Study on Axial Spondylarthritis for Effective Treatment Policy

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Summary

Herein contains a proposal is detailed that outlines the background and methodology used to investigate and model a treatment policy model based on an existing rheumatic diseases' dataset, obtained with permission from the Royal National Hospital for Rheumatic Diseases in Bath, England

A proposal submitted in partial fulfilment of the requirements for a Master of Science in Data Science & Statistics

Contents

1 Introduction

1.1 Background

Axial spondyloarthritis (AxSpA) is an inflammatory arthritis disease that affects the joints in a patient's axial skeleton such as the spine, pelvis, and chest. The inflammation and damage to the sacroiliac joints and spine often cause inflammatory back pain, inflammation in the eyes, skin conditions, cardiovascular problems, breathing difficulties, fatigue, bowel problems, and other conditions that lead to an overall impaired quality of life as up to 59% of patients experienced mental health problem according to National Health Service (NHS). Usually, symptoms of AxSpA starts in early adulthood and diagnosis may requires several years. Which is further complicated by the fact that AxSpA patients often have other health problems compared to their age-match counterpart without AxSpA, which will affect treatment choices (Zhao et al., 2023). According to NHS, it is a disease that could potentially affect anyone with an estimation that 1 in 200 of the adult population in the United Kingdom is afflicted by AxSpA. The actual cause of AxSpA is unknown, although there is evidence that it is heavily link to a genetic antigen known as human leukocyte antigen B27 (HLA B27) (Inman, 2015). However, it is not a certainty as there are cases of those who do not have HLA B27 but still developed AxSpA and vice-versa.

According to NHS, diagnosis usually involves a rheumatologist who will conduct a series of interviews, joint examinations, X-Ray, magnetic resonance imaging (MRI), and blood test. X-ray is conducted to check for any changes to bone growth or loss, signs of calcification which is a build-up of calcium in body tissue, signs of bones being fused together, or signs of chronic inflammations, which if last for years, will likely be visible on an X-ray. MRI is conducted too as it is a useful tool for visualising ligaments, tendons, or showing inflammatory changes within a patient's bones. MRI is conducted jointly with X-ray as it is possible for some patients to develop non-radiographic AxSpA which causes inflammations to be visible on MRI but not on X-ray images. It should be note that MRI can be a useful diagnosis tool to detect signs of early changes which are not visible on X-ray images. Blood test are done to check for markers of inflammation such as C-reactive Protein (CRP) and erythrocyte sedimentation rate (ESR). CRP is a direct measure of inflammatory response by checking the level of a plasma protein known as C-reactive protein produced by the liver cell when experiencing acute inflammation or infection. Conversely, ESR is an indirect measure of the level of inflammation in the body by checking the rate at which red blood cells settle in a specially designated tube of anticoagulated blood, an effect that is altered by proteins associated with an inflammatory response (Assasi et al., 2015).

There is no definite cure for AxSpA and current methods involving management on the disease using a combination of medications and exercises. According to NHS guidelines, the range of medication and management strategies involves:

- Painkillers such as paracetamol for pain management during AxSpA flare-ups
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and etoricoxib to reduce inflammation and pain caused by AxSpA
- Corticosteroids are injected into the joints when there is a flare-up on the arm and legs or patients are being prescribed corticosteroid tablets such as prednisolone. Sometimes, patients are injected with methylprednisolone to the muscle. It should be note, however, that steroids are known to cause side effects and are generally not included in a long-term treatment plan.

- Targeted Synthetic/Biological Disease-Modifying Anti-Rheumatic Drug (ts/b-DMARD) are drugs that target specific cells in the immune system that cause inflammation. The difference between ts-DMARD and b-DMARD is unlike biologic medicines, targeted ts-DMARDs is not made of living cells. ts/b-DMARDs are the next level of escalation by a rheumatology clinician if a patient's arthritis condition could not be resolved with conventional synthetic disease modifying anti-rheumatic drugs (cs-DMARDs).

- Exercise improve overall patient's condition at all stages of AxSpA and is considered a vital part of a treatment regime. Depending on the patient, physiotherapy may be recommended as well.

- Patients are advised to abstain from alcohol and smokes as both cause AxSpA to worsen.

- A healthy diet to maintain a healthy weight to reduce strain on joints and to reduce risk of cardiovascular diseases.

- Relaxation, meditation, and mindfulness to improve a patient's overall mental health.

Recent years have seen significant advancements in healthcare for AxSpA as pharmacological management has introduced new classes of ts/b-DMARDs and treatment strategies such as drug tapering. Even then, Das et al. (2023) asserts that knowing which b-DMARD or ts-DMARD would be most effective for a particular patient remains an area of active investigation. As mentioned above, patients with AxSpA starts with NSAIDs and treatments are escalated to targeted therapies if it is inadequate. According to Holdsworth et al. (2021), the following list below are some of the various therapeutic options available for managing the disease:

- Glucocorticoids and DMARDs including cs-DMARDs: methotrexate, sulfasalazine, and leflunomide

- b-DMARDs: tumor necrosis factor inhibitors (TNFis) such as etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, and non-TNF biologics: tocilizumab, sarilumab, abatacept, anakinra, and rituximab

- ts-DMARDs: Janus kinase inhibitors (JAKis) such as tofacitinib, baricitinib, and upadacitinib

Even then, targeted therapies are no guarantee as up to half of patients starting their first b-DMARD do not response positively to it (Zhao et al., 2023). Despite these advancements, the treatment of axSpA remains complex, particularly in difficult-to-treat cases where patients may exhibit resistance to multiple classes of ts/b-DMARDs. The papers by Di Giuseppe et al. (2022) and Fakih et al. (2023) delve into the challenges of managing such cases. Fakih et al. (2023) mentioned that despite recent advancements, efficacy is not present in all cases and there are a portion of patients that have failed several treatments directed against the same or different targets. They also suggests that phenotypic presentation may play a role that causes targeted therapies to have different efficacies for different axial, peripheral, and enthesitic symptoms.

1.2 Motivation & Significance of this Research

A common problem when working with AxSpA patients is the complexity involved in deciding on which treatment to consider, when is the best time to perform a treatment switching, and how long should a treatment last. Not to mention, the decision on which treatment to consider, when is the best time to perform a treatment switching, and how long should a treatment last are weighted against multiple considerations such as a patient's clinical characteristics such as age, gender, smoking status, etc. as well as past treatment(s) and diagnosis. Especially in difficult-to-treat patients, multiple treatment switching are common and it is often heuristical. This supported by Di Giuseppe et al. (2022), "... *only a few studies have previously described multiple switching in routine care axSpA and have typically not explored outcomes beyond the second (or third) treatment course. Thus, how multiple switching should best be defined and how often it occurs are poorly understood.*

To find what is the best treatment recommendations for AxSpA patients, there are many factors and complications that requires a rheumatologists to take in consideration. Given the nature of AxSpA, while a specific for a treatment for an AS patient may produce positive results in the beginning (*Could be measured using assessment such as Margolis Pain Data, BASDAI, BASFI, and other relevant assessment available in the dataset*), it might not be best for the patient in the long run. And vice versa, a treatment that deteriorates a patient's condition might in reality, be the best option for the patient's long term recovery given the patient's clinical characteristics and background. In short, switching treatment complicates observational studies. Thus, the author proposed to perform a statistical study to model a treatment policy based on existing data.

A statistical study to create a model can helps inform healthcare professionals and researcher on what is the best treatment combination policy. A pseudonymised clinical dataset provided by The Royal United Hospitals Bath NHS Foundation is used to model effective treatment policy based on the dataset. The model consists of 3 stages that model a patients' initial stages, intermediate stages, and final stages as described in the ***Methodology*** section.

By mapping out the frequency of success/failure in the dataset, we are able to estimate the probability of success for a given treatment based on a patient's clinical characteristic (*such as past treatment, age, gender, HLA B27 status, year of diagnosis, smoking status in the dataset*).

It is necessary to distinguish between Randomised controlled trials (RCTs) and observational studies for this research. According to Toews et al. (2024), RCTs are a type of healthcare experiment where participants are allocated at random to one of two (*or more*) treatment groups. One group is given an experimental treatment known as an 'intervention' while the other remains as the 'control' group without given the intervention. RCTs test how effective and safe an experimental treatment is under ideal conditions while observational studies try to measure the effectiveness of an intervention in non-experimental, 'real world' scenarios such as the dataset in this research.

Other than prescribing only a single treatment, researchers may run treatment trials in one or more stages also known as 'phases'. Usually, the early phases aim to find out more about the safety and side effects of a new treatments while later phases aim to see if a new treatment works better than the current treatment or if a new treatment works better than a placebo (*a dummy drug*). For trials that compare two or more treatments, participants are put into a treatment group at random in a randomised trial. Randomised trial are the best way to obtain information the effectiveness of a treatment reliably. A multi-arm multi-trial (MAMS)

is a trial considers several treatment groups as well as the control group. It is a more complex type of trial that has control group all the way through while the other treatment groups can change as the trial goes on.

From Concato's (2013) paper, a brief overview of the strength and limitations of RCTs and observational studies are as follow:

- Randomised Controlled Trials (RCTs)
  - Strengths
    1. Randomisation balances baseline characteristics (as prognostic factors)
    2. "Prospective" infrastructure collects pertinent data
    3. Methods of analysis can be simple and straightforward
  - Limitations
    1. RCTs on the same topic are often contradictory
    2. Meta-analyses and large RCTs often disagree
    3. RCT can have limited generalisability (applicable to broader populations)
- Observational Studies
  - Strengths
    1. Rigour of observational studies is enhanced by specific methodological strategies
    2. Observational studies and RCTs with the same focus provide consistent results
    3. Treatments evaluated in non-randomised studies are safe and effective
  - Limitations
    1. Baseline characteristics (as prognostic factors) are usually imbalanced
    2. Quality of data pertinent to research question can be variable
    3. Accompanying methods of analysis can be complex and obscure

It should be note that research on the dataset is an observational study.

1.3 Data Source

The pseudonymised clinical dataset is provided by The Royal United Hospitals Bath NHS Foundation. The dataset contains patients' clinical information, routine information, and relevant axSpa information *(known as SpA Biobank)*:

1. ID
2. Age
3. Gender
4. Diagnosis
5. Year of diagnosis
6. Year of onset of symptoms
7. HLA B27 status

   Full form: Human leukocyte antigen (HLA) B27

   Note: Approximately 90% of patients with AS carry this antigen (Inman, 2015). As described in the ***Background*** section, presence of HLA B27 is tested by blood tests.

8. Smoking status
9. Margolis Pain Data

   Note: An instrument for assessing pain which can be used by AxSpA patients (Nishtala et al., 2020). In the original study by Margolis et al. (1986), it is a rating system to use with patient pain drawings that detailed 45 body areas. Scorers in that study managed achieved a high rate of inter-rater agreement despite having relatively little training.

10. ASQoL

    Full form: Ankylosing spondylitis Quality of Life

    Note: An AS-specific quality of life (QoL) by Doward et al. (2003) that asks 18 questions regarding the patient's daily activities and mental well-being. Each statement on the ASQoL questionaire is given a score of "1" or "0". A score of "1" is given where the item is affirmed, indicating adverse QoL. All item scores are summed to give a total score or index. Scores can range from 0 (good QoL) to 18 (poor QoL).

11. AS patient global
12. AS back pain
13. BASDAI

    Full form: Bath Ankylosing Spondylitis Disease Activity Index

Note: The standard for measuring and evaluating disease activity in Ankylosing Spondylitis by Garrett et al. (1994). It is a self-administered instrument that consists of six 10 cm horizontal visual analog scales to measure severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative). The final BASDAI score has a range of 0 to 10.

14. BASFI

    Full form: Bath Ankylosing Spondylitis Functional Index

    Note: A validated instrument to assess the degree of functional limitation in patients with AS (Haywood, 2010). It is a self-assessment instrument was designed by Calin et al. (1994) that consists of 8 specific questions regarding function in AS and 2 questions reflecting the patient's ability to cope with everyday life. Each question is answered on a 10 cm horizontal visual analog scale, the mean of which gives the BASFI score (0-10).

15. FACIT

    Full form: Functional Assessment of Chronic Illness Therapy

    Note: A collection of health-related quality of life (HRQOL) questionnaires targeted to the management of chronic illness (Webster, Cella, and Yost, 2003). It is a compilation of general questions divided into four primary domains (*Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being*) used with patients with any form of cancer. However, other variants and extensions of it have been used and validated in other chronic illness condition such as HIV/AIDS, sclerosis, Parkinson's disease, and in our case, rheumatoid arthritis.

16. Jenkins sleep scale

    Note: A brief (*4 items*), reliable, and standardised scale for sleep disturbance by Jenkins et al. (1988). The questions ask patients regarding their sleep activity in the past month which range from difficulty falling asleep, frequent awakenings during the night, trouble remaining asleep, to patients' subjective feelings of fatigue and sleepiness despite receiving a usual amount of night's rest. In the original paper, it asserts that a reliable and standardised scale could also be used to evaluate the impact of different therapies upon sleep problems. Despite the briefness of this scale, the authors also assert that it offers advantages such as stability, potential administration of this Jenkins sleep scale which is not limited to a specific clinical group or circumstances, the fact that this sleep scale focused on the more common occuring symptoms of poor sleep quality, and lastly, the fact that sleep scale offers high reliability while requires less time commitment compared to other instruments such as Parrott and Hindmarch (*10 items*) and the Evans instrument (*33 items*).

17. WPAI

    Full form: Work Productivity and Activity Impairment

    Note: According to Zhang et al. (2010), WPAI is a validated instrument to measure impairments in work and activities that measures absenteeism, presenteeism

as well as the impairments in unpaid activity because of health problem. In addition, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical studies and trials or between subjects with different disease severity levels. There are multiple versions of WPAI which have been validated to quantify work impairments for numerous diseases such asasthma, psoriasis, irritable bowel syndrome (IBS), Crohn's disease, and in our case, ankylosing spondylitis (AS).

18. ts/b-DMARD start & stop dates

    Full form Targeted Synthetic/Biological Disease-Modifying Anti-Rheumatic Drugs

    Note: As described in the ***Background*** section, ts/b-DMARDs is prescribed by rheumatologists when conventional treatments is inadequate.

2 Methodology

2.1 Data Cleaning and Preparation

Check for presence of untidy data in the dataset. If present, Excel and R with 'tidyverse' packages will be used to clean it:

1. Check for missing value and depending on the circumstances, make a judgement call to perform mean/median imputation or outright drop the data row.
2. Check for presence of inconsistencies or typo or incorrect manual entry.
3. Standardisation of data to transform datatype such as yes/no, true/false to 0 or 1 depending on the circumstances.
4. Transformed the data as necessary to fit the programming functions such as defining the variable types or changing it to a usable format as required by the programming functions.

2.2 Descriptive Analysis

Using ggplot packages in R:

1. Perform descriptive statistics from the dataset to get an overview of our data.
2. Using data visualisation methods such as correlation matrix, histogram, scatterplot, pie chart etc. to explore the data and form hypotheses.
3. Run correlation analysis to measure the strength of the linear relationship between two variables and compute their association. There are many type of correlation analysis that are suited for different situation. A correlation usually refers to measure of the degree to which a pair of variables are related and there are many different type of correlation formula for different situations which the author will used depending on the dataset.

   The most common correlation is the Pearson's correlation where for the sample correlation form is $r = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2 \sum_{i=1}^{n}(y_i - \bar{y})^2}}$ where:

   - n: The sample size
   - x_i, y_i: Individual sample points with index i
   - $\bar{x}$, $\bar{y}$: Sample mean of x and y

   In R, correlation analysis is done via '*cor(...)*' function.
4. Run PCA on continuous data and use cluster analysis as a visualisation tool to find possible hidden patterns in the dataset.

   PCA is a dimensional reduction technique that transforms a large set of variables into smaller principal components while retaining most of the original information to simplify the dataset. PCA works by first performing standardisation so that each variable can contribute equally to the analysis after scaling. Next, the covariance matrix is computed before eigen-decomposed. The next step is to find the the eigenvectors

(direction of principal components) and ordering them by their eigenvalues (amount of variance of principal components) to determine the principal components. Next, we discard the unnecessary components to form a feature vector and replot it for further analysis.

In R, PCA is done via '*princomp(...)*' function.

Cluster analysis is a technique to group similar datapoints together to find hidden patterns in the dataset. There are many clustering algorithm but the most common one is the k-means algorithm. K-means works by first specifying the optimal number of cluster, k value. This is done by iteratively assigning data points to clusters and updates cluster centroids to minimise the within-cluster sum of squares (WCSS) for different values of k. After plotting the k-value to WCSS graph, the location where there is an "elbow" or bend point usually indicates that adding more k does not reduce the WCSS and improve clustering quality.

In R, k-means is done via '*kmeans(...)*' function.

2.3 Statistical Modelling and Statistical Inference

According to Davison (2008), statistics concerns what can be learned from data. Applied statistics comprises a body of methods for data collection and analysis to test, or confirm theories, or to inform decisions. Theoretical statistics underpins this by providing a framework for understanding the properties and scope of methods used in applications. A statistical model is a probability distribution constructed to enable inferences to be drawn or decisions made from data. The key idea in statistical modelling is to treat the data as the outcome of a random experiment.

Statistical inference consists in the use of statistics to draw conclusions about some unknown aspect of a population based on a random sample from that population. While some preliminary conclusions may be drawn by the use of exploratory data analysis (EDA) or by the computation of summary statistics as well, formal statistical inference uses calculations based on probability theory to substantiate those conclusions (Sinharay, 2010).

A conditional model could be applied in this research. According to Taboga (2021), in a conditional model, the sample is partitioned into input and output data and the relation between the two kind of data is studied by modelling the conditional probability distribution of the outputs given the inputs. The statistical model is obtained by placing some restrictions on the conditional probability distribution of the outputs given the inputs.

Initially, the author will recorded all the known information about the patient and model the possible treatment strategies for them based on the following formula:

Initial Stage, 0:

Let m be the number of treatment in the dataset, where

- no. of treatment: $1, ..., m$
- Response of the treatment at the start, Y_0

where the response of the patients, Y_0 are based on Margolis Pain Data, ASQoL, AS patient global, AS back pain, BASDAI, BASFI, and FACIT with formulations:

$$
\begin{aligned}
&P(\text{Treatment 1} \mid \text{ID}, \text{Age}, \text{Gender}, \text{HLA B27 status}, \text{Year of diagnosis}, \text{Smoking status}) \\
&\qquad\qquad \vdots \\
&P(\text{Treatment m} \mid \text{ID}, \text{Age}, \text{Gender}, \text{HLA B27 status}, \text{Year of diagnosis}, \text{Smoking status})
\end{aligned} \tag{1}
$$

Intermediate Stage, 1:

At the intermediate stage, the author would model the first stage outcomes. Based on treatment selection i from the initial stages, the outcome is denoted as $Y_{i,1}$. Next, the author will compute the probability of '*receiving another treatment*' or '*no treatment switching*' for each patient:

Let t be the number of treatment in the dataset, where

- no. of treatment: $1, ..., m$
- Response of the treatment at the start, Y_0
- Response of the treatment after selecting treatment i at the initial stage, $Y_{\text{treatment selection i, 1}}$

where the response of the patients, Y_1 are based on Margolis Pain Data, ASQoL, AS patient global, AS back pain, BASDAI, BASFI, and FACIT with the following probabilistic formulations:

$$
\begin{aligned}
&P(\text{Treatment 1} \mid Y_{\text{treatment selection i, 1}}, \text{ID}, \text{Age}, \text{Gender}, \text{HLA B27 status}, \text{Year of diagnosis}, \\
&\qquad\qquad \text{Smoking status}, \text{Treatment duration}) \\
&\qquad\qquad \vdots \\
&P(\text{Treatment m} \mid Y_{\text{treatment selection i, 1}}, \text{ID}, \text{Age}, \text{Gender}, \text{HLA B27 status}, \text{Year of diagnosis}, \\
&\qquad\qquad \text{Smoking status}, \text{Treatment duration})
\end{aligned} \tag{2}
$$

Final, 2:

At the final stage, the author will model the second stage outcomes. Recorded outcome in this stage will be denoted as $Y_{\text{treatment selection j, 2}}$, where

- no. of treatment: $1, ..., m$
- Response of the treatment at the start, Y_0
- Response of the treatment after selecting treatment i at the initial stage, $Y_{\text{treatment selection i, 1}}$
- Response of the treatment after selecting treatment j at the intermediate stage, $Y_{\text{treatment selection j, 2}}$

The results of this analysis will be used for further discussion and to make inference what would be the best treatment policy at different stages for a patient's conditions (*based on age, gender, HLA B27 status, etc.*) and response outcomes at different stages (Y_0, $Y_{i,1}$, and $Y_{j,2}$).

2.4 Q-Learning

According to Sutton and Barto (2018), reinforcement learning is machines "*learning what to do, how to map situations to actions, so as to maximise a numerical reward signal. The learner is not told which actions to take, but instead must discover which actions yield the most reward by trying them*. Discussed in their book, Q-learning was introduced as one of the early breakthroughs in reinforcement learning by Watkins, C.J.C.H. and Dayan, P. (1992). It is a control algorithm that in its simplest one-step form is defined by:

$$Q(S_t,A_t) = Q(S_t,A_t) + \alpha[R_{t+1} + \gamma \max_a Q(S_{t+1},A) - Q(S_t,A_t)]$$

where:

- $Q(S_t,A_t)$ is the Q-value for state S_t and action A_t at time t
- α as the step size, $0 \leq \alpha \leq 1$
- R_{t+1} is the reward received after taking action A_t in state S_t
- γ is the discount rate parameter which controls how much future rewards are valued, $0 \leq \gamma \leq 1$
- $\max_a Q(S_{t+1},A$ is the maximum Q-value for the next state S_{t+1} over all possible actions A

According to Watkins, C.J.C.H. and Dayan, P. (1992), Q-learning is a form of model-free reinforcement learning that provides agents with the capability of learning to act optimally in Markovian domains by experiencing the consequences of actions, without requiring them to build maps of the domains. The algorithm for Q-learning is as follow:

Algorithm 1 Q-Learning (*extracted from Sutton and Barto's 2nd edition (2018) Reinforcement Learning: An Introduction book*)

Initialize $Q(s,a)$, $\forall s \in \mathscr{S}$, $a \in \mathscr{A}(s)$, arbitrarily, and $Q(terminal\text{-}state,\cdot) = 0$
repeat
  (*For each episode*)
  Initialise S
  repeat
    (*For each step of the episode*)
    Choose A from S using policy derived from Q (e.g., ε-greedy)
    Take action A, observe R, S'
    $Q(S,A) \leftarrow Q(S,A) + \alpha[R + \gamma \max_a Q(S',a) - Q(S,A)]$
    $S \leftarrow S'$
  until S is terminal
until convergence criterion is met

Given the nature of this research, Q-learning could potentially be used in to learn the optimal treatment policy for patients with AxSpA.

By having the:

- State Space, S

- Each state S at time t can be represented as a combination of patient characteristics and treatment history, S_t.
- Formulated as: $S_t =$ Age, Gender, HLA-B27, Year of diagnosis, Smoking status, Treatment duration, $\text{Treatment}_{t-1}, \text{Response}_{t-1}$
- Treatment_{t-1} is the treatment administered at the previous time step for non-initial stages
- Response_{t-1} is the patient's response to the previous treatment

- Action Space, A
  - The set of all possible treatment decisions.
  - Let m be the number of possible treatments.
  - Formulated as: $A =$ Treatment_1 , ..., Treatment_m
  - where each treatment is the chosen treatment administered to the patient

- Rewards
  - A function that assigns a reward to each state-action pair based on the patient's outcome. The reward function $R(S_t, A_t)$ assigns a reward based on the transition from state S_t to S_{t+1} after taking action A_t
  - A possible reward function $R(S_t, A_t)$ could be:
    * Let r be the number of indicator selected based on relevancy and suitability after understanding the dataset (*could be a combination of BASDAI, BASFI, and other suitable responses that synergise well with one another*).
    * Multiple combinations could be attempted here and depending on the nature of the responses, some transformations may be needed to prepare it for our reinforcement learning attempt)
    * For each combination, the equation is formulate as: $R(S_t, A_t) =$ $w_1 \Delta$ Indicator $1 + ... + w_r \Delta$ Indicator r
    * where $w_1, ..., w_r$ are the weight assigned to each outcome to reflect their relative importance
    * Δ Indicator could also be defined as a binary indicator for adverse events (e.g., 1 if an adverse event occurred, 0 otherwise).

3 Work Plan

1. **Understanding the dataset and data preparation**
    - Duration: 03 June – 07 June
    - Understand the dataset and if necessary, perform cleaning and transformation to prepare the dataset for further analysis
    - Using R and Excel to format and clean the dataset to prepare for further analysis
    - Perform exploratory data analysis on the dataset
2. **Descriptive Analysis**
    - Duration: 08 June – 20 June
    - Perform descriptive analysis to get a high-level overview of the dataset
    - Make use PCA and cluster analysis as visualisation tools to uncover potential hidden pattern(s) in the dataset
    - Based on what will be learnt on the dataset, conduct appropriate statistical analysis
3. **Statistical Modelling and Statistical Inference**
    - Duration: 21 June – 31 July
    - Perform analysis on the dataset based on decided approaches
    - Evaluate the appropriateness and limitation of the analysis
    - Create a model based on the dataset
    - Draw inferences from the dataset
    - Evaluate feasibility and scope of Q-learning implementation based on the nature of the dataset
    - Implement Q-learning to learn the optimal treatment policy for patients with AxSpA
4. **Pre-feedback report writing and presentation**
    - Duration: 15 July – 30 August
    - Writing the report, 5-minutes video, and presentation before submitting for first round of feedback
5. **Post-feedback report writing and presentation**
    - Duration: 30 August – 12 September (*Submission Deadline*)
    - Finalising the report for submission

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