Use of immunoglobulins: an observational study

Statistical Analysis Plan

version 0.1 (18 February 2022)

1. List of abbreviations

HUB: Hospital Universitari de Bellvitge
HGTiP: Hospital Germans Trias i Pujol
HUVH: Hospital Universitario Vall d'Hebron
RPT: Registro de pacientes tratados
SAP: Sistema de Gestión Administrativa de Pacientes
SISCAT: Sistema Sanitario Integral de utilización pública de Cataluña

2. Responsible parties

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3. Updates and amendments

Overview of SAP Amendments and Updates

Number	Date	Section	Amendment or update	Reason
1	30/03/22			

4. Introduction

4.1. Preface

Immunoglobulins are a derivate of plasma proteins used as therapeutic treatment for patients with antibody-deficiencies and for a wide range of diseases, such as immunomodulatory or replacement therapies (Ruiz-Antorán, 2010)(Vallejo Rodríguez, 1999). Its use has increased over the last few years, especially since the COVID-19 outbreak (AminJafari, 2020). They have been used to try to combat respiratory infection by SARS-CoV-2. However, only some indications have been authorized by the Spanish Medicines Agency (AEMPS) based on contributed evidence. Immunoglobulins are not only used for these indications but are also used for several conditions not included in the regulatory approvals but for which substantial clinical evidence exists (Farrugia, 2001). Moreover, there has been a significant increase in the price per unit of immunoglobulins, due to the increased complexity of manufacturing processes, including safety enhancements and stringent regulatory requirements (N'kaoua, 2021). The use of immunoglobulins for non-approved indications without evidence, the increase in consumption and its high costs have already promoted the rationalization of its use through a

consensus in other countries. Different consensus and guidelines have attempted to establish priorities and to optimize the use of immunoglobulins (Ruiz-Antorán, 2010).

In 2014 a register was implemented in Catalonia to carry out the task of monitoring data on the use of high-cost drugs in normal clinical practice conditions: the Registry of Patients and Treatments (RPT). Its objective is to measure the quality criteria of the care process and health outcomes through the systematic collection of data on the effectiveness and safety of drugs under normal clinical practice conditions. From September 2019 on it is obligated to report immunoglobulins in the RPT (Roig Izquierdo, 2020).

4.2 Purpose of the specific analyses

Immunoglobulins represent a therapeutic option with high economic costs and limited availability. Therefore, by describing the use of immunoglobulins through RPT, evaluating the indications for which they are being used and by comparing the usage with clinical recommendation guidelines, risks can be limited and the best possible clinical results can be obtained. The protocol of this study and the approval form (CEIm) are attached in annex 1 and 2.

5. Study objectives

objective 1: to describe the use of immunoglobulins in the HUVH, HUB and HGTiP.
objective 2: to validate the indications for use of the non-specific immunoglobulins in the RPT of the HUVH, HUB and HGTiP.

6. Study Methods

6.1. General study design

We will perform an observational, retrospective, multi-centered study in a cohort of users of non-specific immunoglobulins. Naive incident users in the RPT registry will be included.

6.1.1. Base population

The inclusion criteria are: all the naive incident users who initiate a treatment with non-specific immunoglobulines (J06BA01 and J06BA02) in the period between September 2019 and December 2021 regardless of their age, sex, indication, dose and duration. And without immunoglobulines use in the year before the treatment initiation date.

A preliminary count of registered treatments indicates that around 500 patients would meet these inclusion criteria.

6.1.2. Registry characteristics

The RPT is a register implemented in Catalonia by health professionals from the Comprehensive Public Health System of Catalonia (SIS CAT) to carry out the task of monitoring the data on the use of high-cost drugs in normal clinical practice conditions. All the hospitals named above participate in the RPT. The general structure of the registry consists of three levels of information: treatment level, initiation level and follow-up level. Treatment level includes basic patient data, the identification of the treatment and identification of the origin of the prescription. The initiation level includes the clinical variables that are required when initiating a treatment such as the

indication. Lastly, the follow-up level includes the clinical variables that are required during the treatment follow-up and the discontinuation variables at the end of the treatment (Roig Izquierdo, 2020). The RPT does not register any concomitant medications or comorbidities.

6.1.3. Participating centers

In this study three third-level hospitals will participate:

- **Hospital Vall d'Hebron (HUVH)** is the largest hospital complex in Catalonia and one of the largest in Spain. It is structured into three main health areas: General Area, Mother and Child Area and Orthopedics and Rehabilitation Area. With 1,146 beds, the hospital is committed to a management model that places patients at the center of its actions and promotes participation in Catalan and Spanish research projects.

- **Hospital Universitari de Bellvitge (HUB)** is a public hospital located in the town of l'Hospitalet de Llobregat. It is specialized in high complexity medical care and has 708 beds. It offers all the medical specialties, except for pediatrics and obstetrics. Bellvitge University Hospital, together with the University of Barcelona, the Catalan Institute of Oncology and the IDIBELL Research Institute, make up the Bellvitge Campus.

- **Hospital Universitari Germans Trias i Pujol (HGTiP)** is one of the large university hospitals (almost 650 beds) located at the foot of the Sierra de la Marina, in the municipality of Badalona. It provides direct healthcare to 250.000 citizens and is a referral center for high-tech care for 820.000 citizens in the surrounding areas. It also has an associated center devoted to research, the Health Sciences Research Institute Germans Trias i Pujol (IGTP).

To facilitate the collaboration between the hospitals, an opperalization tasks document was created to estimate workload and provide data sharing instructions (Annex 3)

6.2. Descriptive use methods (objective 1)

All patients starting a treatment with non-specific immunoglobulines (naive incident users) in the period between September 2019 and December 2021 regardless of their age, sex, indication, dose and duration of treatment.

6.2.1. Exposures

All the patients included in the study are exposed to non-specific immunoglobulines, this could be an extra- (J06BA02) or intravascular (J06BA01) administration.

List of definitions:
Naive incident user: a patient who isn't exposed to immunoglobulines (intra- or extravascular) a year prior to the start of the treatment with a non-specific immunoglobulin.
Immunoglobulin switching: the patients who changed immunoglobulin therapy from extravascular to an intravascular administration or vice versa during the study period providing that the period in between therapies is less than a year, regardless of the indication. In cases where two immunoglobulin types overlap in time, we won't consider them as switchers.
Immunoglobulin concomitance: if an overlapping use of an intravascular and an extravascular immunoglobulin of at least one day, regardless of indication. If cases are found they will be narratively described.
*Immunoglobulin discontinuatio*n: the patients who stopped the use of any type of non-specific immunoglobulins (J06BA01 and J06BA02) for a year or longer.
Duration of treatment: When there is a certain period between the start date and end date of the use of immunoglobulin.

Patients with multiple indications: In RPT each treatment initiation is linked to a single indication. When a patient meets multiple treatment initiations, different diagnosis for each may be found. In this case, if the patient does not meet any of the previous definitions (switching or discontinuation) and is treated with the same type of IGG administration (extra- or intravascular), they will be reviewed case by case. From this review, it will be decided based on medical criteria whether diagnoses are a specification of the other (e.g., transplant versus transplant rejection), or if they are clearly referring to different clinical entities. For both situations, if cases are found they will be narratively described.

These group of patients will not be taken into account during the validation of the RPT (see 6.3).

6.2.2. *Diagnoses*

The system that is used to classify and code all the diagnoses for indication, is the International Classification of Diseases (ICD-10).

Definition of indications: could be classified into three groups of indications; authorized, unauthorized with scientific evidence, unauthorized without scientific evidence and indications with unknown evidence.

An analysis of the indications for immunoglobulins will be carried out, for which the indications will be classified into three groups based on a bibliographic review of the current guidelines of UK and of CatSalut, see annexes 4 and 5.

- authorized indications (group 1): authorized by the EMA
- unauthorized indications with scientific evidence (group 2): not authorized by the EMA and used off-label with scientific evidentiary support (level A) (Oxford Centre for Evidence-based Medicine): at least one controlled and randomized clinical trial (UK Ia, Ib)
- unauthorized indications without scientific evidence (group 3): not authorized by the EMA and unaccepted indications
- indications with unknown evidence (group 4)

The trade names of immunoglobulines relating to approved indications are shown in annex 6.
The proportion of patients for each indication will be calculated as well as the proportion of patients in each group.

6.2.3. Costs

To estimate the costs of a certain indication per patient the yearly mean costs per gram of immunoglobulins are used.

The following calculation is used:
Weight of a patient (kg) x dosage (0,4-0,8g/kg) x price (€/g) = price per months per patient (€)
Price per administration (€) x 13 administration = price per year per patient (€)
Total cost (€) per person-month over the whole study period

With this, the costs per patient per month and per year could be calculated. At the end, the costs of different indications could be estimated through the mean costs per indication per patient and per person-month.

For the Vall d'Hebron Hospital the costs are as following:

Year	€/g overall	€/g intravascular	€/g extravascular

2019	42,75	42,77	42,33
2020	42.33	42,33	42,32
2021	41.60	41,53	42,36

These costs are obtained through the sum of the total costs per brand divided by the total stock per brand multiplied by the grams per brand.

The costs per year (€/g) could be different between hospitals due to institutional agreements with the pharmaceutical industry providers.

6.2.4. Statistical analysis

Standard descriptive calculations for qualitative and quantitative variables will be used. The median of general characteristics such as age, follow-up period and treatment duration will be calculated. The gender distribution is also mapped out. Furthermore, calculations are also made with the patients who switch, *see paragraph 6.2.1*. Here, the number of switches, the mean time between switching and the number of switches per patient are mapped out. This will be visualized with a Kaplan Meier curve.

The proportion of patients for each indication will be calculated as well as the proportion of patients in each group. Information will also be calculated by person-month.
The analysis will be stratified following the variable list in the next section.

The result tables of this objective are shown in annex 7.

6.2.4.1. *Variables*

The following covariates are used for stratification and postcalculation.

- Gender: female or male
- *Age*: will be calculated as the difference between the data of start of treatment and the birth month and year (for all patients considered the 1st of every month).
- Weight: the weight of an included patient a prior to the start of treatment with immunoglobulins

6.2.4.2. Stratification variables

Stratification by gender with strata:

- men
- women

The patients will be stratified based on age, yielding two strata:

- Age ≥ 16
- Age < 16

Extravascular + intravascular stratification with strata:

- Extravascular
- Intravascular

Stratification by hospital with strata:

- HUVH

- HUB
- HGTiP

Stratification on ICD10-codes*

- A00-B99 Certain infectious and parasitic diseases
- C00-D49 Neoplasms
- D50-D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
- E00-E89 Endocrine, nutritional and metabolic diseases
- F01-F99 Mental, Behavioral and Neurodevelopmental disorders
- G00-G99 Diseases of the nervous system
- H00-H59 Diseases of the eye and adnexa
- H60-H95 Diseases of the ear and mastoid process
- I00-I99 Diseases of the circulatory system
- J00-J99 Diseases of the respiratory system
- K00-K95 Diseases of the digestive system
- L00-L99 Diseases of the skin and subcutaneous tissue
- M00-M99 Diseases of the musculoskeletal system and connective tissue
- N00-N99 Diseases of the genitourinary system
- O00-O9A Pregnancy, childbirth and the puerperium
- P00-P96 Certain conditions originating in the perinatal period
- Q00-Q99 Congenital malformations, deformations and chromosomal abnormalities
- R00-R99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
- S00-T88 Injury, poisoning and certain other consequences of external causes
- U00-U85 Codes for special purposes
- V00-Y99 External causes of morbidity
- Z00-Z99 Factors influencing health status and contact with health services

**ICD-10 dictionary corresponds to its Spanish version named CIE-10.*

6.3. Validation of the RPT (objective 2)

Validation is often reported as a quality marker for both the results of the research and of the records used (Nicholson, 2011). Validation indicates the process of assessing and improving register quality. One of the objectives is to validate the indications for use of the non-specific immunoglobulins of the RPT of the HUVH, HUB and HGTiP. The RPT plays a crucial role in this multi-centered study. Obtaining reliable results requires valid diagnosis. Data are considered valid if the data represent what they claim to represent. This external validation will measure the accuracy of the data in the RPT. For the RPT validation of the diagnosis the information recorded in the electronic health record, SAP of the participating hospitals, will be used as “gold standard”. In validity studies, the gold standard is assumed to represent the true value and thus to be free of error. The validation of the RPT will be stratified by age, indication and hospital.

6.3.1. *Sample size calculation*

For the sample size calculation for the validation of the indications in the RPT, the Granmo online calculator was used (https://www.imim.es/ofertadeserveis/en_granmo.html). It was determined that for a total of 500 RPT records, a random sample of 173 individuals was sufficient to estimate the validity of the register with a confidence interval of 95% and a precision of +/- 5%. The expected proportion was 78%, based on a similar previous study (R. Izquierdo et al 2020) and a replacement rate was not taken into account due to study validation design.

Of the 500 records, 224 belong to the Vall d'Hebron Hospital. This means that, with the same conditions as mentioned above, the sample size of the validation for the Vall d´Hebron Hospital will be 122. The number of validations is calculated in the same way for the other hospitals.

6.3.2. *Validation form*

A validation form has been built using RedCap (RedCap, 2019). This standard validation form is user-friendly and should be used across multiple centers to ensure proper validation and uniformity of information. The form includes sex, year of birth, indication of RPT (including ICD10) and indication(s) of SAP (including ICD10). Finally, the reviewer can mark the matching status as correct, missing, incorrect and doubtful. If the **full** code in the RPT corresponds with the code in the clinical history the status could be classified as correct. Missing means that the reviewer has not enough information in either RPT or SAP to draw a conclusion. The reviewer can mark a case as incorrect when the two diagnoses are not equivalent or do not belong to the same ICD subgroup. When there is no code in the clinical history the diagnosis would be written down as free text, these cases will be reviewed case by case. In case of doubt, the reviewer can specify the doubt in the form. Doubtful cases will be discussed and a consensus will be reached within the research team. All cases will be reviewed by two different observers in order to map out the reliability of the validation *[see paragraph 6.3.3.].* This form can be found in Annex 8.

6.3.3. *Specific methods for validation*

There are different methods used for the assessment of validity. Which index or technique is used depends on the type of variable. In this case, the variable is categorical. The positive predictive value is used for validation of the RPT. To make sure the validation is reliable the Cohen's kappa score and percent agreement will be calculated. There are other methods that could be used for validation but cannot be applied in the validation of the RPT (Szklo, 2014). These methods can be found in annex 9.

6.3.3.1. *Positive predictive values*

The positive predictive value is a measure used in the context of the evaluation of screening and diagnostic procedures, in addition to sensitivity and specificity [annex 9], the positive predictive value (PVV) is the proportion of patients truly diagnosed as positive to all those who had positive test results (Szklo, 2014). In this validation, the PVV is calculated by dividing the cases with diagnosis in RPT which are equivalent to the clinical history to all the cases of RPT indications (*A/(A+B)),* according to figure 1.

		CLINICAL HISTORY (CH)		
		YES	NO	TOTAL

RPT REGISTER	YES	**A** Diagnose in RPT equal* to CH (VP)	**B** Diagnose in RPT different than CH or absent	POSITIVES
	NO	**C** No Diagnose in RPT	**D** No Diagnose in RPT and no DX in CH	NEGATIVES
	TOTAL	DX in CH		

Figure 1: measures of validity of categorical data. Sensitivity: A/(A+C); specificity B/(B+D); positive predictive value: A/(A+B); negative predictive value D/(C+D).

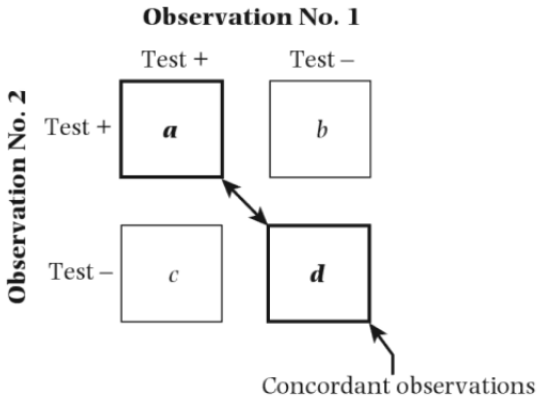
*If the **full** code in the RPT corresponds with the code in the clinical history the status could be classified as correct. When there is no code in the clinical history the diagnosis would be written down as free text, these cases will be reviewed case by case.

6.3.3.2. *Reliability of the validation*

In addition to validity, reliability is also taken into account. The reliability says something about the extent to which the results can be reproduced when the research is repeated under the same conditions. It is assessed by checking the consistency of results across time, across different observers, and across parts of the test itself (Szklo, 2014).

6.3.3.2.1. Percent agreement

Percent agreement is a simple method of summarizing agreement for categorical variables and thus could be used to examine the reliability of the validation of the RPT. Percent agreement between two sets of observations is obtained by dividing the number of paired observations in the agreement cells by the total number of paired observations. The percent agreement calculation is shown in figure 2. The observation numbers could be obtained by two different reviewers or by the same reviewer at two different points in time (Szklo, 2014). To check the reliability of the RPT validation two different reviewers will fill in the validation form (annex 8) for the same case. The cases of the two different reviewers will be compared and divided into groups according to figure 3.



$$\text{Percent agreement: } \frac{(a+d)}{(a+b+c+d)} \times 100$$

Figure 2: Percent agreement for paired binary test

	Observer 2		
		Correct	**Incorrect**
Observer 1	**Correct**	**A** Correct by both	**B** Correct by observer 1, incorrect by observer 2
	Incorrect	**C** Correct by observer 2, incorrect by observer 1	**D** Incorrect by both

Figure 3: Percent agreement to check reliability of the validation of RPT

6.3.3.2.2. Cohen Kappa

The kappa statistic is defined as the fraction of the observed agreement not due to chance in relation to the maximum non-chance agreement when using a categorical classification of a variable (Szklo, 2014). This method is used in this specific validation to measure the percentage agreement between the RPT and SAP beyond that expected by chance alone.

The formula for Cohen's kappa is defined as:

$$k = (p_o - p_e) / (1 - p_e)$$

where **Po** is the relative observed agreement among raters (= percent agreement calculated above) and **Pe** is the hypothetical probability of chance agreement.

The chance agreement is the agreement that would be expected if both observers rated the responses at random. The total chance agreement is the sum of the chance agreement for each cell on the diagonal. The number expected in each cell by chance alone is the product of the corresponding marginal totals divided by the grand total. Using the notation in figure 2 the following calculation is given:

$$Pe = (a + c) \times (a + b) + (b+d) \times (c+d) / (a+b+c+d)^2$$

Kappa = 0: the amount of agreement that can be expected from random chance
Kappa = 1: perfect agreement between the raters

6.4. *Data* management overview

6.4.1. *Missing* data

Since the underlying data represent attended medical care we generally assume that absence of information of diagnoses means absence of that condition. No imputation will be done for missing data.

6.4.2. *Relational* model building

Each PI of each center will get data extracted. Locally they will run an RStudio script hosted in a private repository in GitHub [https://github.com/JR-Farcli/test_private/tree/main/RPT_IGG]. This script will be adapted if required to center particularities by PI from HUHV. The variable extraction table is shown in Annex 10.

This script will codify the information to prevent identification risk (see next section), and also harmonization of each hospital data (Figure 4). It has been set to assign an automatic random study code to each patient, each time it runs; thus, even if someone tries to run the coding script in the same sample, the identification numbers will not be the same. Consequently, the only possibility to traceback patients is through the codification table guarded by each PI.

Moreover, the addition of further tables (such as medical dictionaries or evidence level equivalences between guidelines) may be eased through this design.

The output will be sent to the coordinating center (HUVH), and its quality will be assessed and analyzed.

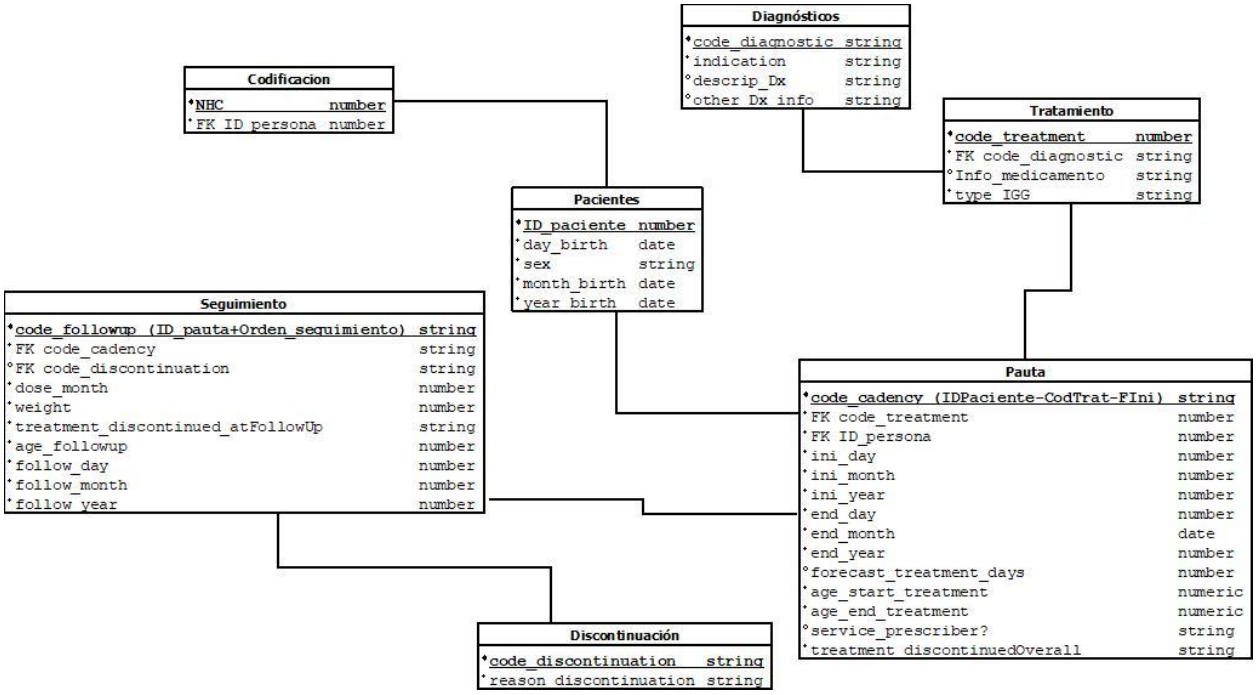


Figure 4. Relational model created from extracted RPT variables.

**The "Codificacion" table will remain locally under responsibility of each in-hospital's PI.*

Table 1. Content of relational-RPT datasets.

Dataset	Content
CODIFICACIÓN	It contains the anonymization codes relating the artificially created "patient identifier" and number of clinical history (NHC).
PACIENTES	It contains demographic information.
TRATAMIENTO	It contains the treatment code, which uniquely identifies the joint typeIGG-indicationDx.
DIAGNOSTICOS	It contains the diagnostic ICD-10 (CIE-10) medical code, and also the description of the indication diagnosis, and some further additions.
PAUTA	It contains a unique identifier by patient-TTcode-iniDate. Information here is about age at start or end of treatment, start and end dates, expected days of treatment and prescribers' service.
SEGUIMIENTO	It contains connecting codes between PAUTA and DISCONTINUATION. Also information retrieved in each follow-up such as weight, date or dose at follow-up.

DISCONTINUATION	it contains an artificially created code for each reason of discontinuation and its full name description.

6.5. *Data* codification and privacy (data exchange between centers)

Data will be codified and converted to the relational model locally and analyzed centrally in HUVH.

The principal investigator will possess a file with the study protocol and data. Patient data will be stored for a period of 18 months from the last extraction in the database in encrypted form and the database will be stored on a computer determined for this purpose. Likewise, the reference investigator by center will keep a list containing the inclusion codes of the cases locally generated by the script, each case with the name of the patients and the medical record number. This is combined with lists of respective included patients. The identification of the patients will be provided to only investigators strictly assigned for the validation of the diagnoses through the clinical history process.

For the analysis, the data, once coded, will be sent to the principal investigator (HUVH) through Excel files encrypted with a password through the ICS secure file delivery platform in the institutional mail (Zimbra). The password and the file will be sent in different emails.

6.6. *Quality* checking

Before moving to analysis, a series of issues will be checked to detect problems in data such as inconsistencies, duplicates, missing variables or categories needed for this study. A report will be generated by the hospital and sent to each. This will contain information on missingness of variables, general counts and distributions and dates consistency. Referees from each center will be asked to revise the information flagged in the Quality Report, and if needed, a meeting will be scheduled with the coordinating center.

Please, find in Annex 11 a template of the Quality Report with the issues that will be checked.

7. *Transparency* and ethics

The study will be carried out in accordance with the principles from the Declaration of Helsinki and according to current legal regulations (Real Decreto 957/2020). The confidentiality of personal data is guaranteed by limited access to sensitive data by the researchers of the study under the responsibility of the principal investigator. The data will remain encrypted in the database. The research team has committed not to carry out any re-identification activities, in addition to a technical and functional separation of the encryption process. This observational study meets the ethical criteria required by the International Guidelines for Epidemiological Studies (2009). All information obtained in the study will be treated confidentially, in compliance with the Ley Orgánica de Protección de Datos de Carácter Personal LOPD 3/2018.

Even if there is no direct patient participation, the participants of the study will not be affected. On the contrary, greater knowledge about the indications for which immunoglobulins are used could actually lead to greater benefit for patients.

None of the investigators participating in this project have any conflicts of interest.

8. Strengths and limitations

8.1. Strengths and limitations of methods

Nonspecific immunoglobulins represent a therapeutic option with a high economic cost and limited availability. Therefore, one of the strengths of the study is that it will obtain knowledge about the use in clinical practice of immunoglobulins in tertiary care centers in Catalonia belonging to the ICS (Institut Català de la Salut) Catsalut. In this way, the description of the use of non-specific immunoglobulins in the hospital and the evaluation of the indications for which they are being used, will make it possible to optimize access to their use, limit the risks and obtain better clinical results.

There are also a few limitations of the study. It is a retrospective study and therefore the information obtained will be based on data in which the quality of the information recorded or collected may be limited. In this study, only the naive incident users are included and not the prevalent users. Finally, within the data extraction, it was not possible to split the information by service nor immunoglobulin brand.

Another strength of this study is that the RPT will be validated. Validation indicates the process of assessing and improving register quality. It is important to validate the RPT because it also plays a crucial role in this multi-centered study (objective 1). Moreover, the validation of the RPT was not done before.

Regarding the validation of the RPT, there were also a few limitations. In this study, the RPT is only validated in terms of the diagnosis, but other variables such as treatment duration are not taken into account. Thus, the conclusion about the validation of the RPT could be less reliable. On the other hand, although the study will be carried out with data from some of the largest hospitals belonging to the ICS, the results may not be extrapolated to other centers or health systems.

8.2. Strengths and limitations because of datasource

The strength of the RPT is that the register is implemented in Catalonia by health professionals from the Comprehensive Public Health System of Catalonia (SIS CAT) to carry out the task of monitoring the data on the use of high-cost drugs in normal clinical practice conditions. It consists of three levels of information: treatment level, initiation level and follow-up level. Just the availability of the RPT represents opportunities for analysis and the generation of support information for management decision-making.

There are also some limitations regarding the data source. The database that is used is specific for Catalonia and only Catsalut hospitals participate, which means that the generalizability is limited. In addition, it has only been mandatory since 2019 to register immunoglobulins in the RPT, for that reason the data source is relatively new and possibly less reliable. This also means that no information was available before 2019 about the use of immunoglobulins in the RPT, which again could lead to decreased reliability of the results. A possible other limitation is that different clinicians provide the RPT with information, the consistency of the database could therefore be questioned. Moreover, there is limited information available about the costs as they may vary across different brands (which are not present in the RPT registry), thus the yearly mean costs are used. Thereby, it is assumed that the administrations are given monthly based on the data extraction (dose/month). The reliability of this information could be questioned: some immunoglobulins require weekly/biweekly administrations.

9. Results spreading plan

The knowledge and results obtained because of this study will be disseminated through conferences, internal talks, journals and as training material.

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Annexes

Annex 1. Protocol

Annex 2. Ethics Committee of medicines' research (CEIm) opinion

Annex 3 . Operativization tasks document

Annex 4. Guideline CatSalut compared to United Kingdom (UK) clinical guidelines

Annex 5. Clinical guidelines for immunoglobulin use (second edition update)

Annex 6. Trade names of immunoglobulines relating to approved indications

Annex 7. Results shell tables

Annex 8. Validation form

Annex 9. Other validation methods

Annex 10. Variable extraction table

Annex 11. Quality check template