# Appendix A

**DALY calculation detail**

The YLL of a population during a given period is

where N is the number of deaths in the population, and L is the population's average remaining life expectancy, in years, at the age of death. Total number of IBD deaths was obtained from the NHS hospital Diagnosis-related group (DRG) database from 2016. The split between UC and CD was calculated using a published mortality ratio for both UC and CD, which was weighted according to IBD population distribution [24–26]. A population’s average remaining life expectancy is

where the average life expectancy is gathered from statistical national data from 2018, and the average age of death is obtained from the NHS hospital DRG database from 2016.

On the other hand, YLD is

where I is the number of incident cases for a particular condition/disease in the population, L is the average length of disability, and W is the disability weight associated with the condition/disease. However, for prevalence-based studies, the Global Burden of Disease (GBD) 2010 [28] study updated the YLD calculation as

where P is the number of prevalent cases and DW is the disability weight. The most conservative forecast methodology of the paper from Santiago and colleagues was used, where researchers estimated the prevalence for 2019 based on a previous study from 2010 [22,27]. Disability weight is a weighting factor that reflects the severity of the disease and is quantified between 0, where no disability is quantified and perfect health is considered, and 1, equivalent to death. This parameter was obtained directly from the GBD 2017 study, as it is the latest report regarding the disability weight for IBD. This value is applicable across the whole population of IBD patients and no distinction is made between diseases or its different stages, such as remission or exacerbations.

A two-way sensitivity analysis was performed for the calculation of YLL using different methods for determining the number of deaths (number of deaths obtained from the mortality ratio published and deaths reported in the NHS hospital DRG data), and age of death (average, adjusted to account for deaths outside hospital and from GBD 2017).

# Appendix B

**Cost calculation detail**

### Direct healthcare costs

This study considered direct costs recorded in hospital settings for the 1,455 patients identified, representing all IBD patients diagnosed and treated in NHS hospitals in 2016 in Portugal. Costs associated with the episodes considered were valued according to the prices set in Portuguese Law [31]. Here, national DRG funding values were used as a proxy for the hospital’s costs for the treatment of these patients. These values vary by DRG code, the episode’s level of severity, and whether the episode occurs in ambulatory or inpatient conditions.

Direct healthcare includes the following components:

1. Medical hospitalisation: all events codified with a medical DRG according to the NHS hospital DRG database were considered. For cost calculation, DRG established prices were used as a proxy for all coded episodes. DRG for immunomodulators administration in day care hospital were costed separately under the IBD-related drugs category.
2. Surgery: surgical DRGs codified for the selected patient pool were analysed, indicating that a given patient underwent a surgical procedure. Like medical hospitalisations, DRG values were used for calculating costs related to surgery.
3. Gastroenterology healthcare professional (HCP) visits: the average number of hospital visits to gastroenterologists by IBD patients was estimated by the local Expert Panel for each of the different disease stages – mild, moderate and severe. According to Portuguese law, hospital groups have a fixed funding price per appointment, which was used to calculate the average price, assuming NHS patient data distribution per hospital group [32]. According to Portuguese law, a patient is exempt from out-of-pocket costs if s/he has a 60% or higher degree of disability [33]. The number of patients that meet this criterion was obtained through the patient study. Regarding the out-of-pocket costs, a fixed price applied to all appointments was also taken into consideration for all patients that where not exempt from this charge [34].
4. Other specialty HCP visits: the average number of hospital visits to surgery, rheumatology, infectiology / immunomodulation, dermatology and other medical specialties was estimated by the local Expert Panel. The same appointment price calculated for gastroenterology HCP visits was applied to determine the costs of other specialty HCP visits, and the same rationale used for out-of-pocket costs was applied [34].
5. Emergency visits: the average number of emergency hospital visits by IBD patients was estimated by the local Expert Panel according to the different disease stages. Emergency visits leading to hospitalisation were not considered in this category as they were accounted for in “hospitalisations”. Only emergency episodes that did not result in an inpatient episode were costed here. Each hospital has a signed contract which comprises the typology of emergencies (*Multi-faceted Emergency Service, Medical-surgical Emergency Service and General Emergency Service*) that each hospital must cover. Fixed funding prices for each type of emergency service were used to determine the cost, assuming NHS patient data distribution per hospital group. Out-of-pocket costs were considered for non-exempted patients and the price was determined by splitting the emergencies according to each emergency type and applying the corresponding legislated price [34].
6. Exams and laboratory tests: the expert panel estimated the most common exams and laboratory tests performed for IBD patients as well as their annual frequency. According to Portuguese law, medical exams and laboratory tests have a fixed funding price for NHS hospitals, as well as a user charge associated, which were used to calculate costs [31].
7. Pharmacologic treatment: for retail, the molecules considered were Azathioprine, Budesonide, Hydrocortisone, Mesalazine, Methotrexate and Sulfasalazine. Molecule share for IBD was based on its allocation to the ATC3 (Anatomical Therapeutic Classification) A07E – Intestinal anti-inflammatory drugs category. Furthermore, patient’s co-payment was assessed, by applying the reimbursement rates defined by law for each drug [36]. In the hospital scope, molecules considered were Adalimumab, Budesonide, Certolizumab, Ciclosporin, Golimumab, Hydrocortisone, Infliximab, Mercaptopurine, Mesalazine, Methotrexate Methylprednisolone, Prednisone, Sulfasalazine, Tacrolimus, Ustekinumab and Vedolizumab. The consumption allocated to IBD was determined by calculating the share of each molecule in the gastroenterology cost centre. Additionally, drugs administration cost in day care facilities was estimated according to the number of day hospital visits in the NHS 2016 database DRG codes. Costs split between UC and CD, for both retail and hospital settings, were estimated with the expert panel, where a treatment algorithm was accessed for each disease and disease stage and thus distributed accordingly.

### Direct non-healthcare costs

This study estimated costs associated with IBD patient transportation due to HCP visits for consultation, emergency visits, treatment sessions, surgery, and hospitalizations. The NHS hospital DRG database concerning hospital production contains data on patients’ residential districts and hospitals visited, enabling the quantification of the number of patients treated outside their district of residence. The transportation cost was then calculated according to four possible situations:

1. Patient residence and treatment hospital in the same district
   1. Programmed appointment;
   2. Emergency visit.
2. Patient residence and treatment hospital not in the same district
   1. Programmed appointment;
   2. Emergency visit.

The maximum NHS payment price for these two situations varies according to the vehicle used by the patient – ambulance vs. private vehicle – and is established in Portuguese law, as shown in table 2 [30]. The allocation of transportation costs to whether patients or NHS, by distributing the types of vehicle used, was attained from the patient study.

For episodes that did not occur in the same district, the patient’s residential address was taken as the district’s main hospital address. An average cost per visit was then calculated according to the number of selected episodes recorded for both programmed and emergency transportations.

### Indirect costs

The employment rate in IBD patients was obtained from the APDI patient study. The average daily wage for the Portuguese population in 2019, €73, was collected from the National Institute of Statistics (INE) and assumed to be similar for IBD patients [35].

As such, indirect costs include the following components:

1. Patient work absences – the average number of days a patient is absent from work was estimated as the sum of the following:
   1. Inpatient time – time spent during medical hospitalisation and surgical hospitalisations, obtained in the NHS DRG 2016 data;
   2. Medical appointment time – time spent in all appointments or emergency visits related to IBD, obtained through the direct costs. A factor of 0.5 days was considered for each event;
   3. Day care facilities time – time spent in all day hospital sessions was obtained from the NHS 2016 data. A factor of 0.5 days was considered for each session;
   4. Sick leave – The number of days patients were on sick leave was collected via patient study;
2. Caretaker work absences: the number of days patients’ caretakers were absent from work was obtained from the APDI patient study, where information regarding the number of patients accompanied by a caretaker was collected, as well as their employment rate and the average number of days used by the caretaker in patient support;
3. Presenteeism: representing the reduced productivity of a patient due to disease, the number of working days patients lost to presenteeism was obtained through the APDI patient study. Specifically, patients reported how many hours they worked and how many of those hours were unproductive due to their IBD condition, generating an efficiency rate which was applied against 220 working days;
4. Premature death: the median age of death obtained from the NHS 2016 data was compared with the national average life expectancy, generating the number of years lost, which was computed with the number of deaths. Costs were obtained by multiplying this figure by the national average social security income per capita, €3,372, a measure of the contribution of each resident per year to the state [35].
5. Early retirement: the number of work lost due to early retirement associated with IBD was collected through the patient study. The average IBD patients’ age of retirement was subtracted from the national average age of retirement, 62.6 years, and multiplied by the number of retired patients. Again, national average social security income per capita was used to determine the cost [35].

# Appendix C

**International Classification of Diseases (ICD-9) codes**

1. Ulcerative Colitis
   * 556.0 - Ulcerative (chronic) enterocolitis;
   * 556.1 - Ulcerative (chronic) colitis;
   * 556.2 - Ulcerative (chronic) proctitis;
   * 556.3 - Ulcerative (chronic) proctosigmoiditis;
   * 556.5 - Left-sided ulcerative (chronic) colitis;
   * 556.6 - Universal ulcerative (chronic) colitis;
   * 556.8 - Other ulcerative colitis;
   * 556.9 - Ulcerative colitis, unspecified.
2. Crohn’s Disease
   * 555.0 - Regional enteritis of small intestine;
   * 555.1 - Regional enteritis of large intestine;
   * 555.2 - Regional enteritis of small intestine with large intestine;

555.9 - Regional enteritis of unspecified site

# Appendix D

**Drug costs detail per molecule**

### Retail costs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Molecule** |  | **UC** |  | **CD** |
| Azathioprine |  | 320,506 € |  | 996,805 € |
| Budesonide |  | 142,619 € |  | 359,752 € |
| Hydrocortisone |  | 56,394 € |  | 142,253 € |
| Mesalazine |  | 10,118,105 € |  | 1,647,133 € |
| Methotrexate |  | 144,550 € |  | 449,564 € |
| Sulfasalazine |  | 531,472 € |  | 86,519 € |

### Hospital costs

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Molecule** |  | **UC** |  | **CD** | | Adalimumab |  | 5,287,393 € |  | 9,552,438 € | | Azathioprine |  | 423 € |  | 1,317 € | | Budesonide |  | 3,085 € |  | 7,781 € | | Certolizumab |  | 864 € |  | 1,561 € | | Ciclosporin |  | 115 € |  | 358 € | | Golimumab |  | 1,536,379 € |  | 0 € | | Hydrocortisone |  | 3,398 € |  | 8,570 € | | Infliximab |  | 6,472,238 € |  | 11,693,033 € | | Mercaptopurine |  | 3,935 € |  | 12,237 € | | Mesalazine |  | 14,232 € |  | 2,317 € | | Methotrexate |  | 1,794 € |  | 5,580 € | | Methylprednisolone |  | 4,223 € |  | 10,652 € | | Prednisolone |  | 3,639 € |  | 9,180 € | | Sulfasalazine |  | 101 € |  | 16 € | | Tacrolimus |  | 15,564 € |  | 48,407 € | | Ustekinumab |  | 0 € |  | 3,754,364 € | | Vedolizumab |  | 2,936,699 € |  | 5,305,570 € | |  |  |  |  |