University of Dublin

TRINITY COLLEGE

Investigation into ICT support for clinical trial enrolment of patients with Motor Neuron Disease

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B.A.(Mod.) Computer Science and Business

Final Year Project

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Declaration

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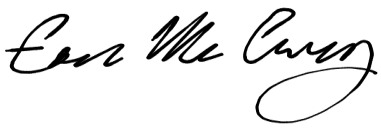
Signed:  Date: _____

Abstract

Motor Neuron Disease (MND) is a progressive neurological condition that attacks the motor neurons, or nerves, in the brain and spinal cord. It is a designated rare disease and currently lacks a cure. Many challenges face MND researchers. These challenges range from the treatment and analysis of patients due to geographic disparity, the disease's heterogenic onset which is complemented by its heterogeneity in progression to the collaborative research challenges embodied by the syntactic, semantic, pragmatic and organisational interoperability problems that pervade the domain.

ADAPT is an SFI funded research centre. The ADAPT MND team are undertaking a project focused on providing a solution to overcome the domain's pervasive interoperability problems. To overcome interoperability challenges, the team are exploring data models and collating MND data to provide an ontology for a semantic web based solution. Research collaboration between ADAPT and another SFI funded centre, FutureNeuro aims to apply semantic web, AI and machine learning data driven solutions to support research into MND.

To contribute to the work of ADAPT, this project focuses on two data sets i.e. patient data and clinical trial data. The project explores the data requirements and existing challenges in order to contribute to an ICT solution that supports the enrolment of patients in MND clinical trials. The enrolment phase of clinical trials is critical to the statistical significance in the trial's outcomes. The nature of the disease coupled with interoperability issues creates many obstacles to MND clinical trial enrolment. To overcome these obstacles a clear set of data requirements is needed for future development of MND enrolment ICT solutions. This project presents the methodology, design decisions and documents the implementation of the final prototype's functionality and user interface. The metadata chosen and functionality implemented were validated by MND clinical professionals and the ADAPT MND team and will contribute to the creation of the MND ontology.

Acknowledgements

I would firstly like to thank my supervisor, Ms. Gaye Stephens, whose expertise was invaluable throughout every aspect of the project. Your feedback, in-depth discussions and support pushed me to develop and improve my academic and technical skills. I feel so fortunate and incredibly grateful to have had your guidance during such a challenging project and academic year.

I would also like to thank every member of the ADAPT MND team for giving me the opportunity to learn from them and improve my project and domain knowledge through many discussions and their amazing feedback.

In addition, I would like to thank my parents for their support and encouragement throughout the project. I am also grateful to my brother, family and friends for providing much needed distractions and extra motivation throughout the writing of this report and the development of the web application.

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Abbreviations

MND	Motor neuron disease
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale - Revised
CDISC	Clinical Data Interchange Standards Consortium

Terminology

Enrolment	The process of entering a patient into a clinical trial
Vital Capacity	The maximum amount of air a person can expel from the lungs after a maximum inhalation
Site of Onset	Location on the body where symptoms of the disease are initially observed
Diagnosis	Type of MND
King's College Staging	Staging system for ALS to map disease progression
El Escorial	A criteria used for the diagnosis of ALS
EudraCTR	European clinical trials register
Clinical Trials.gov	US clinical trials register
Eligibility criteria	Requirements that must be met for a patient to be included in a trial
Inclusion criteria	Specified characteristics that must be met for study entry
Exclusions criteria	Specified characteristics that disqualify patients from entry in the study
Clinical trial investigator	An individual who conducts a clinical investigation. In the event an investigation is conducted by a team of individuals, the investigator is the leader of the team.
Data model	An abstract model that organises elements of data and standardises how they relate to one another and to the properties of real-world entities
Interoperability	The ability of computer systems or programs to exchange information

1. Introduction

This project involves the investigation of MND patient data items, clinical trial data items and functionality required to create a web application that supports the enrolment of MND patients in clinical trials. The project was carried out in collaboration with the ADAPT MND team that are currently developing an AI and machine learning data driven solution to support research into MND. The web application was built using the CodeIgniter web development framework and MySQL database technology. The data values used to test the web application were synthetic and based on discussions with the ADAPT MND team.

This project report outlines the approach adopted, the technologies employed and the explorative research that was carried out to achieve the objectives of the project. It will then describe the web application's development decisions from the user interface, to the functional and non-functional requirements, and also the database's design. Following the development decisions, the implementation and resultant application will be examined through the web pages, components and query functions. In closing, the project's evaluation and concluding remarks will be discussed.

1.1 Motivation

The main factors that motivated the author to undertake this project are outlined below.

1.1.1 **Personal Motivation**

The personal motivation for being involved in this project came from understanding the importance of clinical trials on healthcare and an interest in developing web development skills. Firstly, the COVID-19 pandemic highlighted the importance of clinical trials as finding an effective vaccine was still ongoing and had been at the forefront of pandemic conversation and public debate. The fact that Motor Neuron Disease (MND) is a disease that currently has no cure also provided motivation as I was interested to understand what prevents more successful research and cure discovery from taking place. This motivation relates to seeing family members who have been affected by diseases which currently have no cure. While carrying out this project, a member of my family died from dementia. Dementia is a disease that affects more people than MND and is not a rare disease but is currently incurable and no treatment can stop its progression. Based on my exposure to and understanding of diseases, I felt that investigating how ICT can be leveraged as a support for helping clinical trials in any way is a hugely interesting and important domain to explore.

I was also interested in developing and improving my technical skills. I had previous experience as an intern in a multi-national insurance company where I worked on the backend of their resource management software. From that experience it was evident how powerful and essential ICT systems are to the decision making and the management of employee workflow. Working on a project that could provide some similar capabilities and potentially afford similar benefits to healthcare researchers was a key motivator. The project was also an opportunity to develop more comprehensive web development skills in a way I have never done before in terms of both database design and query handling and user interface design.

1.1.2 **Research Motivation**

There were two main research motivations with this project. The first was developing and gaining experience using interdisciplinary skills that would help me become a more rounded researcher and thinker. This project provided an opportunity to collaborate with information engineers and clinical researchers within a complex domain. This would allow me improve my T-shaped skills (Brown et al. 2015) which are essential for the career path I have chosen to pursue and necessary for the modern ICT landscape. The experience I gained on this project and developing these interdisciplinary skills will support my career to go in many different directions.

The ADAPT MND team is developing an AI and machine learning data driven solution to support research into MND. Some ADAPT researchers are focusing their research to overcome the interoperability problem. This interoperability problem is prevalent in a lot of healthcare research and many domains outside of healthcare. Even with a $27 billion stimulus bill, President Barack Obama was unable to overcome the hurdles of interoperability during his time in office (Kliff 2017). So the opportunity to learn from the ADAPT MND team's approach and their collaborative working methods towards solving this problem seemed invaluable to me.

1.2 Objectives

To clarify the aims and objectives of this project the author iteratively created and refined a research canvas which was agreed with the project supervisor. Figure 1.2 below outlines the final refined canvas of agreed upon aims, objectives and summarised approach of the project.

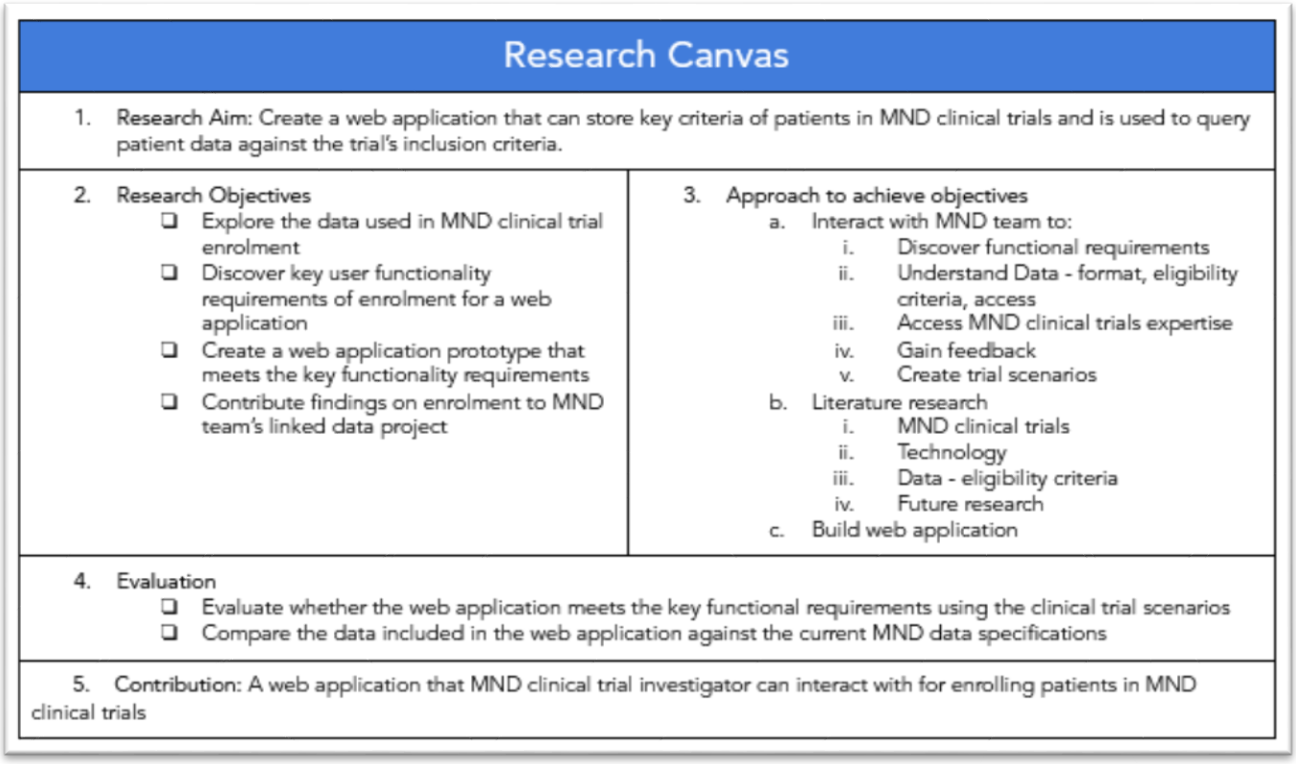

Figure 1.1 Research Canvas 1

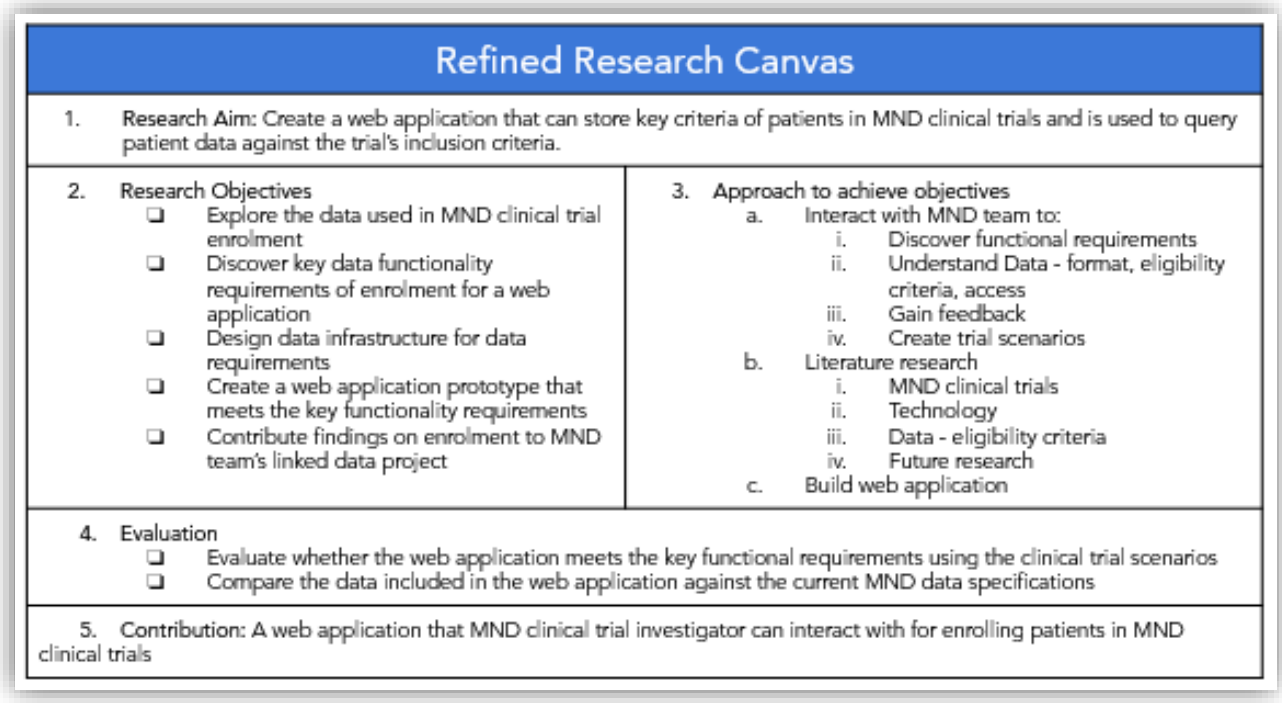

Figure 1.2 Refined Research canvas

The refined research canvas gives an overview of the projects main aim which was to explore the data requirements for MND clinical trial enrolment through the creation of an artefact that can capture patient

data items for MND clinical trials and capture clinical trial inclusion criteria to then match patients to MND clinical trials.

To fulfil the primary aim of the project, five research objectives were outlined.

1. To explore the data used in MND clinical trial enrolment
2. To discover key data functionality requirements of enrolment for a web application
3. To design data infrastructure for data requirements
4. To create a web application prototype that meets the key functionality requirements
5. To contribute findings on enrolment to ADAPT MND team's linked data project

The third objective was added during the research of the project where non-functional requirements like extensibility and flexibility were highlighted which required designing the database to cater for future data extensions as MND research is constantly leading to data being revised or updated.

1.3 Project Methodology

1.3.1 Participatory Design Approach

The design of the web application used a participatory design process where MND team members and my supervisor participated in highlighting the needs of potential users, proposed application features and helped with evaluation. This approach was necessary due to the specialised domain knowledge required to satisfy user functionality and data requirements.

Specifically, this approach enabled the learning required for an interdisciplinary project and the development of T-shaped skills that allowed the author to gain the depth of knowledge needed to execute a project in new domain. Figure 1.1 shows the co-creative and journey to constructive dialogue and deeper understanding of a different discipline. The participatory approach emphasis the co-creative and dialogue driven implementation for the project and supports a design science research method.

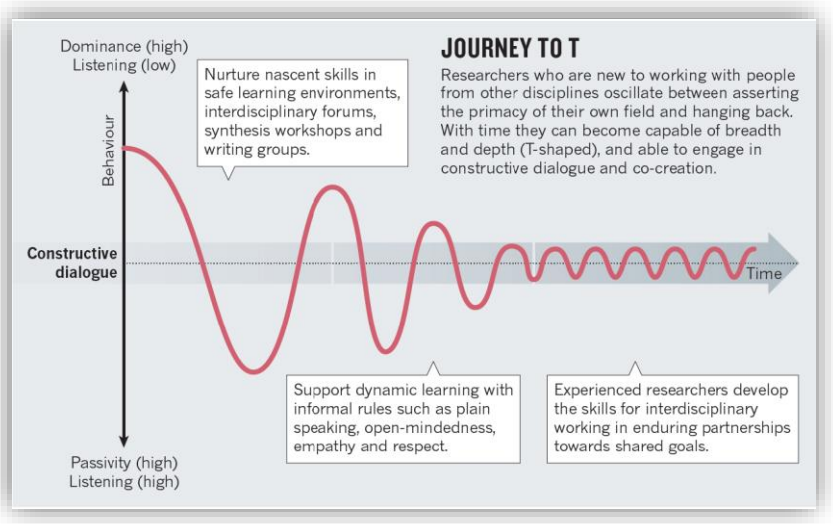

Figure 1.3 Journey to T (Browne et al. 2015)

1.3.2 **Design Science as an overarching research method**

Table 1. Design-Science Research Guidelines

Guideline	Description
Guideline 1: Design as an Artifact	Design-science research must produce a viable artifact in the form of a construct, a model, a method, or an instantiation.
Guideline 2: Problem Relevance	The objective of design-science research is to develop technology-based solutions to important and relevant business problems.
Guideline 3: Design Evaluation	The utility, quality, and efficacy of a design artifact must be rigorously demonstrated via well-executed evaluation methods.
Guideline 4: Research Contributions	Effective design-science research must provide clear and verifiable contributions in the areas of the design artifact, design foundations, and/or design methodologies.
Guideline 5: Research Rigor	Design-science research relies upon the application of rigorous methods in both the construction and evaluation of the design artifact.
Guideline 6: Design as a Search Process	The search for an effective artifact requires utilizing available means to reach desired ends while satisfying laws in the problem environment.
Guideline 7: Communication of Research	Design-science research must be presented effectively both to technology-oriented as well as management-oriented audiences.

Figure 1.4 Design science research guidelines (Hevner et al. 2004)

Design science refers to extending the boundaries of our capabilities through the creation of "new and innovative artifacts" (Hevner et al. 2004, p.75). Hevner et al. (2004) also highlight that with design science, devising a solution while gaining knowledge and understanding of a problem domain can only be achieved though the development and testing of the created artefact. Therefore, this project used the guidelines of design science as an overarching methodology to investigate and create an ICT support for MND clinical trial enrolment. Some guidelines followed are outlined below:

Guideline 1 was followed by creating a web application that can be used for interrogating data, entering data and querying data against each other.

Guideline 2 was satisfied based on the importance of MND research and the fundamental importance of the enrolment process in contributing to the statistical significance of clinical trial outcomes.

Guideline 5 was followed by employing a participatory design approach where the ADAPT MND team played a significant role in the feedback and reviews of each prototype's data decisions, as well as the functional and non-functional aspects of the artefact.

Guideline 6 was a core feature in the project as thorough data exploration was necessary to find the current standards for MND and clinical trial metadata with its corresponding data values. The exploratory nature of the project was factored into the project's iterative development process by using the spiral software development model which focuses on risk consideration during the planning of each prototype.

1.3.3 Spiral Software Development Model

There were risks to consider throughout development as the project was influenced by exploring data, refining data interactions and site functionality. The risks and continuous refinements based on feedback required using the spiral development model that supports a risk driven cyclic approach where an evolutionary prototyping model was used to support development and feedback within each spiral cycle.

Each cycle consists of identifying objectives, evaluating risks and alternative solutions, developing and taking in feedback followed by planning the next cycle to refine and implement additional features to the web application.

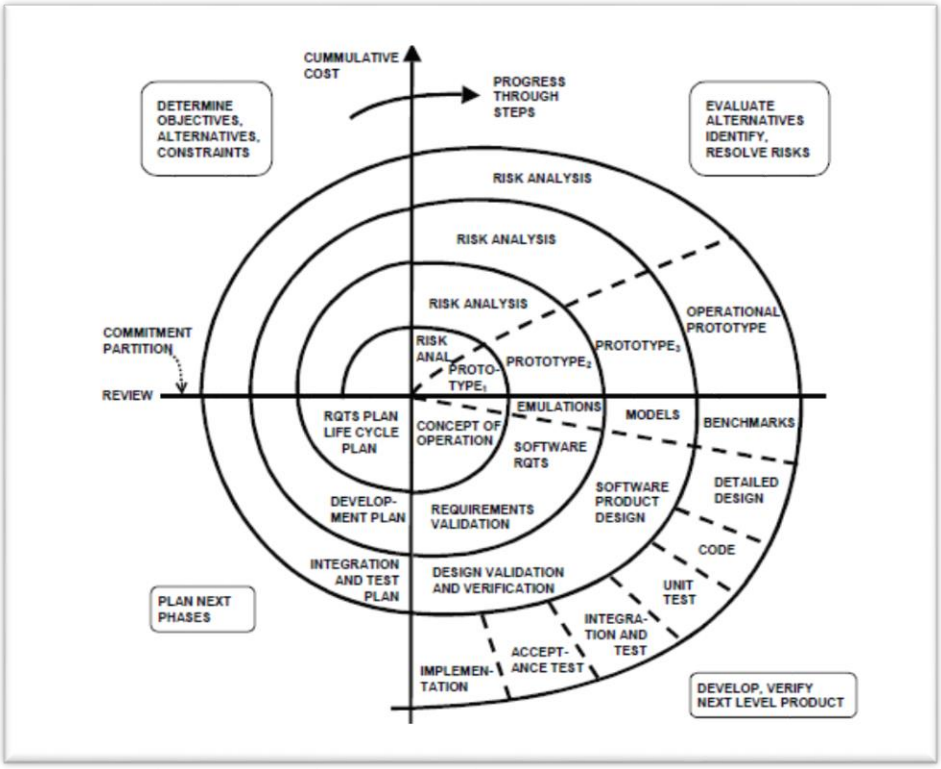

Figure 1.5 Spiral Software Development Model (Boehm 2000)

The approach involved MND team members and my supervisor highlighting the needs of potential users, proposed application features and iteratively evaluating the work. The evaluations involved feedback sessions on many prototypes which were developed to meet the functional and non-functional requirements identified during research and data exploration with the ADAPT MND team. The prototype development was therefore driven by the use case's requirements, domain-specific feedback and background research.

1.4 Report Structure

Chapter 1. Provides an introduction to the aims and objectives of the project and the approach taken to the design and development of the project.

Chapter 2. Provides background research on MND, clinical trials and the technologies used in the website development.

Chapter 3. Describes the design of the system functionality, user interface and database.

Chapter 4. Describes the implementation of the system.

Chapter 5. Provides the evaluation of the project and its limitations.

Chapter 6. Presents the conclusion and highlights future work.

2. Background

This chapter discusses the research and data items that were explored in order to capture the data and functional requirements for the web application's prototype planning, risk assessments and in its validation and testing. The ideas that arose from the research and participation of the ADAPT MND team influenced the technology decisions. These decisions, which are detailed within this chapter, reference the wireframing, web development framework, styling and database technologies utilised to create the web application.

2.1 Spiral Model and Design Science in Research

The design science method and guidelines are characterised by exploring solutions and improving domain knowledge through the creation of an artefact. The artefact for this project was a web application that supports patient enrolment in an MND clinical trial. The creation of the artefact was supported by an iterative risk-based software development model. For this project's iterative risk-based development, the author used the spiral model complemented by an evolutionary prototyping development process. Each spiral centred on planning a prototype and assessing the risks associated with implementing the prototype. In each iteration (spiral), risks referred to the knowledge gaps that the author had to bridge in order to complete the iteration's prototype. This project began with risks relating to a technological learning curve. However, the most significant risk for each iteration was the possibility of not finding, understanding and validating the domain-specific data and functionality requirements. These risks were navigated through consistent dialogue and collaboration with the ADAPT MND team. Feedback and refinements were given on the artefact which directed and improved the project's research and supported the validation of the research. The validated research and the data still to be explored were the basis of the next prototype's plans.

2.2 Research

2.2.1 Motor Neuron Disease

A disease is an abnormal condition that has a specific set of signs and symptoms (Nature 2021). Diseases are caused by either external causes or internal causes. External causes can refer to infections which range from common colds to COVID-19. Internal causes can refer to autoimmune diseases where the immune system is directed at the body's own tissues and consequently damages the tissue (Nature 2021).

In Europe, diseases can be defined as rare when no more than 1 in 2,000 people are affected. There are over 6000 unique rare diseases that collectively affect between 3.5% to 5.9% of the world's population. The definition for rare diseases comes from the European Union Regulation on Orphan Medicinal Products (1999). Orphan medicinal products are designated to medicines that may aid the diagnosis, prevention or treatment of rare diseases (RD) (EMA 2021). The orphan designation also extends to any condition that occur so infrequently that the costs of developing and providing the medicine to patients outweighs the expected sale returns. The European Medicines Agency regulates and incentivises orphan medicines to help overcome the challenges of researching RD. The characteristics of rare diseases engenders the financial and research challenges associated with curing RD.

The common characteristics of rare diseases are (Nguengang Wakap 2020):

- Low prevalence
- Lack of knowledge exists
- Scarcity of expertise
- Chronic, progressive, degenerative and life-threatening
- Heterogeneous in nature
- Geographically disparate

Motor Neuron Disease (MND) is a progressive neurological condition that attacks the motor neurons, or nerves, in the brain and spinal cord (IMNDA 2021). MND is a rare disease. There are five known types of MND listed below (NINDS 2021). MNDs are hereditary but the causes of most MNDs are still unknown. ALS is the most common form of MND.

- Amyotrophic Lateral Sclerosis (ALS)
- Progressive Bulbar Palsy
- Primary Lateral Sclerosis
- Progressive Muscular Atrophy
- Kennedy's Disease

Due to the heterogeneous nature of the onset symptoms and the progression of the disease there is no single test to diagnose MND. MND patients cannot yet receive treatment to cure their MND. Current treatment methods can only offer medication or therapies to help reduce the speed of neurodegeneration. In terms of survival, 70% of patients diagnosed with ALS die within three years of the onset of symptoms and only 10% live more than 5 years (HSE 2021). The specific characteristics of MND added to the characteristics related to rare diseases make discovering a cure and gaining a deeper understanding of the disease challenging for researchers. Technology presents a pathway to

overcome the research challenges that arise from low prevalence. Using technology to enable aggregation of data from many sites means more data becomes accessible to researchers. The data can be used to improve the insights and statistical significance of MND research. However, the lack of standardisation surrounding MND data collection and data storage present challenges to linking remote patient data records together.

2.2.2 **Patient Data**

There are a lot of data requirements associated with the diagnosis, clinical care and study of MND patients. The importance of the data items changes as discoveries are made or different research hypotheses are posed. This is due to the nature of MND. Research aimed at collating the MND patient meta-data in Ireland approximates that 350 data points are captured across 32 data groups (Impey et al. 2019).

The clinical trial enrolment process involves matching some of these data points with the criteria set out in the clinical trials. So, it was necessary to investigate the data in the register and select which items were relevant for the clinical trials recruitment process.

The data table below is the meta-data and corresponding data values that were selected based on discussions with the ADAPT MND team and exploring the MND Register Data Dictionary. The data selection was based on common clinical trial criteria for MND patient enrolment in clinical trials. The sources for researching MND clinical trial criteria were the EU (Eudra) clinical trial register and US clinical trial register (ClinicalTrials.gov). Trials that were studied were selected by their recency to try to ensure that up to date MND terms were considered when the trial's inclusion and exclusion criteria were created in the database.

Table 1 Selection from the MND Register Data Dictionary

SECTION OF REGISTER	VARIABLE NAME (SHOW MODE)	VARIABLE NAME (EXPORTED DATA MODE)	POSSIBLE VALUES
Personal Details	Patient ID	ID	Numerical (four digits)
Personal Details	Sex	Gender	Male, Female
Personal Details	Date of birth	DOB	DD/MM/YYYY

Onset Details	Site of Onset	Site of onset	Bulbar, Spinal, Thoracic/ Respiratory, Cognitive/ Behavioural
Onset Details	Type of MND	Diagnosis	ALS, ALSFTD, PLS, PMA, Kennedys, PBP, Unknown
Onset Details	Phenotype	Phenotype	UMN Predominant ALS, LMN Predominant ALS, Flail Arms, Flail legs, Bulbar, Classical ALS
Onset Details	El Escorial category at diagnosis	El Escorial	Suspected, Possible, Lab Supported Probable, Probable, Definite
Onset Details	Date of Diagnosis	Date of Diagnosis	DD/MM/YYYY
Onset Details	Medical history	Medical History	Alcoholism, Alzheimer's Disease, Autism, Bipolar Disorder, Dementia, Depression, Multiple Scleroisis, Parkinson's Disease, Psychosis, Schizophrenia, Suicide, Other Neurological, Other Neuropsychiatric, IVDA, FTD
Clinic Visits	Vital Capacity	Vital Capacity(%)	Numerical
ALSFRS-R	Total	Total	Numerical
Clinic Visits	Stage (King’s College system)	Stage (King’s College system)	Stage 1: symptom onset (involvement of first region), Stage 2A: diagnosis, Stage2B: involvement of second region, Stage 3: involement of third region, Stage4A: need for gastrostomy, Stage 4B: need for non-invasive ventilation

Medication	Riluzole	Riluzole	Yes / No
Medication	Riluzole Date	Riluzole date	DD/MM/YYYY

Table 2 Selected Patient Data

SELECTION OF PATIENT DATA TAKEN FROM THE LIST ABOVE:
Patient ID
Sex
Date Of Birth
Site Of Onset
Diagnosis
El Escorial
Date Of Diagnosis
Vital Capacity
ALSFRS-R Total
Stage (King's College System)

Vital capacity is described as "the maximum amount of air a person can expel from the lungs after a maximum inhalation" (MND Register Data Dictionary 2021). It is important to note that the MND register does not specify whether their vital capacity value refers to forced vital capacity or slow vital capacity. Even though the two measurements are highly correlated they are not the same. The MND Register and clinic use the sniff nasal inspiratory pressure (SNIP) measure which is a non-invasive test of inspiratory muscle function. This is one of the examples of the semantic interoperability problem that exists in MND research.

ALSFRS Total has been revised and is now known as ALSFRS-R Total. There are sub-scores that are measured to give the ALSFRS-R Total. Those sub-scores were not included in the selection as they were not present as clinical trial criteria in the clinical trials checked within the EU and US clinical trials registers. Phenotype, Medical History, Riluzole and Riluzole date were not included in the final selection as the selected data was deemed sufficient for achieving the objectives of the project.

2.2.3 **Clinical Trials**

Clinical trials refer to tests that study the efficacy, safety and appropriate prescription dosage of specific therapeutic interventions for humans. The participants selected for trial must meet the predetermined eligibility criteria. It is difficult for clinical trials that focus on a rare disease intervention to find a sufficient number of patients that meet the eligibility criteria in a timely manner. This is the case for MND clinical trials.

The low prevalence results in a geographically scattered population of participants that meet a given trial's eligibility criteria. For clinical trial investigators, the scattered population's data is not openly accessible and difficult to quickly interrogate due to variance in meta-data and data storage practices in MND clinics. Impey (2021) describes the MND clinical trial enrolment process in Ireland. Firstly, patient data is captured on paper and then digitally stored in excel spreadsheets. To enrol MND patients in clinical trials these excel spreadsheets are manually checked against the MND trial's criteria. This process is currently very slow, often taking over twenty-four hours, and reliant on the expert knowledge of Professor Orla Hardiman.

MND clinical research is affected by the current pace of patient enrolment in MND clinical trials as many patients once diagnosed with a type of MND have a short life expectancy. A solution to speed up and potentially increase the number of patients enrolling in MND clinical trials would be to connect all the MND patient registers into one database and giving MND researchers a controlled level of access to query this database. To implement and interact with such a system requires overcoming an array of interoperability problems. These problems are described in the next section.

2.2.4 **Interoperability**

According to Maciel et al. (2017) there are four types of interoperability; syntactic, semantic, pragmatic and organisational. MND research experiences semantic interoperability problem where there is a divergence of similar concepts having different definitions or names. MND research also experiences syntactic interoperability problems where no common data model and data storage format is in place. The MND team in Trinity are currently engaging in solving MND interoperability problems by creating a standard data model, ontology and using semantic web technologies.

There are two datasets where interoperability poses a problem for MND clinical trial enrolment. The first is the patient metadata and the second is the clinical trial metadata. The variance in MND patient

metadata across different registers is one of the main challenges in creating interoperable solutions for MND researchers. Work is ongoing across Europe to harmonise this metadata. A similar variance is present in MND clinical trial inclusion and exclusion criteria and in how clinical trials are described. The Eudra (EU) clinical trials register and ClinicalTrials.gov (US) clinical trials register require different information for the descriptions and details of clinical trials. To overcome the potential issues that could result from these variances the World Health organisation (WHO) and CDISC, which is standards development organisation, created a clinical trial registry model that consolidates both the EU and US clinical trial registers differences. See table below with CDISC Clinical Trial Registry Model including mappings to the US and the EU metadata.

Table 3 CDISC Clinical Trial Register Model

TRDS NO.	WHO	EUDRA CT REGISTRY	CLINICALTRIAL. GOV
1	Primary Registry and **Trial Identifying Number**	EudraCT number	ClinicalTrials.gov NCT number
2	Date of Registration in Primary Registry		Study Start Date
3	Secondary Identifying Number	Secondary ID, Secondary ID Type, Secondary ID Issuing Organization	
4	Sources of Monetary or Material Support		
5	Primary Sponsor	Sponsors / monetary_supports	Sponsors/ Collaborators (lead_sponsor)
6	Secondary Sponsor(s)		
7	Contact for Public	Sponsor Contact (Section B of Protocol Spreadsheet)	Recruitment Information, Contacts, Contact
8	Contact for Scientific Queries		
9	**Public Title**	Full Title, Lay Person Title, Abbreviated Title	Brief Title (protocol title intended for the lay public)
10	Scientific Title	Full Title	Official Title
11	Countries of Recruitment	Planned_region	Location_countries

12	Health Condition(s) or Problem(s) Studied	Medical conditions	Conditions or Keywords (using NLM Medical Subject Heading (MeSH) terms)
13	Intervention Name and Intervention Description by arm	Medicinal_product_information / medicinal_product	Intervention Description / Intervention Name
14	Key Inclusion and Exclusion Criteria	Principal Inclusion Criteria, Principal Exclusion Criteria	Eligibility Criteria
15	Study Type (“Interventional” or “Observational”)	Trial Type	Study Type “Interventional”, “Observational”, “Expanded Access” (component of Study Identification)
16	Anticipated or Actual date of enrollment of first participant	Study Start Date, Study End Date	Study Start Date, Study End Date
17	Planned number of participants to be enrolled	Population Planned numbers in member state and in EEA in trial as whole	Study Design / Enrollment
18	Recruitment status of this trial (Pending, Recruiting, Suspended, Complete, Other) per country or worldwide	Not required	Study Status / Overall Recruitment Status (Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, Completed, Suspended, Terminate, Withdrawn
19 **20**	Primary and Secondary Outcome(s): Name of the outcome, metric of method of measurement, timepoint(s) of interest	Primary Endpoint, Endpoint Timepoint	Primary and Secondary Outcome Measures: Title, Time Frame,Description, Safety Issue Indicator

Based on this background research which was conducted by consulting literature and using the participatory design method the following ideas were brought forward to the design phase.

1. The relevant selection of patient metadata from the MND register.
2. The metadata relevant to clinical trials selected from the CDISC standard.
3. A requirement for a flexible and extensible system to support a variety of clinical trials.
4. A requirement for data integrity.
5. A variety of technologies.

2.3 Technology

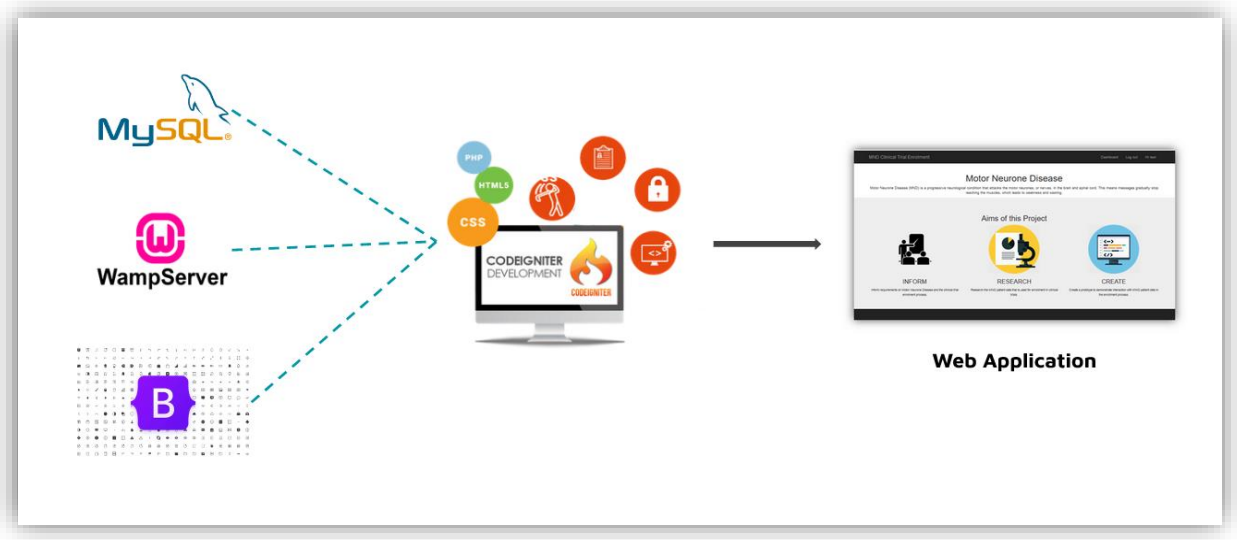

Figure 2.1 Diagram of web application's technologies

2.3.1 **MySQL**

The main focus of this project was an exploration of data requirements. The exploration occurred through the development of a website. The website demonstrated both functional and more importantly the data requirements required for MND clinical trial enrolment supported by ICT. To keep the focus on exploration MySQL was chosen as the author had experience working with SQL queries and databases. This technology decision was suitable and allowed more focus to be placed on the data exploration than on a technology learning curve.

2.3.2 **CodeIgniter Framework**

To create a web application that works well with a MySQL database the scripting language used was PHP. According to G2 (2021), CodeIgniter is the market leader in PHP web development frameworks and therefore was the most suitable web development framework to use with the project's choice of database. CodeIgniter is an open source toolkit for PHP web development licensed under the MIT license. It provides a lightweight package, with small library requirements, rich built-in query handling functionality and strong performance. CodeIgniter adopts the Model View Controller approach but allows flexibility in the structure of the web application's files. The CodeIgniter packages enable simple database configuration, session tracking and form validation. CodeIgniter is also well documented which is essential for developers.

2.3.3 **WAMP server**

WAMP server is a windows web development environment for Apache, MySQL and PHP web applications. It provides easy database management and web application access for MySQL databases through PhpMyAdmin. Due to the author using a Microsoft Windows operating system, as well as the web application being built on top of PHP and a MySQL database, WAMP server was chosen as the local web development server.

2.3.4 **Bootstrap**

Bootstrap is an open source CSS framework that provides CSS templates and user interface components that was first started by Twitter as an internal tool for consistent and responsive front-end web developers. Bootstrap's library allowed the author to create a flatter user-friendly layout and responsive user interface through the use of components like tables, navigation bar, forms, tabs and panels as well as specific form handling classes and input fields. Bootstrap was chosen as the styling library as it supports data table and form components which were the main UI features required for the web application.

2.3.5 **AdobeXD**

AdobeXD is a user experience design tool for web applications and mobile applications. It is the most used prototyping tool by UI professionals and has out-of-the-box features that look similar to real web development library components. For the initial prototyping and wireframing it was important for the author to create a realistic design to work from and progress with into the project implementation and functional prototypes.

3. System Design

This chapter demonstrates how the background research translated into the web application's design considerations and decisions. The design considerations highlighted below range from ethics, initial prototype planning, functional and non-functional requirements, to the user interface design, web application architecture and database design. The metadata selected, the range in data values, and protecting the integrity of that data along with allowing for extensibility and flexibility were the key considerations in the database's design and web application's architecture. The clinical trial enrolment process outlined by Impey (2021) and weekly discussions with the ADAPT MND team helped to define the use case and functionality required of the web application.

3.1 Spiral Model and Design Science in Design

The design science method and guidelines are characterised by exploring solutions and improving domain knowledge through the creation of an artefact. The design of the artefact was supported by an iterative risk-based software development model. For this project, the author used the spiral model complemented by an evolutionary prototyping development process within the boundaries of the spiral model. Each spiral centred on planning a prototype and assessing the risks associated with implementing the prototype. The most significant risk for each iteration was the lack of knowledge on domain-specific data and functionality requirements which became more defined with every iteration. These risks were navigated through consistent dialogue and collaboration with the ADAPT MND team and domain experts. Feedback and refinements were given on each iteration of the artefact which directed and defined the application's design considerations and ultimately the design itself.

3.2 Ethics Canvas

It is important to understand the ethical implications surrounding software development. To do so requires understanding how all the parties are positively and negatively affected both directly and indirectly. This ethical review uses the Ethics Canvas developed by the ADAPT Centre. The ethics canvas was important to consider before the development process. Feedback from the project supervisor and considerations taken from ADAPT MND team members shaped the ethics canvas points detailed below.

This project did not involve human participants. However, I am still morally obliged to conduct my project in an ethical way. This involves giving credit to authors of the literature that were sourced and used within this report and project presentations. It was also important to interpret the explored data

and research in an accurate way, without “falsifying” and “distorting” the original author’s research (British Educational Research Association, 2018, p.33).

<table>
<tr><th>Individuals Affected</th><th>Behaviour</th><th>What can we do?</th><th>World Views</th><th>Groups Affected</th></tr>
<tr><td rowspan="3">MND clinical trial investigators

MND clinic staff

Trinity MND team

MND patients

MND researchers</td><td>Reduce time from 24 hour process to seconds

Less reliant on paper based record keeping</td><td rowspan="3">Ensure GDPR compliant

Ensure conforms with information storage standards for healthcare

Form handling that protects data integrity and consistency

Follow CDISC CTR model

Follow Single Research Document and MND register data mapping</td><td>Change MND clinic outlook on patient data storage

From time-consuming to valuable aspect of their workflow</td><td rowspan="3">Population-based register</td></tr>
<tr><th>Relations</th><th>Group Conflicts</th></tr>
<tr><td>More collaborative matching process

Less reliant on expert knowledge

More clarity in decision making trail for patients and clinical investigator</td><td>MND clinic staff may be reluctant to move away from paper-based administrative practices

Gender categorisation for male/ female data values is resolved with sex data label</td></tr>
<tr><th colspan="2">Product or Service Failure</th><th colspan="3">Problematic Use of Resources</th></tr>
<tr><td colspan="2">Non-compliant with data storage standards

Database security breach in web application

Inconsistent data values and incorrect data labelling with clinical trial and patient data</td><td colspan="3">Additional time, effort and costs in supporting and extending the web applications functionality

Additional time, effort and costs in moving storage and conforming to future developments in MND and clinical trial information models</td></tr>
</table>

Figure 3.3.1 Ethics Canvas for MND Clinical Trial Enrolment web application

3.2.1 **Individual and Groups Affected**

The users will be MND clinical trial investigators. Non-users that are affected; Trinity MND team, MND patients and researchers. In terms of inclusivity, the data collected in the Irish MND register is population-based (Westeneng et al. 2018). In the MND register, male and female meta-data is called gender. To follow the correct identification and use Impey et al.’s (2019) categorisation, the web application uses sex to store male and female data values.

3.2.2 **Behaviour**

The web application would reduce the time it takes clinical trial investigators to check each MND patient’s medical information against the inclusion criteria set for their respective trial. It would also reduce the risk of excluding suitable MND patients in a clinical trial for MND research due to the decentralised and dispersed nature of currently stored MND patient data. Clinical trial investigators

would interact with all their eligibility criteria in one place rather than checking individual medical reports on MND patients. The web application would also provide a clearer decision making trail for investigator to communicate with MND patients or use as basis to carry out further tests to reduce the gaps in the patient's data in the MND register.

3.2.3 **Relations**

Clinical trial investigators may have less reliance on the personnel under them during the enrolment phase. The web application may enable a more collaborative workflow to the matching of patients to clinical trial due to the web application taking less time and affording more people the opportunity to interrogate potential clinical trial patients.

3.2.4 **Worldviews**

The web application could change MND clinical trial investigators' outlook on the record-keeping and matching process from a primarily time-consuming activity to an efficient valuable activity that can help improve the statistical significance of a clinical trial.

3.2.5 **Group Conflicts**

The clinical trial investigators may be resistant to change from a paper-based record keeping format and excel-based manual matching process. There may be initial adoption issues for investigators navigating and using the application.

3.2.6 **Product or Service Failures**

The application would fail if issues arise relating to non-compliance with GDPR and information storage standards for healthcare. A security breach in the web application could compromise the data set, the web server or result in loss of the dataset. Query breaks down due to incorrect data values and inconsistent naming conventions.

3.2.7 **Problematic Use of Resources**

There may be additional time, energy and costs associated with the technical support and further development for the web application. This may result in exceeding current resources and efforts required to carry out MND clinical trials.

3.2.8 **What Can We Do?**

Ensure compliance with GDPR with clear procedures required when interacting with the web app. Consider a cloud web server based on reliability and cost.

3.2.9 **Ethics Summary**

The ethical canvas detailed above outlined the importance of using the correct meta-data while ensuring the integrity of data values for both the performance of the web application's matching functionality and also importance of security of access to the web application's database. Understanding the difficulty for clinic staff in moving from their current behaviours and relations around a paper-based workflow highlights the need for simple navigation within the web application to encourage its adoption.

3.3 Wireframe

Wireframing is a fundamental and primitive prototyping stage that can direct layout of content and webpage functionality while taking the user needs and journey into account. A high-fidelity wireframe (Figure 3.2) was created to help guide and refine the interface layouts to suit the scope and relationships of the web applications functionality.

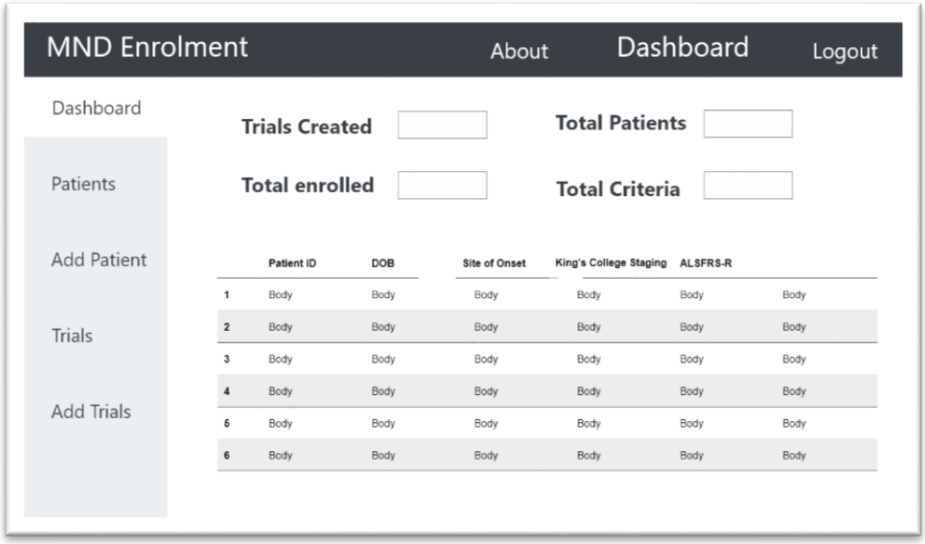

Figure 3.2 High-fidelity wireframe of MND enrolment dashboard made using AdobeXD

The design of the wireframe is based on enterprise resource management applications and modern clinical trial management applications. Experience with a management software platform called

ServiceNow (Figure 3.3 and 3.5) while on an internship in a multi-national insurance company was helpful in structuring the layout and user journey on the web application and also the data entry form layouts. Medidata (Figure 3.4) is one of the best clinical trial management systems according to G2 (2021) was also considered in the wireframe. The focus is on simple, user-friendly navigation and follow a layout that users would find familiar and intuitive.

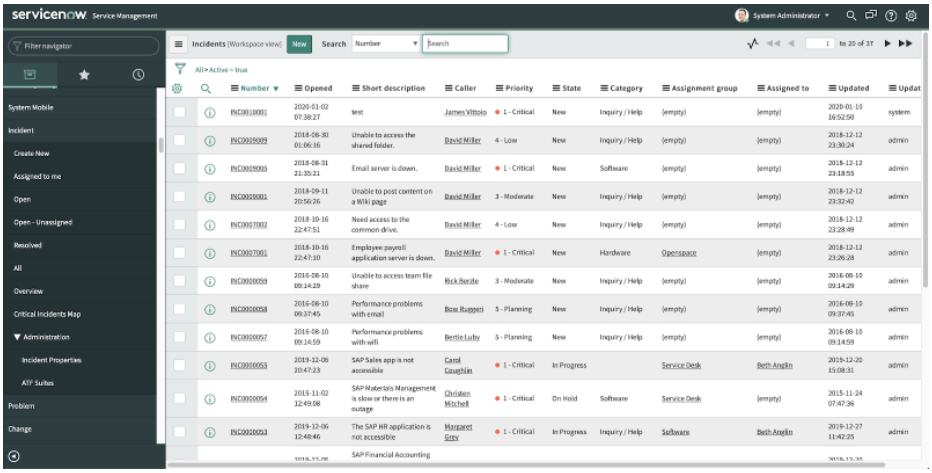

Figure 3.3 Service Now service management platform (Wang, C. 2020)

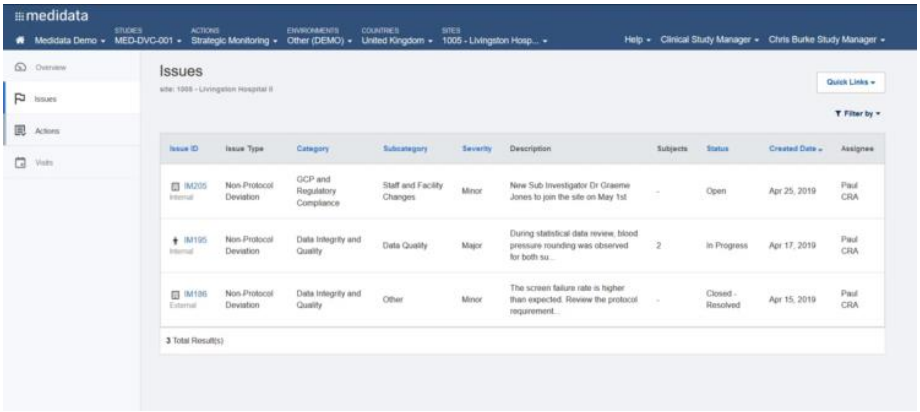

Figure 3.4 Medidata clinical trial management system (Capterra 2021)

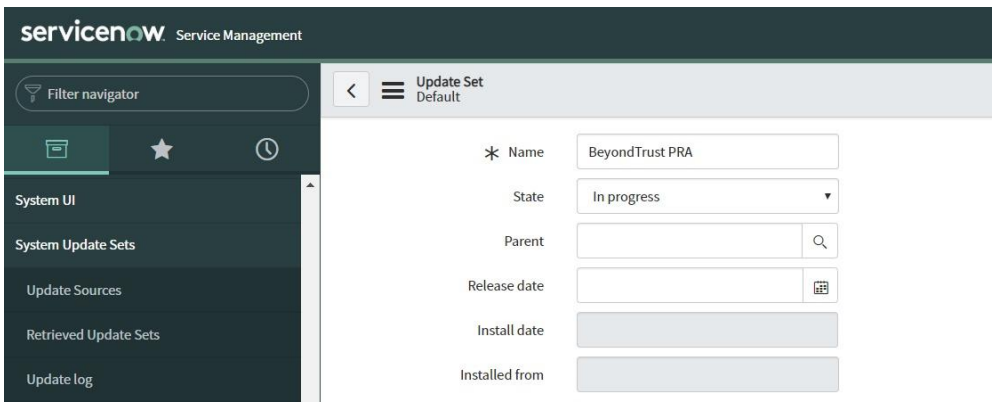

Figure 3.5 Service Now data entry form layout (Beyond Trust 2021)

3.4 Design Requirements

The project's main focus was to provide an MND clinical investigator an application to enter and find patients that would be eligible for their clinical trial.

3.4.1 **Functional requirements**

The functional requirements for the application as agreed with my supervisor, domain experts and ADAPT MND team members:

- Login / logout
- Register
- Home page that explains the uses of the application
- User can add a patient to the application
- User can add a trial to the application
- User can interact with patient data
- User can see patients who meet their trial criteria
- User can update their trial criteria to include more patients
- User can save different versions of their trials on the application

These functional requirements provide essential capabilities that would allow a clinical trial investigator to have patients automatically added to their trial based on the investigator's defined trial eligibility criteria.

3.4.2 **Non-functional requirements**

The non-functional requirements for the application are:

- **Usability**

  The web application needs to provide a clear user journey for navigating and interacting with the application. The functionality should be clear through simple and consistent design layout.

- **Extensibility**

  The project fulfilled key functionality for a use case that requires data model validation. It was important to consider extensibility for changes and additional features to be built on to the application that would cater future data model evolutions that would impact the functionality and data on the application.

- **Performance**

  The web application should provide responsive and easy navigation while also inserting, retrieving, updating, displaying and filtering the data in a quick manner. CodeIgniter framework ensures fast performance and claims to be one of the best performing frameworks available (CodeIgniter 2021).

- **Security**

  It is important for the application to prevent changing and removing of the data within the application as allowing any user registered to use the application could compromise the integrity of the data. Delete or edit functionality of patient data or deletion of trial data was not implemented on the web application to support this non-functional requirement.

- **Flexibility**

  The project focused on a selection of data and not all possible 350 data points recorded in the MND register. Database normalisation was carried out to accommodate further expansions and volume of data that would be added in real-world settings.

- **Data integrity**

  The consistency and accuracy of the data is critical for MND research and for future processing of data. The forms must ensure users insert correct data values under the correct meta-data fields in order to protect the integrity of data for clinical trial investigators.

3.5 Use Case

This section details the MND clinical trial enrolment web application's use case diagram and the use case's textual description.

3.5.1 **Use Case Diagram**

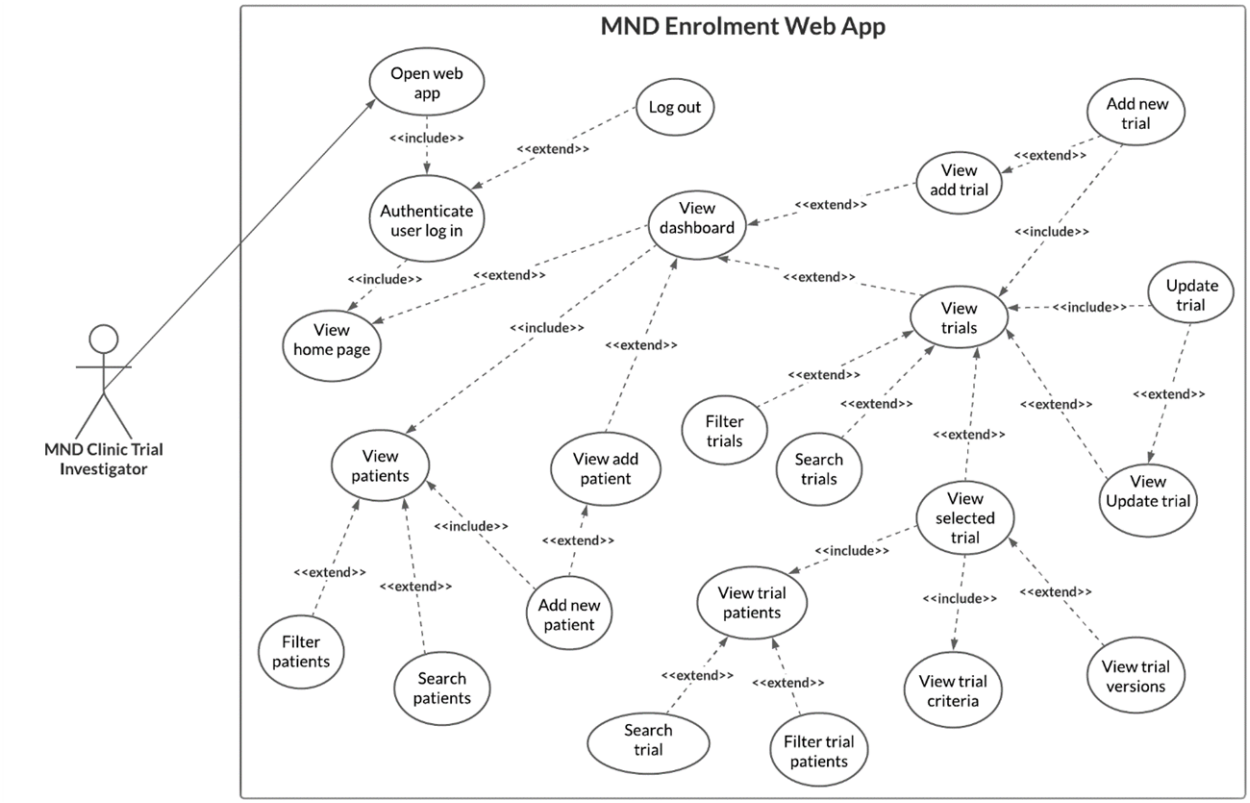

Figure 3.6 Use case diagram for MND clinical trial enrolment web application

The UML use case diagram above describes the scope and relationships of the actor's interactions with the web application. The functionality requirements guided the possible use cases while the use case diagram was extended and refined throughout the spiral development cycles. There is one primary user in the diagram which is a MND clinical trial investigator who would have responsibilities for enrolling patients in a MND clinical trial. To begin using the web application, the user opens the web application and is shown the login page. Once their login username and password are authenticated the user is taken to the home page and can move to the dashboard page or log out from any web page in the web application. The home page use case has the <<include>> tag as it is where the user is always taken upon login authentication.

Opening the dashboard page includes a list of all the patients but also provides the option to go to the patient page, add patient page, trials page and add trial page. From the patient page, the user can interrogate the patient data by filtering or searching through it. In the add patient page, the user can fill out the new patient's information to then add this patient to the database and is taken to the patient page to see the patient has been added successfully. In the trial page, the user can filter or search through the trials that are on the web application, the user can also select a trial to view or update a specific trial. In the selected trial page, the user can view the trial patients and the selected trial's inclusion criteria. While viewing the trial patients from the selected trial page, the user can interrogate the trial patient data. From the view trial page, the user can also update the trial. Once the user inputs the trial details in the form and clicks update, they are taken back to the view trial page.

3.5.2 **Use Case Textual Description**

Table 4 Textual description of use case

Use case title	**MND Clinical Trial Enrolment Web Application**
Actors	MND Clinical Trial Investigator
Preconditions	The user has an authenticated email and password login.
Trigger	The use case is triggered when the user opens the web application.
Description	This use case is an overview of the possible user interactions within the web application. Once the user is logged in, the user is taken to the Home page. From the home page the user can navigate to the Dashboard or Log out. From the dashboard the user can navigate to the Patients page, Add Patient page, Trials page or Add Trial page. From the Trials page, the user can choose to view a selected trial or update a trial. Adding or updating a new trial populates a trial's patient table by checking which patients match the trial's criteria. From the Patients, Trials and selected trial pages the user can interrogate the data using filtering or searching components.
Normal scenario	The user is logged in successfully and uses the web application as needed.
Error scenario	The user cannot log in successfully. In this case they can register a new password for their username.

Conclusion	The use case is completed once the user logs out of the web application.

3.6 Architectural Design

3.6.1 Model View Controller (MVC)

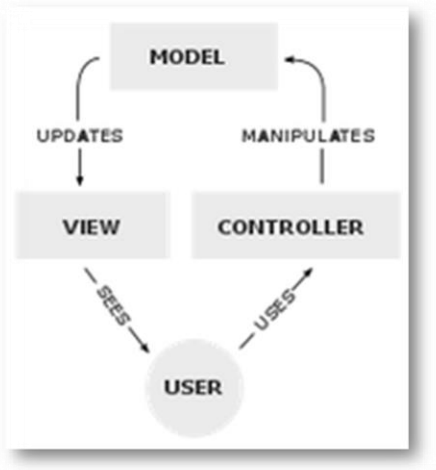

Figure 3.7 Model View Controller software design pattern (Wikipedia 2021)

The software architecture of the web application uses the Model View Controller (MVC) development pattern. This approach separates the presentation and logic of the application. The model represents the data structures that handle the insertion, retrieval and updating of information with the database. The view handles the information that is displayed to the user. The controller is the mediator between the model and view.

CodeIgniter encourages the MVC development architecture to help separate code logic from presentation in a way that provides a lightweight, flexible and high-performing application (CodeIgniter 2021).

3.7 Database Design

Database design involves any process that focuses on the structure of the database that enable the effective management and storage of end-user data (Coronel and Morris 2019). The first step in designing a database requires a data model that outlines the entities, attributes, relationships and constraints (Coronel and Morris 2019). Entity Relationship Modelling was used to provide a graphical representation of the web application's data model. To protect data integrity and make the database more flexible it was crucial to prevent data anomalies and prevent data redundancy. To fulfil this requirement database normalisation was carried out on the web application's database design.

The four stages of database normalisation carried out on the web application's data model are illustrated below. Red text indicates that the values are either primary keys or foreign keys.

3.7.1 First Normal Form

Frist normal form requires atomic valued attributes and for all column names in a single table to be unique.

Trial Details Table
Trial ID
Trial Version
Public Title
Sex
Minimum DOB
Maximum DOB
Site of Onset
Diagnosis
El Escorial
Minimum Date of Diagnosis
Maximum Date of Diagnosis
Minimum Forced Vital Capacity
Maximum Forced Vital Capacity
Minimum ALSFRS-R Total
Maximum ALSFRS-R Total
King's College Stage

Patients Table
Patient ID
Full Name
Sex
Date of Birth
Site of Onset
Diagnosis
El Escorial
Date of Diagnosis
Forced Vital Capacity
ALSFRS-R Total Score
King's College Stage

Trial Patients Table
Trial ID
Trial Version
Patient ID
Full Name
Sex
Date of Birth
Site of Onset

Diagnosis
El Escorial
Date of Diagnosis
Forced Vital Capacity
ALSFRS-R Total Score
King's College Stage

3.7.2 **Second Normal Form**

Second normal form requires the database tables to be in first normal form and to not have partial dependencies. Partial dependency occurs when an attribute is dependent on only a portion of the primary key.

Trial Criteria Table
Trial ID
Trial Version
Criteria ID
Criteria Value

Patient Criteria Table
Patient ID
Criteria ID
Criteria Value

Criteria Table
Criteria ID
Criteria Name

Trial Patients Table
Trial ID
Trial Version
Patient ID
Criteria ID
Criteria Value

Trial Details Table
Trial ID
Trial Version
`Public Title

Patient Table
Patient ID
Full Name

3.7.3 **Third Normal Form**

Third normal form requires the database tables to be in second normal form and also not have any transitive dependencies. Transitive dependencies occur when a non-key column is dependent on another non-key column.

Trial Criteria Table
Trial ID
Trial Version
Criteria ID
Criteria Value

Patient Criteria Table
Patient ID
Criteria ID
Criteria Value

Criteria Table
Criteria ID
Criteria Name

Trial Patients Table
Trial ID
Trial Version
Patient ID

Trial Details Table
Trial ID
Trial Version
`Public Title

Patient Table
Patient ID
Full Name

3.7.4 **Boyce-Codd Normal Form**

Boyce-Codd normal form requires the database to be in third normal form and also not have any non-prime column derive a prime column. The database tables in third normal form already satisfies Boyce-Codd normal form.

3.7.5 **Fourth Normal Form**

Fourth normal form requires the database to be in Boyce-Codd normal form and also not have any multi-valued dependencies. Multi-valued dependencies do not exist in the third normal form of this normalised data model as evident in the Normalised Database's ERD (Figure 3.8).

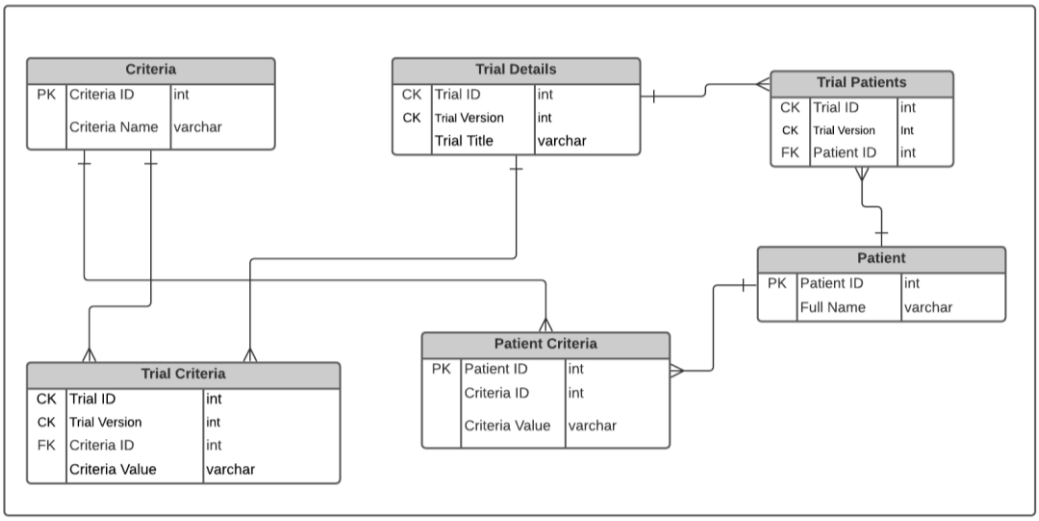

Figure 3.8 Normalised Database Entity Relationship Diagram (ERD)

4. Implementation

This chapter describes the implementation of the design decisions and requirements illustrated above. The final prototype's functionality and site navigation are detailed along with the underlying technological components programmed to produce the MND Clinical Trial Enrolment web application. The web application was developed using the CodeIgniter Framework. The CodeIgniter project was created by installing the CodeIgniter package into the folder that will store all of the web application code files. Next the CodeIgniter folders and files were uploaded to the server. This project's server was a Windows Apache MySQL PHP (WAMP) server that acts as a web development environment for a windows operating system. WAMP server allows local hosting of the web application and database storage. The application is styled using components and grid layouts imported from Bootstrap such as buttons, tables, forms, panels, navigation bar, side bar, dropdown menus, checkboxes and tabs.

4.1 Spiral Model and Design Science in Implementation

As stated previously throughout the report, the design science method and guidelines are characterised by exploring solutions and improving domain knowledge through the creation of an artefact. The implementation of this project's artefact was supported by an iterative risk-based software development model. The iterative risk-based development used was the spiral model complemented by an evolutionary prototyping development process. Each iteration began with planning and assessing the risks associated with prototype implementation. In each iteration (spiral), risks referred to the knowledge gaps that the author had to bridge in order to complete the iteration's prototype. This project's risks revolved around technical aspects with also understanding the domain-specific data and functionality requirements. These risks were navigated through consistent dialogue and collaboration with the ADAPT MND team. Feedback and refinements were given on the artefact which directed and improved the project's implementation and supported the validation of each prototype.

4.2 Final Prototype's Functionality and Technical Implementation

This section of the report describes the current version of the MND Clinical Trial Enrolment web application by describing each web page in detail.

4.2.1 Configuration of Technology Used

To set the default loading configuration for CodeIgniter packages, libraries, drivers, helper files, custom 'config' files, language files and models, the 'autoload' file is altered to suit the requirements of the web application. To create the settings required to access the database, the database file in the 'config'

folder of the application is specified with the database's hostname, username, password, database and database driver. To set the root of the web application, the 'config' file requires the base URL to be specified. The CodeIgniter framework is also based on MVC architecture so the type of files described below follows the expected separation in function between the model, view and controller files.

Table 5 Web Application's Use Cases

Use case No.	Use case name
1	User Login
2	View Home page
3	View Dashboard
4	View Patients
5	View Add Patient
6	View Trials
7	View Add Trials
8	View Selected Trial
9	View Update Trial

4.2.2 **Use Case 1 - User Login**

Use case 1 discusses the implemented functionality on the interface and the underlying technical aspects of the login, log out and register.

4.2.2.1 Login interface functionality

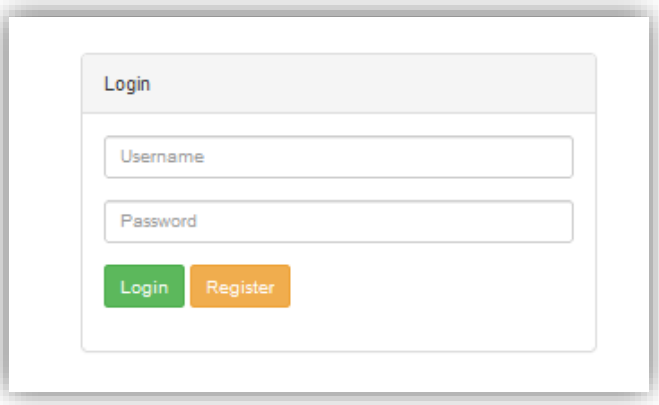

Figure 4.1 Login page user interface

The login page follows conventional UI design for web application login functionality using a simple form layout. The register form is the same with Register labelled in the panel heading of the form. The form prompts the user to enter their username and password by having placeholders within the form's input grids. If the user successfully enters the correct username and password, they are taken to the home page of the web application. If they are unsuccessful, they must re-enter their correct username and password combination or in the current web application, the user is allowed to register under a new username and password. As this was focused on the data and matching of patients without aims of hosting the web application, a fully developed error and two-factor authentication was not required.

4.2.2.2 Log out interface functionality

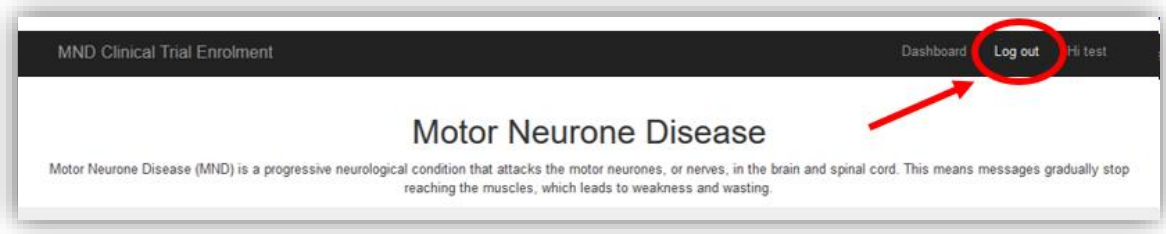

Figure 4.2 Log out user interface

Once logged in, the user can log out from any web page by clicking on log out in the navigation bar. By clicking log out, the user is taken back to the login page.

4.2.2.3 Login technical implementation

The login page consists of a login form and an authentication function to check user's credentials. The view file that creates the user interface components is the 'home.php' file. The login form takes two inputs from the user; a username and password. When the user clicks the login button the login form information is submitted and processed by the login_process() function. This function is called in the controller file named 'Home.php'. The function checks whether the username and password combination exists in the MySQL database 'users' table. The password is decrypted using an md5 function that is included in the CodeIgniter library. If the user submits incorrect details they are not logged in and reverted back to the login page. In the controller file a session value is started when the user is logged in.

4.2.2.4 Register technical implementation

The register page consists of a register form that requires an email, username and password. The view file that creates the user interface components is the 'register.php' file. When the user click the register button the register form information is inserted into the database by the register_process() function in the controller file 'Home.php'. The function encrypts the password using an md5 hash function that is included in the CodeIgniter library. This is processed and redirects the user back to the login page.

4.2.3 **Use Case 2 – View Home Page**

Use case 2 discusses the implemented functionality on the interface and the underlying technical aspects of the home page and navigation bar.

4.2.3.1 View home page interface functionality

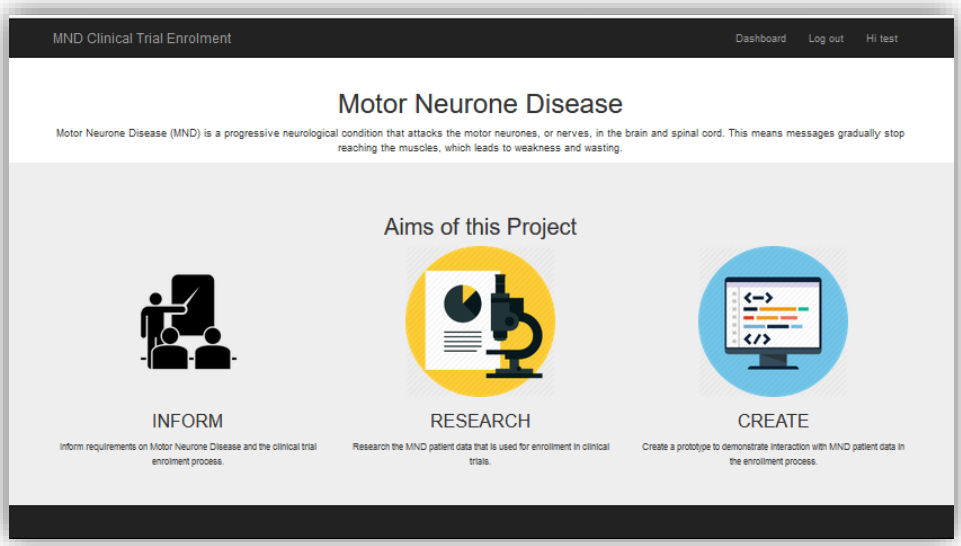

Figure 4.3 Home page user interface

Once the user's login is authenticated, they are brought to the home page. The home page gives a definition of what motor neuron disease is and the purpose for the web applications existence. From the home page the user can navigate to the dashboard page or log out.

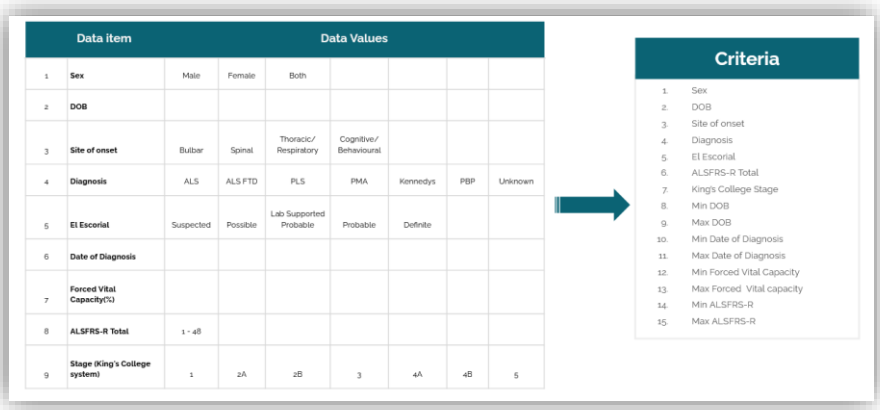

Figure 4.4 Home page user interface

Directly below the aims of the project, the home page has tables that highlight the patient data that can be captured by the web application and provides the array of values available to be entered for each data item. The home page includes how this patient data translates into the trial inclusion criteria a user can use while trying to match and query potential MND patients to enrol in their clinical trial.

CDISC Clinical Trial Register Data Model

TRDS No.	WHO	EudraCT Registry	ClinicalTrial.gov
1	Primary Registry and **Trial Identifying Number**	EudraCT number	ClinicalTrials.gov NCT number
2	Date of Registration in Primary Registry		Study Start Date
3	Secondary Identifying Number	Secondary ID, Secondary ID Type, Secondary ID Issuing Organization	
4	Sources of Monetary or Material Support	Sponsors / monetary_supports	Sponsors/ Collaborators (lead_sponsor)
5	Primary Sponsor		
6	Secondary Sponsor(s)		
7	Contact for Public	Sponsor Contact (Section B of Protocol Spreadsheet)	Recruitment Information, Contacts, Contact
8	Contact for Scientific Queries		
9	Public Title	Full Title, Lay Person Title, Abbreviated Title	Brief Title (protocol title intended for the lay public)
10	Scientific Title	Full Title	Official Title
11	Countries of Recruitment	Planned_region	Location_countries
12	Health Condition(s) or Problem(s) Studied	Medical conditions	Conditions or Keywords (using NLM Medical Subject Heading (MeSH) terms)
13	Intervention Name and Intervention Description by arm	Medicinal_product_information / medicinal_product	Intervention Description / Intervention Name
14	Key Inclusion and Exclusion Criteria	Principal Inclusion Criteria, Principal Exclusion Criteria	Eligibility Criteria
15	Study Type ("Interventional" or "Observational")	Trial Type	Study Type "Interventional", "Observational", "Expanded Access" (component of Study Identification)
16	Anticipated or Actual date of enrollment of first participant	Study Start Date, Study End Date	Study Start Date, Study End Date
17	Planned number of participants to be enrolled	Population Planned numbers in member state and in EEA in trial as whole	Study Design / Enrollment
18	Recruitment status of this trial (**Pending**, **Recruiting**, **Suspended**, **Complete**, **Othe**r) per country or worldwide	Not required	Study Status / Overall Recruitment Status (Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, Completed, Suspended, Terminate, Withdrawn
19	Primary and Secondary Outcome(s): Name of the outcome, metric of method of measurement, timepoint(s) of interest	Primary Endpoint, Endpoint Timepoint	Primary and Secondary Outcome Measures: Title, Time Frame,Description, Safety Issue Indicator

Figure 4.5 Home page user interface

Directly below the MND patient data and trial criteria table on the home page, there is a table that shows the CDISC Clinical Trial Register model that provides a clear mapping for users familiar with either EU or US clinical trial register data models to understand how that translates into the trial entry forms on this web application.

4.2.3.2 View home page technical implementation

The home page is a view file that includes an imported navigation bar view file. A bootstrap container is used for inserting the text that defines motor neuron disease. This is followed by another container that provides the aims of the project with imported image files that were stored in the image folder within the asset folder of the CodeIgniter package. The image of the MND Data and CDISC CTR model are within their own containers and both images were also imported from the image folder. The home page view file also includes a check for the session value to ensure the user is logged in while on the home page. If the session value check in figure 4.6 sees the user is not logged in it will redirect the user back to the login page. This session check is included within every page on the web application.

```php
if ( !$_SESSION['u_name'])
{
  redirect('home', 'refresh');
}
```

Figure 4.6 Session check

4.2.3.3 Navigation bar technical implementation

The navigation bar is created using the bootstrap navbar class in 'nav.php' view file. Within the navbar class, a container that includes the buttons and labels for each web page. The labels are set with a bootstrap toggle feature which highlights them when the user hovers the mouse over the label. Each label contains the corresponding link for routing to the web page the user wants to go to. Each link contains the base URL defined in the 'config.php' file and then has the relevant file path to get to the correct view for the page the user is trying to navigate to. The navigation bar view file does not call the controller files with functions.

```php
<nav class="navbar navbar-inverse">
  <div class="container">

    <!-- Brand and toggle get grouped for better mobile display -->
    <div class="navbar-header">
      <button type="button" class="navbar-toggle collapsed" data-toggle="collapse" data-target="#bs-example-navbar-collapse-1" aria-expanded="false"></button>
      <a class="navbar-brand" href="<?php echo site_url('dash'); ?>">MND Clinical Trial Enrolment</a>
    </div>

    <!-- Collect the nav links, forms, and other content for toggling -->
    <div class="collapse navbar-collapse" id="bs-example-navbar-collapse-1">
      <ul class="nav navbar-nav navbar-right">
        <li><a href="<?php echo site_url('patient/dashboard'); ?>">Dashboard</a></li>
        <li><a href="<?php echo site_url();?>home/logout">Log out</a></li>
        <li><a href="<?php echo site_url('dash'); ?>">Hi <?php echo $_SESSION['u_name']; ?></a>
      </ul>
    </div>

  </div>
</nav>
```

Figure 4.7 nav.php view file

4.2.4 **Use Case 3 – View Dashboard**

Use case 3 discusses the implemented functionality on the interface and the underlying technical aspects of the dashboard page and sidebar.

4.2.4.1 View Dashboard Interface Functionality

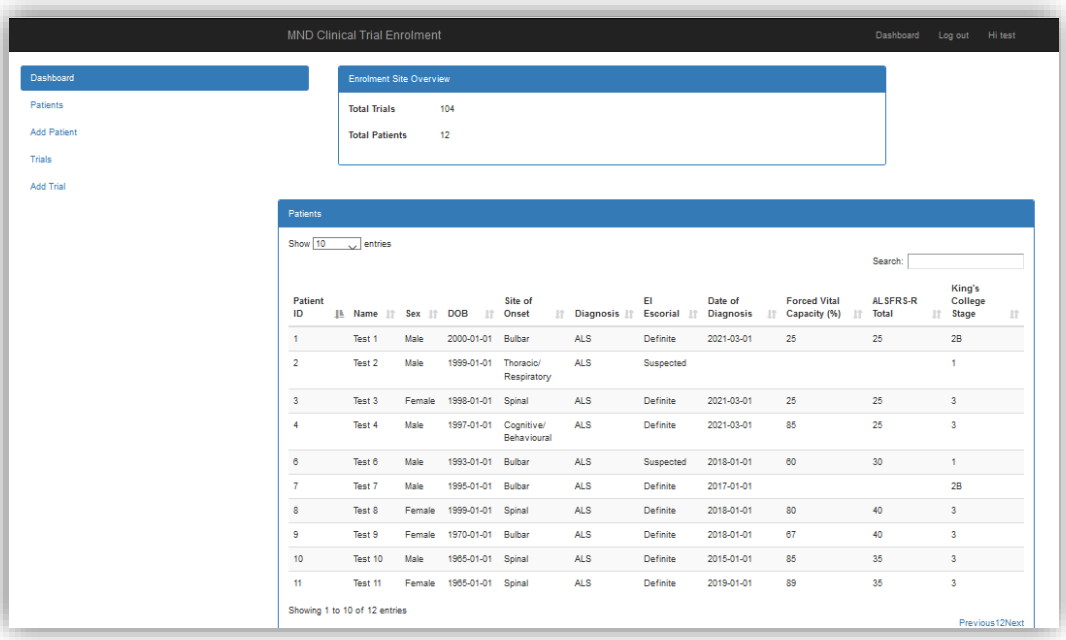

Figure 4.8 Dashboard page user interface

The dashboard page provides an overview of the total patients and total trials on the web application and also displays patient data. The patient data can be interrogated by searching or filtering each column. The patient table by default displays 10 patients at a time and provides pagination to move to the next 10 patients by clicking on the bottom right of the patient table. If the user would rather see more than 10 patients per page, they can decide to display either 25, 50 or 100 patients and also use the pagination where each next page includes the chosen number of patients.

4.2.4.2 View Dashboard Technical Implementation

The dashboard page is a view file that includes an imported navigation bar view file and an imported sidebar view file. The dashboard view file also contains bootstrap components; a panel within a container that provides real-time total number of trials and total number of patients currently stored in the database. To get those totals, CodeIgniter supports quick database query handling for counting all results in a database table. Within the view file PHP script, which is supported by CodeIgniter libraries, is used to directly generate those totals. Figure 4.9 below shows the CodeIgniter $this method which

is used for loading libraries, views or in this case the database to then call a library function that counts all the results in the ‘trial details’ table in the database.

The dashboard also includes a container and panel with a responsive data table component that connects to the patient table in the database. The responsive data table is implemented using an imported jQuery plug in data tables library that is built on top of bootstrap. The jQuery data table plug in provides pagination, multi-column ordering, vertical and horizontal scrolling along with searching functionality. The table is given an ID and is initialised within the dashboard view file.

The patient data is retrieved using the CodeIgniter CI_DB_query_builder get function seen in figure 4.10. The results are stored in an array. To display the patient data, the array is looped through using a PHP for each loop. Firstly, the patient ID and full name are taken from the patient table in the database. Then using the for each loop for each patient ID in the patient table, a get where function is called to the ‘Patients criteria’ table to get all the criteria ID and criteria values for each patient ID. These results then populate the responsive data table.

```
<?php echo $this->db->count_all_results('trial_details'); ?>
```

Figure 4.9 CodeIgniter PHP count all results function

```
<?php
$patient_list = $this->db->get('patient');
foreach ($patient_list->result() as $patient)
{?>
  <tr>
  <td><?php echo  $patient->patient_id; ?></td>
  <td><?php echo  $patient->full_name; ?></td>
```

Figure 4.10 CodeIgniter get function and for each loop

4.2.4.3 Sidebar Technical Implementation

The sidebar is created using the bootstrap nav-stacked class in ‘sidebar.php’ view file. Within the nav class, a container that includes the buttons and labels for each web page. The labels are set with a bootstrap nav-pills component which highlights them when the user hovers the mouse over the label. Each label contains the corresponding link for routing to the web page the user wants to go to. Each link contains the base URL defined in the ‘config.php’ file and then has the relevant file path

to get to the correct view for the page the user is trying to navigate to. The sidebar view file does not call the controller files with functions.

4.2.5 Use Case 4 - View Patients

Use case 4 discusses the implemented functionality on the interface and the underlying technical aspects of the patients page.

4.2.5.1 View Patients Interface Functionality

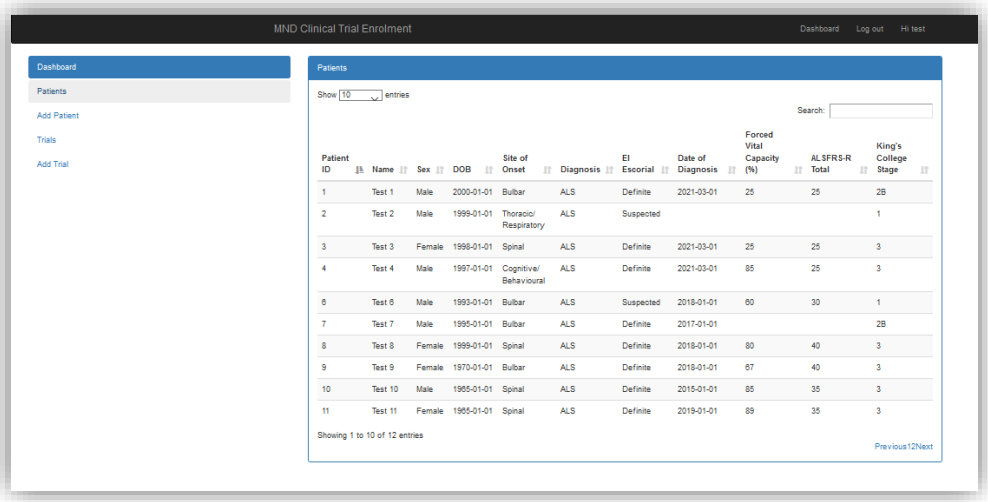

Figure 4.11 Patients page user interface

The user can move to the Patients page from the dashboard. It provides the same responsive data table functionality as the patient table in the dashboard page.

4.2.5.2 View Patients Technical Implementation

The patients page is a view file that includes an imported navigation bar view file and an imported sidebar view file. The patients view file also contains bootstrap components; a panel within a container that includes the same responsive data functionality used in the dashboard page.

4.2.6 Use Case 5 – View Add Patient

Use case 5 discusses the implemented functionality on the interface and the underlying technical aspects of the add patients page.

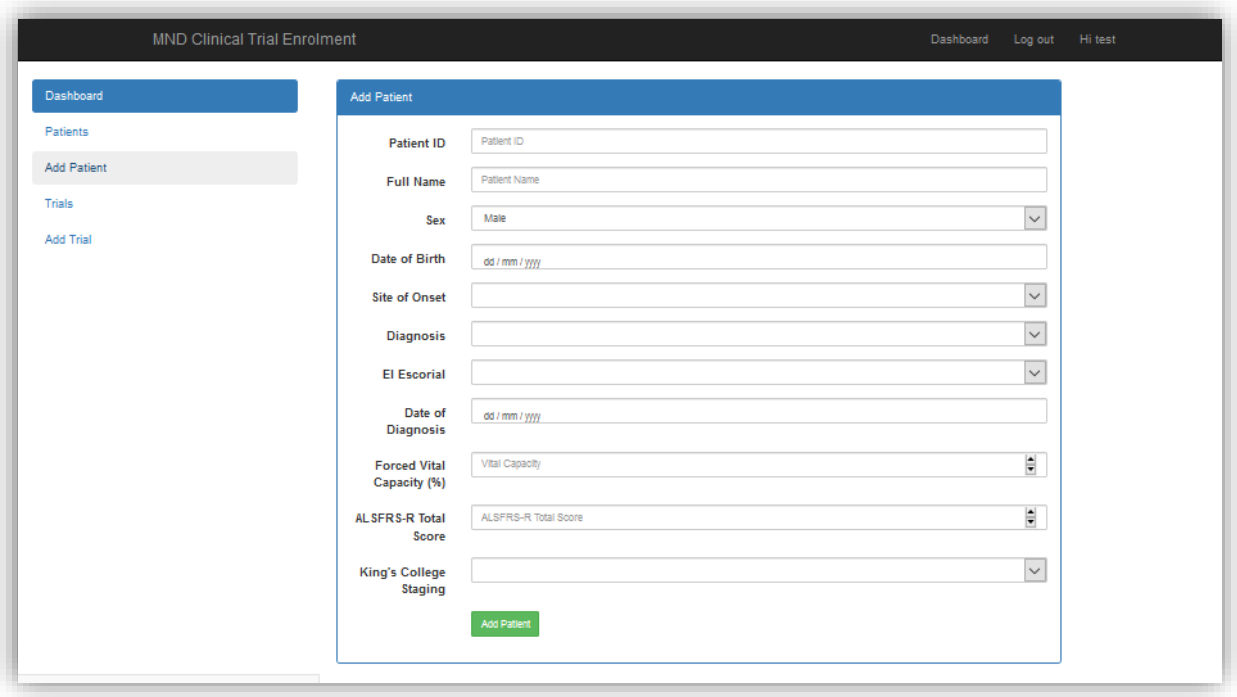

Figure 4.12 Add Patient page user interface

The patients page is a view file that includes an imported navigation bar view file and an imported sidebar view file. The patients view file also contains bootstrap components; a panel within a container that includes the same responsive data functionality used in the dashboard page.

The dropdowns display the possible data value options that accompany each data entry field. The dropdown selection options protect the integrity of data and allow efficient and accurate query handling. The form also prevents inputs that go over the range for Forced Vital Capacity % and also ALSFRS-R Total Score.

4.2.6.1 View Add Patient Technical Implementation

The add patient page is a view file that includes an imported navigation bar view file and an imported sidebar view file. The add patients view file also contains a bootstrap container and panel with a form made up of form group classes that each have a label and input fields for text inputs and select class for the sex, site of onset, diagnosis, el Escorial and King's College stage. Each form element stores the inputted or selected data value and stores which are sent to the add_patient_process() function in the patient model file. The patient controller file processes the data and then submits it as arrays of patient data to be inserted in the database in the 'Patient_list.php' model file. The insert_patient() function in the 'Patient_list.php' model file adds the patient ID and full name to the patient details table in the database. The insert_patient_criteria() function in the same model file mentioned above, adds the arrays of patient data from sex to King's College Stage as shown in figure 4.14. The add patient page redirects the user to the Patients page once the form is submitted.

```php
<?php
defined('BASEPATH') OR exit('No direct script access allowed');


class Patient_list extends CI_Model
{

  public function insert_patient( $patient_details )
  {
    $this->db->insert('patient', $patient_details);
  }

  public function insert_patient_criteria($p_sex, $p_dob, $p_site_of_onset,  $p_diagnosis, $p_el_escorial, $p_date_of_diagnosis, $p_vital_capacity, $p_alsfrs_score, $p_k_c_stage)
  {
    $this->db->insert('patients_criteria', $p_sex);
    $this->db->insert('patients_criteria', $p_dob);
    $this->db->insert('patients_criteria', $p_site_of_onset);
    $this->db->insert('patients_criteria', $p_diagnosis);
    $this->db->insert('patients_criteria', $p_el_escorial);
    $this->db->insert('patients_criteria', $p_date_of_diagnosis);
    $this->db->insert('patients_criteria', $p_vital_capacity);
    $this->db->insert('patients_criteria', $p_alsfrs_score);
    $this->db->insert('patients_criteria', $p_k_c_stage);
  }
```

Figure 4.14 Patient_list.php model file

4.2.7 **Use Case 6 – View Trials**

Use case 6 discusses the implemented functionality on the interface and the underlying technical aspects of the trials page.

4.2.7.1 View Trials Interface Functionality

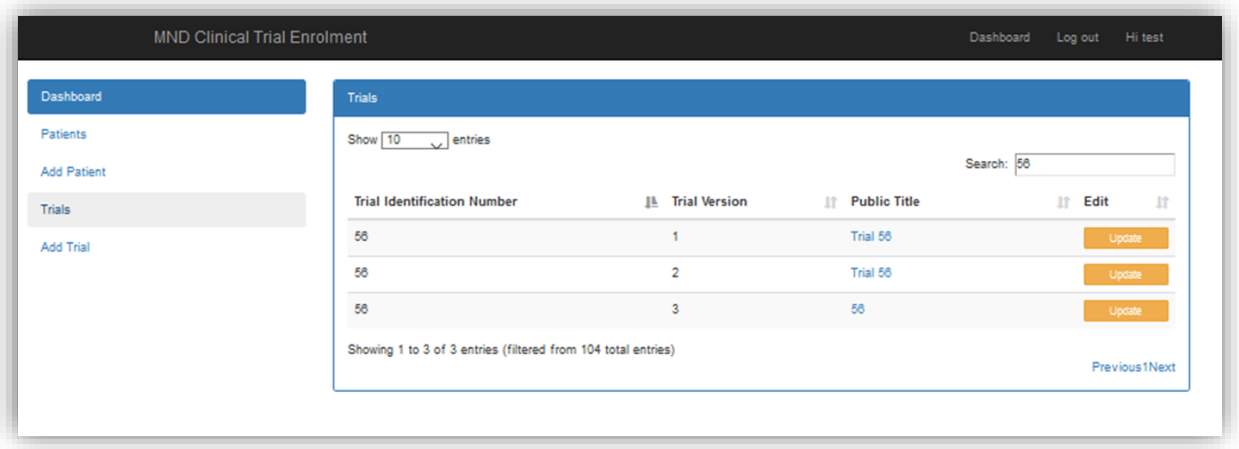

Figure 4.15 Trials page user interface

The trials page includes a data table that allows the user to interrogate the trial data by filtering and searching through the trial id and public title. The data table also has the pagination and default number of trials displayed as the Patients page's data table. The user can also update a trial by clicking on

update. The user can also click on the trial's public title to see that trial's details and criteria as well as the patients who meet that trial's criteria.

4.2.7.2 View Trials Technical Implementation

The trials page is a view file that includes an imported navigation bar view file and an imported sidebar view file. The trials view file also contains bootstrap components; a panel within a container that includes the same responsive data functionality used in the dashboard and patient page. The table displays the trial ID, trial version and public title and also an update button for every trial. If the update button is pressed the user is taken to the Update trial page. If the user clicks on a trial's public title they can view that selected trial's criteria and the patients that matched that criteria. Figure 4.16 shows the constructed link to take a user to a selected trial page or the update trial page. When the public title of a trial is clicked, the view_selected_trial() function in the 'Trials.php' controller file is called which then directs the user to the 'selected_trial.php' view file.

```
<?php
  $trial_list = $this->db->get('trial_details');
  foreach ($trial_list->result() as $trial)
  { ?>
  <tr>
    <td><?php echo $trial->trial_id; ?></td>
    <td><?php echo $trial->trial_version; ?></td>
    <td><a href="<?php echo site_url(); ?>trials/view_selected_trial/<?php echo $trial->trial_id; ?>/<?php echo $trial->trial_version ?>"><?php echo $trial->public_title; ?></a></td>
    <td><a href="<?php echo site_url(); ?>trials/update_trial/<?php echo $trial->trial_id; ?>/<?php echo $trial->trial_version ?>" class="btn btn-warning btn-block btn-xs">Update</a></td>
```

Figure 4.16 Links to navigate to either view a selected trial or update a trial in the Trials view file

4.2.8 Use Case 7 - View Add Trial

Use case 7 discusses the implemented functionality on the interface and the underlying technical aspects of the add trials page.

4.2.8.1 View Add Trial Interface Functionality

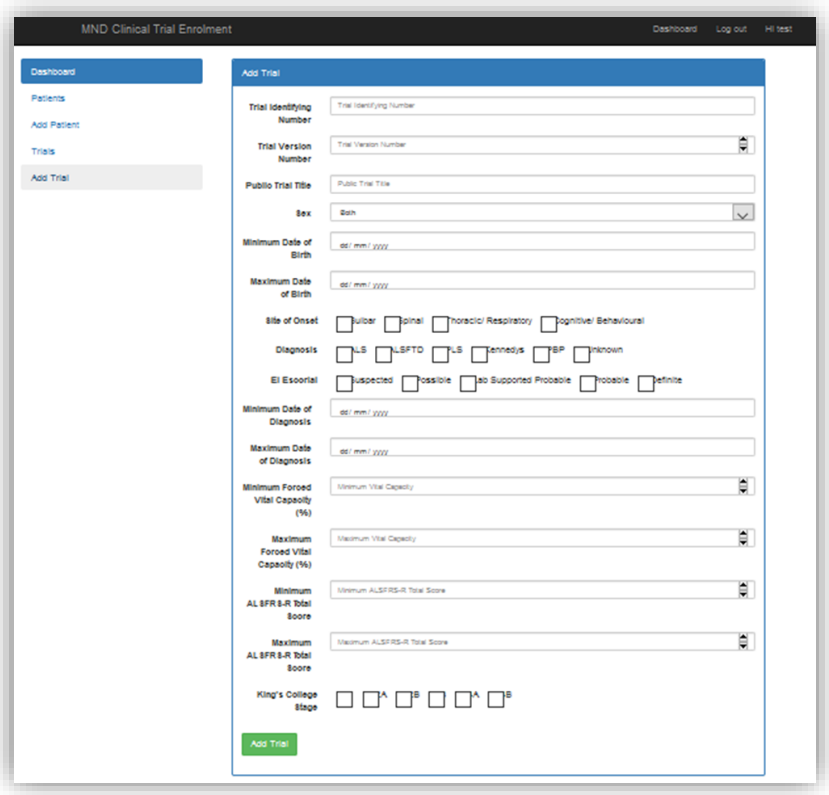

Figure 4.17 Add Trial page user interface

The user can click on multiple Site of Onset, Diagnosis, El Escorial and King's College Stage by clicking on multiple check boxes. Once the user clicks the add trial button, they are taken to the Trials page where they can select their newly added trial.

4.2.8.2 View Add Trial Technical Implementation

The add trial page also include a navigation bar and sidebar. A bootstrap container panel holds the form (Figure 4.17) that takes inputs, selects and checkbox values to populate the database with the entered trial information. There are three different queries being carried out once the trial is added. The trial ID, trial version and public title are added to the trial details table in the database. The specific inclusion criteria are stored in the trial criteria table in the database. There is also a query that checks patients who match the criteria and adds those patient IDs into the trial patients table in the database along with the trial ID of the trial the patient matched. This involves checking each patient's criteria against the corresponding trial criteria. To ensure efficiency in the query, as soon as a patient does not match a criterion, the function moves directly on to the next patient. The use of for each loops and the fact that php returns rows where each data value from the row can be taken without additional loops provides a similar process to a hash table. This significantly reduces the amount of loops required to fulfil the

checking process which helps with the performance of the query. If a patient passes each criteria check, then they are added to the trial patient table in the database. Once the data has been inserted to the respective tables in the database the user is redirected to the Trials page. The controller file that handles these queries is included in Appendix A. This function is included in the report as it was the most important function to enable the matching patients to trial functionality. It is also presented in the report as it could be improved as part of future work to make the matching query more efficient and it was the most technically challenging and incorporated all the domain data items selected for the project.

4.2.9 **Use Case 8 – View Selected Trial**

Use case 8 discusses the implemented functionality on the interface and the underlying technical aspects of the selected trial page.

4.2.9.1 View Selected Trial Interface Functionality

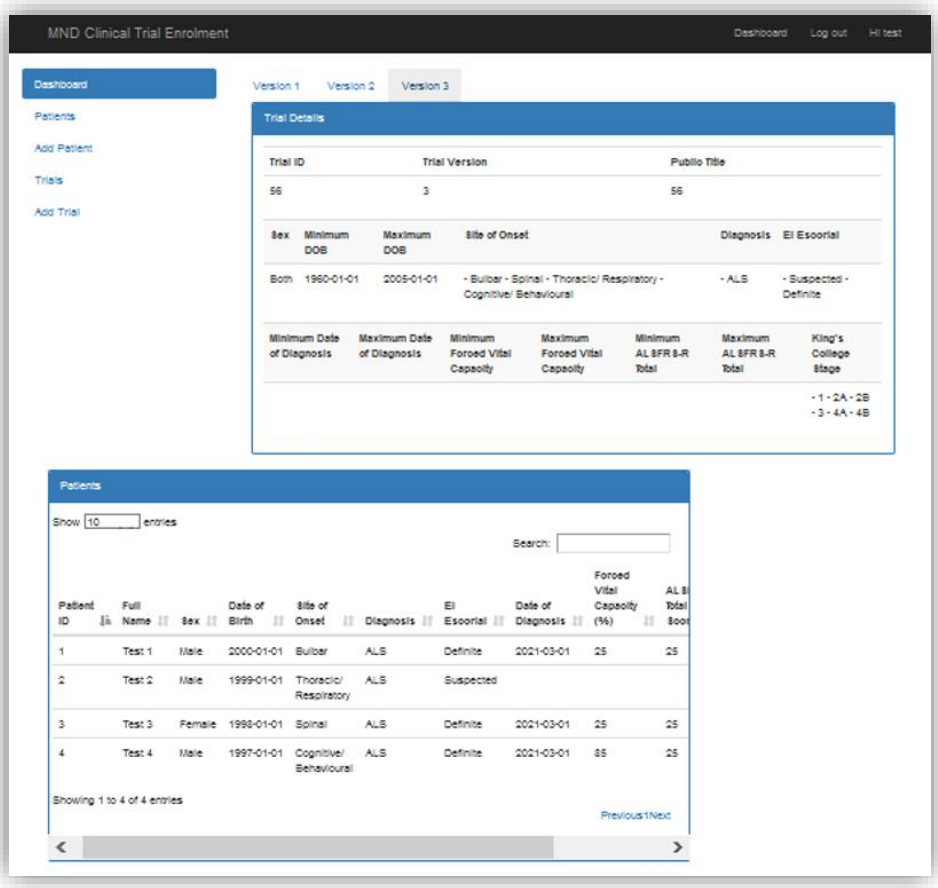

Figure 4.18 Selected Trial page user interface

The user can click between other versions of the trial and also can see the trial details and criteria of the selected version of that clinical trial. For each version there is a 'Trial Patients' data table that provides the same data table interrogation present in the Patients page data table. The Trial Patients data table is labelled as 'Patients' in the container's heading and displays the patients that meet the trial inclusion criteria specified by the user when filling out the add trial or update trial forms.

4.2.9.2 View Selected Trial Technical Implementation

The user navigates to this page by clicking on a trial's public title in the Trials page. The select trial view file includes the navigation bar, sidebar, bootstrap tab components that allow the user to see the version associated with the selected trial's trial id, that trial's details and criteria in a static table within a container as well as a responsive data table in a panel below with the patients who matched the trial criteria.

4.2.10 Use Case 9 – View Update Trial

Use case 9 discusses the implemented functionality on the interface and the underlying technical aspects of the update trial page.

4.2.10.1 View Update Trial Interface Functionality

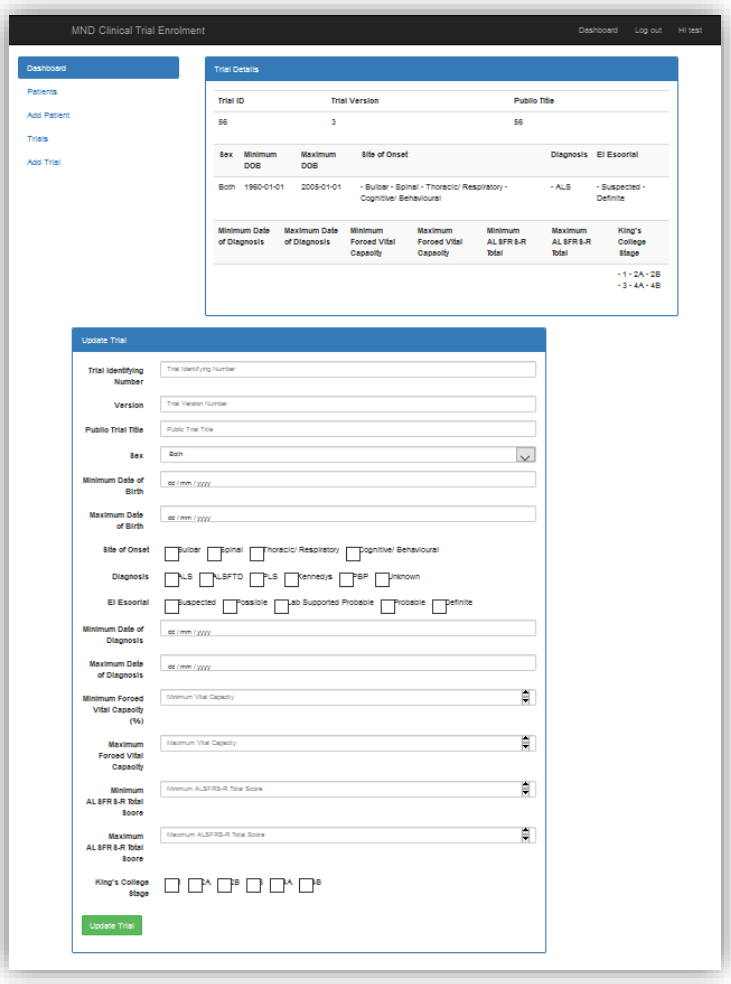

Figure 4.19 Update Trial page user interface

The update trial page displays the previous trial version's trial details and criteria as a reference for the user to fill out the update trial form. Once the user fills in the form and click update trial they are redirected to the Trials page where they can select the new version of their trial.

4.2.10.2 View Update Trial Technical Implementation

The update trial page is a view file that includes an imported navigation bar and sidebar. The update trial page takes the trial ID and trial version to display the criteria from the previous trial version. The previous trial version's criteria are displayed in a static table within a panel. The same form from the add trial page is included in a panel underneath. The queries performed for adding a trial are recycled for performing the update trial form functions.

5. Evaluation

The nature of the project required consistent communication and collaboration with decision making regarding data decisions and the web application's functionalities. Using an evolutionary prototyping process within a spiral development method required feedback for each prototype and considering the implications and risks collectively when planning refinements to implement for the next prototype. This chapter highlights the results, testing, limitations and challenges faced throughout the project and prototype development.

5.1 Results

Through many prototypes a web application was developed that captures patient data and trial criteria to then match patients to the trial based on a function that checks the trial criteria against patient data. Taking a design science approach, by creating a web application artefact while exploring the domain resulted in deeper knowledge of the domain and developing stronger interdisciplinary skills (see figure 5.1). The requirements and approach towards protecting the integrity of data through form handling and following validated data models can be used to inform future MND web applications. The approach to extensibility and flexibility through the database design also highlights the specific needs of the domain in relation to web application development. The database design could be used as a template and extended to provide future web application solutions within the domain. The application and discovery of data models, specifically the CDSIC Clinical Trial Register model, used to support the web application can be applied to also support future web applications in the domain.

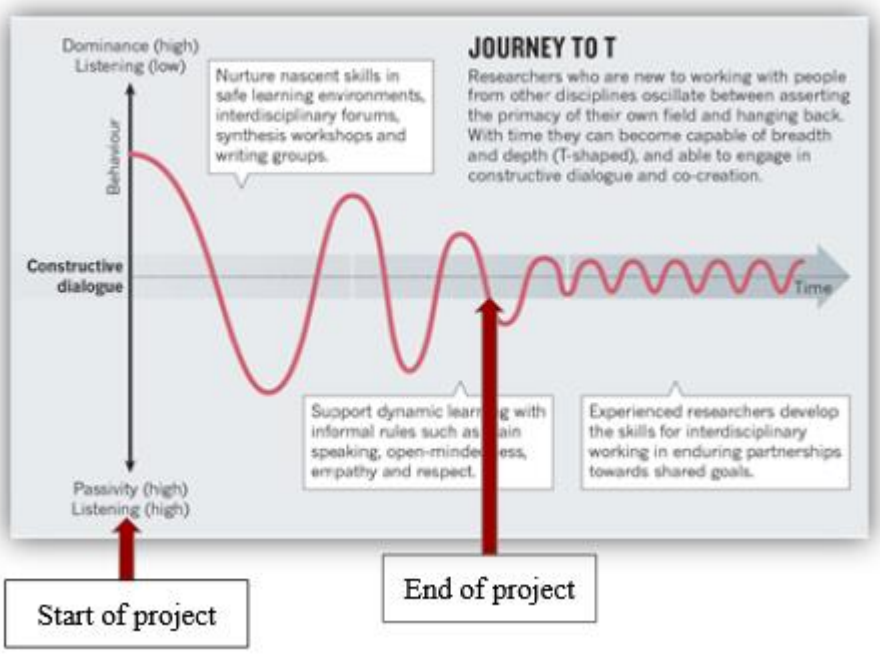

Figure 5.1 Journey to T - development of interdisciplinary skills

5.2 Testing

Each prototype of the web application was demoed and tested to ensure the new functionality and added data worked as expected and outlined before beginning the latest prototype's development. This provided clear suggestions and refinements that were compatible with the current prototype and helped the author correct errors early. Capturing and understanding errors early and quickly enabled the development process to progress as expected and provide the functionality required from the web application.

5.3 Requirements Fulfilment

It is evident from testing and project demonstrations that the web application satisfies all functional and non-functional requirements as described in Section 3.4 above. Potential users can capture patient data, trial data and match patients to clinical trials based on the criteria entered by the user. The user can also interrogate data and update trial versions to refine their clinical trial criteria and also easily understand their patient population.

Table 6 Functional requirements fulfilment

Functional Requirement	Successfully Implemented and Tested
Login/ log out	Yes
Register	Yes
Home page explaining web app	Yes
Add patient	Yes
Add trial	Yes
Interact with patient data	Yes
Match patients to trial	Yes
Update trial criteria	Yes
Trial version control	Yes

Specifically, the non-functional requirements were satisfied during the project implementation and also in demonstration and testing. Using the bootstrap components and responsive grid layouts provides a consistent and

adaptable user interface design that resembles similar software solutions researched and specified in section 3.3. The security of the data is satisfied using an authentication login process and preventing deletion of any data in the front-end of the web application. This security along with the strict form handling ensures correct data value entries in the database and conforms with the standard data models available at the time of project development. The normalisation of the database and the flexibility of the MVC architecture that CodeIgniter allows satisfies the extensibility and flexibility needed in the web application and the database for future MND use cases and data model developments. The performance was satisfied from testing and demonstrating where the responsiveness in form submission and data table interrogation was instant, reliable and accurate. The structure of the database, correct and reliable data value entry, CodeIgniter's query builder library and the author's implementation of the add_trial function enabled strong performance as when testing the application the performance is immediate from the perspective of the user.

Table 7 Non-functional requirements fulfilment

Non-functional Requirement	Successfully Implemented and Tested
Usability	Yes
Extensibility	Yes
Flexibility	Yes
Data integrity	Yes
Security	Yes
Performance	Yes

5.4 Limitations of the Web Application

5.4.1 Amount of data items included

Due to the nature of the disease and domain there is a vast amount of data items that could be included in the web application. For demonstration and exploration of functional requirements the number of data items included was limited. For the web application to be used effectively in a clinical trial it would require more criteria options and need to capture more patient data. Due to a lack in standardised MND patient data models, there would be a limit to the amount of additional data included in the site as the Single Research Document and data dictionary used require validation against other European MND research groups.

5.4.2 **Connecting to MND patient database**

As the current MND patient data is stored in excel format in the MND register there was no database for the web application to connect to and be built around. The synthetic data used to test the web application's functionality were based on the author's knowledge of data values based on research and conversations with the project supervisor and the domain experts who were Sinead Impey and Mark Heverin. As the web application is a standalone artefact with synthetic data it cannot be validated against real Irish MND patient data or be used to interrogate real MND patient data.

5.4.3 **Data visualisation needs for MND clinical trial investigators were not explored**

The web application was built around MND clinic staff who deal primarily with clinic care aspects for MND research. For the web application to fully satisfy the needs of MND clinical trial investigators there would need to be input from investigators who have experience in enrolment of patients in MND clinical trials. The matching patients to trials functionality was the main focus, however additional data analytics and visualisation features may be valuable to clinical trial investigators and were not considered until the project's last prototype review.

5.4.4 **Update patient data**

It was decided that editing of patient data would not be necessary for achieving the objectives of the project and may result in risk to the integrity of the data so the edit patient data functionality was removed after one of the prototype reviews. In real-world use cases, patient data is updated and can change significantly in short periods of time due to severe disease progression. Catering to versions of patient data and controlling who is permitted to edit patient data would be required to guarantee that the patients who met a trial's criteria are the most recent version of data recorded on those patients.

5.5 Challenges Faced

5.5.1 **Understanding the domain of MND and clinical trials**

Prior to the project the author had no experience with any terminology and ICT requirements in the healthcare and clinical research domain. From the outset of the project, many articles and research papers were provided along with guidance on navigating the steep learning curve. My knowledge and understanding on the domain was gained through extensive reading of the articles and papers provided,

researching beyond those articles and also having many conversations and meetings with the ADAPT MND team. It was critical to gain a comprehensive appreciation of the data captured and the processes involved in collecting MND patient data and also enrolling patients in clinical trials in order to gather the appropriate data and functionality requirements.

5.5.2 **Data exploration and decisions**

There is a vast amount of data stored for each MND patient. The MND register data dictionary includes 151 data items and Impey's (2019) Single Research Document includes 350 data points for a single MND patient. It was challenging to thoroughly explore that amount of data and was made even more challenging after realising that there can be variability in the meaning or in some cases the names of meta-data. This variability was evident between the MND register's data dictionary and the Single Research Document. It was also evident in the author's exploration of inclusion and exclusion criteria in EU and US MND clinical trials. This semantic interoperability was the biggest challenge faced during the project. To overcome semantic interoperability a standardised data model is required. Currently no such data model exists for MND. Therefore, data decisions were made based on the guidance of the domain experts Sinead Impey, Mark Heverin, listening to the ADAPT MND team's information engineers and using the meta-data from both the MND register's data dictionary and the Single Research Document.

While exploring clinical trial inclusion and exclusion criteria, the author discovered that there was also differences in how US and EU clinical trial information was captured in their respective clinical trial registers. The CDISC clinical trial register provided a data model that mapped the differences between US and EU clinical trial information models. This model was used to enable both EU and US clinical trials to be entered into the web application.

5.5.3 **Skills gap**

The author had experience using SQL and MySQL databases. However, the author had no experience developing a fully integrated web application. Learning the CodeIgniter framework and PHP was challenging. Following many online tutorials, CodeIgniter's documentation and through exhaustive trial and error, the author was able to implement the required functionality and operations in the front-end and back-end of the application. The skills gained are incredibly valuable for the current employment landscape as the scope of the project provided an interdisciplinary context and information gathering experience as well as learning full web development stack skills that are transferable in any IT focused career path.

6. Conclusion

6.1 Future Work

Even though the objectives of the project were achieved, the project highlighted future work and extensions that can be made to the web application and MND research.

6.1.1 Further explore criteria

For the web application to satisfy all potential MND data criteria it requires expanding the data items stored in the database. This would also require the web application to provide more form options for the user to select criteria without filling out all of the possible MND data criteria in the web application.

6.1.2 Standardised data model for MND patient data

For the web application to overcome potential semantic interoperability around MND patient data, a globally validated MND data model is required.

6.1.3 Connect to a real database

Overcome syntactic interoperability and accessing real patient data is required for this web application to be used by Irish MND researchers to match patients to real MND clinical trials. Currently this matching process is done manually through excel spreadsheets so for the web application to carry out the matching process it needs to access the MND patient register data. The ADAPT MND team are currently working on a project to uplift this excel data and make it openly accessible to MND researchers using the semantic web technologies like RDF databases, SPARQL querying and then building a user interface on top of this technology.

6.1.4 Create access control and permissions protocols

A web application that allows interactions with MND patient data and overseeing clinical trial enrolment will require role assignments and access controls to give certain users restricted permissions for inserting patients or deleting data from the web application.

6.1.5 **Explore data visualisation aspects for MND clinical trial investigators**

Future work should also consider more visualisations that affect the user's workflow or can generate more insights with clinical trial enrolment. One suggestion was a traffic light system that kept track of patient data not yet captured and also features that monitored the patients that match a user's trial criteria in a way that highlights the amount of patients still required to meet the trial's enrolment sample size requirements. This type of system could be displayed in a user's personal dashboard to direct their trial progression and potential gaps in their dataset.

6.1.6 **Explore complementary functionalities**

If the web application was connected to a real MND database, the functionality and database could be extended to provide ways for MND researchers and clinical trial investigators to monitor patients enrolled in clinical trials or track the progression of patients who may become suitable for future MND clinical trials. There are also opportunities to analyse the patient journey by incorporating patient version control similar to the trial criteria versions currently implemented with this project's web application.

6.1.7 **Domain Transferability**

The web application's most complex and primary functionality is in taking trial criteria and matching patients that meet the criteria to that trial. This functionality is transferrable across many domains. Some examples identified include; resource management system that seeks employees that fit specified skill set for projects, consumer relations management software that matches consumers who meet a specified demographic or target market, or used by educational institutions to analyse student populations against specific criteria.

6.2 Concluding Remarks

The overall aim and project objectives were achieved successfully and generated positive feedback. The web application was created to explore the data requirements and challenges in order to contribute to future ICT solutions that support the enrolment of patients in MND clinical trials. The MND and clinical trial register data models explored and used within the web application were validated by the ADAPT MND team and domain experts. The approach to data integrity, web application extensibility and flexibility as well as the discovery and exploration of data models can help inform the development of future web applications within the project's explored domain.

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Appendix A

Appendix A includes the function add_trial() that is in the Trial.php controller file. This function is included in the report as it was the most important function to enable the matching patients to trial functionality. It is also presented in the report as it could be improved as part of future work to make the matching query more efficient and it was the most technically challenging and incorporated all the domain data items selected for the project.

Full source code of the web application files discussed within the report can be viewed through this link:

https://github.com/mccroare/fyp-mnd-enrolment-web-app

```php
public function add_trial()
{
  if ( $this->input->post('add_trial') )
  {
    $trial_id = $this->input->post('trial_id');
    $trial_version = $this->input->post('trial_version');
    $public_title = $this->input->post('public_title');
    $minimum_dob = $this->input->post('minimum_dob');
    $maximum_dob = $this->input->post('maximum_dob');
    $sex = $this->input->post('sex');
    $site_one = $this->input->post('site_one');
    $site_two = $this->input->post('site_two');
    $site_three = $this->input->post('site_three');
    $site_four = $this->input->post('site_four');
    $diagnosis_als = $this->input->post('diagnosis_als');
    $diagnosis_alsftd = $this->input->post('diagnosis_alsftd');
    $diagnosis_pls = $this->input->post('diagnosis_pls');
    $diagnosis_kennedys = $this->input->post('diagnosis_kennedys');
    $diagnosis_pbp = $this->input->post('diagnosis_pbp');
    $diagnosis_unknown = $this->input->post('diagnosis_unknown');
    $el_suspected = $this->input->post('el_suspected');
    $el_possible = $this->input->post('el_possible');
    $el_lab_supported = $this->input->post('el_lab_supported');
    $el_probable = $this->input->post('el_probable');
    $el_definite = $this->input->post('el_definite');
    $min_date_of_diagnosis = $this->input->post('min_date_of_diagnosis');
    $max_date_of_diagnosis = $this->input->post('max_date_of_diagnosis');
    $min_vital_capacity = $this->input->post('min_vital_capacity');
    $max_vital_capacity = $this->input->post('max_vital_capacity');
    $min_alsfrs_score = $this->input->post('min_alsfrs_score');
    $max_alsfrs_score = $this->input->post('max_alsfrs_score');
    $k_c_one = $this->input->post('k_c_one');
    $k_c_two_a = $this->input->post('k_c_two_a');
    $k_c_two_b = $this->input->post('k_c_two_b');
    $k_c_three = $this->input->post('k_c_three');
    $k_c_four_a = $this->input->post('k_c_four_a');
    $k_c_four_b = $this->input->post('k_c_four_b');

    $trial_details = array(
      'trial_id' => $trial_id,
      'trial_version' => $trial_version,
      'public_title' => $public_title
    );

    $this->Clinical_Trials->add_trial($trial_details);

    $trial_criteria = array(
      'trial_id' => $trial_id,
      'trial_version' => $trial_version,
      'criteria_id' => 1,
      'criteria_value' => $sex
    );

    // Min DOB
    $trial_criteria_min_dob = array(
      'trial_id' => $trial_id,
      'trial_version' => $trial_version,
      'criteria_id' => 10,
      'criteria_value' => $minimum_dob
    );

    // Max DOB
    $trial_criteria_max_dob = array(
      'trial_id' => $trial_id,
      'trial_version' => $trial_version,
      'criteria_id' => 11,
      'criteria_value' => $maximum_dob
    );
```

```
92
93          $this->Clinical_Trials->add_trial_criteria($trial_criteria, $trial_criteria_min_dob, $trial_criteria_max_dob);
94
95          // Site of Onset
96          if($site_one == "Bulbar"){
97            $trial_site_one = array(
98              'trial_id' => $trial_id,
99              'trial_version' => $trial_version,
100             'criteria_id' => '3',
101             'criteria_value' => $site_one
102           );
103           $this->Clinical_Trials->add_trial_kc($trial_site_one);
104         }
105
106         if($site_two == "Spinal"){
107           $trial_site_two = array(
108             'trial_id' => $trial_id,
109             'trial_version' => $trial_version,
110             'criteria_id' => '3',
111             'criteria_value' => $site_two
112           );
113           $this->Clinical_Trials->add_trial_kc($trial_site_two);
114         }
115
116         if($site_three == "Thoracic/ Respiratory"){
117           $trial_site_three = array(
118             'trial_id' => $trial_id,
119             'trial_version' => $trial_version,
120             'criteria_id' => '3',
121             'criteria_value' => $site_three
122           );
123           $this->Clinical_Trials->add_trial_kc($trial_site_three);
124         }
125
126         if($site_four == "Cognitive/ Behavioural"){
127           $trial_site_four = array(
128             'trial_id' => $trial_id,
129             'trial_version' => $trial_version,
130             'criteria_id' => '3',
131             'criteria_value' => $site_four
132           );
133           $this->Clinical_Trials->add_trial_kc($trial_site_four);
134         }
135
136         // Diagnosis
137         if($diagnosis_als == "ALS"){
138           $trial_diagnosis = array(
139             'trial_id' => $trial_id,
140             'trial_version' => $trial_version,
141             'criteria_id' => '4',
142             'criteria_value' => $diagnosis_als
143           );
144           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
145         }
146
147         if($diagnosis_alsftd == "ALSFTD"){
148           $trial_diagnosis = array(
149             'trial_id' => $trial_id,
150             'trial_version' => $trial_version,
151             'criteria_id' => '4',
152             'criteria_value' => $diagnosis_alsftd
153           );
154           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
155         }
```

```
156
157         if($diagnosis_pls == "PLS"){
158           $trial_diagnosis = array(
159             'trial_id' => $trial_id,
160             'trial_version' => $trial_version,
161             'criteria_id' => '4',
162             'criteria_value' => $diagnosis_pls
163           );
164           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
165         }
166
167         if($diagnosis_kennedys == "Kennedys"){
168           $trial_diagnosis = array(
169             'trial_id' => $trial_id,
170             'trial_version' => $trial_version,
171             'criteria_id' => '4',
172             'criteria_value' => $diagnosis_kennedys
173           );
174           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
175         }
176
177         if($diagnosis_pbp == "PBP"){
178           $trial_diagnosis = array(
179             'trial_id' => $trial_id,
180             'trial_version' => $trial_version,
181             'criteria_id' => '4',
182             'criteria_value' => $diagnosis_pbp
183           );
184           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
185         }
186
187         if($diagnosis_unknown == "Unknown"){
188           $trial_diagnosis = array(
189             'trial_id' => $trial_id,
190             'trial_version' => $trial_version,
191             'criteria_id' => '4',
192             'criteria_value' => $diagnosis_unknown
193           );
194           $this->Clinical_Trials->add_trial_kc($trial_diagnosis);
195         }
196
197         // El Escorial
198         if($el_suspected == "Suspected"){
199           $trial_el = array(
200             'trial_id' => $trial_id,
201             'trial_version' => $trial_version,
202             'criteria_id' => '5',
203             'criteria_value' => $el_suspected
204           );
205           $this->Clinical_Trials->add_trial_kc($trial_el);
206         }
207
208         if($el_possible == "Possible"){
209           $trial_el = array(
210             'trial_id' => $trial_id,
211             'trial_version' => $trial_version,
212             'criteria_id' => '5',
213             'criteria_value' => $el_possible
214           );
215           $this->Clinical_Trials->add_trial_kc($trial_el);
216         }
217
218         if($el_lab_supported == "Lab Supported Probable"){
219           $trial_el = array(
220             'trial_id' => $trial_id,
221             'trial_version' => $trial_version,
222             'criteria_id' => '5',
223             'criteria_value' => $el_lab_supported
```

```
        );
        $this->Clinical_Trials->add_trial_kc($trial_el);
      }

      if($el_probable == "Probable"){
        $trial_el = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '5',
          'criteria_value' => $el_probable
        );
        $this->Clinical_Trials->add_trial_kc($trial_el);
      }

      if($el_definite == "Definite"){
        $trial_el = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '5',
          'criteria_value' => $el_definite
        );
        $this->Clinical_Trials->add_trial_kc($trial_el);
      }

      // Min Date of Diagnosis
      if($min_date_of_diagnosis != ""){
        $trial_dod = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '12',
          'criteria_value' => $min_date_of_diagnosis
        );
        $this->Clinical_Trials->add_trial_kc($trial_dod);
      }

      // Max Date of Diagnosis
      if($max_date_of_diagnosis != ""){
        $trial_dod = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '13',
          'criteria_value' => $max_date_of_diagnosis
        );
        $this->Clinical_Trials->add_trial_kc($trial_dod);
      }

      // Min Vital Capacity
      if($min_vital_capacity != ""){
        $trial_v_c = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '14',
          'criteria_value' => $min_vital_capacity
        );
        $this->Clinical_Trials->add_trial_kc($trial_v_c);
      }

      // Max Vital Capacity
      if($max_vital_capacity != ""){
        $trial_v_c = array(
          'trial_id' => $trial_id,
          'trial_version' => $trial_version,
          'criteria_id' => '15',
          'criteria_value' => $max_vital_capacity
        );
        $this->Clinical_Trials->add_trial_kc($trial_v_c);
      }
```

```
291
292         // Min ALSFRS-R Total
293         if($min_alsfrs_score != ""){
294           $trial_als_score = array(
295             'trial_id' => $trial_id,
296             'trial_version' => $trial_version,
297             'criteria_id' => '16',
298             'criteria_value' => $min_alsfrs_score
299           );
300           $this->Clinical_Trials->add_trial_kc($trial_als_score);
301         }
302
303
304         // Max ALSFRS-R Total
305         if($max_alsfrs_score != ""){
306           $trial_als_score = array(
307             'trial_id' => $trial_id,
308             'trial_version' => $trial_version,
309             'criteria_id' => '17',
310             'criteria_value' => $max_alsfrs_score
311           );
312           $this->Clinical_Trials->add_trial_kc($trial_als_score);
313         }
314
315
316         // King's College Staging
317         if($k_c_one == "1"){
318           $trial_k_c_one = array(
319             'trial_id' => $trial_id,
320             'trial_version' => $trial_version,
321             'criteria_id' => '9',
322             'criteria_value' => $k_c_one
323           );
324           $this->Clinical_Trials->add_trial_kc($trial_k_c_one);
325         }
326
327         if($k_c_two_a == "24"){
328           $trial_k_c_two_a = array(
329             'trial_id' => $trial_id,
330             'trial_version' => $trial_version,
331             'criteria_id' => '9',
332             'criteria_value' => $k_c_two_a
333           );
334           $this->Clinical_Trials->add_trial_kc($trial_k_c_two_a);
335         }
336
337         if($k_c_two_b == "28"){
338           $trial_k_c_two_b = array(
339             'trial_id' => $trial_id,
340             'trial_version' => $trial_version,
341             'criteria_id' => '9',
342             'criteria_value' => $k_c_two_b
343           );
344           $this->Clinical_Trials->add_trial_kc($trial_k_c_two_b);
345         }
346
347         if($k_c_three == "3"){
348           $trial_k_c_three = array(
349             'trial_id' => $trial_id,
350             'trial_version' => $trial_version,
351             'criteria_id' => '9',
352             'criteria_value' => $k_c_three
353           );
354           $this->Clinical_Trials->add_trial_kc($trial_k_c_three);
355         }
356
```

```
        if($k_c_four_a == "4A"){
          $trial_k_c_four_a = array(
            'trial_id' => $trial_id,
            'trial_version' => $trial_version,
            'criteria_id' => '9',
            'criteria_value' => $k_c_four_a
          );
          $this->Clinical_Trials->add_trial_kc($trial_k_c_four_a);
        }

        if($k_c_four_b == "4B"){
          $trial_k_c_four_b = array(
            'trial_id' => $trial_id,
            'trial_version' => $trial_version,
            'criteria_id' => '9',
            'criteria_value' => $k_c_four_b
          );
          $this->Clinical_Trials->add_trial_kc($trial_k_c_four_b);
        }


        $trial_criteria = $this->db->get_where('trial_criteria', array('trial_id' => $trial_id, 'trial_version'  => $trial_version));
        $false_id_array = array();
        $match = "True";
        $count = "0";
        $p_id = "0";
        $patient_details = $this->db->get('patient');
        foreach($patient_details->result() as $patient)
        {
          echo print_r($patient);
          $criteria_count = 0;
          $check_count = 0;
          $match = "True";
          $p_id = $patient->patient_id;
          $p_c = $this->db->get_where('patients_criteria', array('patient_id' => $p_id));
          foreach($p_c->result() as $p)
          {
            //echo $p->criteria_value;
            $criteria_count++;
          }
          foreach($p_c->result() as $p)
          {

            $check_count++;
            if($check_count != ($criteria_count+1))
            {

              foreach($trial_criteria->result() as $trial)
              {
                foreach($false_id_array as $false)
                {
                  if($p_id == $false)
                  {
                    $match = "False";
                  }
                }
                if($match == "True")
                {
                  // CHECK sex, site of onset, diagnosis, el,escorial, kings college stage
                  if($p->criteria_id == $trial->criteria_id)
                  {
                    // CHECK SEX
                    if($p->criteria_id == "1")
                    {
                      $match = "False";
                      if($trial->criteria_value == $p->criteria_value)
                      {
                        $match = "True";
                      }
```

```
                if($trial->criteria_value == "Both" and $p->criteria_value == "Male")
                {
                  $match = "True";
                }
                if($trial->criteria_value == "Both" and $p->criteria_value == "Female")
                {
                  $match = "True";
                }
                if($match == "False")
                {
                    array_push($false_id_array, $p_id);
                }
            }

            // CHECK SITE OF ONSET
            if($p->criteria_id == "3")
            {
                $site_array = array();
                foreach($trial_criteria->result() as $t)
                {
                    if($t->criteria_id == "3")
                    {
                        array_push($site_array, $t->criteria_value);
                    }
                }
                $true_count = 0;
                foreach($site_array as $site_value)
                {
                    if($p->criteria_value == $site_value)
                    {
                        $true_count++;
                    }
                }
                if($true_count != 0)
                {
                  $match = "True";
                }
                else
                {
                    array_push($false_id_array, $p_id);
                }
            }


            // CHECK DIAGNOSIS
            if($p->criteria_id == "4")
            {
                $diagnosis_array = array();
                foreach($trial_criteria->result() as $t)
                {
                    if($t->criteria_id == "4")
                    {
                        array_push($diagnosis_array, $t->criteria_value);
                    }
                }
                $true_count = 0;
                foreach($diagnosis_array as $diagnosis_value)
                {
                    //echo $diagnosis_value;
                    if($p->criteria_value == $diagnosis_value)
                    {
                        $true_count++;
                    }
                }
                if($true_count != 0)
                {
                  $match = "True";
                }
```

```
                    else
                    {
                        array_push($false_id_array, $p_id);
                    }
                }

                // CHECK EL ESCORIAL
                if($p->criteria_id == "5")
                {
                    $el_array = array();
                    foreach($trial_criteria->result() as $t)
                    {
                        if($t->criteria_id == "5")
                        {
                            array_push($el_array, $t->criteria_value);
                        }
                    }
                    $true_count = 0;
                    foreach($el_array as $el_value)
                    {
                        if($p->criteria_value == $el_value)
                        {
                            $true_count++;
                        }
                    }
                    if($true_count != 0)
                    {
                      $match = "True";
                    }
                    else
                    {
                        array_push($false_id_array, $p_id);
                    }
                }

                // KINGS COLLEGE STAGE
                if($p->criteria_id == "9")
                {
                    $kings_array = array();
                    foreach($trial_criteria->result() as $t)
                    {
                        if($t->criteria_id == "9")
                        {
                            array_push($kings_array, $t->criteria_value);
                        }
                    }
                    $true_count = 0;
                    foreach($kings_array as $kings_value)
                    {
                        if($p->criteria_value == $kings_value)
                        {
                            $true_count++;
                        }
                    }
                    if($true_count != 0)
                    {
                      $match = "True";
                    }
                    else
                    {
                        array_push($false_id_array, $p_id);
                    }
                }
            }
```

```
559                 // CHECK DATE OF BIRTH
560                 if($p->criteria_id == "2")
561                 {
562                     if($trial->criteria_id == "10")
563                     {
564                         if($p->criteria_value >= $trial->criteria_value)
565                         {
566                           $match = "True";
567                         }
568                         else
569                         {
570                             array_push($false_id_array, $p_id);
571                         }
572                     }
573                     if($trial->criteria_id == "11")
574                     {
575                         if($trial->criteria_value >= $p->criteria_value)
576                         {
577                           $match = "True";
578                         }
579                         else
580                         {
581                             array_push($false_id_array, $p_id);
582                         }
583 
584                     }
585                 }
586 
587                 // CHECK DATE OF DIAGNOSIS
588                 if($p->criteria_id == "6")
589                 {
590                     if($trial->criteria_id == "12")
591                     {
592                         if($p->criteria_value >= $trial->criteria_value)
593                         {
594                           $match = "True";
595                         }
596                         else
597                         {
598                             array_push($false_id_array, $p_id);
599                         }
600                     }
601                     if($trial->criteria_id == "13")
602                     {
603                         if($trial->criteria_value >= $p->criteria_value)
604                         {
605                           $match = "True";
606                         }
607                         else
608                         {
609                             array_push($false_id_array, $p_id);
610                         }
611 
612                     }
613                 }
614 
615                 // CHECK VITAL CAPACITY
616                 if($p->criteria_id == "7")
617                 {
618                     if($trial->criteria_id == "14")
619                     {
620                         if($p->criteria_value >= $trial->criteria_value)
621                         {
622                           $match = "True";
623                         }
624                         else
625                         {
626                             array_push($false_id_array, $p_id);
627                         }
```

```
                    }
                    if($trial->criteria_id == "15")
                    {
                        if($trial->criteria_value >= $p->criteria_value)
                        {
                          $match = "True";
                        }
                        else
                        {
                            array_push($false_id_array, $p_id);
                        }

                    }
                }

                // CHECK ALSFRS_R TOTAL SCORE
                if($p->criteria_id == "8")
                {
                    if($trial->criteria_id == "16")
                    {
                        if($p->criteria_value >= $trial->criteria_value)
                        {
                          $match = "True";
                        }
                        else
                        {
                            array_push($false_id_array, $p_id);
                        }
                    }
                    if($trial->criteria_id == "17")
                    {
                        if($trial->criteria_value >= $p->criteria_value)
                        {
                          $match = "True";
                        }
                        else
                        {
                            array_push($false_id_array, $p_id);
                        }

                    }
                }

              }
            }
          }
        }

        if($match == "True")
        {
          $trial_p = array(
            'trial_id' => $trial_id,
            'trial_version' => $trial_version,
            'patient_id' => $p_id
           );
          $this->Clinical_Trials->add_trial_patients($trial_p);
        }

        }

      // Redirect to list of trials when form is submitted
      redirect('trials/view_trials', 'refresh');
    }
  }

```