visit, allowing them to freely edit the visit details. Along with this option, the investigator is required to fill in the fields depicted in fig 2.19. These fields are as follows: the periodicity ("Períodicidade") that can be turned ON in case the visit is a reoccurring one with the ability to schedule at a custom interval in days; the type of visit ("Tipo de visita"), that has three possible inputs, Screening, indicating the first visit, Monitoring ("Monitorização") indicating a motoring visit and finally a Closeout visit, which indicates the final visit done to a participant. In case the visit is periodic the field of end date ("Data fim") becomes mandatory to fill.

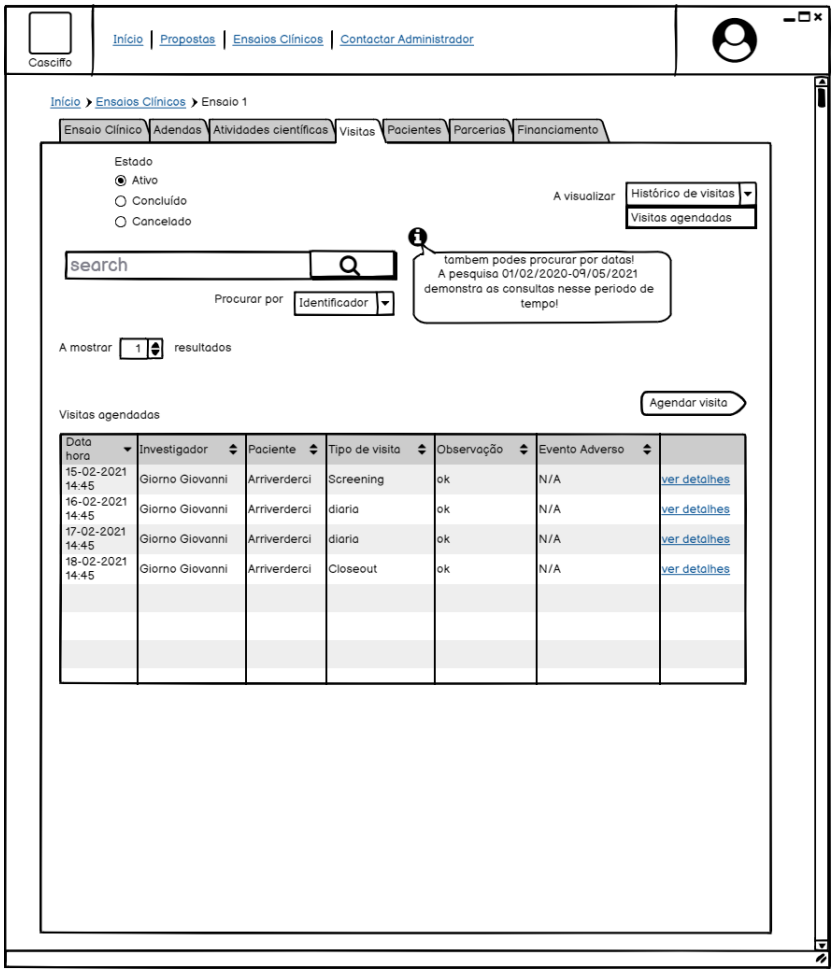

Figure 2.19: Mock overview of visits scheduled in the clinical trial

When a visit occurs, the associated investigators are given access to the observations ("Observações") field and adverse event ("Evento adverso") warning. In

addition to this, the field "Marcar presença" is now available to mark attendance.

Bibliography

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Webografia

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