Anemia Control Model

Instructions for Use

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1 Important information

1.1 Introduction

This User Manual (i.e. Instructions for Use) contains information necessary for the use of the Anemia Control Model (ACM). Before using the software, users must have been instructed by the manufacturer on how to use the software and must be thoroughly familiar with the contents of the User Manual. Training is required for safe use of the medical device. The first trained users have the responsibility of handing down the knowledge they have acquired to other future users.

This manual serves as a reference guide should questions arise during day-to-day work.

The software must only be used by persons who can prove that they have been instructed on its proper use and handling.

ACM is a software application that provides physicians with optimal dosage recommendations for the erythropoiesis stimulating agent (ESA) and iron pharmacological treatments to maintain patient hemoglobin and ferritin levels within the targeted range in dialysis patients. Medical supervision is required for validating ACM suggestions and turning them into actual prescriptions.

ACM consists of two (2) major components:

- The ACM Recommendation Engine (hereinafter referred to as the “ACM service”), an online component fully managed by Fresenius Medical Care (FMC)
- The ACM Application (optional) (hereinafter referred to as the “Application”), a local web application that interfaces with the customer’s healthcare information system (HIS) and provides a user interface (UI) via an ordinary internet browser

ACM obtains patient information from the customer’s HIS. Healthcare professionals can access ACM in the following ways:

- Via the ACM Application when the HIS only provides patients’ data but does not handle the ACM response
- Via an HIS when ACM is integrated into that HIS (consequently disabling the Application)

1.2 How to use the User Manual

Purpose. This manual is intended for study and reference purposes.

Identification. The document can be identified by the following information on the title page:
– Edition of the technical document
– Date of issue

Page identification. Page identification “Page 3 of XXX” refers to page 3.

Changes. Changes to this manual will be released as new editions, supplements, or product information.

Version

The current issue of the Instructions for Use is valid as of ACM version 4.0.

Illustrations and photos of parts, as well as screenshots, used in the documents may differ from the actual parts if they are not relevant for proper functioning.

NOTE: This document is subject to change without notice.

Reproduction and distribution of parts of this manual or of the programs for any purpose whatsoever is strictly prohibited without express written permission. Copies may only be made to the extent permitted by applicable law. Disclosure to third parties is prohibited.

This documentation was prepared with great care and attention to detail. However, we cannot exclude the possibility that errors or inadequacies may still exist. We ask the reader to notify us of any such errors so that they can be addressed in the next version.

Important notice
Fresenius Medical Care AG shall not be liable for any damages caused by improper use of the product. Liability for consequential damages is excluded, as far as this is legally permissible. Using the product in vital systems (i.e. those in which breakdowns or malfunctions pose a threat to human life) without prior written consent of the manufacturer is prohibited.

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1.2.1 Significance of warnings

Advises the operator of hazards that carry the risk of serious to potentially life-threatening bodily injury to persons, unless the measures for avoiding the risk described are followed.

Warning

Type and cause of risk

Possible consequences of exposure to the risk

→ Measures for avoiding the risk

Warnings can deviate from the above template in the following cases:
– If a warning describes several risks
– If no specific risks can be described in the warning

1.3 Identification label

No packaging is available as the “Anemia Control Model” product is a software installed remotely. The “About Box” of the ACM client software serves as the label. For details, see the chapter entitled “About ACM”.

1.4 Glossary

ACM	Anemia Control Model
CKD	Chronic kidney disease
Erythropoiesis stimulating agent therapy	Erythropoiesis stimulating agents are erythropoietin synthetic analogs that act like natural hormone-enhancing RBC production in the bone marrow. All ESAs share the same mechanism of action, but differences in pharmacokinetic, pharmacodynamic, and receptor-binding properties affect their clinical potency, efficacy, and modality of use.
ESA	Erythropoiesis stimulating agent
ESRD	End stage renal disease. In this terminal phase of chronic kidney disease (CKD), kidney failure is irreversible; transplant or continuous renal replacement therapy are essential for patient survival.
FME	Fresenius Medical Care
Hb	Hemoglobin
HD	Hemodialysis
HIS	Healthcare information system used for clinical data management
IIS	Internet Information Services
Iron therapy	Iron therapy in patients with CKD-secondary anemia is in some cases enough to achieve and maintain a target-range Hb level. Iron agents may therefore serve as primary therapy or be used in combination with ESAs. When administered as adjuvants to ESAs, iron agents prevent iron deficiency and serve to minimize the ESA dose needed to achieve target-range Hb levels
MAE	Mean absolute error
OS	Operating system
RBC	Red blood cell
RDBMS	Relational database management system
Secondary anemia	Anemia may be caused by a reduction in the number of RBCs or by a decreased RBC content of iron-hemoglobin (Hb; the functional oxygen transporter elements). Many pathological conditions may disrupt the balance between RBC production and loss, leading to anemia. When anemia is caused by a primary disease, it is called “secondary anemia.” ESRD patients usually suffer from secondary anemia predominantly due to an iron deficiency and inadequate renal production of the hormone erythropoietin in response to decreasing levels of plasma Hb
UI	(Graphical) user interface
WS	Web service

1.5 Product description

ACM is a software application that provides physicians with optimal dosage recommendations for the erythropoiesis stimulating agent (ESA) and iron pharmacological treatments to maintain patient hemoglobin and ferritin levels within the targeted range in dialysis patients.

Medical supervision is required for validating ACM suggestions and turning them into actual prescriptions.

ACM consists of two (2) major components:

- The ACM Recommendation Engine (hereinafter referred to as the “ACM service”), an online component fully managed by Fresenius Medical Care (FMC)
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ACM obtains patient information from the customer’s HIS. Healthcare professionals can access ACM in the following ways:

- Via the ACM Application when the HIS only provides patients’ data but does not handle the ACM response
- Via an HIS when ACM is integrated into that HIS (consequently disabling the Application)

A new Hb test and/or subset of lab tests that needs to be available with the new Hb is the ACM trigger. When a new hemoglobin measurement is recorded in a third-party HIS, ACM processes a pool of important patient information and provides a dosage suggestion for ESA and iron. Based on a patient’s historical clinical data, ACM generates a monthly prediction on the hemoglobin level as a function of possible ESA prescriptions. ACM suggests the best monthly dose to achieve the targeted hemoglobin range (10–12 g/dL) while avoiding wide hemoglobin fluctuations. ACM also generates the optimal iron prescription to achieve the ferritin target (500 µg/L).

The ACM Recommendation Engine receives pseudonymized[1] patient data as input and responds with the suggested ESA and iron dose values. The ACM Recommendation Engine is an online web service provided and managed by FMC (or a provider sub-contracted by FMC). The web service allows ACM functionality for all active clinics in the clinical system and can operate centrally to serve multiple sites.

The Application is an optional module which must be installed and configured by FMC (or a provider sub-contracted by FMC) at the end user’s or the healthcare provider’s locations. When this module is enabled, the Application will interface with the customer’s HIS, receive and store data, and provide nephrologists with a user interface (UI) to view and manage the dosage recommendations, patients, and system configuration. The Application UI is accessed from the customer’s local network via a web browser.

ACM is a computer program and therefore:

- No material has been used to manufacture it
- It does not include any component other that the software itself
- It is not composed of any medicinal substance, tissue, or blood product
- It comes neither into direct nor indirect contact with the human body
- Factors like sterile conditions do not apply

[1] This is the process by which an alphanumeric identity code (i.e. a Patient Key ID) is used to group all data related to each specific patient (e.g., laboratory tests, drug administrations), but identity-related data (e.g., name, surname, HIS patient ID) will never be transferred over the internet.

1.6 Intended purpose

1.6.1 Intended medical purpose and medical indication

Intended purpose
Decision support for anemia drug therapy for dialysis patients.

Medical indication
The Anemia Control Model (ACM) is a software application that provides physicians with dosage recommendations for Erythropoiesis Stimulating Agent (ESA) and iron for adult patients with End Stage Renal Disease (ESRD) undergoing dialysis and affected by secondary anaemia.
ACM suggestions must be validated by a doctor who makes the ultimate decision on whether to apply the ACM's recommendations when prescribing. Doctors are required to evaluate the safety of the ACM's suggestion for each patient on a case-by-case basis. ACM is intended to assist in, and is not a substitute for, a doctor's clinical judgment.

1.6.2 Intended patient population
The intended patient population is composed of adult ESRD patients undergoing chronic dialysis and affected by secondary anemia.

1.6.3 Intended user group and intended environment
ACM is intended for use by trained medical personnel such as nephrologists and doctors in dialysis clinics or other settings where anemia management for hemodialysis patients is conducted.

1.6.4 Side effects
None.

1.6.5 Contraindications
ACM will not provide an ESA or iron suggestion for a patient whose current condition matches one of the ACM's exclusion criteria (see Chapter 2).

1.6.6 Principles of operation and mode of action
ACM receives patients' data from their HISs via network connection and derives therapy suggestions from these. Therapy suggestions are made available to nephrologists in one of the two ways described in Chapter 1.5.

1.7 Indication for use
The Anemia Control Model is intended to be used by clinicians to manage anemia in adult end stage renal disease (ESRD) patients. The Anemia Control Model is designed to obtain, track and trend patient data pertaining to the management of anemia by providing erythropoiesis-stimulating agent (ESA) and iron dosage recommendations to achieve and maintain patient hemoglobin and ferritin levels within a targeted range in dialysis patients.

1.8 Condition of use
The ACM Recommendation Engine must be installed on dedicated servers and accessed remotely either by the Application or by the clinical system where ACM is integrated.

ACM should be operated under standard climate conditions with respect to humidity, temperature (15°C–40°C) and pressure.

1.8.1 Clinical considerations and medical aspects

ACM suggestions cannot become actual prescriptions without medical authorization. ACM use must conform to and respect the following:

- Physicians must consider the patient's overall clinical condition in order to evaluate the ACM's ESA and iron suggestions and to select the best individual therapy
- ESA and iron therapies are just one part of anemia treatment. Physicians must take all necessary measures to optimally treat the patient's anemic status (for example, anemia may be caused by gastrointestinal bleeding; this condition must be checked for and, if possible, treated independently of ACM suggestions)
- When a patient is in a critical anemic condition (i.e. hemoglobin < 8 g/dL), the ACM suggestion must be carefully evaluated because erroneous ESA and iron dosages may put the patient at risk
- ACM is not designed to treat patients in critical conditions. ACM only suggests how to adjust the pharmacological therapy, which might be insufficient for some patients.
- In accordance with international anemia guidelines, specific upper and lower limits for ESA and iron dosages, as well as upper hemoglobin and ferritin limits for ESA and iron therapy interruption, have been set in the machine. Dangerously high drug doses are automatically blocked and no ESA and/or iron therapy is administered.
- In accordance with guidelines for the treatment of anemia in chronic kidney disease, ACM recommends interrupting ESA therapy when hemoglobin > 13 g/dL. For patients dialyzing via a fistula, physicians must carefully evaluate ACM suggestions when the hemoglobin level is close to 13 g/dL.
- If patient hemoglobin levels change abruptly, the physician must investigate the possible causes and carefully evaluate ACM suggestions
- Should ACM fail to provide dosage recommendations, physicians must determine ESA and iron prescriptions based on available patient information
- The ACM's algorithms have been developed based on retrospective data from real patients (i.e., actual biochemical and clinical data together with actual administered drug quantities)
- ACM provides reliable therapy recommendations when all of the following conditions are met:
  - Hemoglobin is measured at least every month
  - Ferritin is measured at least every six (6) months
  - Biochemical parameters are assessed from samples taken before a dialysis treatment
- No more than 15 days should elapse between the Hb measurement that triggers the ACM recommendation and its translation into an ESA prescription. There is currently no evidence to support ACM use when ESA prescriptions occur 15 days after their associated serum hemoglobin determination.

- ACM recommendations for iron therapy pertain to ferritin determinations taken in the past 1–3 months. If serum ferritin is measured less frequently (e.g., once every 4 months), iron prescriptions after the validity period should be carefully revised by the attending physician.
- Accurate data is of fundamental importance because erroneous or inaccurate data will result in incorrect recommendations
- There is insufficient evidence for the benefit of using ACM among patients with porphyria. A physician should evaluate the appropriateness of an ACM suggestion on a case-by-case basis. Continuous medical attention may be necessary when using ACM for patients with porphyria.

1.9 Interaction with other systems

ACM works in conjunction with the patients' data source (i.e. third-party HIS used for clinical data management).

1.10 System requirements

ACM must be installed by an authorized technician.

Warning

Risk for the patient as a result of incorrect data
Risk for the patient as a result of an incorrect therapeutic decision

If the ACM Application is not properly configured, data cannot be transferred correctly

→ ACM must be installed and configured by authorized service technicians
→ It is the responsibility of technical support to verify that the interface between the ACM Application and the ACM Recommendation Engine is functioning properly

1.11 IT environment

The clinic is responsible for managing the IT infrastructure that hosts the ACM Application (hardware, network, OS, and RDBMS) and the security monitoring and alert systems for the machine and the network.

FME is responsible for the management and security of the ACM Recommendation Engine and the ACM web service updates. FME arranges access management, the system, updates, and backups with the data center sub-contractor. Network, system, and application security monitoring and alerting functions are in place to check for anomalous access patterns.

FME manages support of the ACM Application, its general maintenance as well as updates.

There are clear IT requirements for ACM. For details on the IT Environment requirements that ACM needs to fulfil, please see the ACM Service Manual, specifically the chapter om the IT Environment.

1.12 Operation

The operator must verify that the parameters entered are correct when changing the settings (e.g., the models), entering parameters or making the decision about whether to apply the ACM's recommendation when prescribing.

ACM use requires continuous clinician supervision and control action so that expert nephrologists do not write prescriptions until viewing both the software outcome and the patient's clinical conditions. In general, ACM is not designed to treat patients in critical conditions.

Warning

Risk for the patient as a result of an incorrect therapeutic decision

Inappropriate prescriptions may change a patient's anemic status from severe to critical

→ Doctors must independently prescribe the ESA dosage in the event of a critical anemic status or an excessive hemoglobin level and the iron dosage in the event of a critical iron deficiency status or an excessive ferritin level

Warning

Risk for the patient as a result of an incorrect therapeutic decision

Inappropriate prescriptions may result in patient not reaching the therapeutic target

→ Doctors are required to prescribe by themselves the ESA dosage in case of critical anemic status or too high hemoglobin level and the iron dosage in case of critical iron deficiency status or too high ferritin level

It is the responsibility of the HIS's IT to deal with any problems caused by local hardware or software (excluding the ACM Application), unreliable internal networks, misconfigurations, security threats, and the local dialysis clinic environment. Because ACM does not provide the hardware and software to run the ACM Application, all problems on the client's operating environment (e.g., bugs, faulty updates, malware protection software) are the responsibility of the HIS's technical support.

Warning

Risk for the patient as a result of incorrect data

Risk for the patient as a result of an incorrect therapeutic decision

If the HIS interface is not properly configured, data cannot be transferred correctly

→ It is the responsibility of technical support to verify that the HIS is functioning properly
→ It is the responsibility of technical support to verify the results after the import process is complete. If the import process detects any problems, please check the attached information and/or the related entities

Warning

Risk for the patient as a result of incorrect data

Risk for the patient as a result of an incorrect therapeutic decision

Data might not be transferred correctly in the event that the input or transmission is impaired by errors in communication

→ It is the responsibility of technical support to verify that the data is correct and that the software is operating properly before authorizing usage
→ It is the responsibility of technical support to verify the results after the export process is complete
→ Issues and risks related to incorrect communication between an HIS and ACM should be assessed and mitigated by a third party because the ACM team has limited control over the ACM Application's operating environment
→ It is the responsibility of the user to verify that the correct data has been imported from the HIS

Warning

Risk for the patient as a result of incorrect data

Risk for the patient as a result of an incorrect therapeutic decision

Should the network fail or the HIS malfunction, patient data and suggestions may not be available

→ Clinic personnel and technical support must take the necessary precautions and countermeasures to ensure hardware and software reliability

Warning

Risk for the patient as a result of incorrect data

Risk for the patient as a result of an incorrect therapeutic decision

If the ACM Application is not properly configured, data cannot be transferred correctly

→ ACM must be installed and configured by authorized service technicians
→ It is the responsibility of technical support to verify that the interface between the ACM Application and the ACM Recommendation Engine is functioning properly

1.13 Referenced documents

- ACM Service Manual

1.14 Reporting of incidents

Within the EU, the user must report any serious incident that has occurred in relation to the device to the manufacturer using the information on the label (🏭) as well as the competent authority of the EU member state in which the device is used.

1.15 Certificates

ACM is a class IIa medical device according to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR).

The current versions of the EC certificates will be provided by your local service support organization on request.

1.16 Disposal regulations

Dispose of the product and its packaging in accordance with local disposal regulations. No special precautions must be taken to dispose of the product and its packaging safely.

1.17 Help and support

Please address any inquiries to:

Manufacturer	Fresenius Medical Care AG Else-Kröner-Straße 1 61352 Bad Homburg +49 6172 609-0 www.fmc-ag.com

Service / Support	For customer service, please contact one of the following e-mail addresses: ACM-Support@fmc-ag.com (second-level support team) 3level-ACM-support@doit.zone (third-level support team)

1.18 General Data Protection Regulation (GDPR)

ACM has been designed, developed, and tested in line with security best practices for software and web applications. The authentication, encryption, integrity verifications and communications protocols used in the ACM Application are industry standard and widely adopted. ACM has been designed and developed to comply with the European General Data Protection Regulation (GDPR).

1.18.1 GDPR-compliant usage

The GDPR (General Data Protection Regulation) is a law in effect in the European Union. ACM version 3.0 or later allows for full GDPR-compliant usage.

The following GDPR-relevant features are implemented in ACM:

- The ACM service runs in a secured facility and is protected by multiple levels of firewalls and a security alert system
- The ACM Recommendation Engine allows only connections secured using the HTTPS protocol. Access to the ACM Application UI (by the user, administrator, or remote support) is protected by a login process. Use of secure connections is mandatory and each user session is authenticated
- User passwords are saved as encrypted hash in the database using the “HMACSHA512.ComputeHash” method
- ACM Application login activities are logged, and these logs should be audited
- A special support user profile without access to patients’ identities is dedicated to support UI-related issues
- Personal patient data in data requests and responses to ACM is pseudonimyzed, connections are made via standard secure protocols, and communication partners’ identities are checked using both client and server certificates and an IP whitelist. The ACM Application database separates patient identity tables from other stored information. Although the other tables store sensitive data, patients are referred to only by their Patient Key ID (a pseudonymized ID). Access to this DB (for support activities) does not expose patient identities.
- ACM defines a system of user access management, which includes user authentication, user authorization, user roles, user permissions, etc. Only users with the respective permission (right) can access a certain function of ACM
- Depending on a configurable level of security defined by the customer, ACM requires users to login when starting the application
- Request and responses between the ACM Application and ACM service are signed and validated
- ACM may be periodically updated to improve performance. This process does not require the use of any customer data
- Software releases are versioned and signed
- All security measures in ACM are implemented and configured by default

1.18.2 Personal patient data processed in ACM

Data import and data export security. The ACM Application does not need access to the customer HIS because no data is sent back to that HIS. The ACM Application does not alter or directly interact with HIS data.

Separating patient identities in a dedicated and secured database table that can only be accessed only by the ACM Application graphical UI from trusted clients and authorized users in the internal network minimizes the risk of patient identity exposure. These identities cannot be accessed during the ACM communication exchanges.

Data privacy policies. The ACM library and log files will be located on a designated server installed at the service provider subcontracted by FME. The data sent to the algorithm and logged to file is pseudonymized.[2] Only the clinic treating the patient has access to that data and can map the alphanumeric ID code to the actual patient. The customer is responsible for ensuring a data privacy check process.

To ensure data privacy, the ACM Application database is managed by the customer's IT.

During the HIS data export procedure, a Patient Key ID is created for use by the ACM Application and the ACM web service communications. The Patient Key ID is used to refer to pseudonymised data of a specific patient. Each Patient Key ID is unique and will remain the same as the one assigned during the initial import.

Patients' identities are displayed only in the ACM Application and never exit the hospital environment.

Data logging. Data sent to the ACM web service for prescription drug suggestions will be logged to allow for subsequent analyses. Logged data will be used for the following:

- Data quality check
- Reproducing ACM suggestions
- Reconstructing decisions made based on suggestions
- Documentation purposes
- Analysis of ACM performance in terms of Hb lab tests within the target range
- Monitoring the software's operation

Logs collected by FME will be backed up.

Cryptography. Communication between the Recommendation Engine and the ACM Application is signed using the "HMACSHA512.ComputeHash" method.

[2] This is the process by which an alphanumeric identity code (i.e. a Patient Key ID) is used to group all data related to each specific patient (e.g., laboratory tests, drug administrations), but identity-related data (e.g., name, surname, HIS patient ID) will never be transferred over the Internet.

2 Basic information about ACM

2.1 Exclusion criteria

There are 2 types of exclusion criteria that render ACM unable to generate a suggestion: General exclusion criteria and ESA- and iron-specific exclusion criteria.

2.1.1 General exclusion criteria

ACM considers a patient ineligible if any of the following general criteria is satisfied:

- Patient Hb laboratory test is missing or its reference date is in the future
- Patient date of birth is missing or the patient is underage
- Patient admission date is missing or it is too close to the suggestion date

2.1.2 ESA- and iron-specific exclusion criteria

ESA or iron suggestions are not generated if:

- The patient's Hb lab test is more than 15 days old (only for ESA suggestions)
- The patient's ferritin lab test is more than 40 days old (only for iron suggestions)

ESA or iron suggestions are not generated if, in the 120 days preceding the last Hb/ferritin lab test:

- The patient has not spent enough time in the clinic as an active HD patient or has received at least 1 blood transfusion (enough time as HD patient = the patient received at least 70% of the expected dialysis sessions during the previous 120 days)
- ESA or iron other than the selected ones have been administered for ESA suggestion. Iron other than the selected ones have been administered for iron suggestion.
- Dosages of the selected drugs (ESA and iron for ESA suggestion, iron for iron suggestion) have been measured in an unexpected unit of measurement
- ACM requires an exact correspondence between the selected drug formulation and the actual route of administration for both ESA and iron (ESA suggestion), and iron only (iron therapy suggestion). If drugs are not administered in accordance with the selected formulation and administration routes, ACM does not generate a suggestion.

2.2 Expected performance

To validate the accuracy of ACM's ability to predict patients' response to anemia therapy, which is the foundation for the elaboration of the optimal therapy, we have performed simulation experiments on actual HD patients' retrospective data; machine results have then been compared to the real patient outcomes.

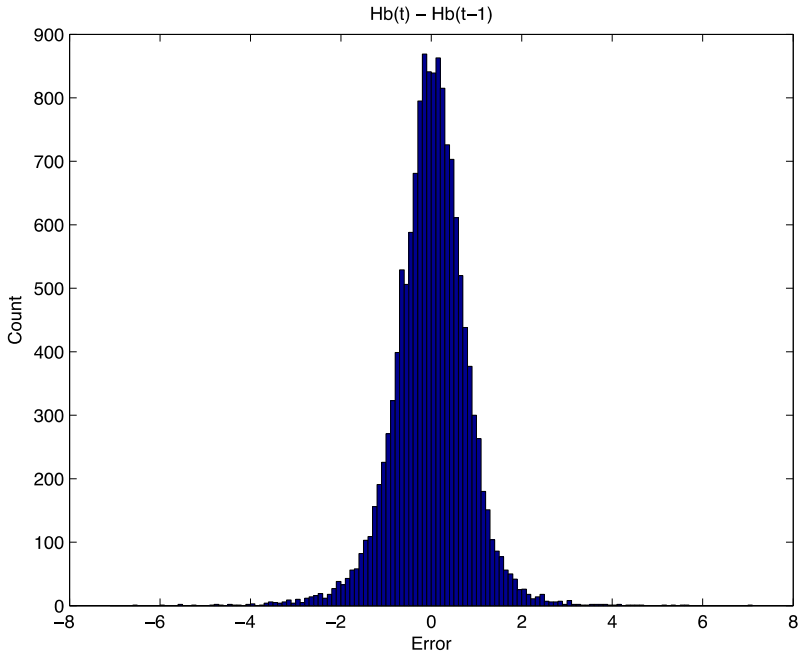
The experimental population was composed of adult ESRD patients undergoing stable HD and satisfying the inclusion criteria (i.e. when none of the exclusion criteria occurs). Pre-dialysis, peritoneal dialysis, intensive care patients and children (age < 18 years) are

excluded from the study. Any other general conditions (such as for instance chronic or acute comorbidities, gender, etc.) do not influence patient inclusion.

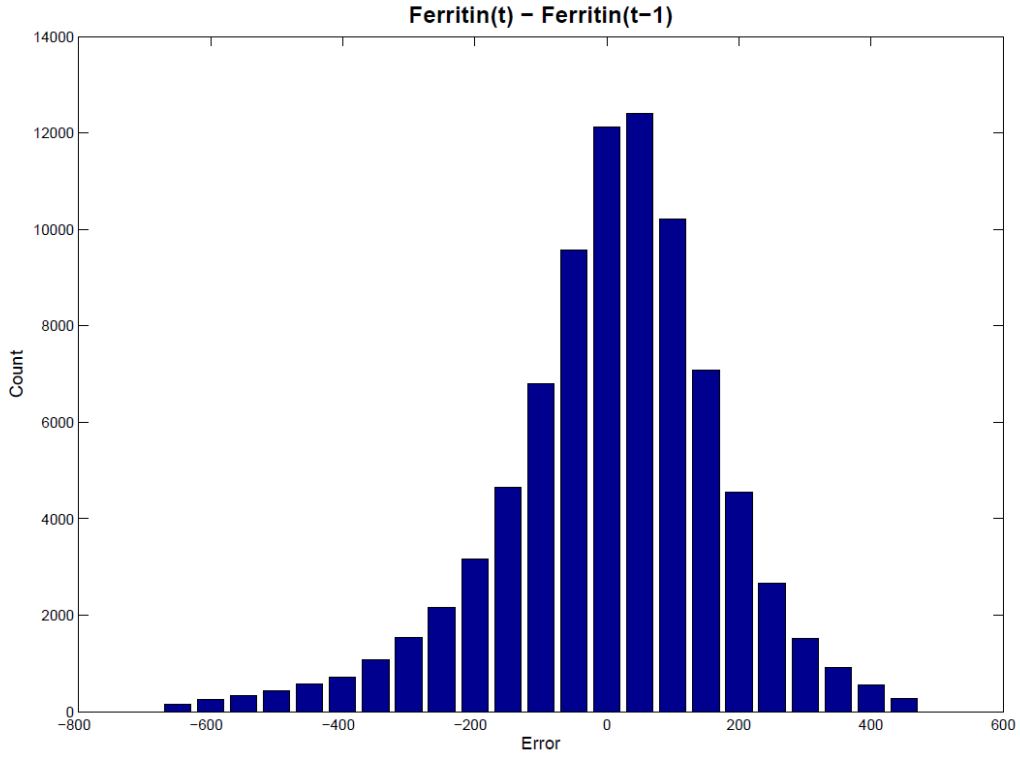
To investigate the strength of the relationship between the predictions and the true outcomes, the mean absolute error (MAE) has been used. The MAE was calculated as the sum of the absolute values of the differences between predicted next hemoglobin/ferritin level and true values (total error), then divided by the total number of measurements.
The results can be summarized as follows:

- HB PREDICTION TASK
  - MAE 0.52 g/dL (on validation dataset)
  - 93% of prediction errors < 1g/dL

The following figure shows the error distribution that is centred on zero. Errors greater than 2 g/dL can be considered outliers; they may be caused either by erroneous values or by the presence of events the algorithm cannot foresee (i.e. transfusions, blood loss, etc.). It is important to remember that these outliers do not influence how the algorithm works; they simply have an impact on the error.



- IRON PREDICTION TASK
  - MAE: 139.1 µg/L (or ng/ml)
  - 79% of prediction errors < 200 µg/L (or ng/ml)



2.3 Available algorithms

ACM version 2.10 or later supplies four suggestion algorithms for ESA therapy:

I. **Darbepoetin** - Considers darbepoetin alfa (Darbo, identified by the unique ATC: B03XA02), measured in mcg (micrograms), as the selected ESA. The admissible administration method is either the intravenous or subcutaneous route. If the selected ESA is intravenously administered darbepoetin, all dosages measured in mcg of subcutaneously administered darbepoetin have to be converted with a conversion factor equal to 1. If the selected ESA is subcutaneously administered darbepoetin, all dosages measured in mcg of intravenously administered darbepoetin have to be converted with a conversion factor equal to 1.
In addition, the set of convertible ESAs consists of:

- Intravenously administered epoetin, whose dosages are measured in IU and converted to mcg with an appropriate conversion factor
- Subcutaneously administered epoetin, whose dosages are measured in IU and converted to mcg with an appropriate conversion factor

Therefore, the accepted past administered ESAs are mcg-iv-darbepoetin or mcg-sc-darbepoetin or IU-iv-epoetin or IU-sc-epoetin.

II. **IV-epoetin** - Considers intravenously administered epoetin (Epo, identified by the unique ATC: B03XA01), measured in IU (international units), as the selected ESA. The selected administration method is the intravenous route.
The set of convertible ESAs is given by:

- Intravenously or subcutaneously administered darbepoetin, whose dosages are measured in mcg and converted to IU with an appropriate conversion factor

- Subcutaneously administered epoetin, whose dosages are measured in IU and converted to iv-epoetin with an appropriate conversion factor

Therefore, the accepted past administered ESAs are IU-iv-epoetin or IU-sc-epoetin or mcg-iv-darbepoetin or mcg-sc-darbepoetin.

III. **SC-epoetin** - Considers subcutaneously administered epoetin (Epo, identified by the unique ATC: B03XA01), measured in IU (international units), as the selected ESA. The selected administration method is the subcutaneous route. The set of convertible ESAs is given by:

- Intravenously administered darbepoetin, whose dosages are measured in mcg and converted to IU with an appropriate conversion factor
- Intravenously administered epoetin, whose dosages are measured in IU and converted to sc-epoetin with an appropriate conversion factor

Therefore, the accepted past administered ESAs are IU-sc-epoetin or IU-iv-epoetin or mcg-iv-darbepoetin or mcg-sc-darbepoetin.

IV. **MPG-epoetin** - Considers methoxy polyethylene glycol-epoetin (MPG-epoetin or shortly MPGepo, identified by the unique ATC: B03XA03), measured in mcg (micrograms), as the selected ESA. The admissible administration method is either the intravenous or subcutaneous route. If the selected ESA is intravenously administered MPG-epoetin, all dosages measured in mcg of subcutaneously administered darbepoetin have to be converted with a conversion factor equal to 1. If the selected ESA is subcutaneously administered MPG-epoetin, all dosages measured in mcg of intravenously administered MPG-epoetin have to be converted with a conversion factor equal to 1.
Therefore, the accepted past administered ESAs are mcg-iv-MPG-epoetin or mcg-sc-MPG-epoetin.

ACM version 2.0 or later supplies two suggestion algorithms for iron therapy according to ferritin lab test availability in each clinic: A 2-month algorithm and a 3-month algorithm.

If ferritin lab tests are less frequent (e.g., every 4, 5, or 6 months), the physician must evaluate the prescription at the end of the period covered by the chosen iron algorithm.

The recommended administration method for iron therapy is intravenous and the expected unit of measurement is milligrams (mg). The admissible iron drugs are identified by the ATC: B03AC**.[3]

The combination of an ESA and an iron algorithm provides the final ACM models:

1. **Darbo IV 1M-IRON IV 2M**: Darbepoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 2 months of validity
2. **Darbo IV 1M-IRON IV 3M**: Darbepoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity
3. **Darbo SC 1M-IRON IV 2M**: Darbepoetin dose suggested with subcutaneous administration and 1 month of validity; iron suggestion with intravenous administration and 2 months of validity

[3] Asterisks refer to the family of iron preparations where the ATC code has been truncated at the 3rd ATC digit. In the past, injectable iron preparations were classified according to a 5-digit ATC system.

4. **Darbo SC 1M-IRON IV 3M**: Darbepoetin dose suggested with subcutaneous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity
5. **Epo IV 1M-IRON IV 2M**: Epoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 2 months of validity
6. **Epo IV 1M-IRON IV 3M**: Epoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity
7. **Epo SC 1M-IRON IV 3M**: Epoetin dose suggested with subcutaneous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity
8. **MPGepo IV 1M-IRON IV 2M**: MPG-epoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 2 months of validity
9. **MPGepo IV 1M-IRON IV 3M**: MPG-epoetin dose suggested with intravenous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity
10. **MPGepo SC 1M-IRON IV 2M**: MPG-epoetin dose suggested with subcutaneous administration and 1 month of validity; iron suggestion with intravenous administration and 2 months of validity
11. **MPGepo SC 1M-IRON IV 3M**: MPG-epoetin dose suggested with subcutaneous administration and 1 month of validity; iron suggestion with intravenous administration and 3 months of validity

2.4 Input data

ACM provides suggestions for ESA and iron therapy. The input data must contain the following fields:

- Clinic code
- Country code
- Number of active prescriptions
- Current hemoglobin* and past hemoglobin, all values in the 120 days prior to the algorithm running
- Admission date*
- Birth date*
- Gender
- Height
- Ferritin°, all values in the 120 days prior to the algorithm running date (ARD)
- Albumin, the last 2 values in the 120 days prior to the ARD
- Calcium, the last 2 values in the 120 days prior to the ARD

- C-reactive protein, the last 2 values in the 120 days prior to the ARD
- Leukocytes, the last 2 values in the 120 days prior to the ARD
- MCH, the last 2 values in the 120 days prior to the ARD
- MCV, the last 2 values in the 120 days prior to the ARD
- Potassium, the last 2 values in the 120 days prior to the ARD
- Phosphate, the last 2 values in the 120 days prior to the ARD
- Sodium, the last 2 values in the 120 days prior to the ARD
- Transferrin saturation, the last 2 values in the 120 days prior to the ARD
- Pre-dialysis weight, all values in the 140 days prior to the ARD
- Dry body weight, all values in the 140 days prior to the ARD
- KtV, all values in the 140 days prior to the ARD
- Administrations of the selected ESA, all dose quantities, measurements units, submission ways and product codes in the 140 days prior to the ARD (for instance, in case of darbepoetin suggestion algorithm, the selected ESA is darbepoetin)
- Administrations of ESAs other than the selected ESA, all dose quantities, measurements units, submission ways and product codes in the 140 days prior to the ARD (convertible ESAs and undesired ESAs fall in this field)
- Intravenous iron administrations, all dose quantities, measurements units, submission ways and product codes in the 140 days prior to the ARD
- Transfusions, if at least one occurs in the 120 days prior to the ARD
- Comorbidity only for the NephroCare clinics, if the patient is currently affected by one of the following pathologies: E80.0, E80.1, E80.2 (see the ICD10)
- Overhydration (not yet used by the algorithm), the last 2 values in the 120 days prior to the ARD

* Mandatory field for the execution of the ESA and iron therapy suggestion algorithms. The patient must be excluded from the ESA and iron therapy suggestion algorithms when data in one of these fields is missing.

° Mandatory field only for the execution of the iron therapy suggestion algorithm. Further specific exclusion criteria must be applied singularly to each drug suggestion algorithm according to its time window. Refer to the specific exclusion criteria.

Optimal dose suggestion is achieved only when values for all fields are entered into ACM.

2.5 User roles

The ACM Application includes four user roles with corresponding privileges and capabilities.

1. Medical:
   - Confirm and reject suggestions

- View patient details and data (including name)
- Manage password

2. Medical Administrator:
   - All of the privileges and capabilities of the Medical role
   - Assign an ACM model after selecting a single patient, a subset of patients, or all patients
   - Assign the ACM model from the patient detail area
   - Define trigger policy parameters in the dedicated view
   - NOTE: The Medical Administrator role does not have access to the administration area (see below).

3. Administrator:
   - All of the privileges and capabilities of the Medical Administrator role
   - Delete data (one patient at a time) or patients (one at a time)
   - Access the administration area to:
     - Set the clinic default ACM model
     - Manage scheduling frequency options used for rejection
     - Manage the list of the models that can be selected and applied to the patients
     - Manage trigger policy options
     - Create new users
     - Manage user privileges
     - Remove users
     - Visualize the log notification, and track the login and the file import process

4. Remote support:
   - All of the privileges and capabilities of the Administrator role except for the ability to:
     - Access patient identities
     - Create new users
     - View and modify the existing user roles
   - The remote support role has been created for troubleshooting the user interface.

After the initial setup is complete, the remote support team will not be able to access the ACM Application. If they need to provide support to the ACM Application server, the customer's IT must set up an ad-hoc connection. That connection must ensure supervision of the remote support team by the customer's IT department.

When a patient's data is used to provide support services, ACM automatically extracts that data and keeps it anonymous.

2.6 How to start the program

Customers using the ACM application-based configuration have access using an internet web browser via a link. A login page appears as shown below.

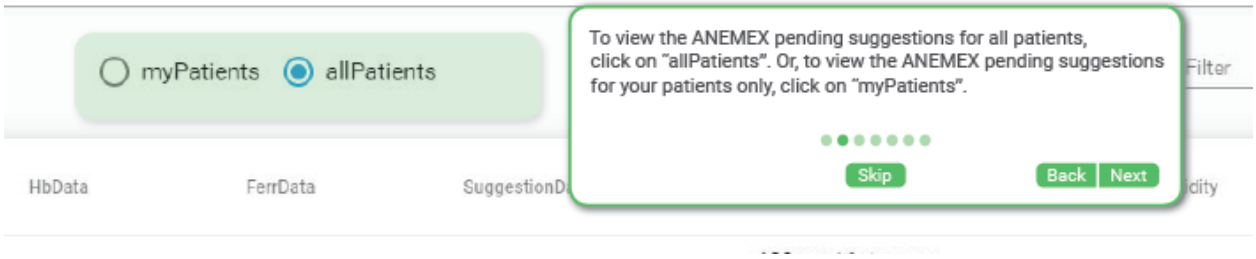
LOGIN
Username *
Dr. Smith
Password *
Login

3 ACM in routine operation

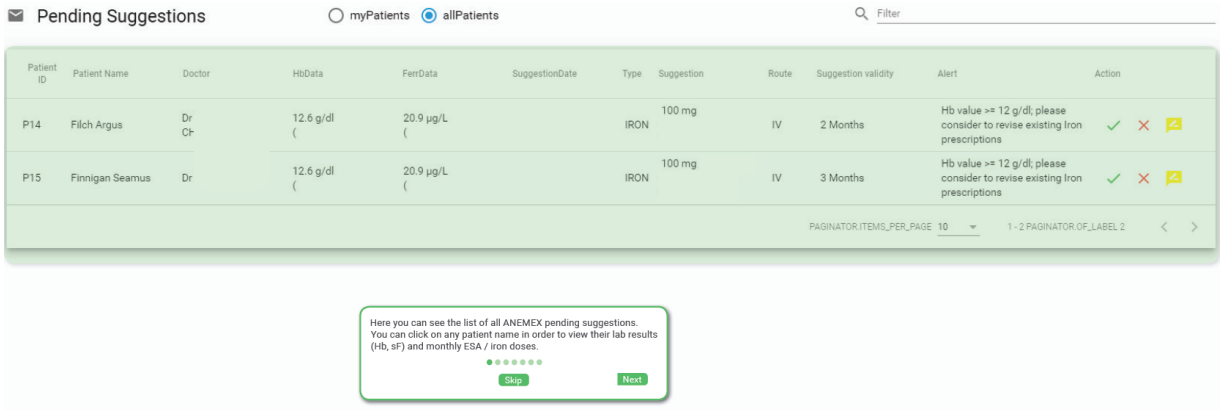
3.1 The main view

The ACM Application displays pending suggestions which the user can confirm (by clicking the green check icon) or reject (by clicking the red x).

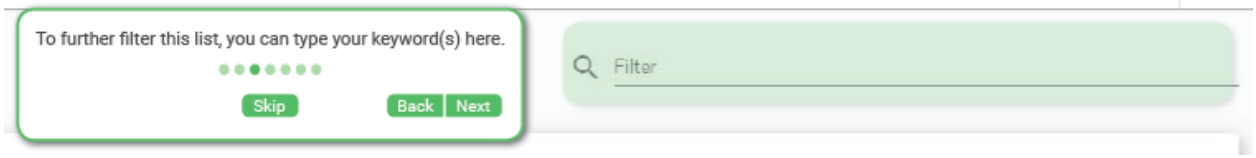
You can view suggestions for “myPatients” or “allPatients” by clicking the corresponding button.



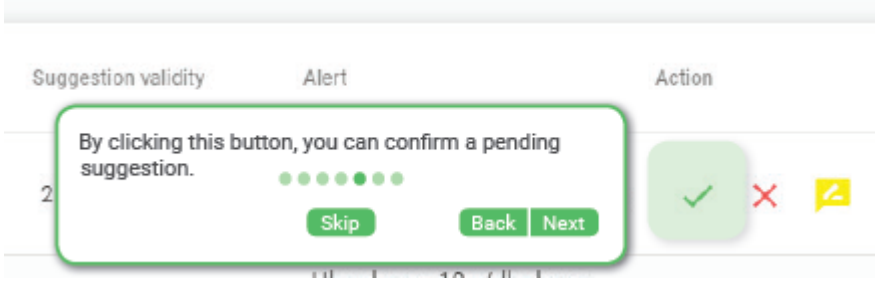
“Pending Suggestions” allows you to view patient lab results and monthly ESA/iron doses.



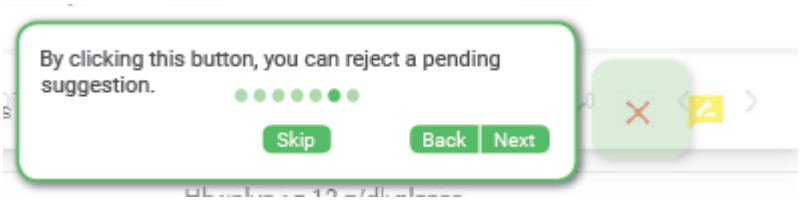
Entering a keyword filters the list.



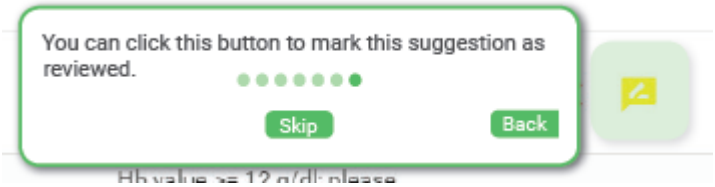
Click the green check icon to confirm a pending suggestion.



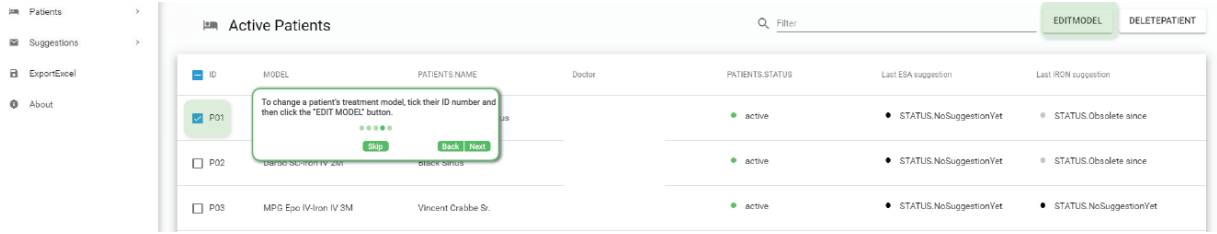
Click the red x to reject a pending suggestion.



The yellow icon automatically appears when users go to the suggestion details for the first time. It remains as “reviewed” until it is accepted or rejected.

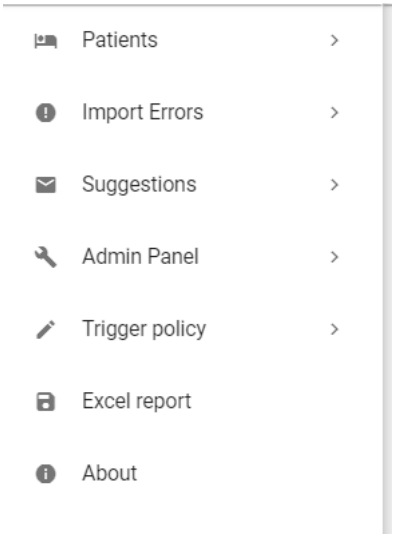


You can change a patient’s treatment model by checking the box next to their ID.

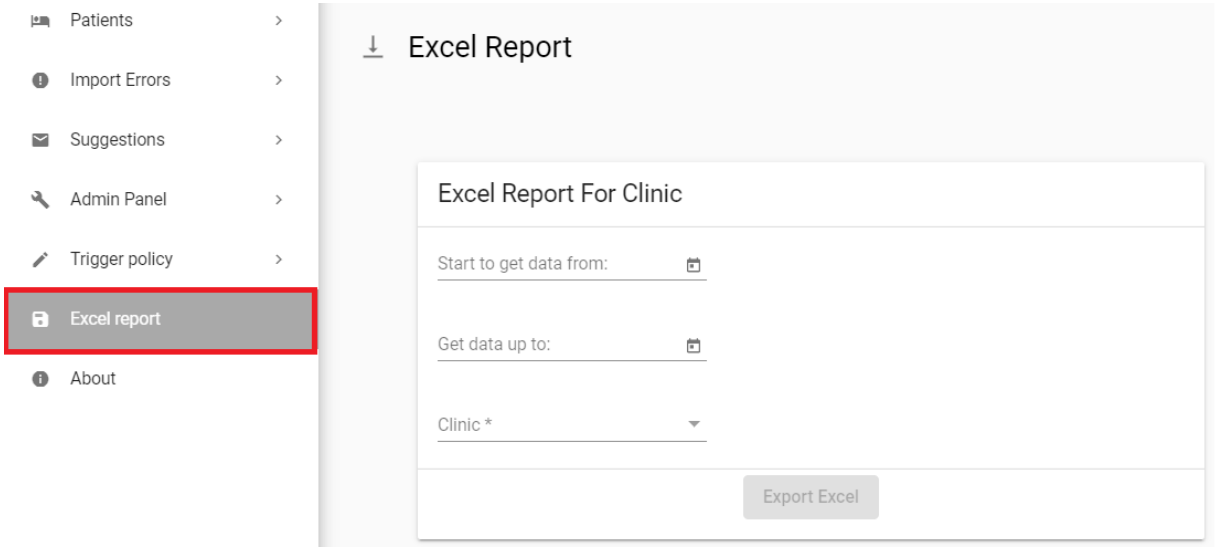


3.1.1 The menu bar

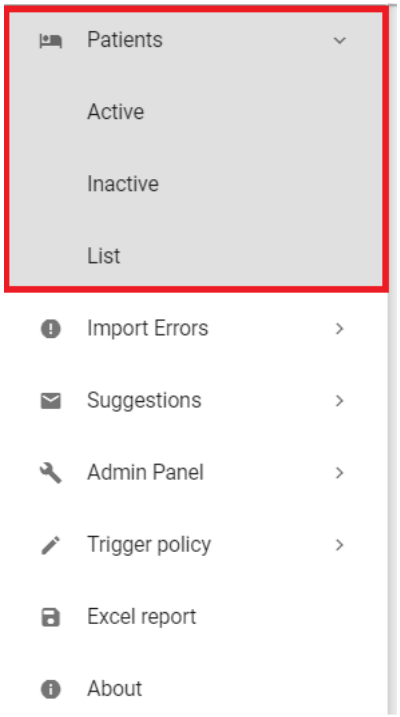
A menu bar is available to allow navigation through the different application areas and access to the different options and commands. Depending on the user role and permissions, some items may be unavailable.



Some menu items direct to a specific module or function, as displayed in the example below:



Some menu items contain sub-menus. Refer to the image below as an example of the available sub-menus:



3.1.2 About ACM

The software Instructions for Use, name of the device, unique device identifier (UDI), version, manufacturer, and manufacture date can be displayed within a dedicated “About” box in the ACM user interface, both in the HIS-integrated configuration and in the application-based configuration, as shown in the following figure.

Product:	**Anemia Control Model**
Version:	**x.y.z.w**
Date of manufacture:	**YYYY-MM-DD**
UDI:	**(01) 04039361116781 (8012) x.y.z.w**

Fresenius Medical Care AG & Co. KGaA
Else-Kröner-Str. 1
61352 Bad Homburg, Germany
+49 6172 609-0

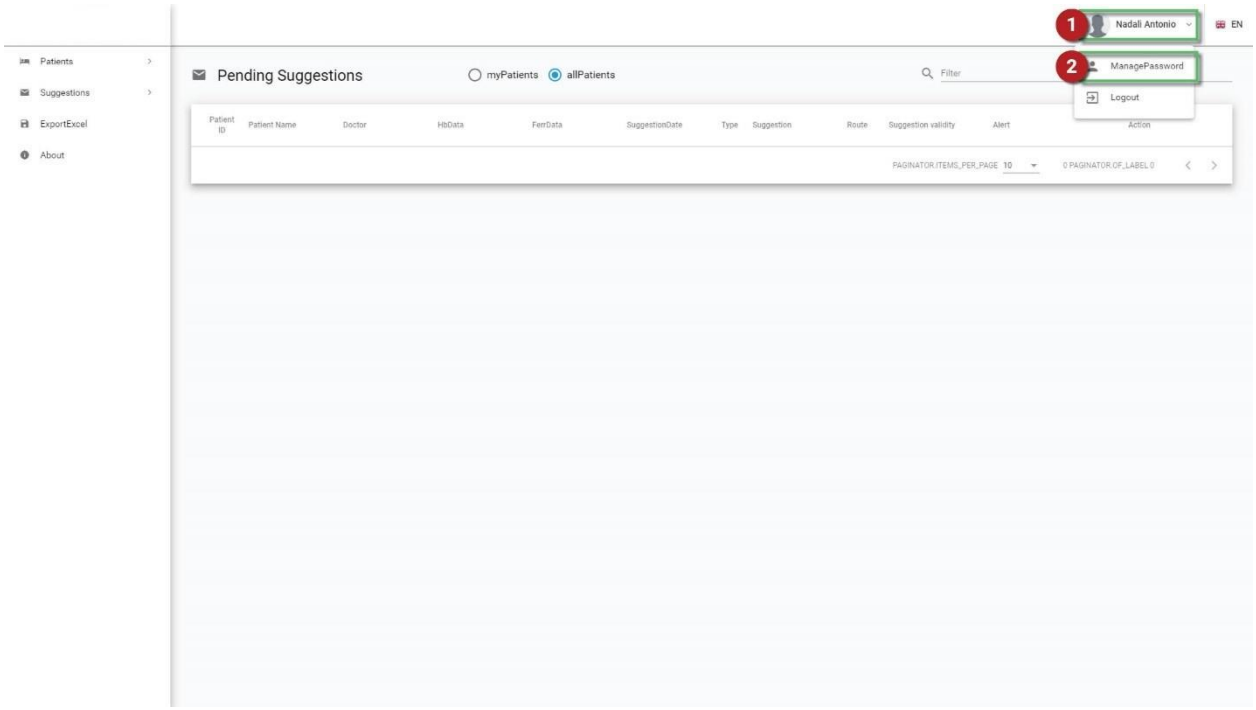
3.2 How to – users

3.2.1 How to retrieve your username and password

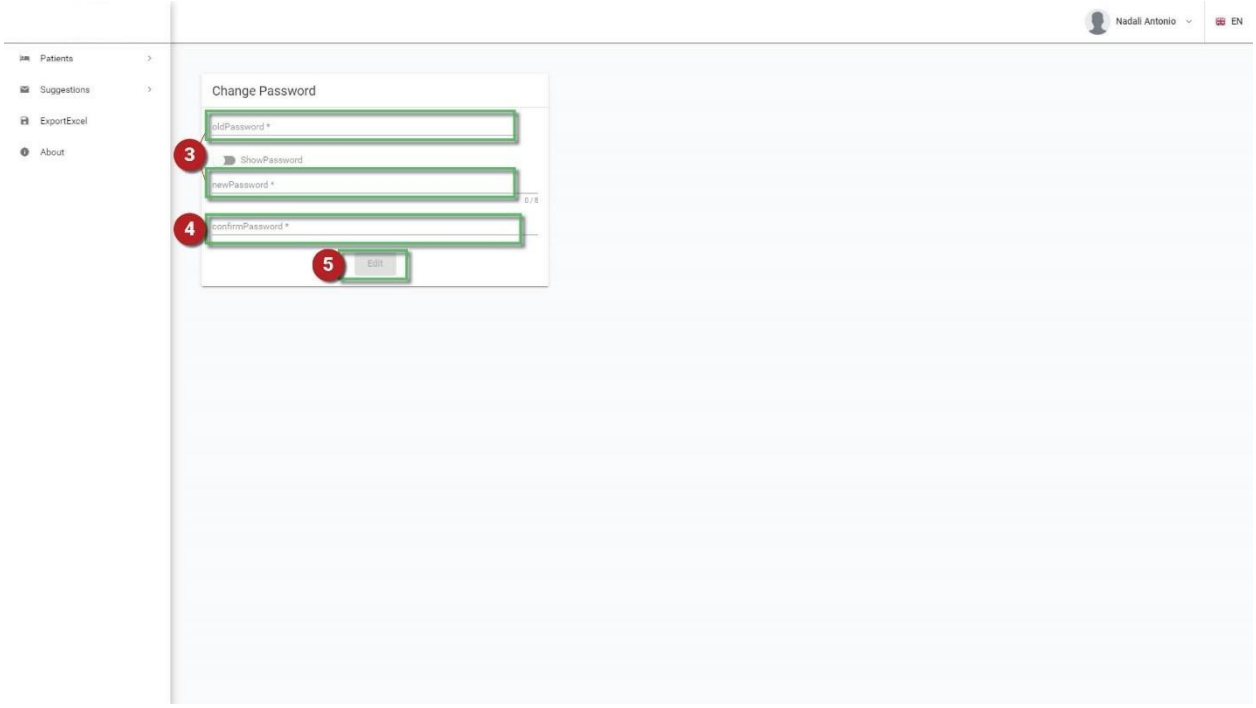
To retrieve your ACM credentials (username and/or password), you should refer to your ACM administrator who will either remind you of them or create new ones for you.

3.2.2 How to change your password

12. Click your username at the top right corner of the screen.
13. In the drop-down menu, click **ManagePassword**.



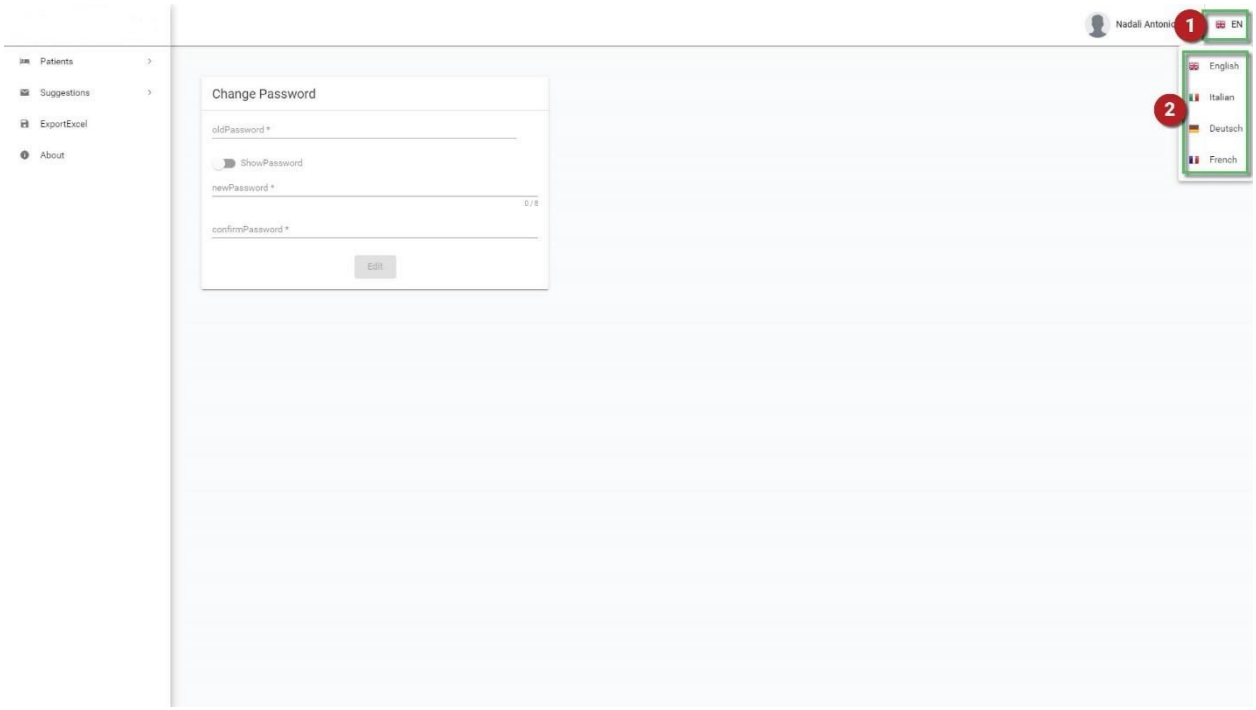
14. Type your current password and then type your new password.
15. Repeat this procedure to confirm your new password.
16. Click **Edit**.



NOTE: By default, and for security reasons, passwords are not displayed while typing. To change this default setting, click the **ShowPassword** button.

3.2.3 How to change the language

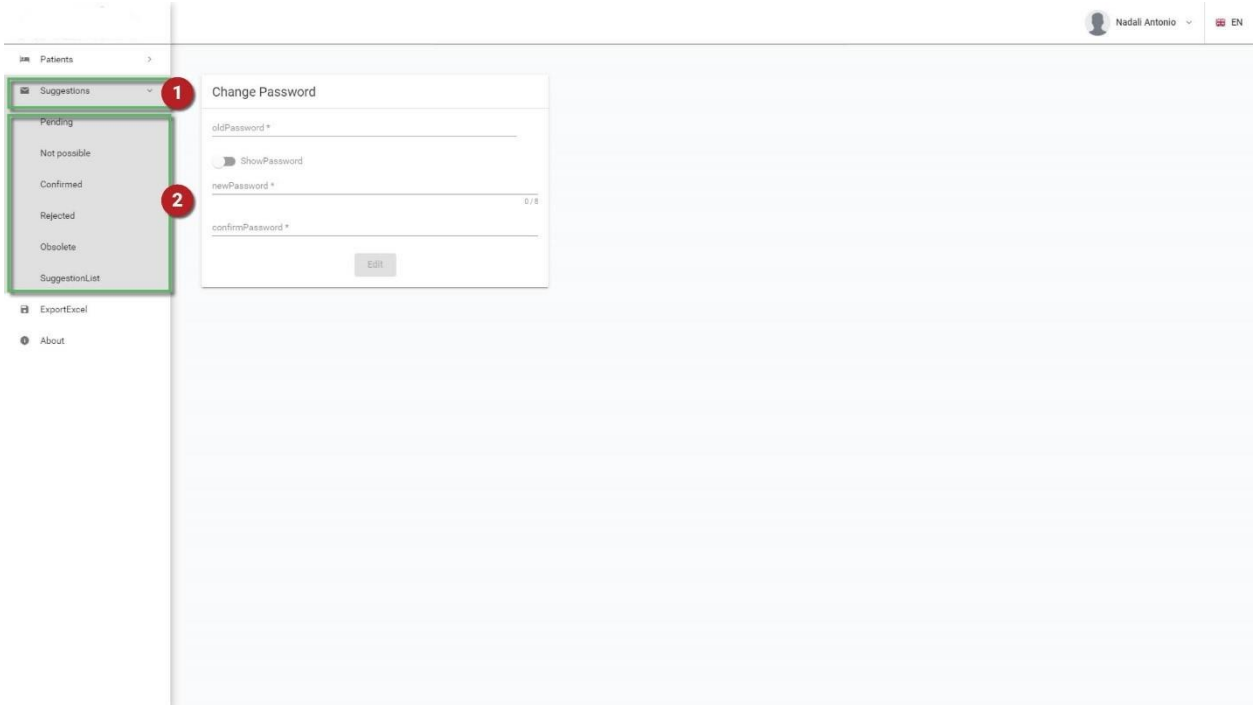
1. Click the flag at the top right corner of the screen.
2. From the drop-down menu, select the desired language.



NOTE: Available languages include English and French.

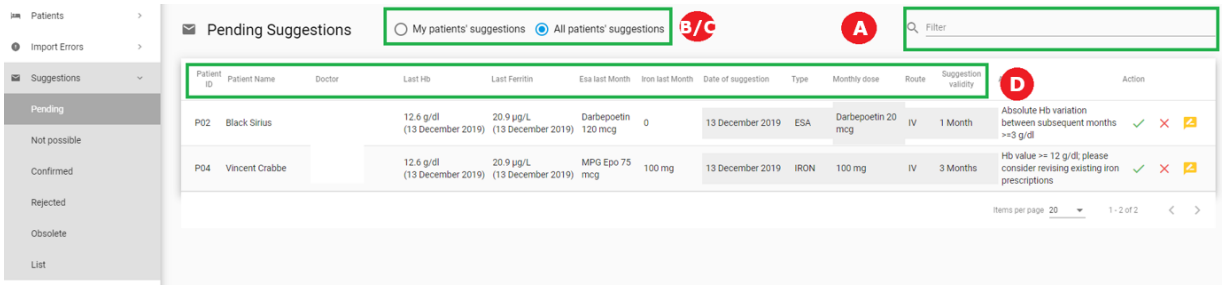
3.2.4 How to find a suggestion

1. On the left-hand side of the screen, click **Suggestions** to expand the suggestions.
2. In the Suggestions sub-menu that appears, click a suggestion status (Pending, Not possible, Confirmed, Rejected, Obsolete) or click **SuggestionList** to view the list of all ACM suggestions, regardless of their status.



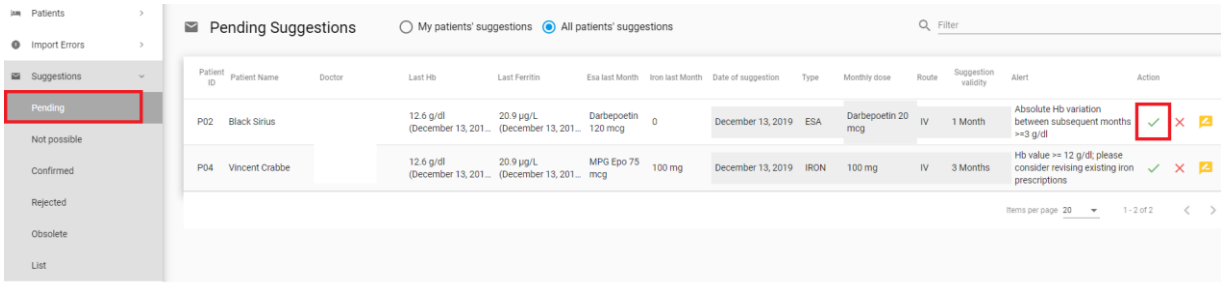
NOTE: On any Suggestions page, you are able to do the following:

a. Filter the suggestion list by typing any keyword(s) in the **Filter** field on the top left corner of the screen (NOTE: Only the following fields can be filtered: Patient ID, Patient Name, Doctor, Type, Route)
b. View a list of suggestions for only your patients by clicking **myPatients**
c. View a list of suggestions for all patients by clicking **allPatients**
d. Sort the suggestion list by clicking each title/header of the first row (Patient ID, Patient Name, Doctor, Type, Route, Suggestion validity, Alert)



3.2.5 How to confirm a pending suggestion

1. Go to the Pending Suggestions page using the main menu at the left-hand side of the screen.
2. In the Pending Suggestions list, click on the green check icon next to each patient's name.



3. In the pop-up window that appears, you can see the patient's name, their treatment suggestion, and the route.
4. Click **Confirm** to confirm the suggestion.

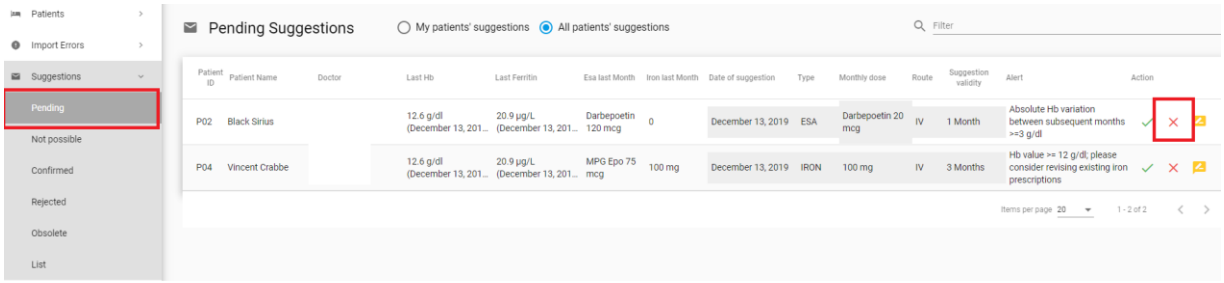
At this point, you also have the option to close the pop-up window without confirming the suggestion by clicking **Cancel**.

NOTE: Once you confirm a suggestion, it automatically appears on the Confirmed Suggestions page, which you can access using the main menu at the left-hand side of the screen.

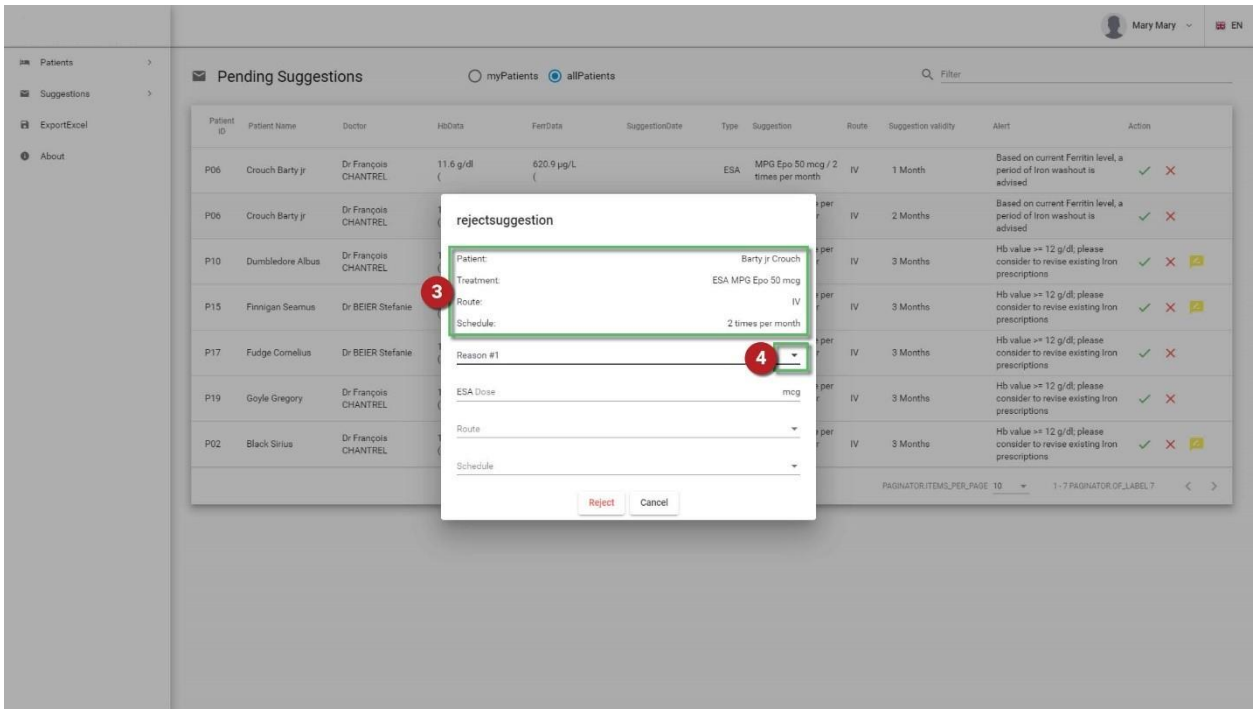
NOTE: In the Pending Suggestions page, you can click on the patient's name to view details of their labs results and monthly ESA/iron doses. You also have the option of clicking on the **View month details** button to view more detailed information about the patient's monthly ESA/iron doses.

3.2.6 How to reject a pending suggestion

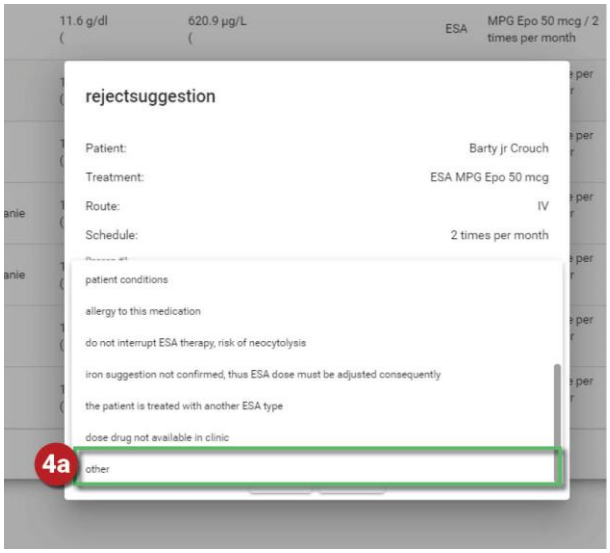
1. Go to the Pending Suggestions page using the main menu at the left-hand side of the screen.
2. In the Pending Suggestions list, click on the red X icon next to each patient's name.

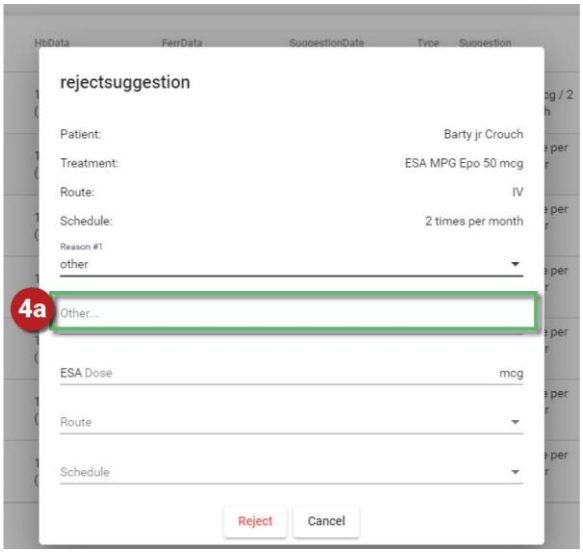


3. In the pop-up window that appears, you can see the patient's name, their treatment suggestion, the route, and the monthly dose.
4. Click the arrow in the **Reason #1** field to select the reason for rejection from the drop-down menu (optional).

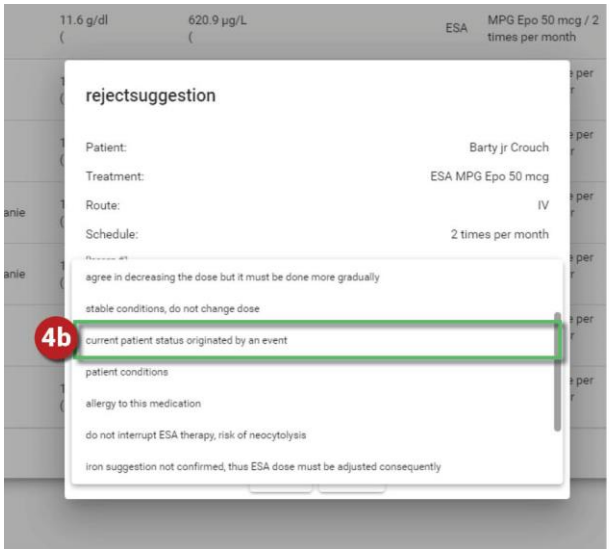


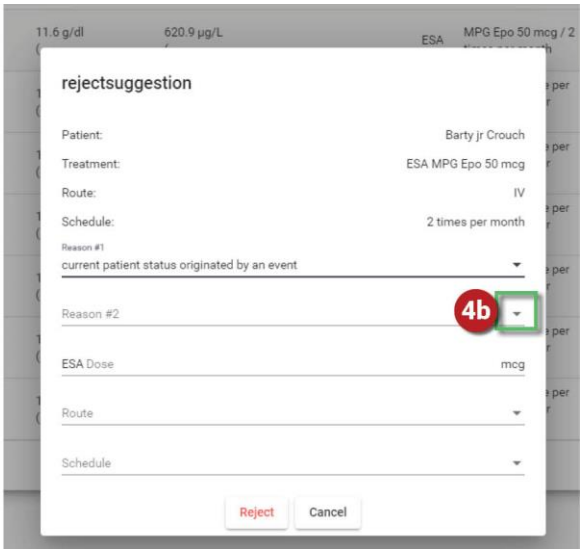
   a. If the reason for rejection does not appear in the drop-down menu, select **other** and type the reason for rejection in the respective field.



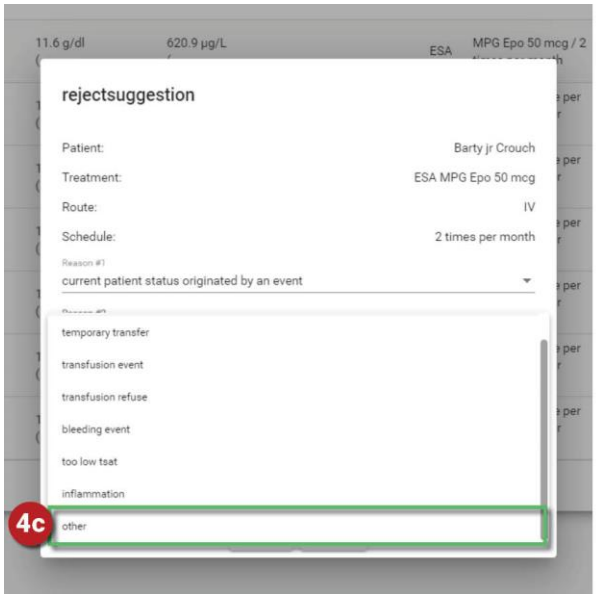


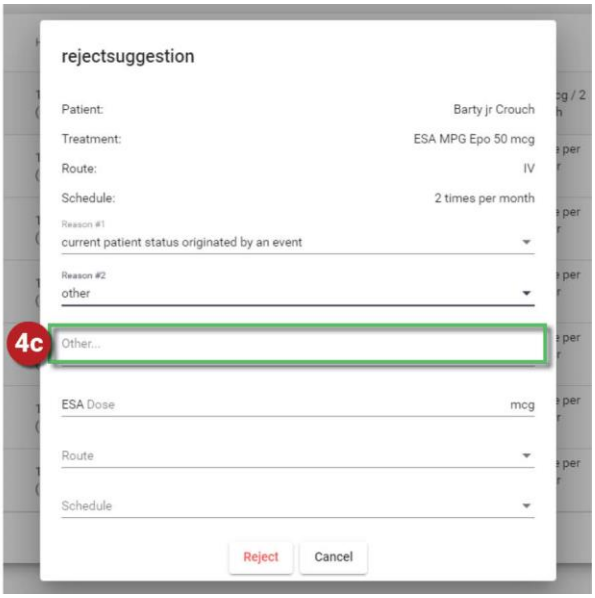
b. If the rejection is due to an event which changed the current status of the patient, select **current patient status originated by an event** and use the arrow to select this event from the drop-down menu.



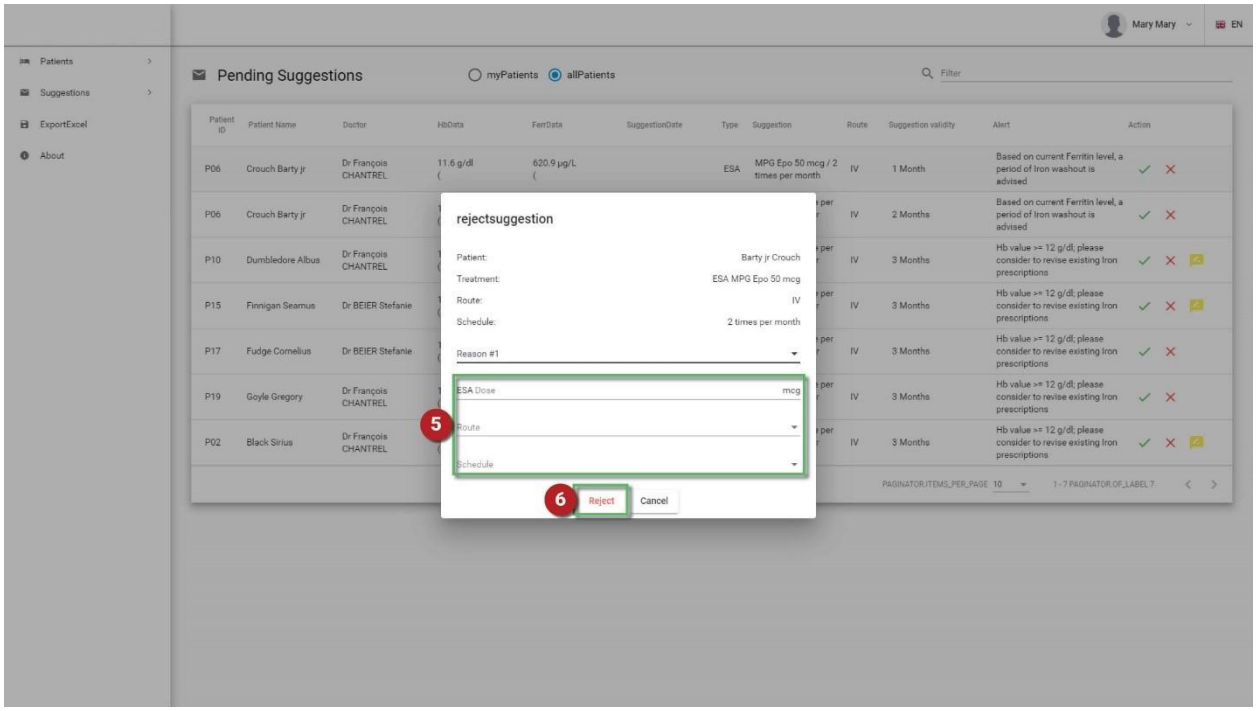


c. If the event which changed the current status of the patient does not appear in the drop-down menu, select **other** and type this event in the respective field.





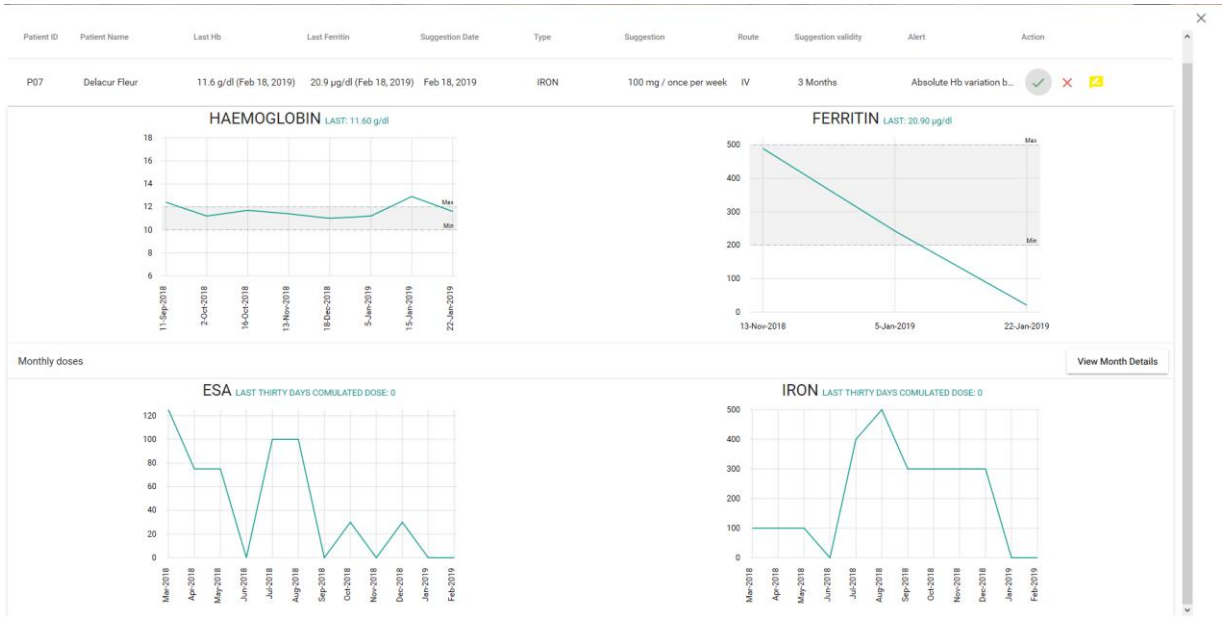
5. Type the ESA/iron dose that you plan to administer, as well as the route and schedule of its administration in the respective fields (optional).
6. Click **Reject** to reject the suggestion.



At this point, you also have the option of closing the pop-up window without rejecting the suggestion by clicking **Cancel**.

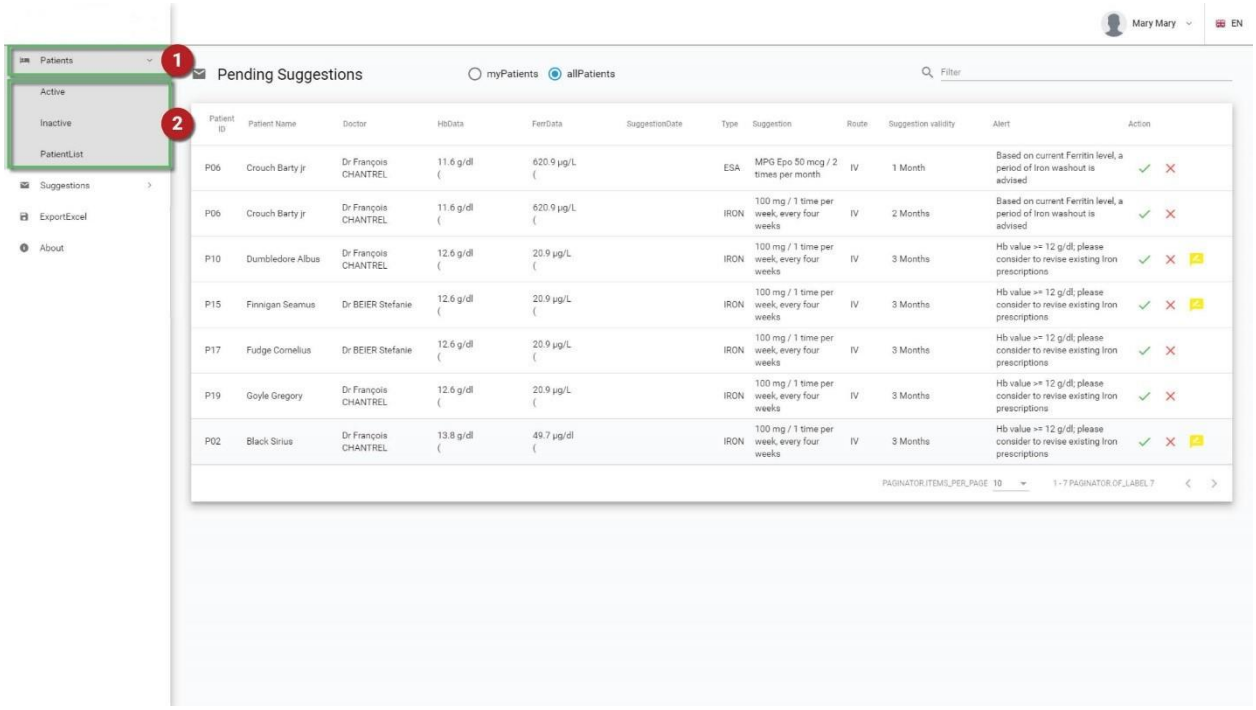
3.2.7 How to find a suggestion detailed view

Selecting a row in the main pending suggestion view displays some detailed patient information. The information may concern laboratory results and drug administrations; the information is displayed in a graph.



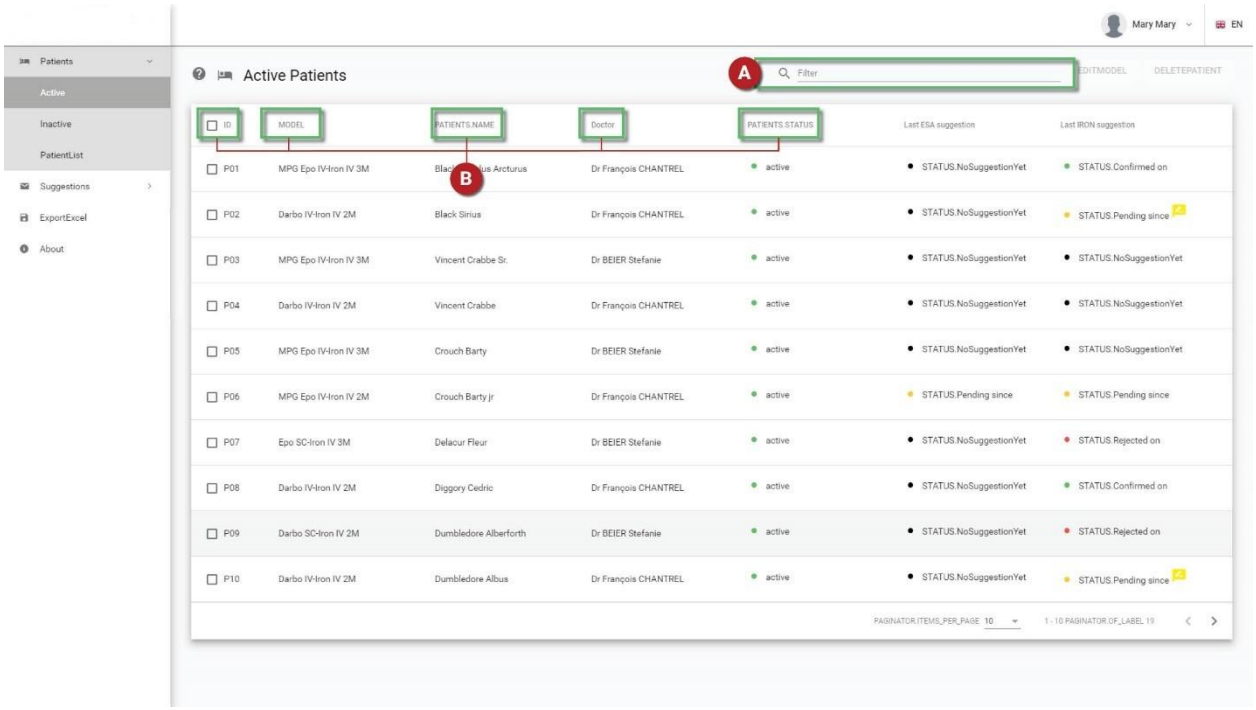
3.2.8 How to find a patient

1. On the left-hand side of the screen, click **Patients** to expand the Patients sub-menu.
2. In the Patients sub-menu that appears, click a Patient Status (Active, Inactive) or click **PatientList** to view the list of all patients, regardless of their status.



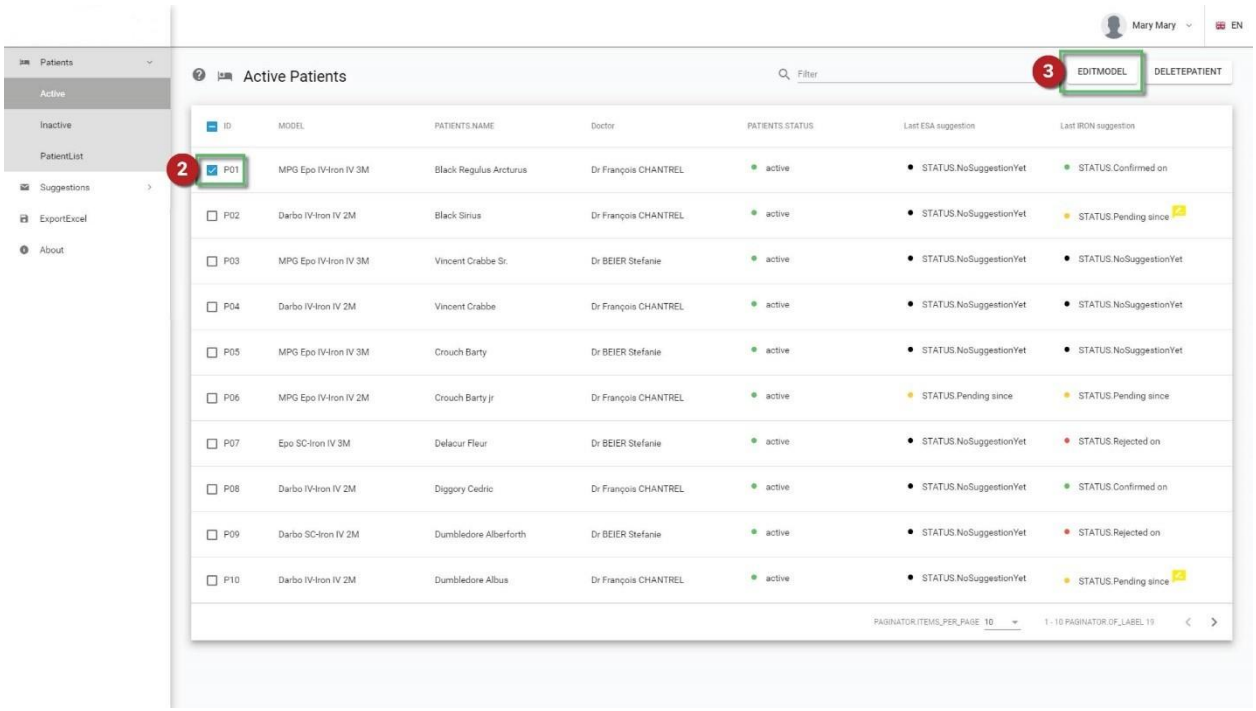
NOTE: On any Patients page, you are able to do the following:

a. Filter the Patients list by typing any keyword(s) in the **Filter** field on the top left corner of the screen
b. Sort the Patients list by clicking each title of the first row (ID, MODEL, PATIENTS.NAME, Doctor, PATIENTS.STATUS)

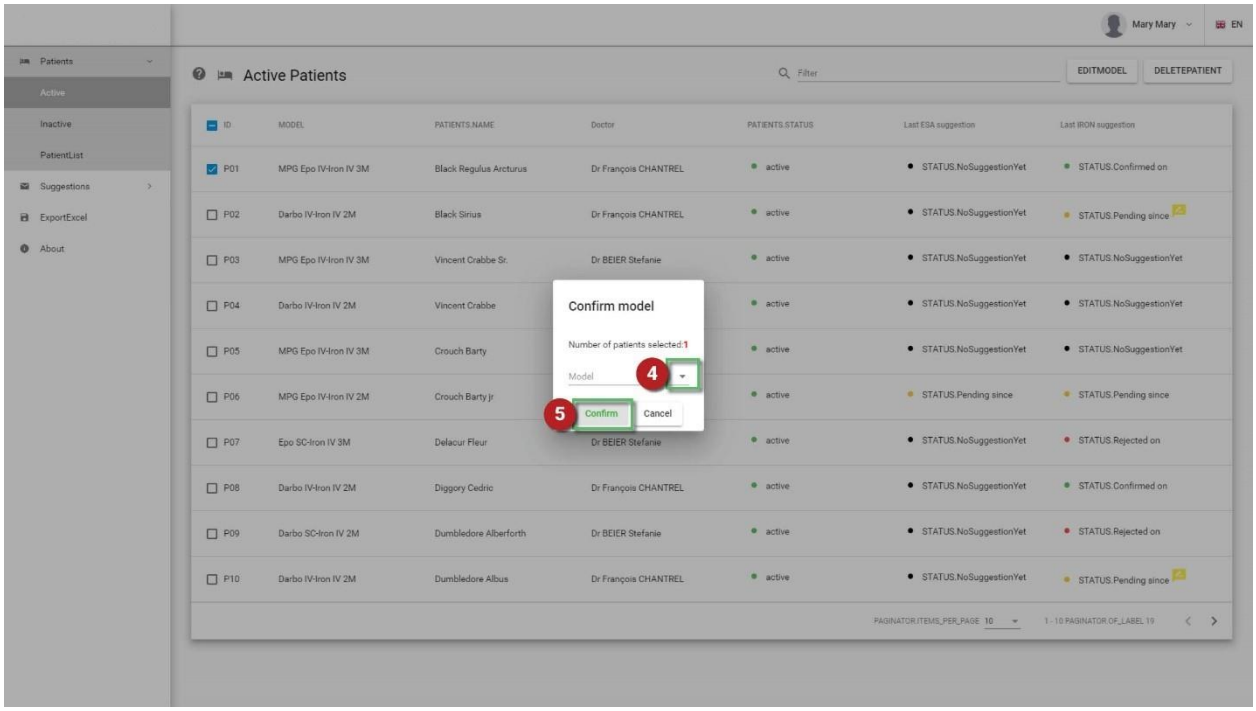


3.2.9 How to edit a patient's treatment model

1. Find the patient's name.
2. Check the box at the left-hand side of the patient's ID.
3. Click the **EDITMODEL** button at the top-right side of the screen.

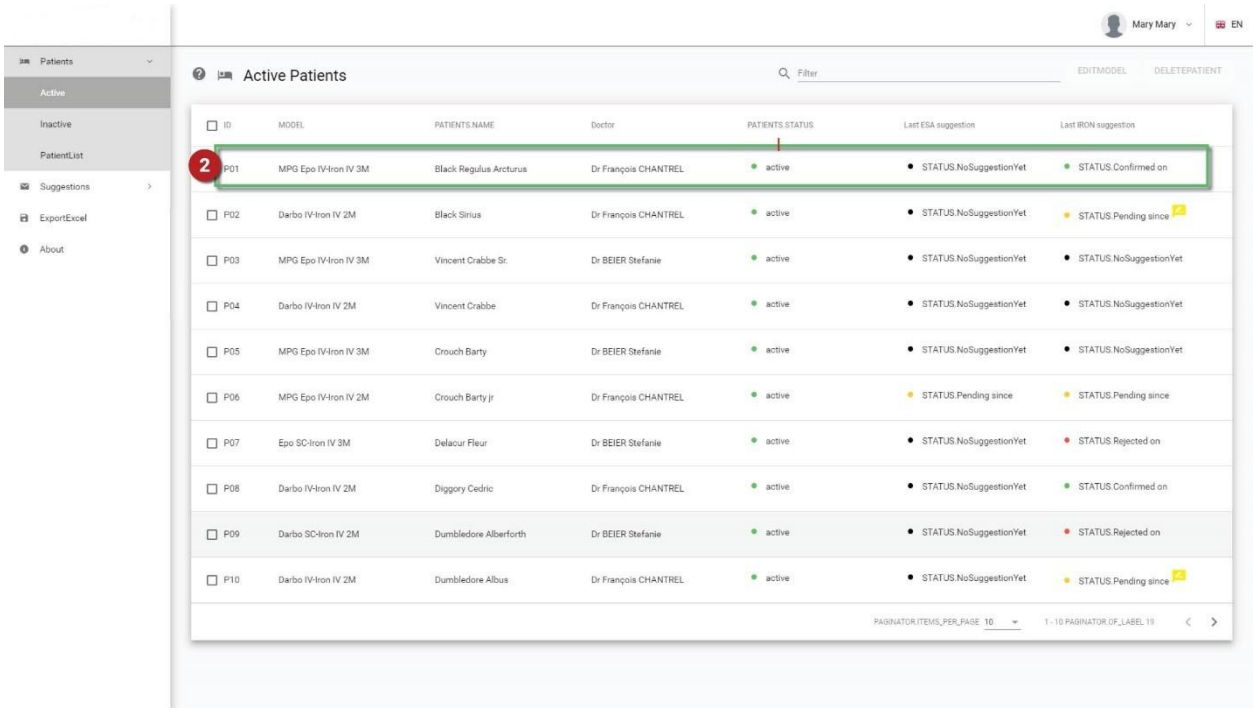


4. In the pop-up window that appears, click on the arrow on the **Model** field and select the desired model from the drop-down menu.
5. Click **Confirm** to confirm your action or **Cancel** to cancel your action.

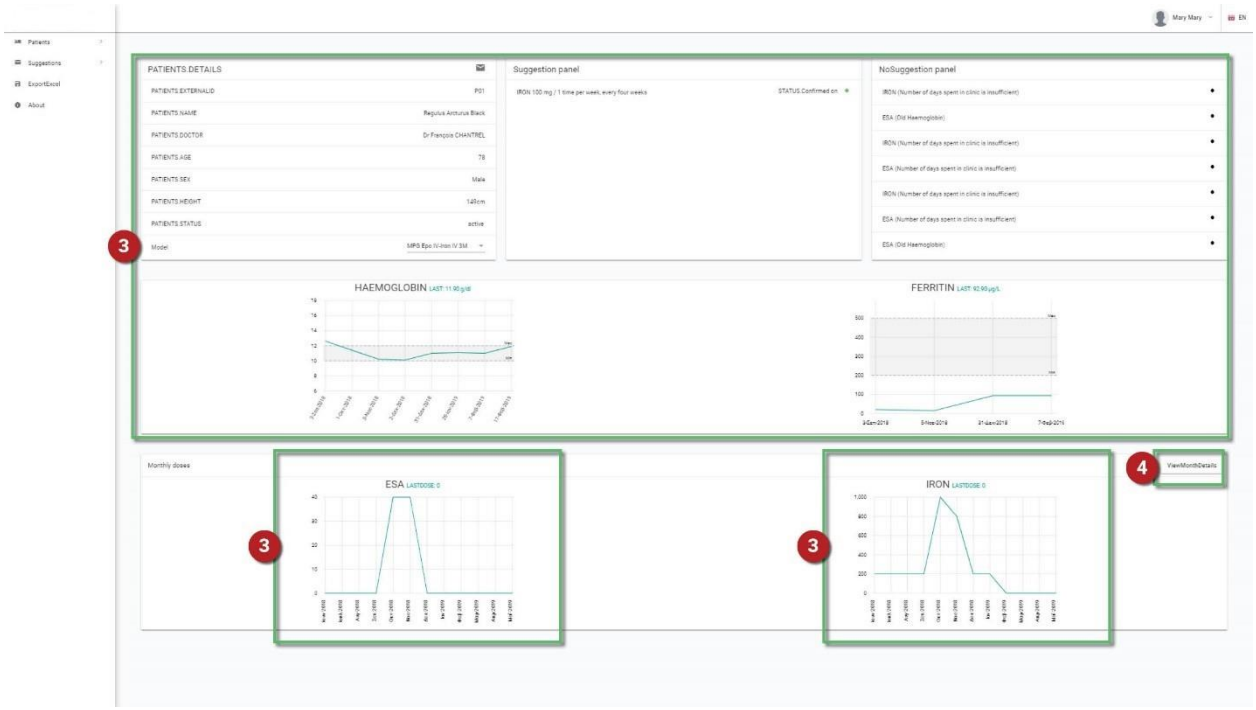


3.2.10 How to view a patient's lab results

1. Go the **Active Patients** page.
2. Click the patient's name.



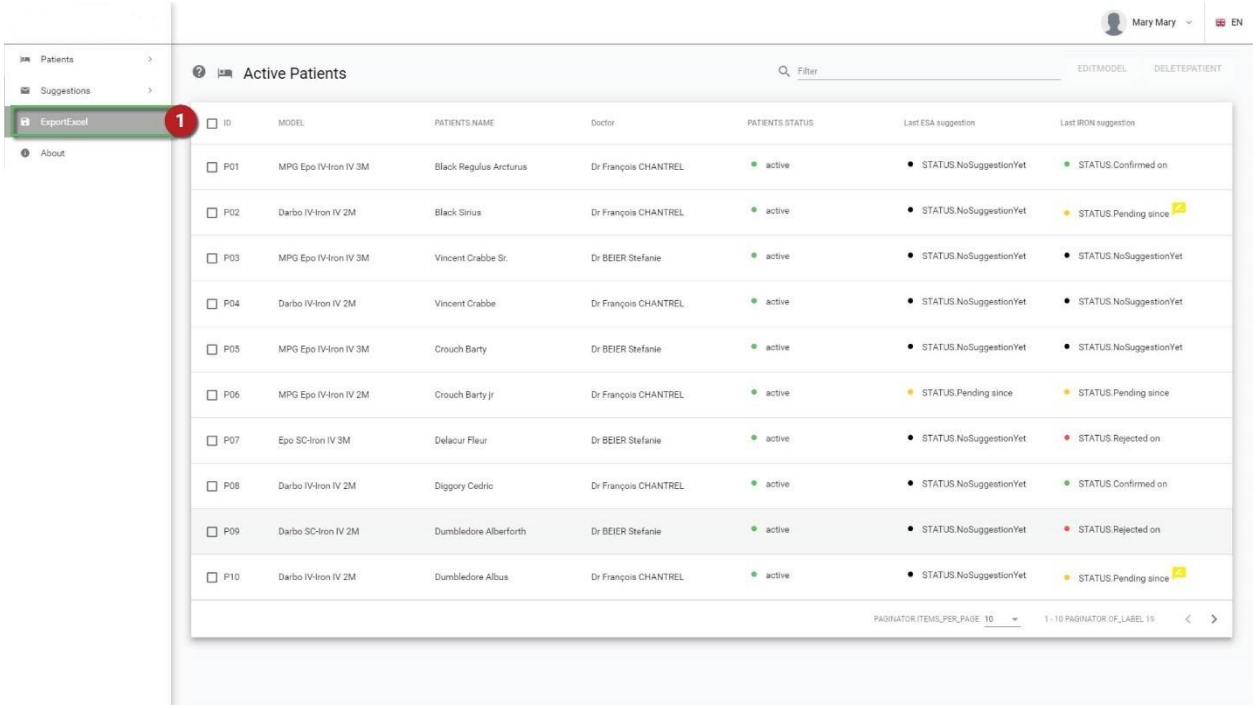
3. In the new page that appears, you can view the patient's details, suggestions, list of non-possible suggestions, the latest labs results and the latest ESA/iron doses of the patient.
4. Click the **ViewMonthDetails** button to view the monthly history of ESA/iron doses of the patient.



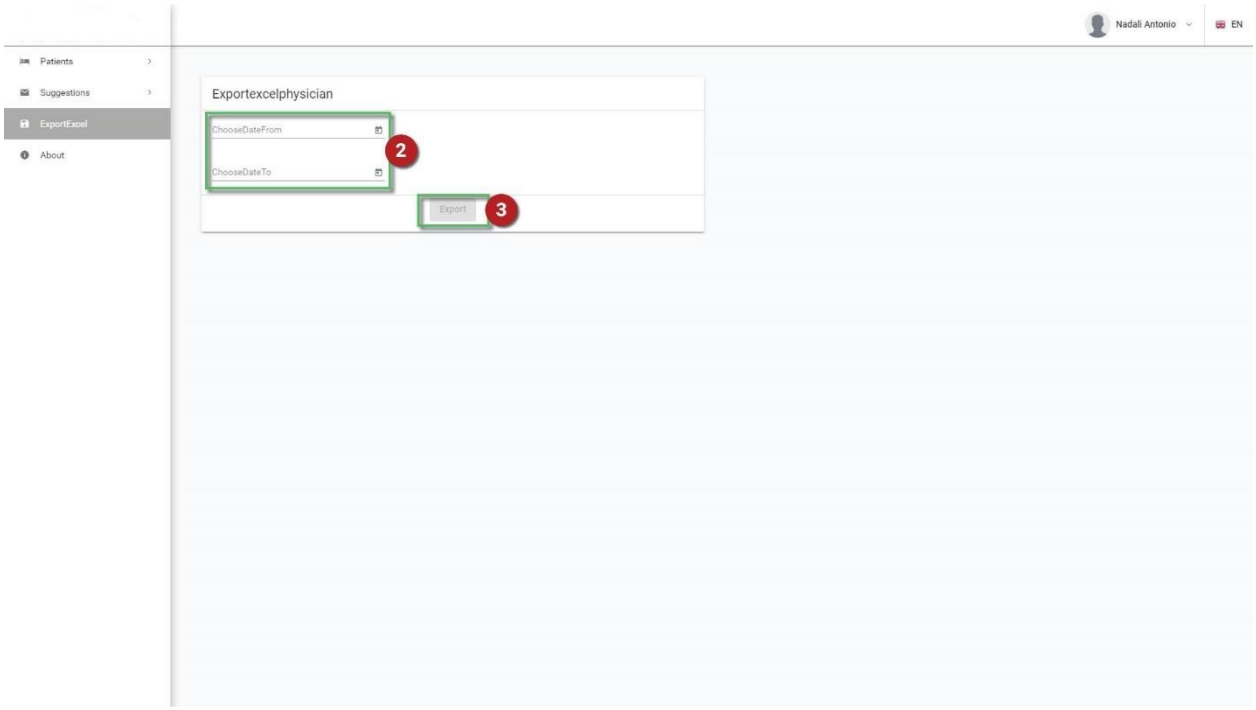
NOTE: Lab results and the monthly history of ESA/iron doses are not available for the inactive patients.

3.2.11 How to export a .xls file of ACM suggestions sorted by date and status

1. Click **ExportExcel** using the menu on the left-hand side of the screen.

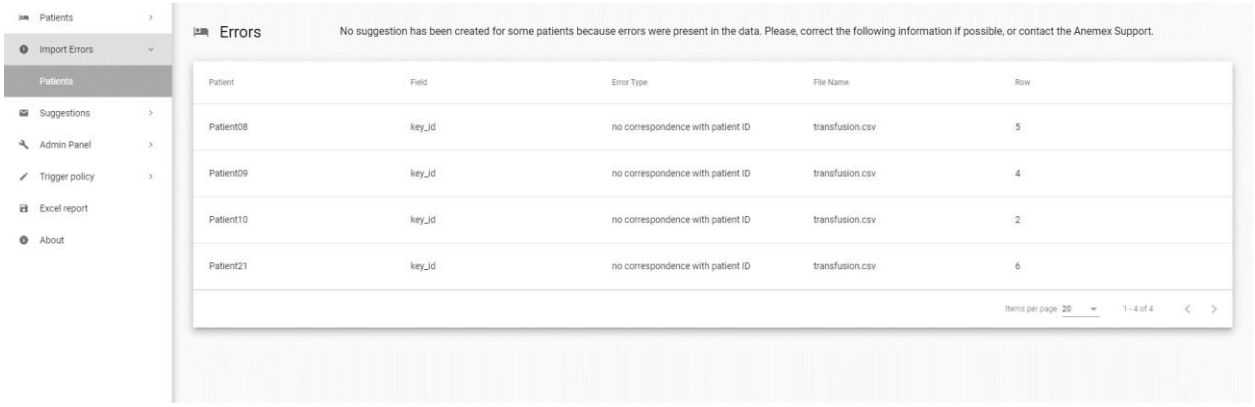


2. In the new page that appears, define a specific time frame by clicking the **ChooseDateFrom** and **ChooseDayTo** buttons.
3. Click **Export** to create and export your .xls file.



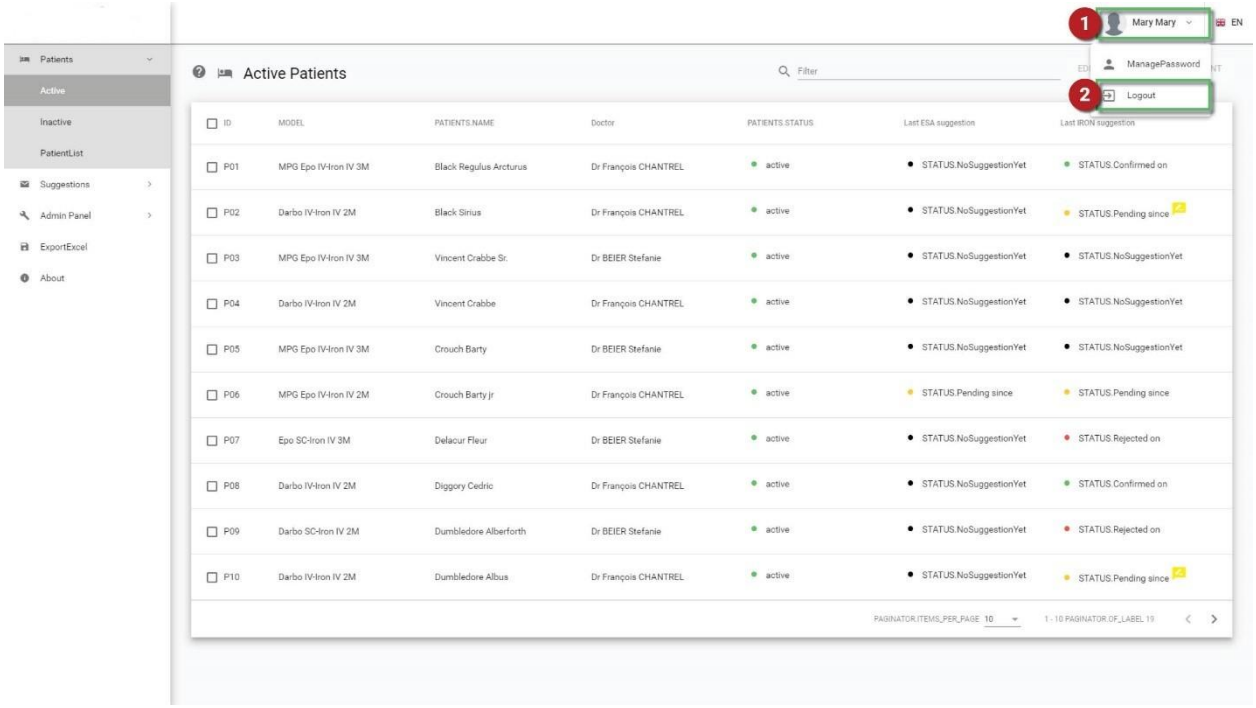
3.2.12 How to visualize the list of possible errors present in the input data

The errors found in the import files are reported in a more readable way for users in a dedicated area. Details on the error type are provided so that it is possible to fix them at the source (i.e. the clinical DB):



3.2.13 How to log out

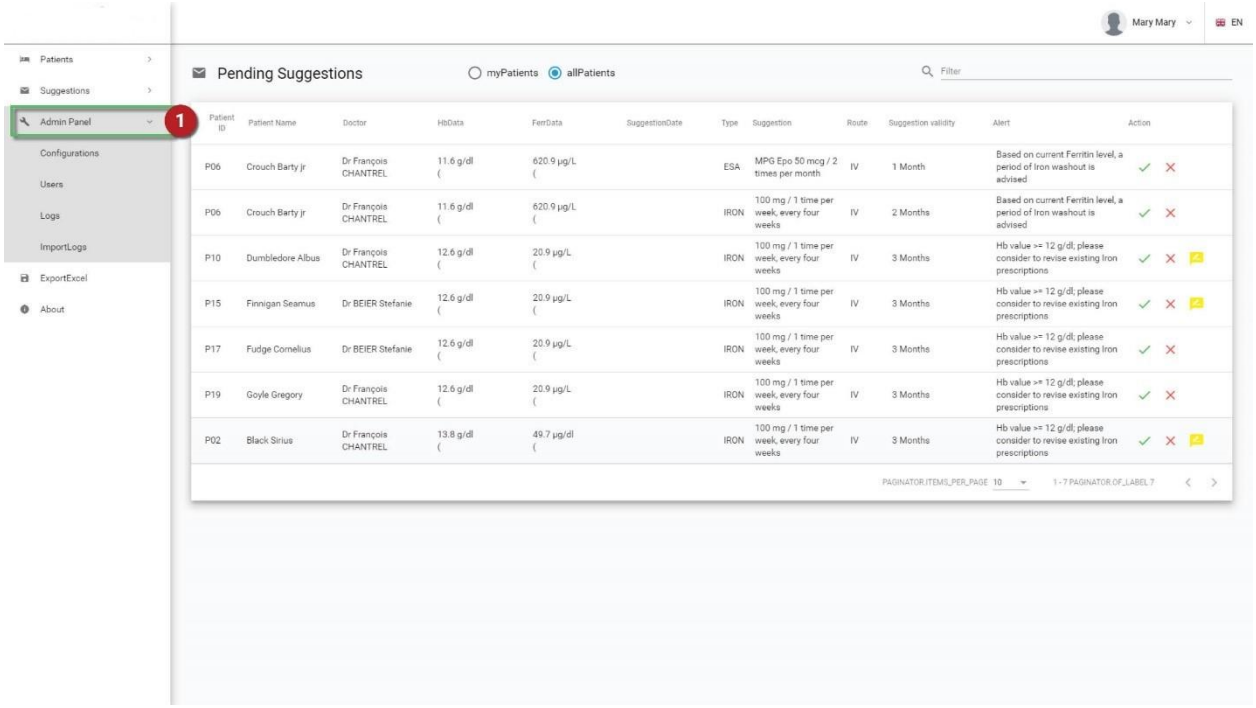
1. Click on your username at the top-right corner of the screen.
2. In the drop-down menu, click **Logout**.



3.3 How to – administrators

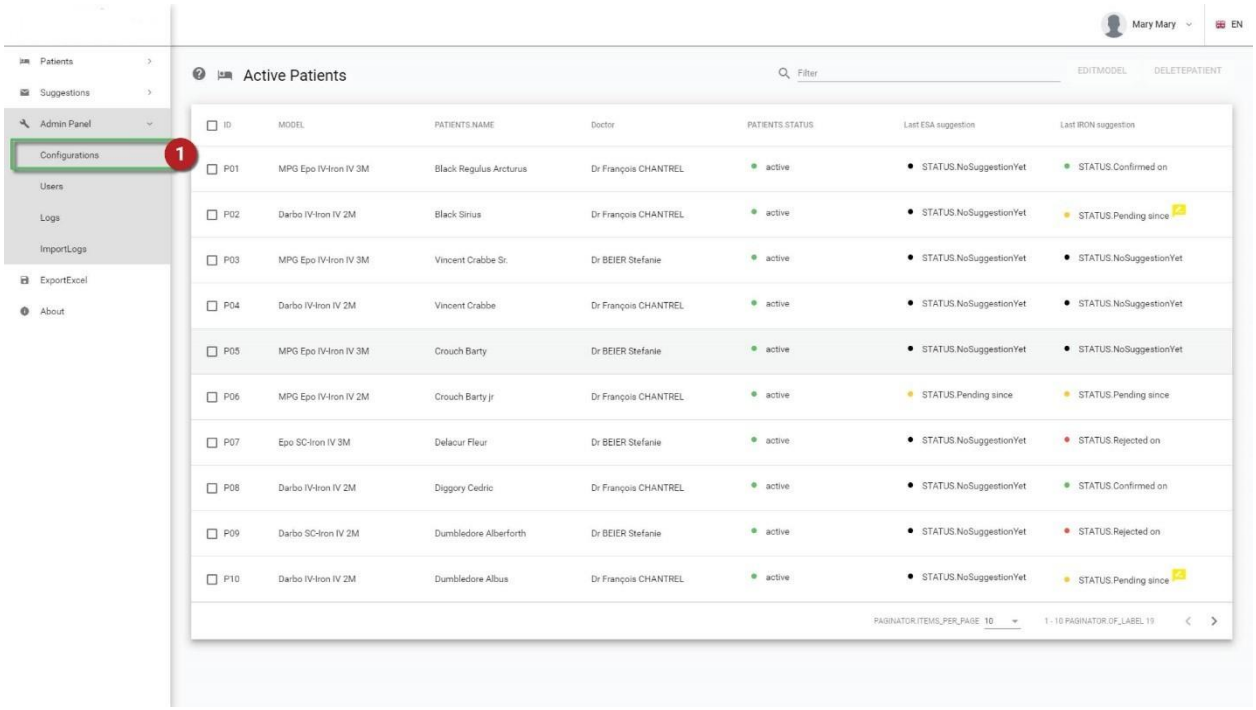
3.3.1 How to access the admin panel

On the left-hand side of the screen, click **Admin Panel** to expand the Admin Panel sub-menu.

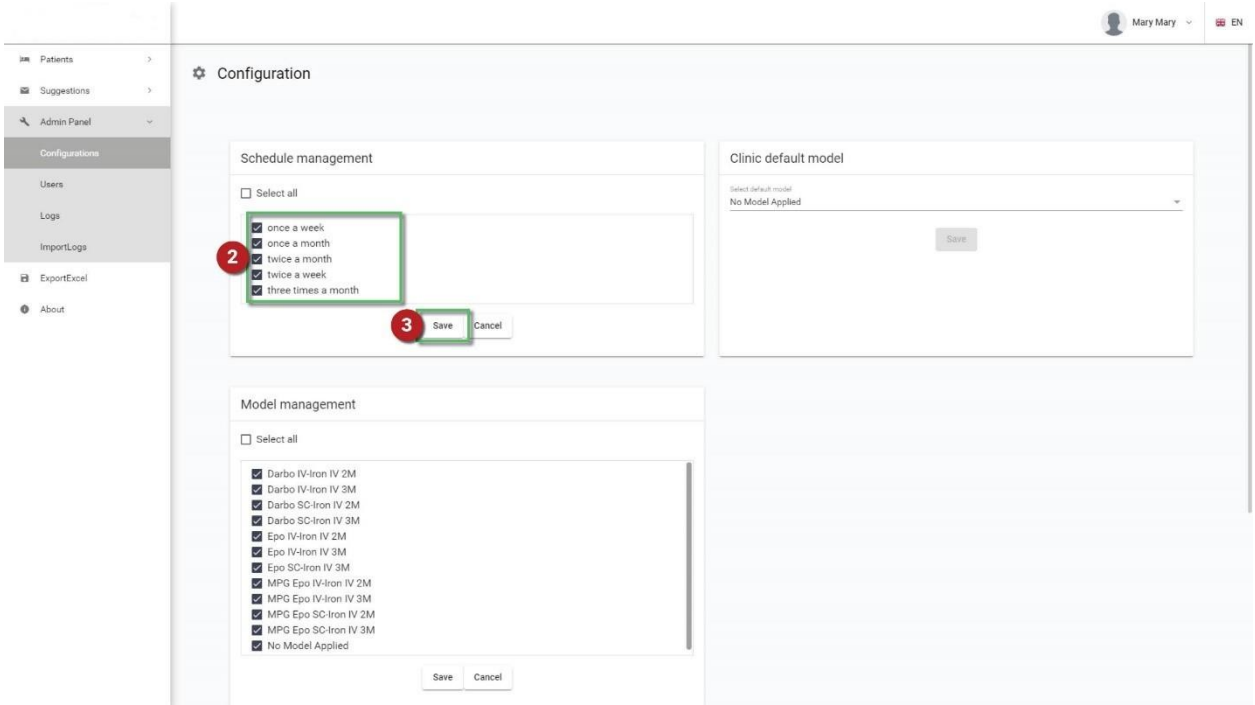


3.3.2 How to configure the schedule of administration

3. Click **Configurations** in the Admin Panel.

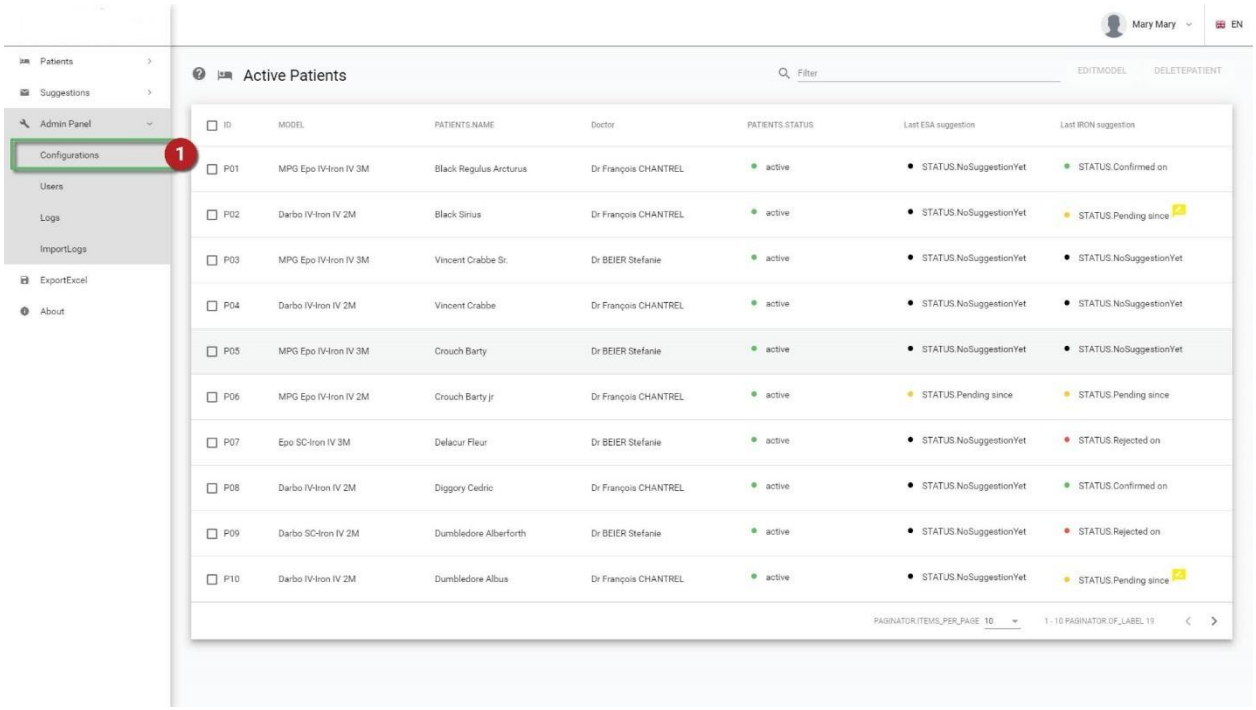


4. In the **Schedule management** tab, tick the desired administration schedule(s).
5. Click **Save**.

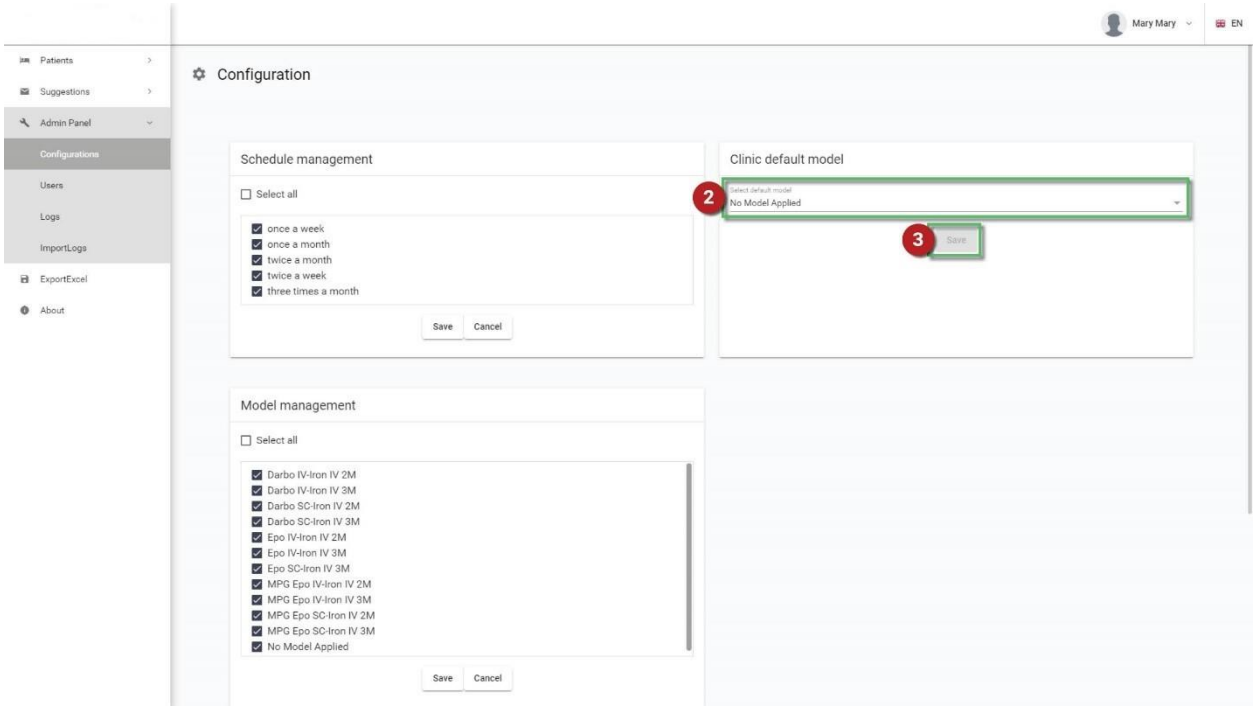


3.3.3 How to change the clinic default model

1. Click **Configurations** in the Admin Panel.

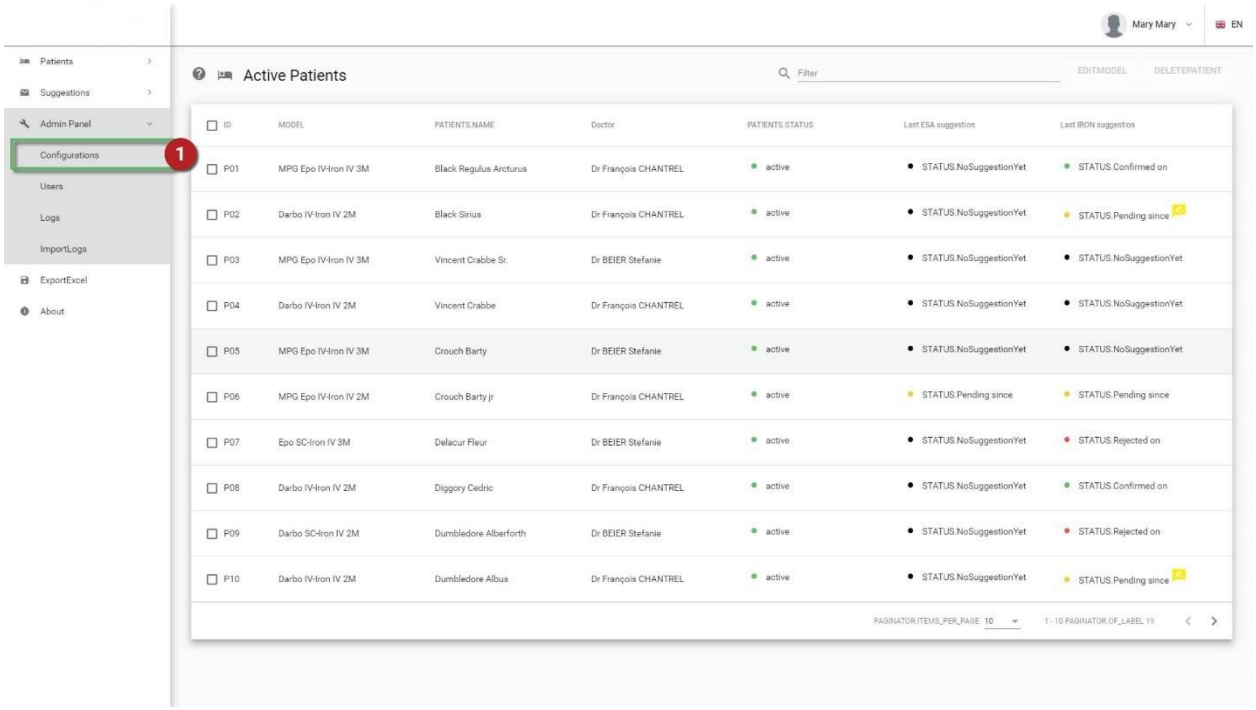


2. In the **Clinic default model** tab, click on the arrow on the **Select default model** field and select the desired model from the drop-down menu.
3. Click **Save**.

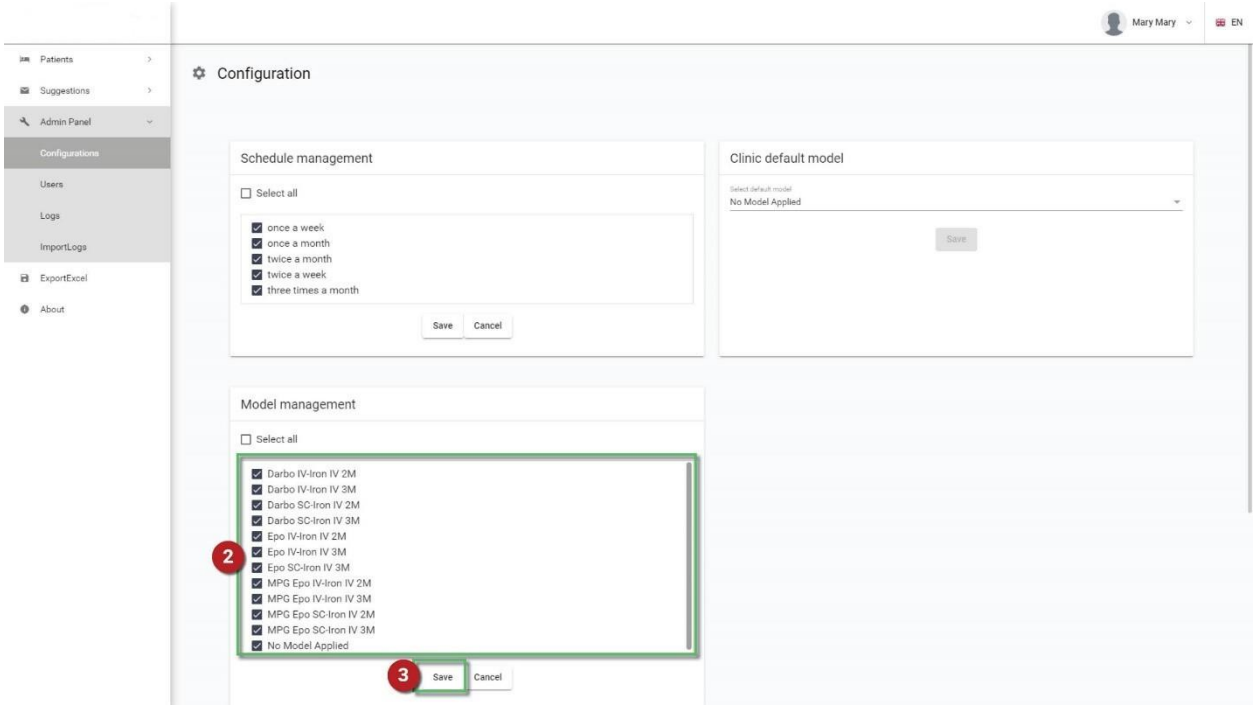


3.3.4 How to configure the available clinic models

1. Click **Configurations** in the Admin Panel.



2. In the **Model management** tab, tick the desired model(s).
3. Click **Save**.



3.3.5 How to set a new trigger policy

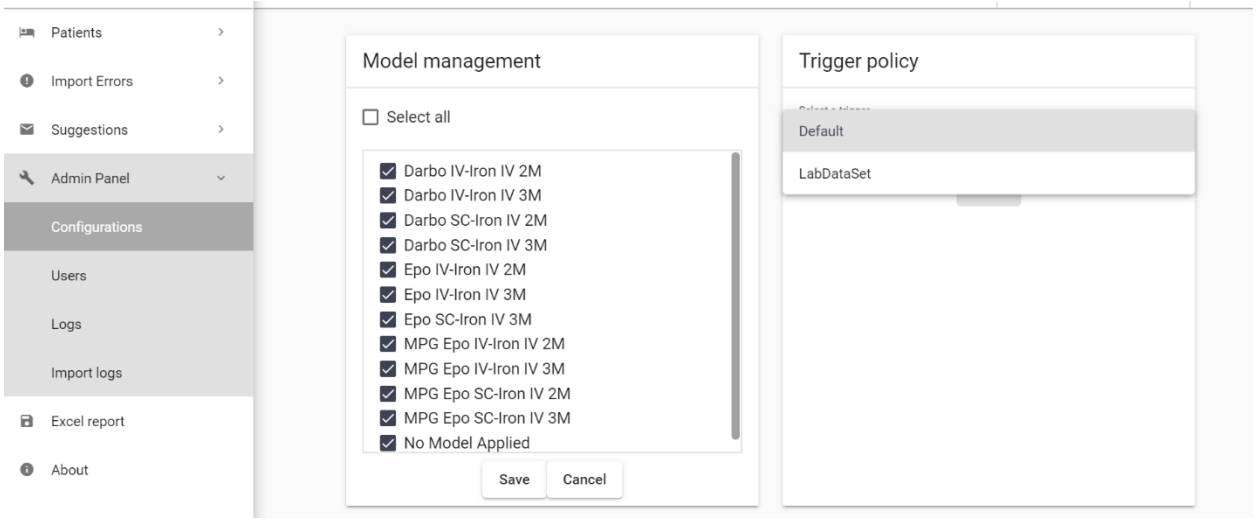
A new suggestion is generated when a new Hb is recorded; however, users can also set a different trigger policy by selecting a subset of lab tests that needs to be present with the new Hb in order to trigger the ACM response.

The trigger of a new suggestion can be:

- Only a new Hb (Default)

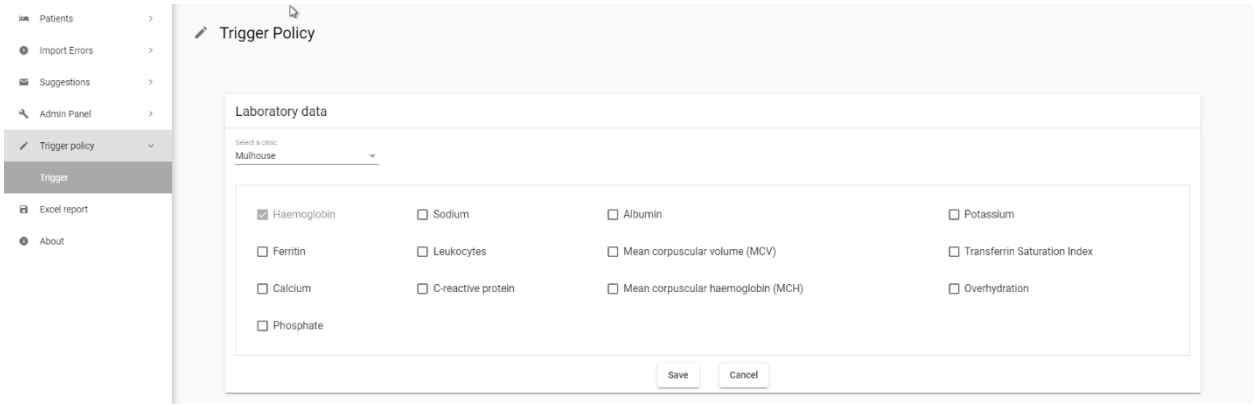
- A new Hb plus other lab tests in the same date (LabDataSet option)

To set a new trigger policy, the Admin user can switch from the Default option to the LabDataSet option from the Configurations menu:



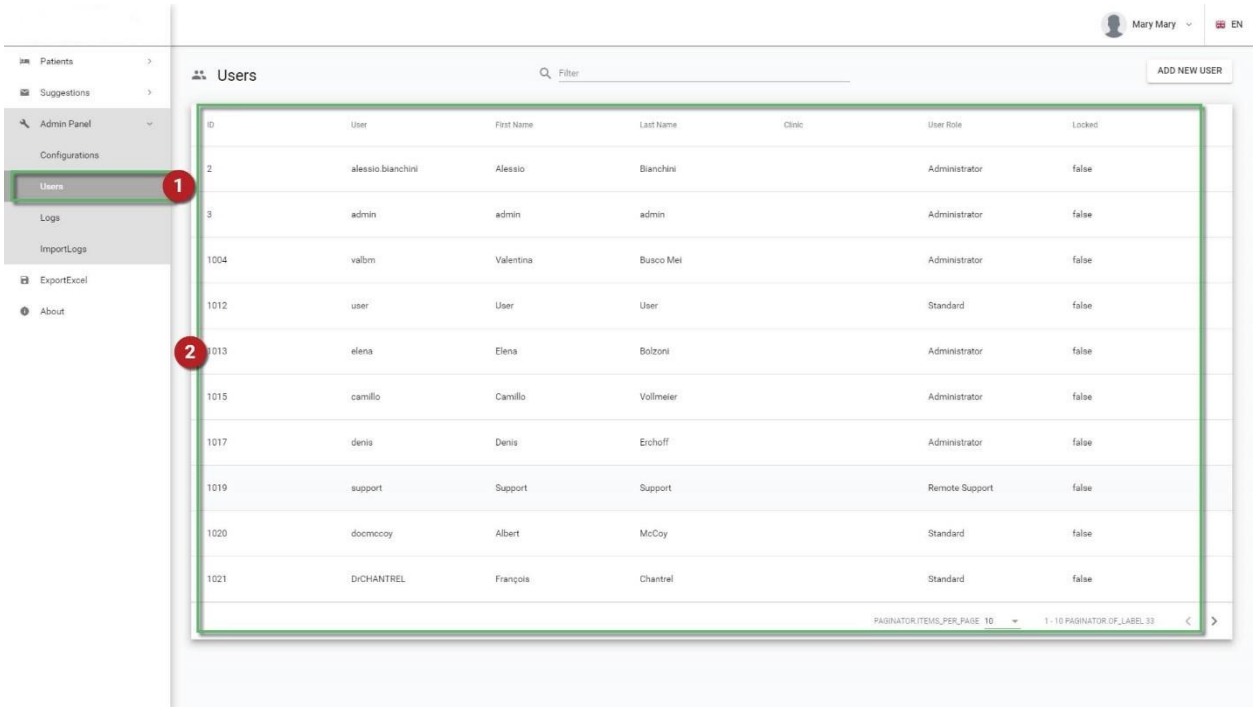
3.3.6 How to select the parameters of the new trigger policy

Once the Admin has set the LabDataSet option, the Medical Admin (and the Admin) can then select the desired subset of lab tests in the available list:



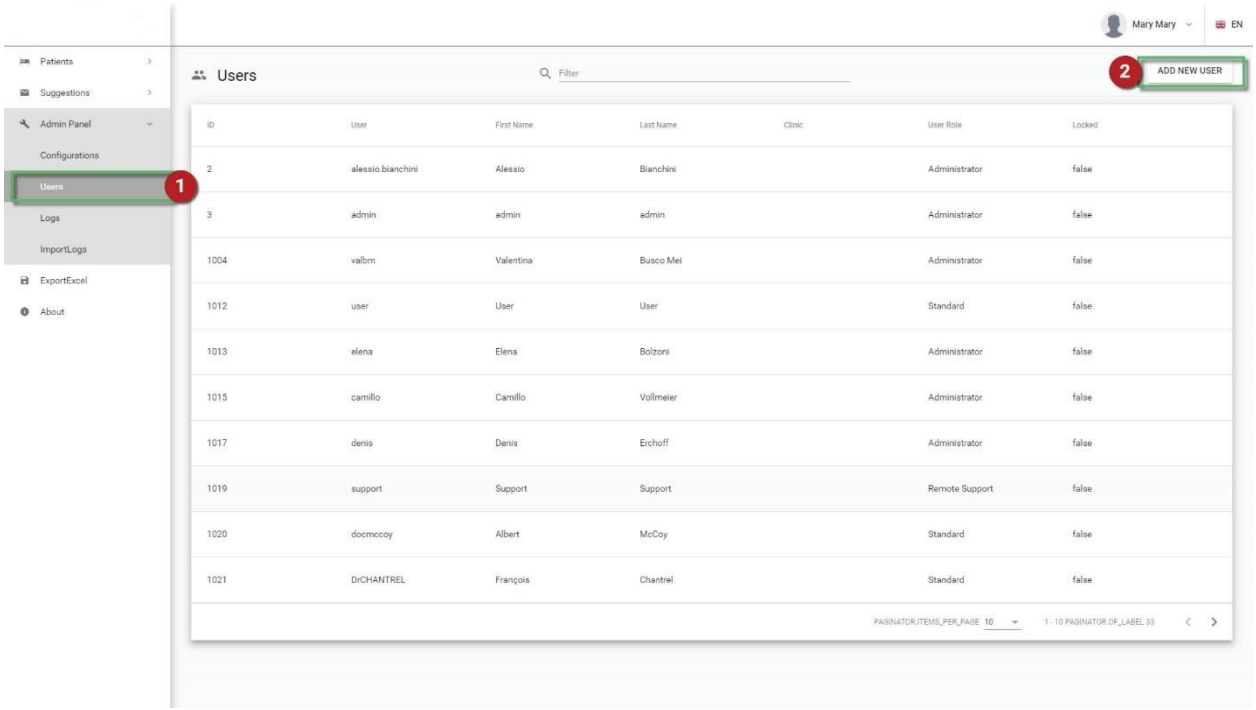
3.3.7 How to find a user

1. Click **Users** in the Admin Panel.
2. In the Users page that appears, you can view the list of all users.



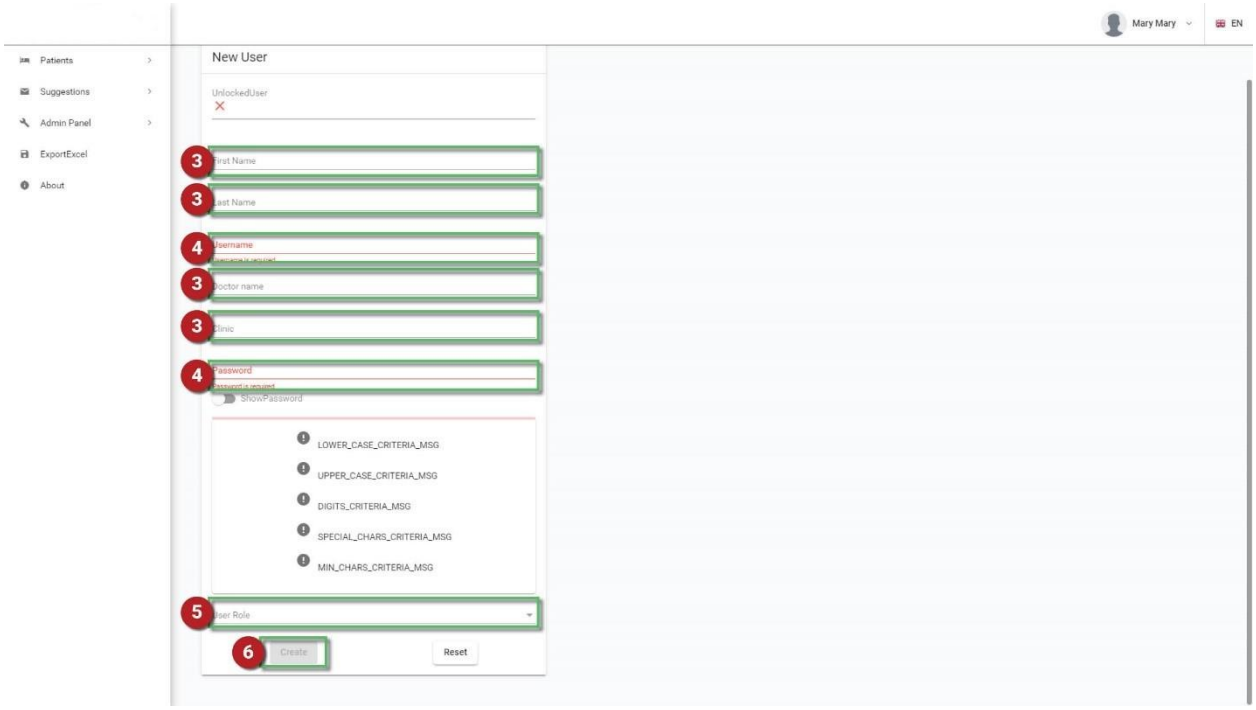
3.3.8 How to add a new user

1. Click **Users** in the Admin Panel.
2. Click the **ADD NEW USER** button at the top-right corner of the screen.



3. In the **New User** tab that appears, fill in the fields **First Name**, **Last Name**, **Doctor name**, and **Clinic**.
4. Set up a username and a password for the new user.
5. Select the role of the new user from the drop-down menu that appears at the bottom of this tab.

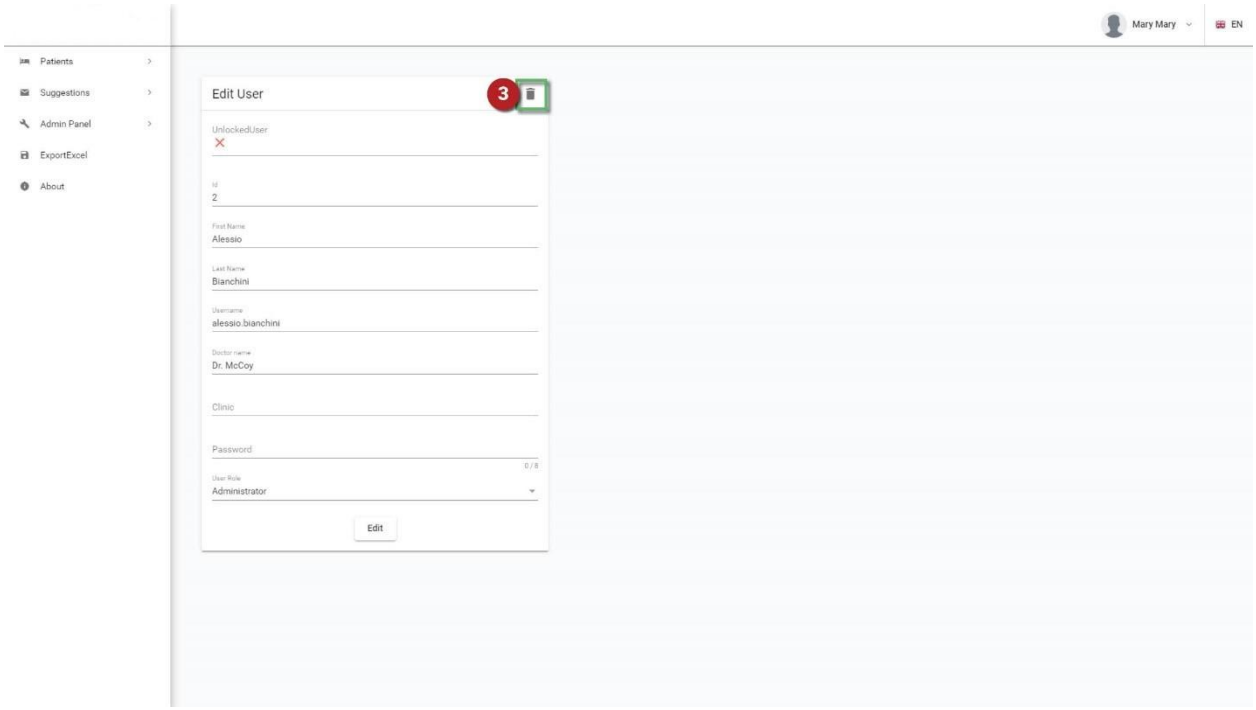
6. Click **Create**.



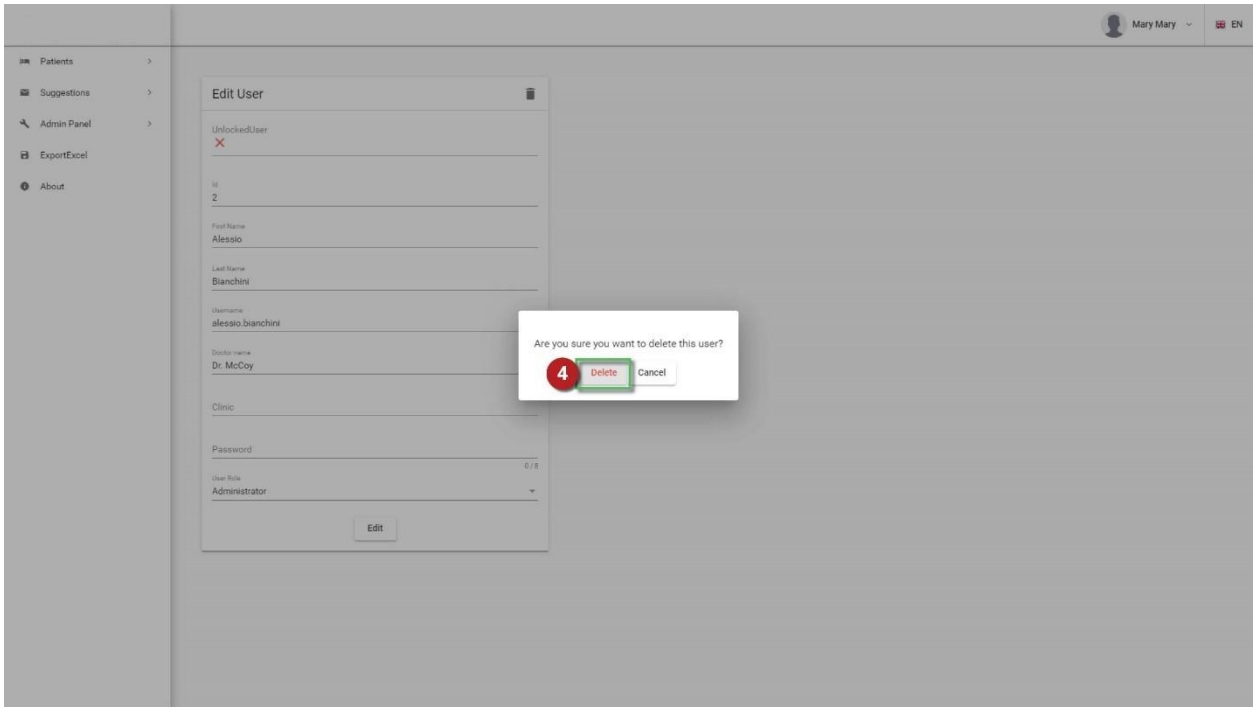
NOTE: At this point, you also have the option to reset the form by clicking **Cancel**.

3.3.9 How to delete a user

1. Find the username.
2. Click on the username.
3. In the Edit User page that appears, click on the **Trash** icon at the top-right corner.



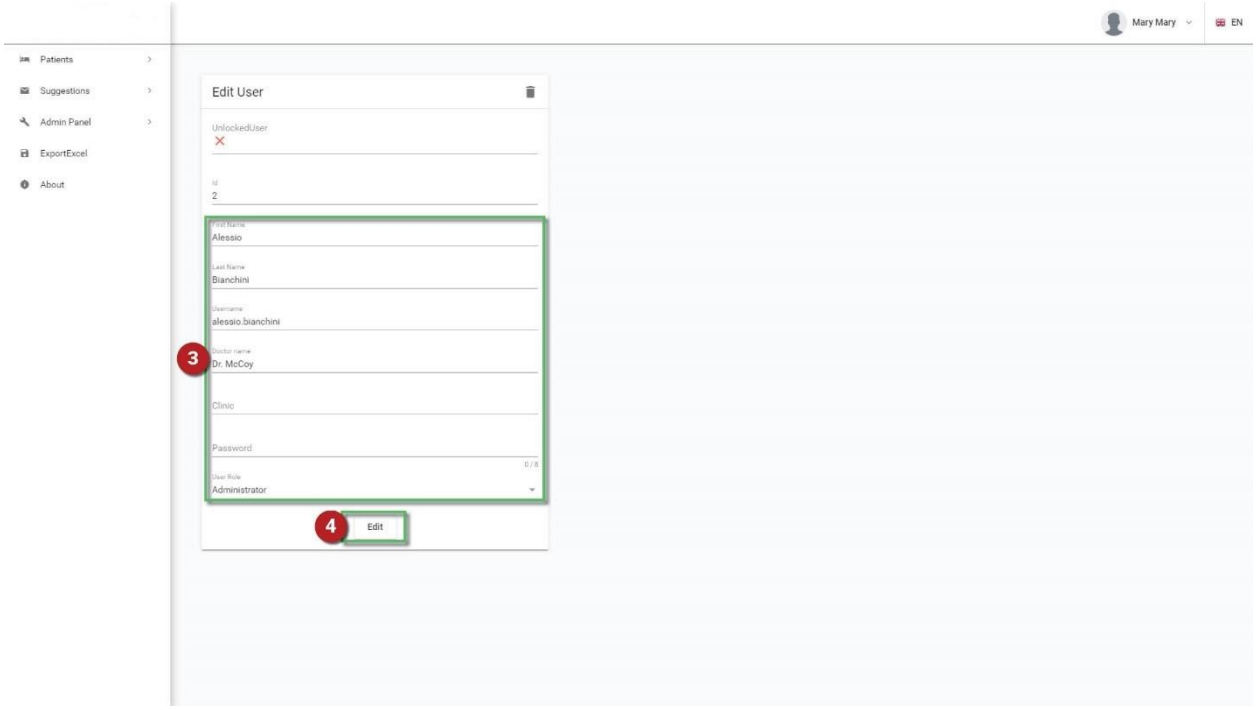
4. In the pop-up window that appears, click **Delete**.



NOTE: At this point, you also have the option not to delete the user by clicking **Cancel**.

3.3.10 How to edit a user's details

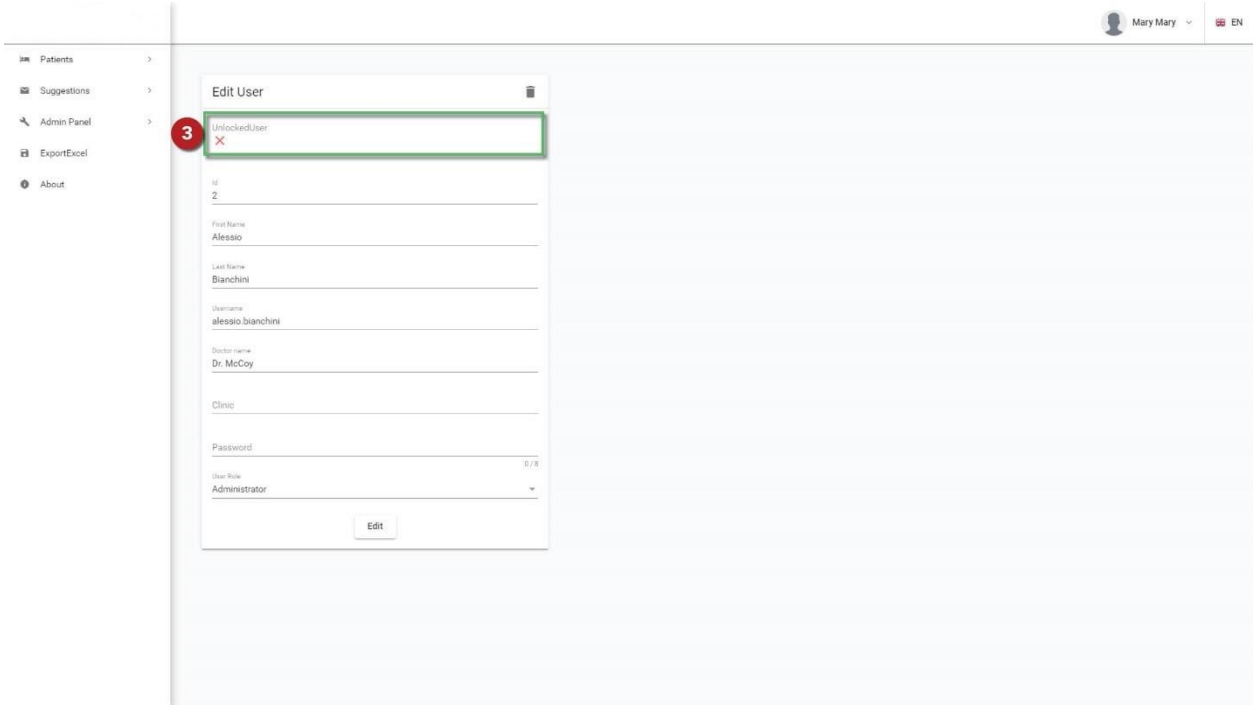
1. Find the username.
2. Click on the username.
3. In the **Edit User** tab that appears, you can edit any field(s), except the **Id** field.
4. Click **Save changes**.



3.3.11 How to lock and unlock a user

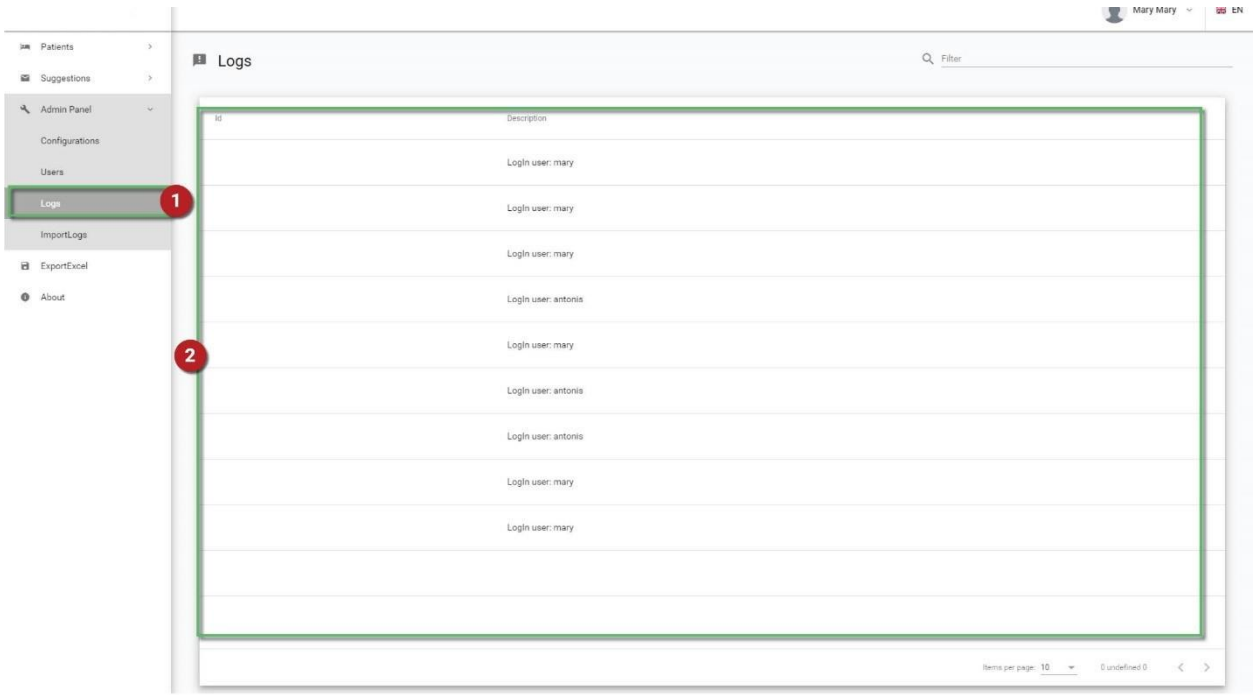
1. Find the username.

2. Click the username.
3. In the **Edit User** tab that appears, click on the icon under the LockedUser or UnlockedUser field.



3.3.12 How to view the history of the users' login activity

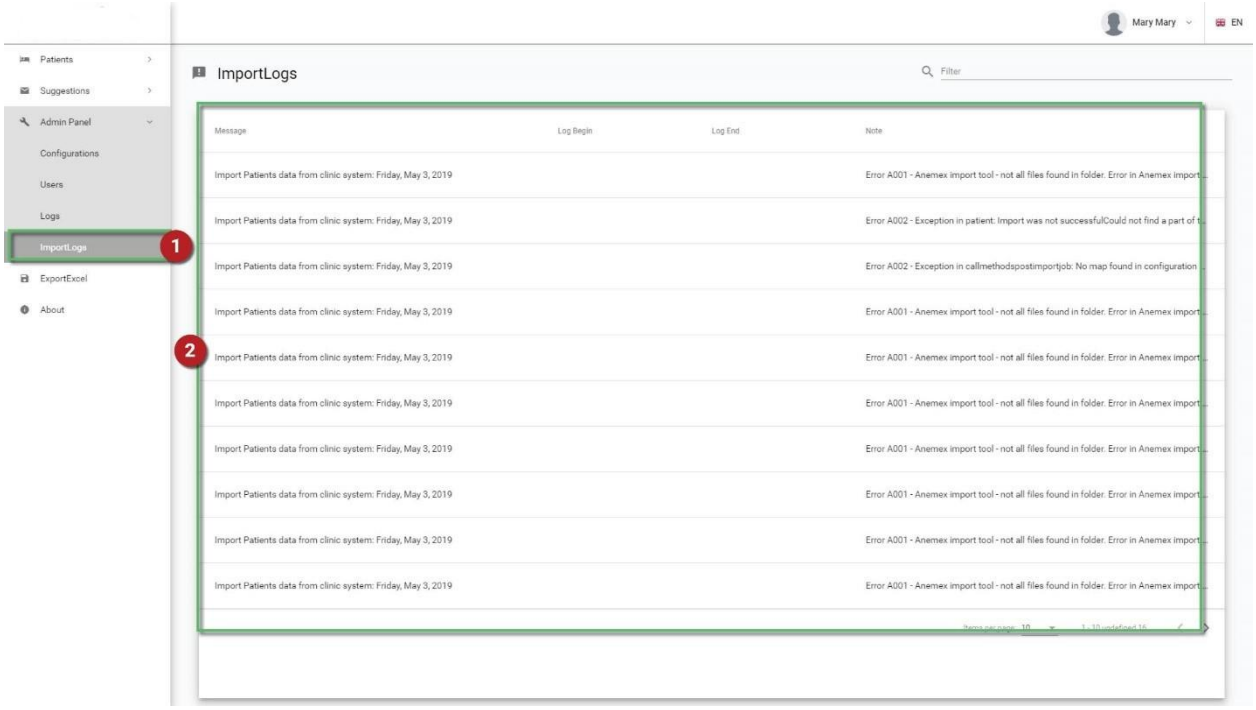
1. Click **Logs** in the Admin Panel.
2. In the new page that appears, you can view the full history of the users' login activity.



3.3.13 How to view import errors

1. Click **ImportLogs** in the Admin Panel.

2. In the new page that appears, you can view the full list of all import errors that have occurred.



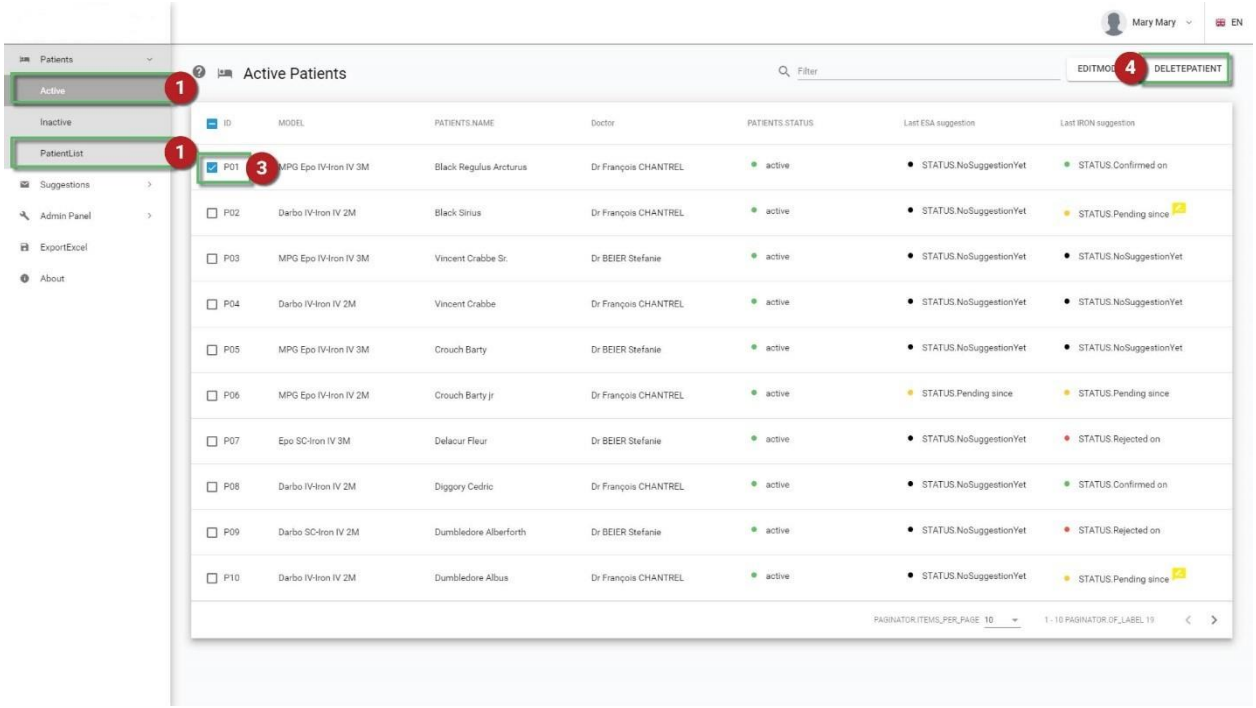
3.3.14 Description of error handling

Error	Explanation	Action	Error prevention
I001	Import procedure is aborted	Check why files are not present	Make sure that files are correctly transferred from the HIS
I002	Pre-import operations failure	Check if the ACM Application database is working properly	Make sure that the ACM Application database is working properly
I003	Import procedure is aborted	Check error logs regarding failure	
I004	Post-import operations failure	Check if the ACM Application database is working properly	Make sure that the ACM Application database is working properly
I005	Import procedure is aborted	Check the integrity of HIS files	Make sure that HIS files were not tampered with or compromised during the transfer
A003	The generation of the ACM request files has failed	Check if the ACM Application or database is working properly	Make sure that the ACM Application and database are working properly
A004	Data transfer to the ACM Recommendation Engine has failed	Check that the ACM Recommendation Engine can be successfully accessed	Make sure that the ACM Recommendation Engine can be successfully accessed

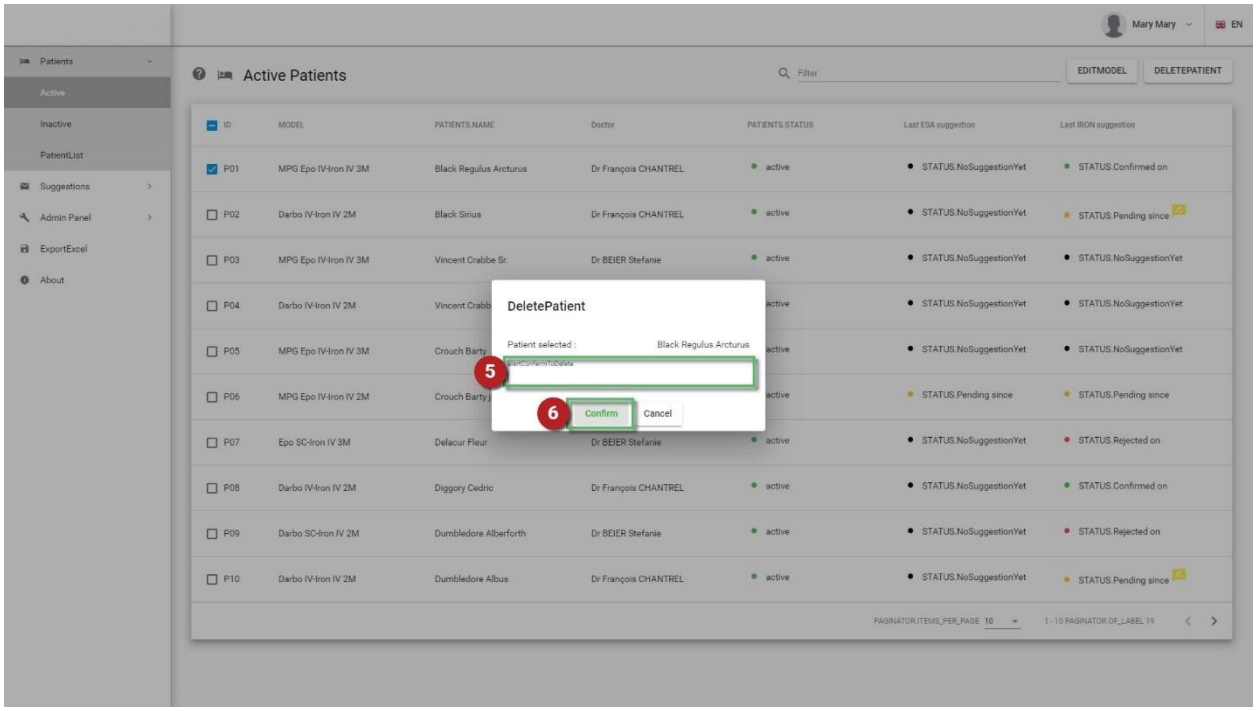
Error	Explanation	Action	Error prevention
A005	The transfer or the save process of the ACM response into the ACM Application has failed	Check that the ACM Application is working properly	Make sure that the ACM Application is working properly and not showing any errors in the interface or in the application log files

3.3.15 How to delete a patient

1. Go to the **Active Patients** page or **PatientList** page using the menu on the left-hand side of the screen.
2. Find the patient that you wish to delete.
3. Click the box on the left of the patient ID.
4. Click the **DELETEPATIENT** button at the top right corner of the screen.



5. In the pop-up window that appears, type the patient ID in the **alertConfirmToDelete** field.
6. Click **Confirm** to confirm the deletion.



NOTE: At this point, you also have the option of closing the pop-up window without deleting the patient by clicking **Cancel**.

3.3.16 Behavior in exceptional situations

Under unfavorable conditions, such as after a disconnected network connection to the server or after the program crashes, deviations between the data on the server side and those in the client program may occur. In this case, we recommend closing and restarting the program.

The following warnings about errors in communication are found in the User and Service Manuals:

Warning

Risk for the patient as a result of incorrect data

Risk for the patient as a result of an incorrect therapeutic decision

Should the network fail or the HIS malfunction, patient data and suggestions may not be available

→ Clinic personnel and technical support must take necessary precautions and countermeasures to ensure hardware and software reliability

3.3.17 Data backup

Data is backed up every day. If you need to access the Application backup DB, please contact the Administrator.

6 Frequently asked questions

6.1 How is patient data security ensured with ACM?

Patient data which reaches the ACM Recommendation Engine is pseudonymized. This is the process by which an alphanumeric identity code (i.e. a Patient Key ID) is used to group all data related to each specific patient (e.g., laboratory tests, drug administrations); however, identity-related data (e.g., first name, last name, HIS patient ID) is never transferred over the internet.

6.2 How often does ACM come up with a new suggestion for a patient?

A new suggestion is generated when a new Hb is recorded; however, users can also set a different trigger policy by selecting a subset of lab tests that needs to be present with the new Hb in order to trigger the ACM response. When triggered, ACM will generate a new pending suggestion.

6.3 How do the alert messages work?

An additional feature of ACM consists of outputting an alert code to signal particular conditions that may require special attention. This provides useful indication to nephrologists so that their attention can be immediately directed to these cases.

The conditions that trigger an alert message are:

- Absolute Hb variation between subsequent months in (1, 2)
- Absolute Hb variation between subsequent months in (2, 3)
- Absolute Hb variation between subsequent months > 3
- Hb value ≤ 8 g/dL
- Hb value ≥ 12 g/dL; please consider revising existing iron prescriptions
- Based on current ferritin level, a period of iron washout is advised

Please note that the last alert message appears when ferritin is in the (500, 650) interval.

In alert message 1, please note that the round brackets mathematically exclude the end points of the interval (i.e. 1 < Hb < 2).

In alert message 2, please note that the square bracket includes the lower end point of the interval (i.e. 2 ≤ Hb < 3).

6.4 Why would ACM not generate a suggestion?

There are 2 types of exclusion criteria that render ACM unable to generate a suggestion: General exclusion criteria and ESA- and iron-specific exclusion criteria (see 2.1).

6.5 Why can’t I find a suggestion I just confirmed?

You confirm a suggestion in the Pending Suggestions page. Once a suggestion is confirmed, it automatically appears in the Confirmed Suggestions page.

7 Definitions

7.1 Symbols

In accordance with the applicable legal and normative requirements, the following symbols are used in the About menu:

	Follow Instruction for Use
	CE mark
	Manufacturer
	Medical Device