AI4CMR

Version 2.1.0
USER MANUAL

AI4CMR

Cardiac MRI reporting:
Simplified. Anywhere. Anytime.

AI4MedImaging

Manufactured by

AI4MedImaging Medical Solutions S.A.

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ISO 13485:2016 Certificate
MD 740465

CE 2797

AI4CMR is qualified as a class IIa medical device. It complies with the requirements of the European Medical Device Regulation MDR 2017/745

MDR Certificate MDR 740464

UDI-DI (01)05600250059039

UKCA 0086

AI4CMR is qualified as a class IIa medical device. It complies with the requirements of the Medical Device Directive 93/42/EEC and UK MDR 2002.

UKCA Certificate UKCA 776320

United States of America

510(k) Cleared

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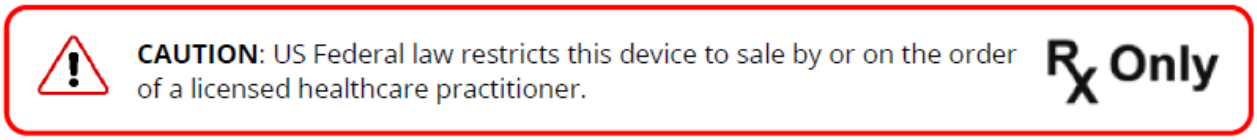

AI4MedImaging shall not be responsible for technical or editorial errors or omissions contained herein.

The information contained herein is subject to change without notice.

The only warranties for AI4MedImaging products and services are described in the express warranty statements accompanying such products and services.

Please contact the manufacturer or authorized representative to request the latest edition of the user manual or consult the latest edition on the AI4MedImaging website.

Table of Contents

1.Terms and Conditions

This User Manual shall be accompanied by the specific plugin User Manual.
The plugin User Manual describes in more detail the features and steps necessary to interact with the AI4CMR service. For clarification purposes only, we present an example of a possible sequence of steps to interact with AI4CMR.

1.1. Intended use

AI4CMR is an image analysis software for post-processing of cardiac magnetic resonance images (CMR), which are used for the assessment of cardiac diseases.

AI4CMR uses artificial intelligence and is intended to automize cardiac segmentation allowing instantaneous quantification of ventricular volumes, myocardial mass, ejection fraction of heart ventricles and to automatically assess left ventricle wall motion*.
AI4CMR also supports clinical diagnostics by calculating flow measurements of vascular structures in 2D phase-encoded cardiac MR images

AI4CMR shall be used by qualified medical professionals, experienced in examining and evaluating magnetic resonance images as a support tool that provides relevant clinical information.

AI4CMR can be integrated with DICOM viewers through a standard communication protocol.

The software is not intended to determine or recommend a course of action or treatment for a patient.

AI4CMR software does not preclude the analysis of the reporting physician. The cine sequences analysed by AI4CMR are only a part of the complete CMR exam and all the data should be integrated with other sequences and the clinical background of the patient to conclude the CMR exam.

The reporting physician holds the responsibility for validating the data provided by the AI4CMR software and performing the final interpretation of the CMR exam.

WARNING: * Wall Motion feature is not available for clinical use in the USA. This module is to be used for research purposes only, and not for primary diagnostics and direct patient care

1.2 Indications for use (United States)

AI4CMR software is designed to report cardiac function measurements (ventricle volumes, ejection fraction, indices etc.) from 1.5T and 3T magnetic resonance (MR) scanners. AI4CMR uses artificial intelligence to automatically segment and quantify the different cardiac measurements. Its results are not intended to be used on a stand-alone basis for clinical decision-making. The user incorporating AI4CMR into their DICOM application of choice is responsible for implementing a user interface.
AI4CMR also supports clinical diagnostics by calculating flow measurements of vascular structures in 2D phase-encoded cardiac MR images

1.3 Intended users

AI4CMR is a medical device and shall be used by qualified medical professionals, experienced in examining and evaluating magnetic resonance images.

Note: Software Developers interact only for technical Integration and Support.

1.4 Conditions for use

AI4CMR is a cloud-hosted service. The system shall be used in association with a third-party DICOM Viewer, which provides the interface between AI4CMR and the intended users (Medical professionals), Software Developers, and Others.

Patients will not be in direct contact with AI4CMR. The CMR images acquired for the patient are fed from the MRI Scanner or PACS (picture archiving and communication system) to the third-party DICOM Viewer.

This system context and interfaces to third-party systems are represented in the diagram of Figure **1**. The AI4CMR system boundaries are defined by the box “AI4CMR”.

The integration between AI4CMR and the DICOM Viewer is established using plugins that implement a standard communication protocol.

The communication between AI4CMR and the third-party system is initiated by the third-party system which posts a request to the AI4CMR in a networked environment. AI4CMR will validate and process the request and return a response via the same medium.

The complete system, including AI4CMR and the third-party systems, as presented in Figure 1, operates as an integrated solution from a clinical workflow standpoint. However, each component is responsible for its own regulatory compliance. Consequently, any DICOM viewer or medical device that interacts with AI4CMR must comply with all applicable requirements under the MDR and another applicable medical device regulations in different markets.

The patient data is anonymized by the third party before being sent to AI4CMR.

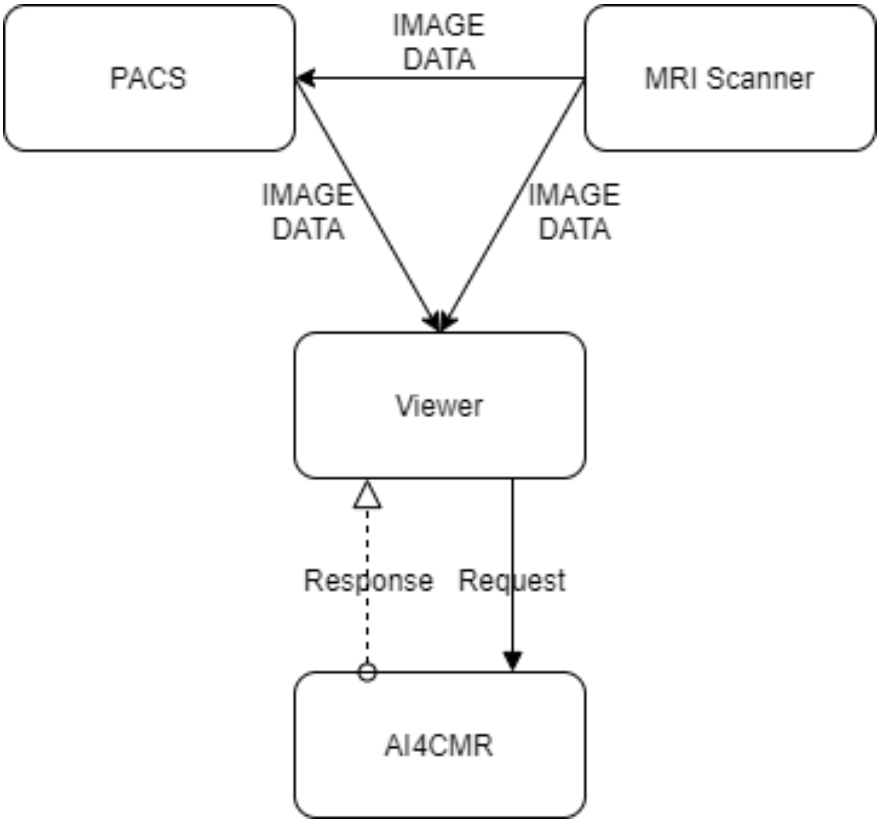

Figure 1. High-level representation of the interoperability between AI4CMR and the third-party systems and services.

1.5 Contraindications

AI4CMR is contraindicated to be used for post-processing of all image modalities other than cine and 2D phase-encoded images of CMR.

1.6 Key Features and Benefits

AI4CMR is intended to support clinicians in the analysis of CMR images. The following benefits may be observed when using the software in accordance with its intended use:

Cine Sequences:

- Fully automated segmentation of left and right ventricles, with possibility of being reviewed in real-time
- Automatic quantification of standard cardiac function parameters:
  - Left ventricle: EDV, ESV, SV, EF, LVM, CO, and BSA-indexed volumes
  - Right ventricle: EDV, ESV, SV, EF, CO, and BSA-indexed volumes.

- High-reliability quantification
- Automatic classification of normal and suspicious left ventricular wall motion*
- Time efficiency, enabling potential reduction of reporting time.

- Compatibility with images acquired from various MRI manufacturers (Siemens, GE, and Philips) - validated across multi-vendor datasets
- Clinical support through standardized, repeatable measurements.

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2D Flow Sequences:

- Semi-automated segmentation of vascular structures via user-placed seed point, with possibility of being reviewed
- Automatic analytical flow quantification, including parameters such as Total Forward/Backward Net Volumes, Regurgitation Fraction, Effective Volume per Minute, Maximum Velocity, Pressure Gradient, and Flow values.
- Clinical support through standardized, repeatable measurements.

General Benefits:

- Cloud-based platform: Offers high availability, scalability, and integration with hospital infrastructure.
- Improves clinical workflow when integrated with PACS or VNAs Viewers (no need for dedicated segmentation software).
- Interoperability: Communicates with other systems via standard protocols.

1.7 Limitations

AI4CMR analysis is limited to Cine CMR and 2D Phase-Contrast CMR acquisitions.

Other studies such as Late Gadolinium Enhancement or Perfusion are not covered.

Image interaction is performed exclusively through DICOM Viewers, encompassing image visualization and annotation, which are fully supported by third-party software.

Studies that rely on direct image interaction through a DICOM Viewer integrated with AI4CMR, such as the extraction of metrics from manually drawn ROIs in sequences like T1, T2, and T2* Mapping can be indirectly supported when AI4CMR is used alongside a compatible DICOM Viewer.

AI4CMR's performance has been tested in three MRI scanner vendors: Siemens, GE Healthcare Systems and Phillips Medical Systems. For new MRI scanner vendors, a message will be returned to the User stating that the vendor is not valid.

AI4CMR's performance has been validated for a range of image characteristics. Cases with image characteristics in the tolerance zone will be processed and a Warning message will be issued notifying the end user of possible performance degradation. Cases that cannot be processed because one or multiple image characteristics fall outside the tolerance range will be rejected.

Alongside unsupported image characteristics, unsupported image types and acquisition conditions may result in processing rejection.

AI4CMR outputs are intended to support qualified medical professionals and must be reviewed and validated within the context of the complete CMR examination and the patient's clinical background prior to clinical interpretation.

1.8 Warnings and precautions

- The physician must always review the cases even when AI4CMR classifies them as normal.
- Quantitative analysis is dependent on the quality and correctness of the image source data acquisition.
- The patient data must be anonymized by the third-party plugin before sending it to AI4CMR.
- The patient data displayed is initially derived from the DICOM information, if available. Editing these values may affect the calculations in all modules. It is the User’s responsibility to verify this data before releasing the final results.
- The user can introduce patient metadata (cine, cine recompute and flow), It is the User’s responsibility to verify this data before releasing the final results.
- The user is responsible for ensuring the seed point (at Flow) is placed precisely within the intended vessel region of interest and on a structure with adequate signal clarity.
- The User must keep a UPS system that provides emergency power when the input power source or mains power fails.
- It is the plugin maintenance team's responsibility to execute the installation procedure to validate the communication between the User and AI4CMR.
- It is AI4MedImaging’s responsibility to update/do maintenance periodically to reduce the probability of AI4CMR SW defects.
- At the installation time, a copy of the digital user manual must be copied to the User’s network, under the domain of the User’s IT Manager.
- In the event of loss of access credentials please follow the procedure in section 4. User account handling.
- AI4CMR outputs must be interpreted in conjunction with the complete CMR examination and the patient clinical context and shall not be used as the sole basis for diagnosis or treatment decisions
- Users should read this manual before using AI4CMR.

1.9 Intended patient population

The software analyses images of patients that were examined by CMR imaging.

Age The use is not recommended for children (age < 18yo) since the clinical evaluation studies targeted a mostly adult population.

Weight No limitations

Height No limitations

1.10 Applicable medical conditions

AI4CMR is an image analysis software for the post-processing of CMR images, used for the assessment of the following cardiac diseases:

- Cardiac failure
- Ischemic heart disease
- Valvular heart disease
- Cardiomyopathy
- Cardiac function and morphology
- Hypertensive cardiac disease
- Congenital heart disease
- Other pathologies that need assessment of cardiac function and morphology

1.11 Safety Instructions

Software AI4CMR is hosted in a cloud. The intended users interact remotely with the software.

The equipment communicating with AI4CMR shall:

- Be connected to a secure network;
- Have an access control system, to ensure that only accredited users can access the device and the AI4CMR service.

AI4CMR requires that the passwords are different from the username and have at least:

- Eight (8) characters;
- One (1) digit;
- One (1) uppercase;
- One (1) lowercase;
- One (1) special character.

It is highly recommended the usage of anti-virus software in all computers interacting with the AI4CMR to protect against cyber-attacks. Periodic backups are also recommended to make sure that no patient data is lost in an unforeseen event.

2 Conventions and Abbreviations

2.1 Conventions

EDV – End-Diastolic Volume [ml]

ESV – End-Systolic Volume [ml]

SV – Stroke Volume [ml]

EF – Ejection Fraction [%]

Mass – Myocardial Mass [g]

CO – Cardiac Output [L/min]

EDV/BSA – End-Diastole Volume/Body Surface Area [ml/m²]

ESV/BSA - End-Systole Volume/Body Surface Area [ml/m²]

SV/BSA – Systole Volume/Body Surface Area [ml/m²]

Mass/BSA – Myocardial Mass/Body Surface Area [g/m²]

CI – Cardiac Index [L/(min m²)]

BSA - Body Surface Area [m²]

TFV - Total Forward Volume (ml)

TBV - Total Backward Volume (ml)

TV - Total Volume (ml)

TNPV -Total Net Positive Volume (PV) (ml)

TNNV - Total Net Negative Volume (NV) (ml)

RF - Regurgitation Fraction (%)

Vol/min- Volume per Minute (Vol/min) (l/min)

Eff. Vol/mi - Effective Volume per Minute (Vol/min effective) (l/min)

Max PG - Maximum Pressure Gradient (mmHg)

Max Vel- Maximum Velocity (cm/s)

Min Vel- Minimum Velocity (cm/s)

Max Mean Vel - Maximum Mean Velocity (cm/s)

Max Flow- Maximum Flow (ml/s)

Min Flow - Minimum Flow (ml/s

2.2 Abbreviations

ED – End-Diastole

ES – End-Systole

MRI – Magnetic Resonance Imaging

CMR – Cardiac Magnetic Resonance

DICOM – Digital Imaging and Communications in Medicine

HTTP – Hypertext Transfer Protocol

SA – Short-axis

LA – Long-axis

LV – Left Ventricle

RV – Right Ventricle

ICC - Interclass Correlation Coefficient

TFV - Total Forward Volume

TBV - Total Backward Volume

TV - Total Volume

TNPV -Total Net Positive Volume (PV)

TNNV - Total Net Negative Volume (NV)

RF - Regurgitation Fraction

Vol/min- Volume per Minute

Eff. Vol/mi - Effective Volume per Minute

Max PG - Maximum Pressure Gradient

Max Vel- Maximum Velocity

Min Vel- Minimum Velocity

Max Mean Vel - Maximum Mean Velocity

Max Flow- Maximum Flow

Min Flow - Minimum Flow

3 Getting Started

3.1 Notice to the user

Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

3.2 System requirements

AI4CMR software runs as a Docker image on the cloud.
The minimum requirements for the ethernet connection are:

- High bandwidth network (50Mbits/s minimum and 100Mbits/s recommended).

3.3 Setup

For customer registration, the customer environment shall be informed to AI4MedImaging: MRI scanner vendor, PACS vendor and version, Viewer vendor and version and third-party plugin ID and version.

A *client_id* and temporary user authentication credentials will be assigned by AI4MedImaging to the customer.

The third-party plugin shall be installed and configured as per its User Manual.

AI4CMR Cine:

To validate the set-up, the following validation protocol shall be followed:

1. Three clinical cases (hereinafter called gold samples GS1; GS2 and GS3) are delivered to the customer by AI4MedImaging. The samples shall be submitted to AI4CMR through the third-party plugin.

   GS1 case is a valid case with all the mandatory and optional data;
   GS2 case is a valid case with all the mandatory data;
   GS3 case is a non-valid case with missing mandatory data.

2. The results displayed by the third-party plugin for each of the golden samples shall be compared with the following expected results:

GS1:

	EDV (mL)	IEDV index (mL/m²)	ESV (mL)	ESV index (mL/ m²)	CO (L/min)	CI (L/min/ m²)	SV (mL)	SV index (mL/ m²)	EF (%)	Mass (g)	Mass index (g/m2)	ED frame	ES frame
LV	116.79	77.57	37.87	25.15	5.05	3.36	78.92	52.42	67.58	77.52	51.49	29	11
RV	117.16	77.82	40.70	27.03	4.89	3.25	76.46	50.79	65.26	-	-	29	12

	Value
Classification	Normal
Confidence	0.95
Final Classification	Normal
BSA	1.51

GS2:
A warning shall be displayed stating CO, CI and other indexed volume metrics were not computed since heart rate, height and weight were not given.

	EDV (mL)	IEDV index (mL/m²)	ESV (mL)	ESV index (mL/ m²)	CO (L/min)	CI (L/min/ m²)	SV (mL)	SV index (mL/ m²)	EF (%)	Mass (g)	Mass index (g/m2)	ED frame	ES frame
LV	219.35	-	110.82	-	-	-	108.53	-	49.48	146.58	-	24	8
RV	203.11	-	91.67	-	-	-	111.44	-	54.87	-	-	24	9

	Value
Classification	Suspect
Confidence	0.69
Final Classification	Suspect
BSA	-

GS3:
The submission shall be disabled. A warning shall be displayed stating there are missing required fields.

3. The customer's IT Manager must send the validation report to AI4MedImaging's Field Support via email. The report must include:
    - A signed statement by the IT Manager confirming if the validation protocol was successful or if it failed.
    - Screenshots of the results obtained for the 3 golden samples.

4. AI4MedImaging's Field Support must confirm reception and sign the report. If the validation protocol is successful AI4MedImaging will provide the final user credentials to the customer. Otherwise, further support must be offered for problem resolution in articulation with the third-party plugin vendor.

Changes to the plugin (release of new versions) must be communicated to AI4MedImaging and a new validation process might be needed depending on the changes done.

AI4CMR 2DFlow:

To validate the set-up, the following validation protocol shall be performed:

1. Three clinical cases delivered to the customer (hereinafter called gold samples GS1Flow; GS2Flow and GS3Flow) shall be submitted to AI4CMR 2DFlow through the third-party plugin.

   GS1Flow case is a valid case with all the mandatory data where ascending and descending aorta are identified for analysis.

   GS2Flow case is a valid case with all the mandatory data where the pulmonary artery is identified for analysis.

   GS3Flow case is a non-valid case with missing mandatory data, specifically the VENC value.

   Note: Since 2DFlow submissions require a seed point on the vessels, which influences the final quantification results, the service will automatically position the seed point at a predefined location, overriding any user-defined seed points. This approach is applied solely for validation during the setup phase to ensure reproducibility.

2. The results displayed by the third-party plugin for each of the golden samples shall be compared with the following expected results:
   GS1Flow:

	Volume (L/min)	**Max Velocity (cm/s)**	**Total Forward Volume (ml)**	**Total Backward Volume (ml)**
Ascending Aorta	8.121	190.137	75.851	-0.457
Descending Aorta	3.057	57.813	40.979	-0.601

   GS2Flow:

	Volume (L/min)	Max Velocity (cm/s)	Total Forward Volume (ml)	Total Backward Volume (ml)
Pulmonary Artery	2.178	20.801	36.308	0.0

   GS3Flow: The submission shall be disabled. A warning shall be displayed stating there are missing required fields.

3. The customer's IT Manager must send the validation report to AI4MedImaging's Field Support via email. The report must include:

   - A signed statement by the IT Manager confirming if the validation protocol was successful or if it failed.
   - Screenshots of the results obtained for the 3 golden samples.

4. AI4MedImaging's Field Support must confirm reception and sign the report. If the validation protocol is successful AI4MedImaging will provide the final user credentials to the customer. Otherwise, further support must be offered for problem resolution in articulation with the third-party plugin vendor.

Changes to the plugin (release of new versions) must be communicated to AI4MedImaging and a new validation process might be needed depending on the changes done.

3.4 User Training

After the setup is validated, the users will partake in individual or group training given by AI4MedImaging through the Microsoft Teams platform. The users must be trained before using AI4CMR.

Additional individual/group training or Demos can be requested and scheduled by contacting our Technical Support (Section 5).

3.5 Software overview

The AI4CMR operating sequence of events is summarized in Figure **2**. The green-colored boxes include the operations executed on the external DICOM Viewer plugin, to initiate AI4CMR processing (blue boxes).

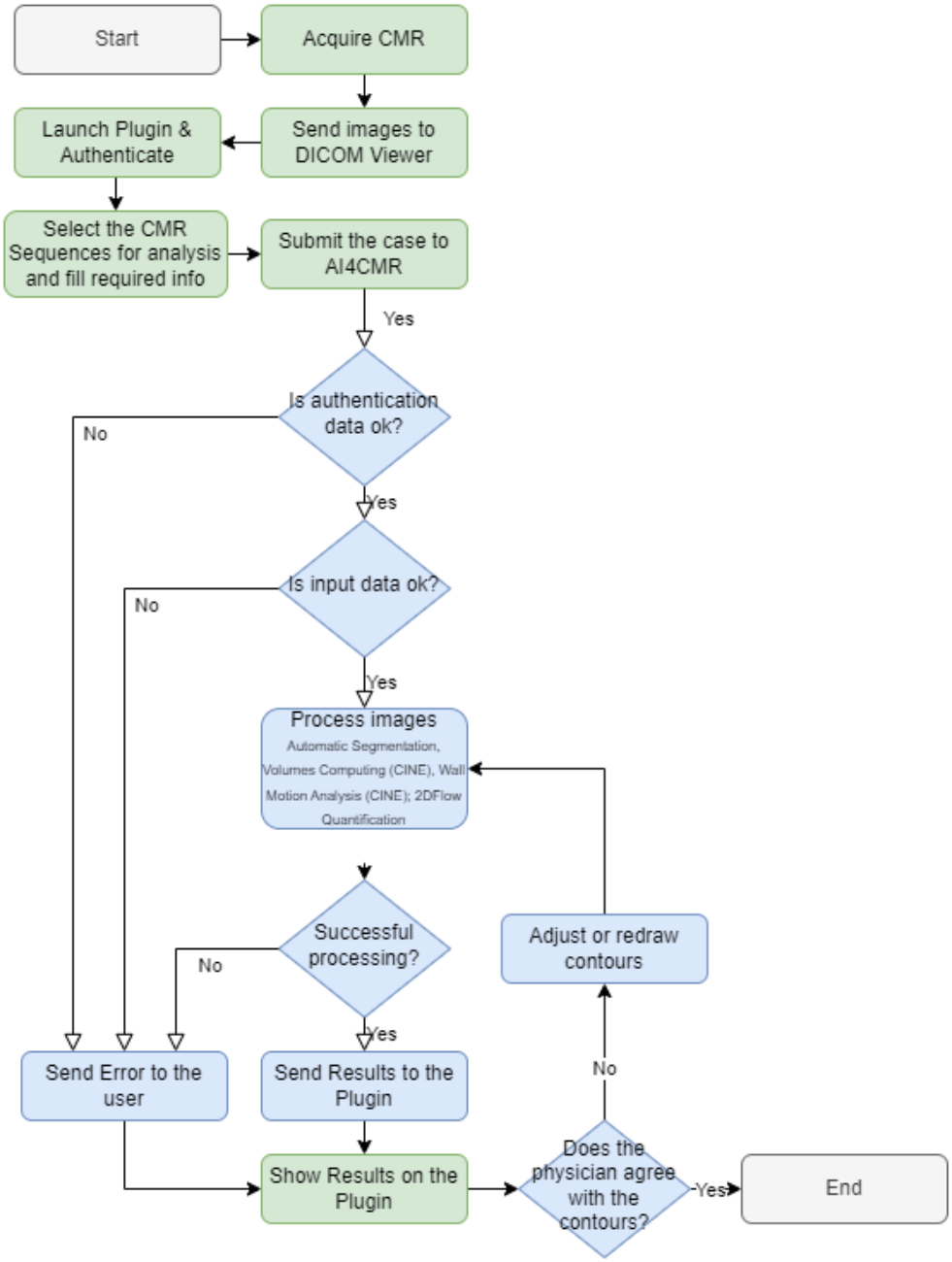

Figure 2. Flowchart of the operating sequence. Green steps are out of AI4CMR's control; blue steps are controlled by AI4CMR.

WARNING: * Wall Motion feature is not available for clinical use in the USA. This module is to be used for research purposes only, and not for primary diagnostics and direct patient care

3.5.1 General operating steps

The general operating steps to use AI4CMR are summarized in the following table:

Operating step	System context
1. The Cardiac Magnetic Resonance is acquired according to standardized protocols	MRI Scanner
2. The images are sent to the third-party software	DICOM Viewer
3. The user launches the dedicated plugin on the third-party software and inserts the user credentials	Plugin
4. The user performs one or more of the following actions: Selection of the correct cine sequence planes and other requested patient data Places a seed point at a cardiac vessel structure in magnitude sequences of 2D Flow CMR.	Plugin
5. The user submits the request form to the AI4CMR cloud service	Plugin
6. The request is subject to authentication	AI4CMR
7. The data on the request is checked for sanity[1] and completion[2]	AI4CMR
8. The patient data is processed by several AI-based image processing modules (Cine: myocardium automatic segmentation, ventricle volumes computation, wall motion* analysis; Flow: vessels segmentation, flow quantification).	AI4CMR
9. The results and log messages (errors, warnings, …) are collected and returned to the plugin via the communication API	AI4CMR
10. The user sees the output of AI4CMR on the dedicated plugin	Plugin
11. The user validates the outputs, or adjusts the contours on the dedicates plugin, prompting the recomputation by AI4CMR.	Plugin/AI4CMR

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A CMR case to be submitted to AI4CMR shall consist of:

Cine:

1. Required:
    - DICOM cine SA with metadata:
        - Image Patient Position;
        - Image Patient Orientation;
        - Pixel Spacing;
        - Slice Thickness;
        - Rows;
        - Columns.
    - Patient metadata:
        - Age (on acquisition date);
        - Sex.
2. Optional:
    - DICOM cine 2ch, 3ch and 4ch (recommended);
    - Height, weight, heart rate.

2D Flow:

- Required:
    - Identification of the vascular structures for analisis: vessel name and ROI
    - DICOM 2DFlow data with metadata:
        - Pixel Spacing;
        - Bits Stored;
        - Manufacturer;
        - VENC;
        - Nominal Interval or TriggerTime or HighRRInterval and LowRRInterval

The outputs of AI4CMR consist of:

- Left Ventricle endo and epicardium contours (coordinates)
- Right Ventricle endocardium contours (coordinates)
- Left Ventricle volumes-derived metrics:
    - EDV – End-Diastolic Volume [ml]
    - ESV – End-Systolic Volume [ml]
    - SV – Stroke Volume [ml]
    - EF – Ejection Fraction [%]
    - Mass – Myocardial Mass [g]
    - CO – Cardiac Output [L/min]
    - EDV/BSA – End-Diastole Volume/Body Surface Area [ml/m²]

  - ESV/BSA - End-Systole Volume/Body Surface Area [ml/m²]
  - SV/BSA – Systole Volume/Body Surface Area [ml/m²]
  - Mass/BSA – Myocardial Mass/Body Surface Area [g/m²]
  - CI – Cardiac Index [L/(min m²)]
  - BSA - Body Surface Area [m²]
- Right Ventricle volumes-derived metrics:
  - EDV – End-Diastolic Volume [ml]
  - ESV – End-Systolic Volume [ml]
  - SV – Stroke Volume [ml]
  - EF – Ejection Fraction [%]
  - CO – Cardiac Output [L/min]
  - EDV/BSA – End-Diastole Volume/Body Surface Area [ml/m²]
  - ESV/BSA - End-Systole Volume/Body Surface Area [ml/m²]
  - SV/BSA – Systole Volume/Body Surface Area [ml/m²]
  - CI – Cardiac Index [L/(min m²)]
  - BSA - Body Surface Area [m²]
- Case classification*:
  - Wall motion class – normal or suspect
  - Wall motion class confidence
  - Final class – normal or suspect

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- 2D flow vessels contours (coordinates)
- 2D flow Measurements:
  - TFV - Total Forward Volume (ml)
  - TBV - Total Backward Volume (ml)
  - TV - Total Volume (ml)
  - TNPV -Total Net Positive Volume (PV) (ml)
  - TNNV - Total Net Negative Volume (NV) (ml)
  - RF - Regurgitation Fraction (%)
  - Vol/min- Volume per Minute (Vol/min) (l/min)
  - Eff. Vol/mi - Effective Volume per Minute (Vol/min effective) (l/min)

- Max PG - Maximum Pressure Gradient (mmHg)
- Max Vel- Maximum Velocity (cm/s)
- Min Vel- Minimum Velocity (cm/s)
- Max Mean Vel - Maximum Mean Velocity (cm/s)
- Max Flow- Maximum Flow (ml/s)
- Min Flow - Minimum Flow (ml/s

See Section 3.5.2 for details on outputs validation.

Notice:

For the Case classification:

1. The final case class takes both wall motion classification* and ejection fraction value into account. A case is only deemed as normal if both criteria are in the normality range.
2. The “confidence” is a probability output (0-1) from the machine learning models used to classify each case. The closer the value is to 1, the greater the confidence in the attributed classification, taking the original training database[1] as a reference.

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3.5.2 Summary of outputs validation

3.5.2.1 Cine:

The studies conducted under the clinical evaluation phases showed high agreement between AI4CMR measurements and the human observers in a set of 146 patients:

- Correlation (ICC) in the measurement of LV EDV is 0.99, LV ESV is 0.99, LV SV is 0.83, LV EF is 0.96 and Mass is 0.96. The other volume metrics are arithmetically derived from the previous.
- The accuracy and precision of the measurement of the volume are given by the bias (mean difference) and the standard deviation:

[1] Training database - Neural networks and other artificial intelligence programs require an initial set of data, called training data, to act as a baseline for further application and utilization. AI4CMR has been trained, validated and tested on a split database of around 1000 patients, labelled by experts.

	LV EDV (ml)	LV ESV (ml)	LV SV (ml)	Mass (g)	LV EF (%)
AI4CMR vs consensus (*)	1.81±17.61	-6.84±17.65	8.36±17.25	3.19±17.37	3.86±5.80

- Correlation (ICC) in the measurement of RV EDV is 0.97, RV ESV is 0.94, RV SV is 0.82 and RV EF is 0.80. The other volume metrics are arithmetically derived from the previous.
- The accuracy and precision on the measurement of the volume are given by the bias (mean difference) and the standard deviation:

	RV EDV (ml)	RV ESV (ml)	RV SV (ml)	RV EF (%)
AI4CMR vs rater1 (*)	1.25±15.99	-13.26±14.63	14.24±15.53	8.34±7.34

(*) The consensus between 2 raters (experts) was obtained by averaging each measurement. The measurements were obtained through a certified software, which computes the volumes based on the raters' manual segmentations.

- For case classification, the sensitivity is 100%, the negative predictive value is 100%, the accuracy is 76.7%, the positive predictive value is 70% and the specificity is 50%.

No uncertainty/error information is shown in the software together with the LV measurements.

3.5.2.2 2D Flow:

The flow quantification performance study was conducted to ensure comparability between AI4CMR and a similar/predicate device, demonstrating a high level of agreement. Vessel segmentation and flow quantification were independent of anatomical structures (e.g., vessel type). The study included 108 independent multivendor samples from real-world cases (covering the ascending aorta, descending aorta, and pulmonary artery) from 66 subjects. These samples were processed by both AI4CMR and the similar/predicate device, and their performance on flow quantification was compared. The key findings were:

- The intraclass correlation coefficients (ICC) for TFV, TBV, and Max Vel were 0.95, 0.82, and 0.95, respectively, highlighting strong agreement in clinically relevant measures.
- The accuracy and precision achieved for TFV, TBV, and Max Vel measurements are given by the bias (mean difference) and the standard deviation:

	TFV (ml)	TBV (ml)	Max Vel (cm/s)
AI4CMR vs Similar/predicate device	-1.65±9.61	-0.47±2.24	-1.24±15.11

- Statistical comparison between AI4CMR and the similar/predicate device was performed using a paired *t*-test for Max Vel (*t* = -0.773, *p-value* = 0. 445), TBV (*t* = -1.039, *p-value* = 0.301) and TFV (*t* = -1.790, *p-value* = 0.076), with all results being non-significant (*p-value* > 0.05).

3.5.3 Plugin

AI4CMR is intended to be integrated with a third party DICOM Viewer. The integration is established via a communication protocol implemented by a Plugin. AI4CMR does not have a User Interface. The end-user will interact with AI4CMR via the Plugin's interface.

The Plugin User Manual or Guide, which accompanies the current manual, describes in more detail the features and steps necessary to interact with the AI4CMR service. The Plugin consists of a user interface to help the User create the request form.
Different viewers can have different user experiences, but the main idea should be the same.

For clarification purposes, this section provides merely indicative (not binding) examples of what the user experience may be like with a third-party Plugin for AI4CMR.

Login

The first step to use the AI4CMR is to successfully authenticate with the service. To do that, there are two options:

- The User shall provide a username and password through the user interface
- The plugin loads credentials/licensing information securely saved in or transmitted by the User's system.

Figure 3. Example of a plugin login window.

Input Data Selection

The input data selection can be done in two ways:

- Manually by the User through the user interface. This option may or may not include automatic prefilling.
- Automatically by the plugin taking advantage of the standard DICOM tags.

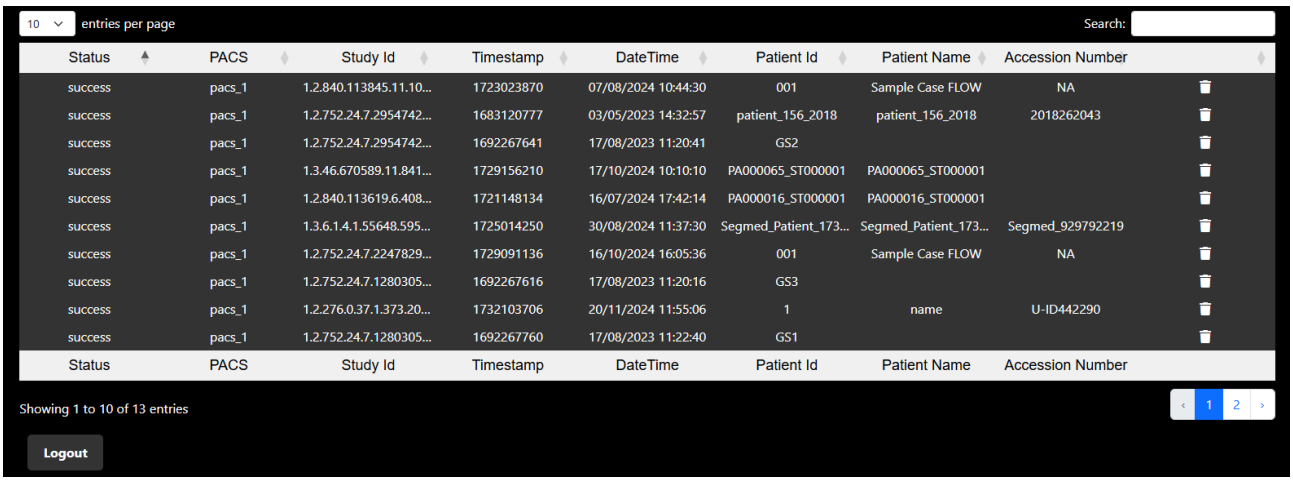


Figure 4. Example of a plugin worklist window.

Form filling

Cine Sequences Analysis

Figure 6 shows an example of an interface for the User to fill in the necessary information. The automation of this step is advised and should allow the edition of the patient metadata (age, sex, heart rate, height, and weight).

AI4CMR's performance has been validated for a range of image characteristics, as shown in the tables[2] below:

Ranges	Number of Pixel Rows	Number of Pixel Columns	Image Size Values	Slice Thickness Values
Error	]-∞, 140[	]-∞, 140[	]- ∞, 26957[	]- ∞, 7.2[
Warning	[140, 156[	[140, 156[	[26957, 29952[	[7.2, 8[
Acceptance	[156, 320]	[156, 320]	[29952, 102400]	8
Warning	]320, 352]	]320, 352]	]102400, 123904]	]8, 8.8]
Error	]352, +∞[	]352, +∞[	]123904, +∞[	]8.8, +∞[

Ranges	Pixel Spacing Values	Number of Slices	Slice Spacing Values	Pixel Intensity Values
Error	]- ∞, 0.8389[	]- ∞, 8[	]- ∞, 7.2[	]- ∞, 28.0069[
Warning	[0.8389, 0.9322[	[8, 9[	[7.2, 8[	[28.0069, 31.1188[
Acceptance	[0.9322, 1.7709]	[9, 16]	[8, 10]	[31.1188, 273.8040]
Warning	]1.7709, 1.9479]	]16, 19]	]10, 11.2]	]273.8040, 355.1480]]355.1480, +∞[*
Error	]1.9479, +∞[	]19, +∞[	]11.2, +∞[	N/A**

**Cases in this range are subject to input normalization prior to processing*
*** Not applicable, meaning that no Warning/Error will be raised*

Cases with image characteristics at the tolerance boundary of the verified algorithm performance will be processed and a Warning message will be issued. Cases that cannot be processed will be rejected because they contain one or more image characteristics outside the acceptance range. In this scenario, the user will be informed of the reason for rejection.

Patient metadata shall be filled in by the User if the Plugin does not automatically fill it based on the DICOM information:

- Mandatory:
  - Patient ID
  - Age
  - Sex
- Optional:
  - Heart rate (if not sent to AI4CMR: CO and CI will not be computed)

[2] The values are the result of a study conducted based on a significative sample of CMR cases.

- Height (if not sent to AI4CMR: no BSA nor indexed metrics (EDV/BSA, ESV/BSA, SV/BSA, Mass/BSA, CI) will be computed)
- Weight (if not sent to AI4CMR: no BSA nor indexed metrics (EDV/BSA, ESV/BSA, SV/BSA, Mass/BSA, CI) will be computed)

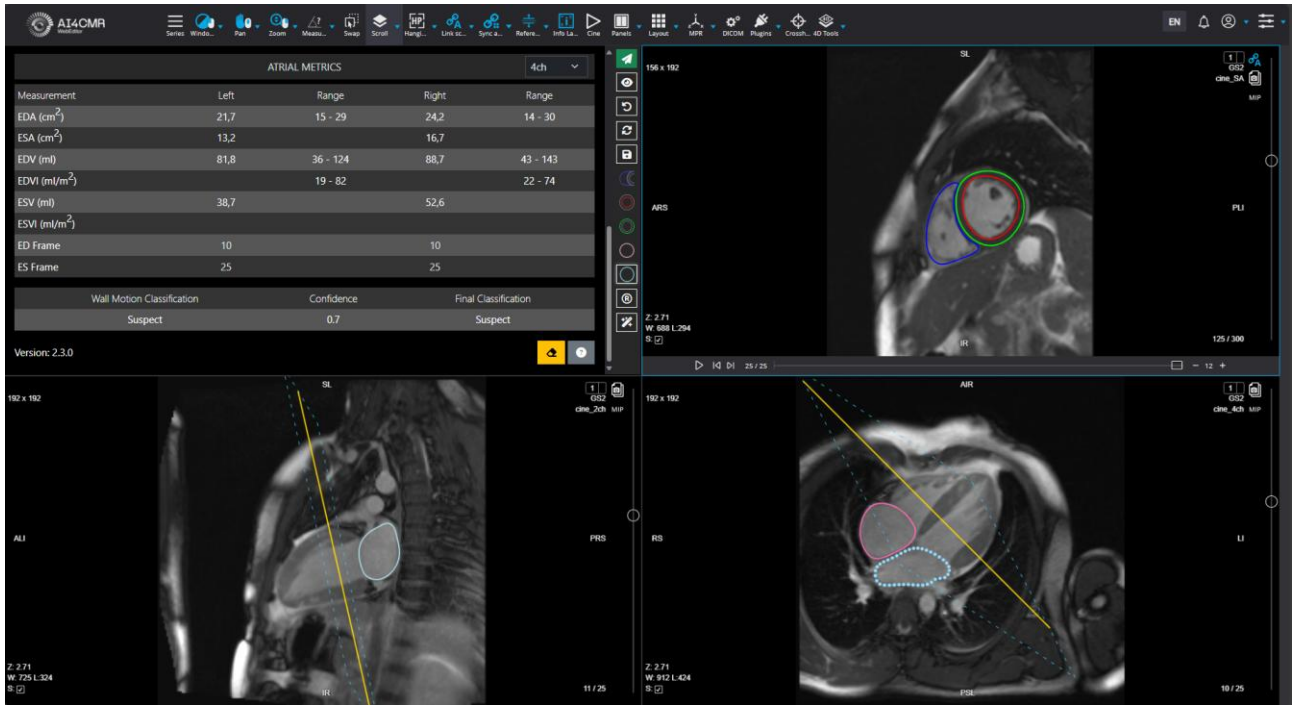


Figure 5. Example of a cine plugin window.

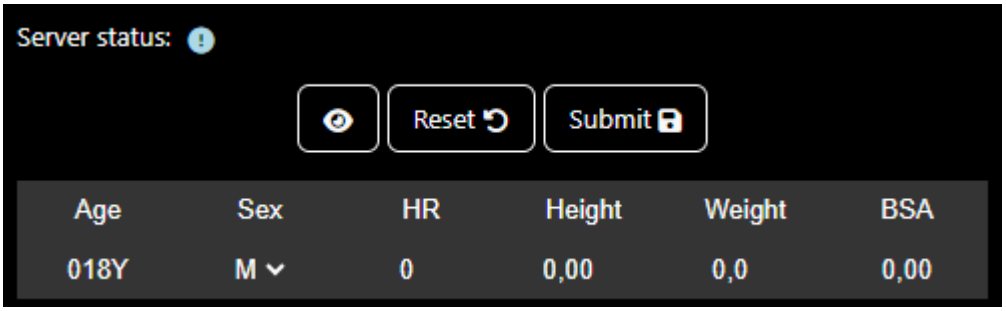


Figure 6. Example of a plugin form filling window.

2D Phase-Contrast Sequences Analysis

AI4CMR 2DFlow's performance has been validated for a range of image characteristics, as shown in the tables[3] below:

Feature	Acceptance	Warning
Pixel Spacing	[1.25, 1.7709]	]- ∞, 1.25[U]1.7709, +∞[
Pixel Intensity	[23.19, 88.55]	]- ∞, 23.19[U]88.55, +∞[

Cases with image characteristics that are outside the boundaries of the verified performance of the algorithms will be processed, but a warning message will be logged to inform that performance can be affected.

In the plugin, the user triggers the AI4CMR 2D Flow to analyze the case by selecting a seed point on the vessels within one of the sequence's magnitude frames to quantify the blood flow of the respective vessel. This allows the tool to quantify the blood flow in the selected vessels. After processing the case, AI4CMR provides the vessels delineation across the entire sequence along with the corresponding flow measurement values.

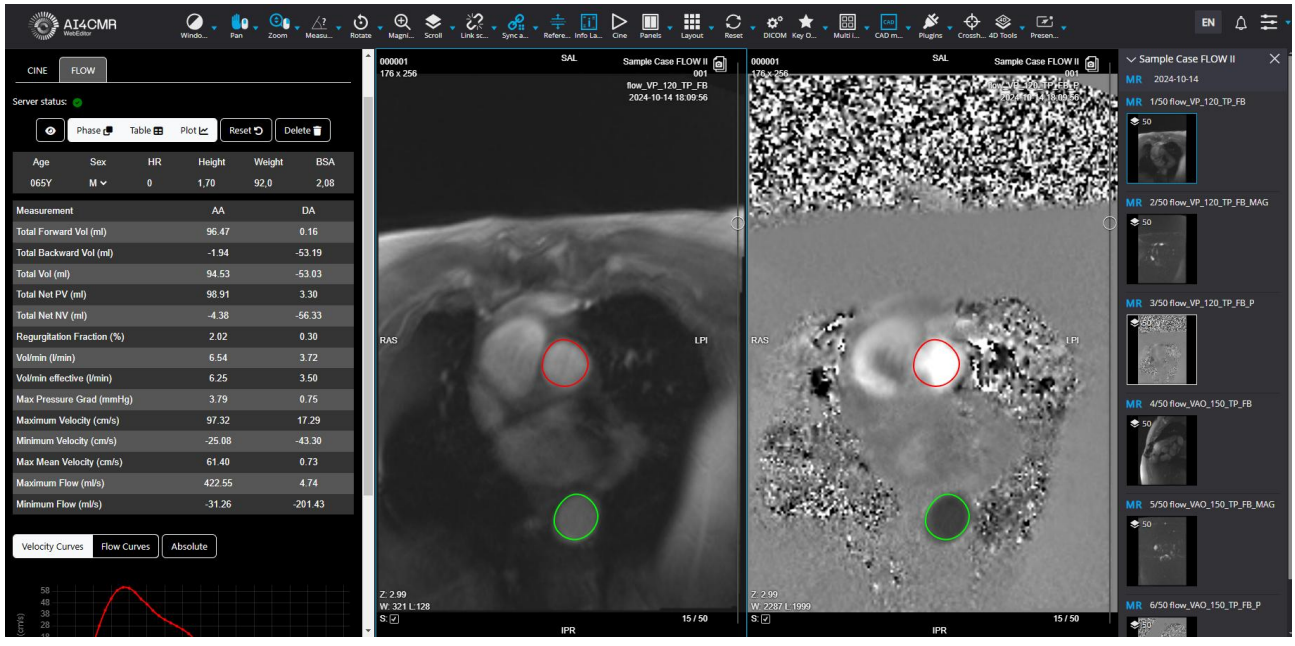


Figure 7. Example of a flow plugin window.

[3] The values are the result of a study conducted based on a significative sample of CMR cases.

T1, T2 and T2* Sequence Analysis

An example of a potential integration between AI4CMR and a DICOM Viewer that supports ROI drawing and metric extraction is shown below. The mean intensity value of the drawn ROIs can then be used to infer the relevent metrics for these Mapping sequences analysis.

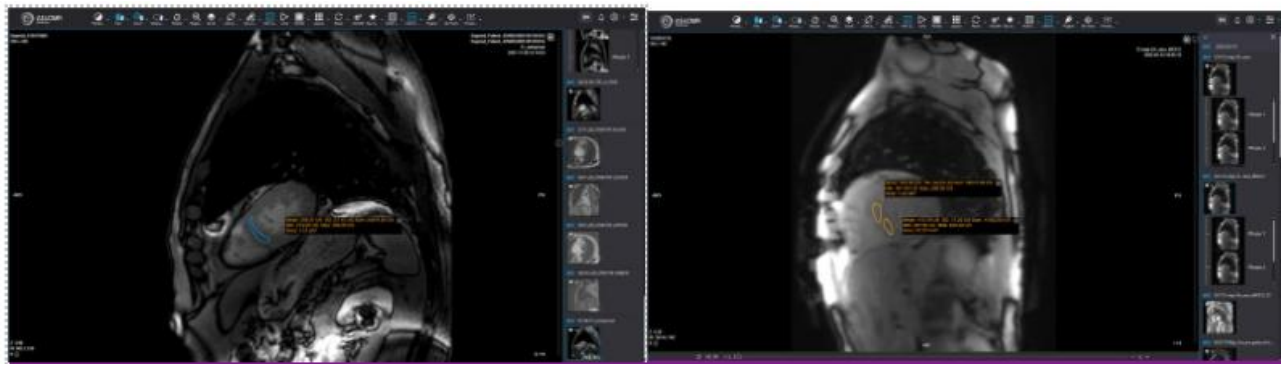


Figure 8. Example of T1 and T2 images analysis.

Results presentation

After successful processing, the plugin presents the results. The results presentation includes someway to show contours and someway to show numerical values and text. In the case of failure, an error message shall be outputted instead of the results.

Cine Sequences Analysis Results

One example of a possible user interface for results reporting is presented in the bottom half of Figure (LV and RV report).

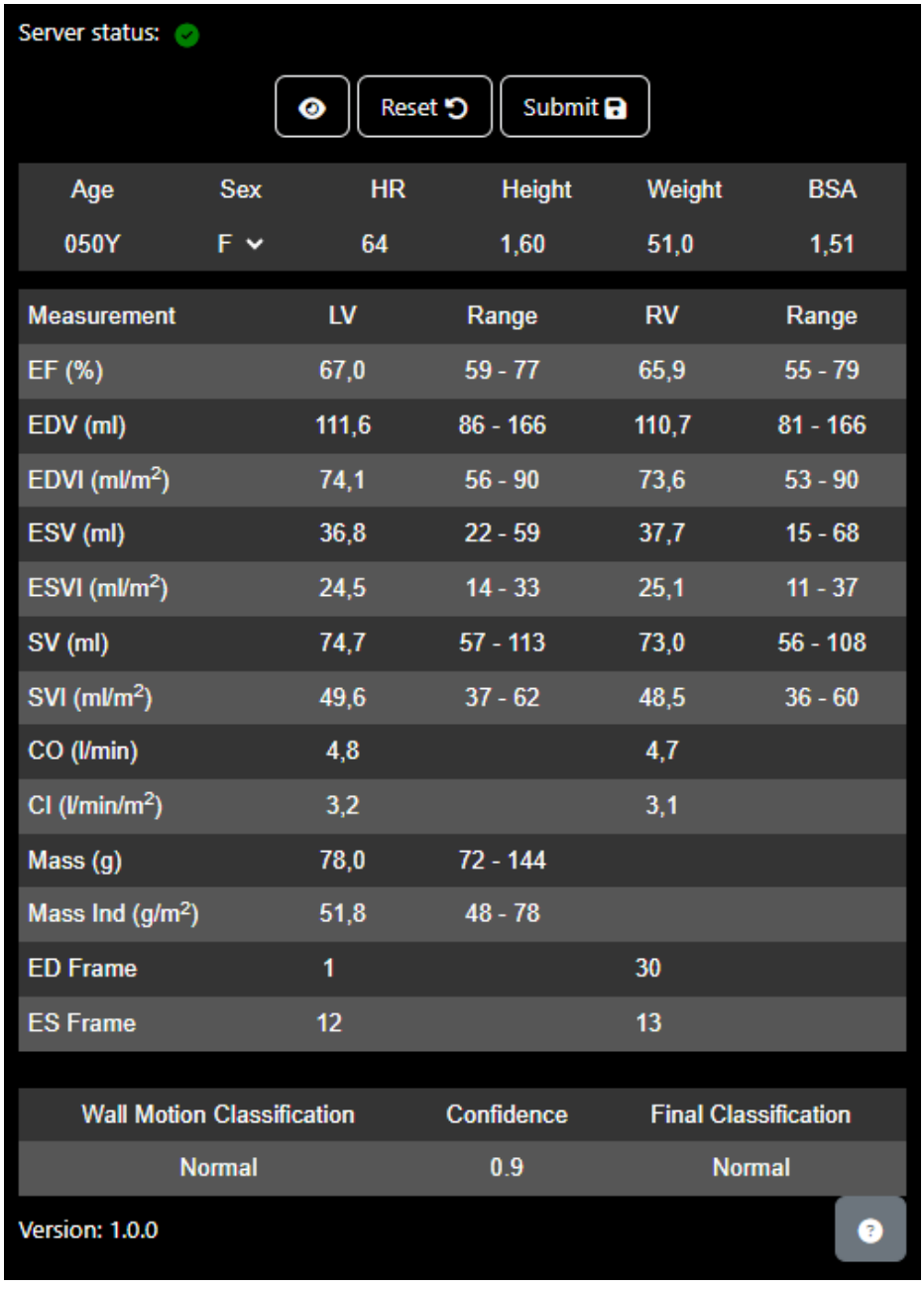
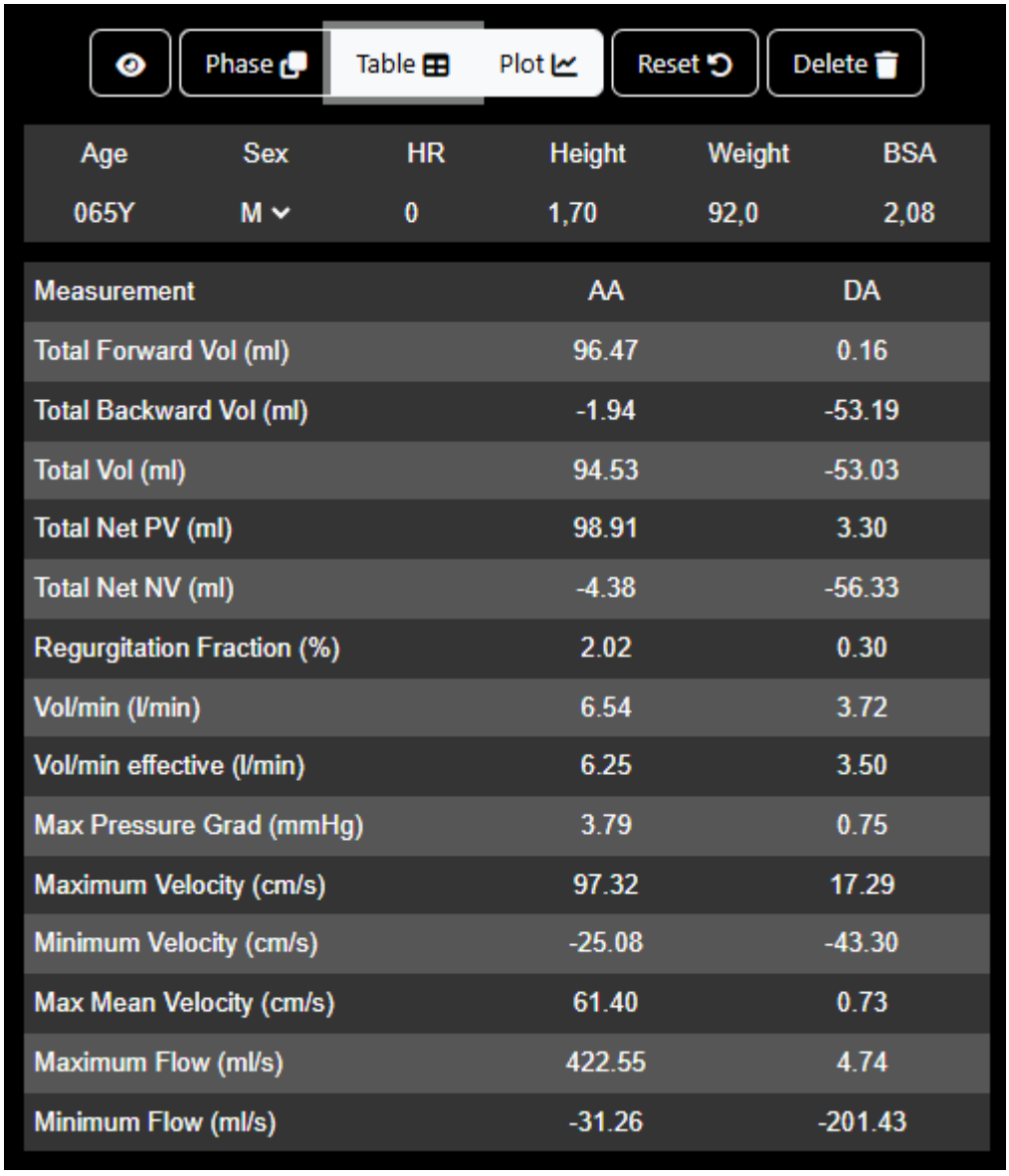


Figure 9. Example of a plugin form filling and results in the presentation window – LV and RV Report.

2D Phase-Contrast Sequences Analysis Results

An example illustrating the results of flow measurements is shown in Figure 10, while Figure 11 illustrates the flow and velocity curves.



Age	Sex	HR	Height	Weight	BSA
065Y	M	0	1,70	92,0	2,08

Measurement	AA	DA
Total Forward Vol (ml)	96.47	0.16
Total Backward Vol (ml)	-1.94	-53.19
Total Vol (ml)	94.53	-53.03
Total Net PV (ml)	98.91	3.30
Total Net NV (ml)	-4.38	-56.33
Regurgitation Fraction (%)	2.02	0.30
Vol/min (l/min)	6.54	3.72
Vol/min effective (l/min)	6.25	3.50
Max Pressure Grad (mmHg)	3.79	0.75
Maximum Velocity (cm/s)	97.32	17.29
Minimum Velocity (cm/s)	-25.08	-43.30
Max Mean Velocity (cm/s)	61.40	0.73
Maximum Flow (ml/s)	422.55	4.74
Minimum Flow (ml/s)	-31.26	-201.43

Figure 10. Example of a plugin metrics results in the presentation– 2D Flow metrics Report.

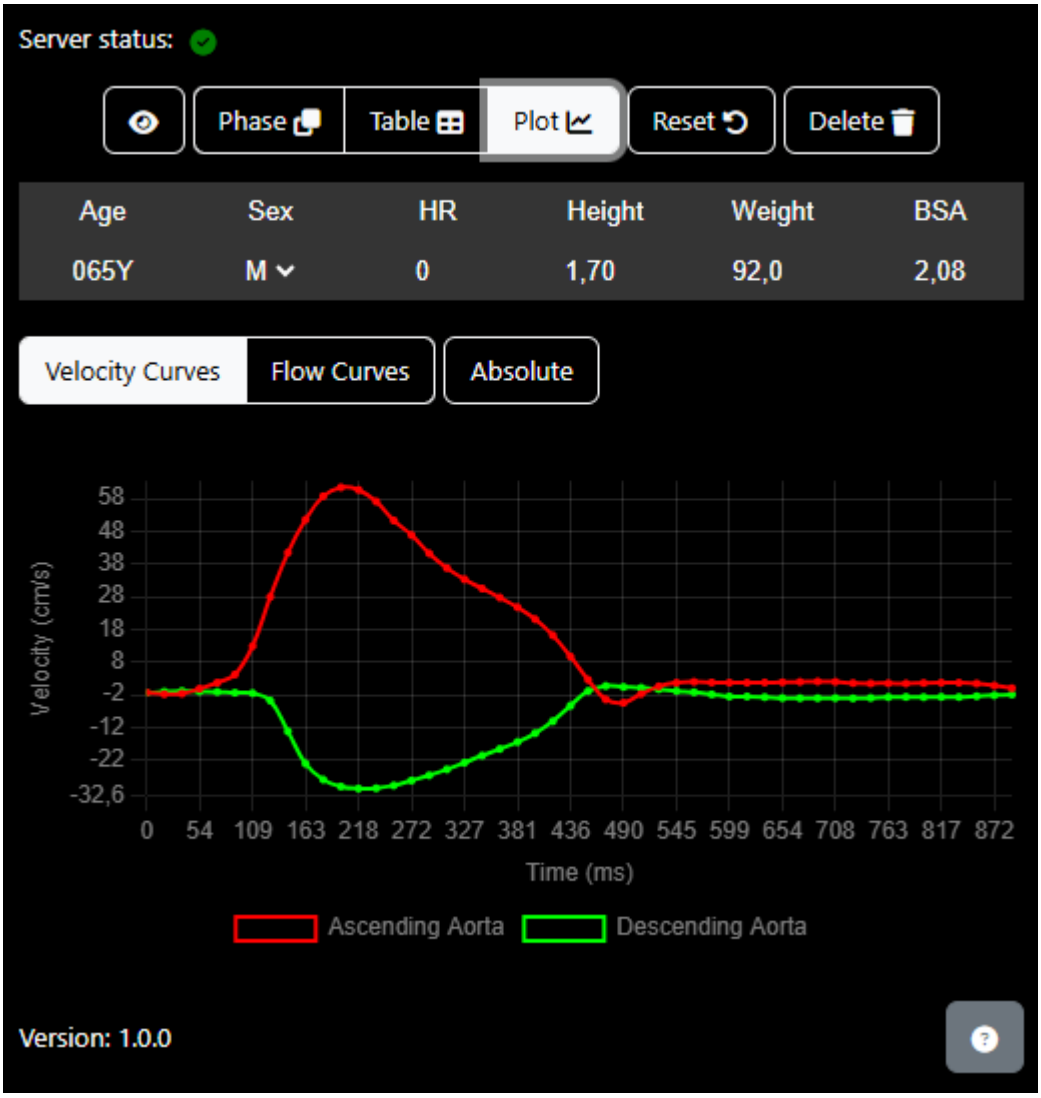


Figure 11. Example of a plugin curves results in the presentation flow window – flow curves

Additional fields

Connection status

This field is used to indicate that the AI4CMR service is available.

If not, the User should be able to force a connection status update. Either by clicking on the status or using any other way. The connection check endpoint of CORE should be used here to test the connection.

Figure 12. Connection status example.

Reset button

The reset button is used to clean all the info from the current request and make it easier for the user to start a new request without cleaning each field individually.

Figure 13. Reset button example.

Info button

This button presents information regarding the plugin and AI4CMR service, such as email, certifications, versions, device labelling and so on.

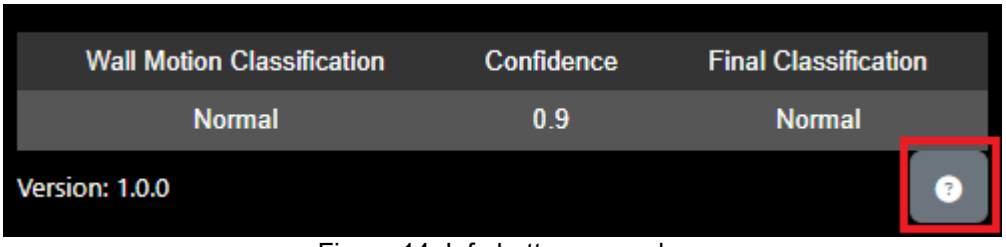


Figure 14. Info button example.

Confidence disclaimer

This button presents information to clarify the wall motion* classification results. When clicked, the button should display the disclaimer text.

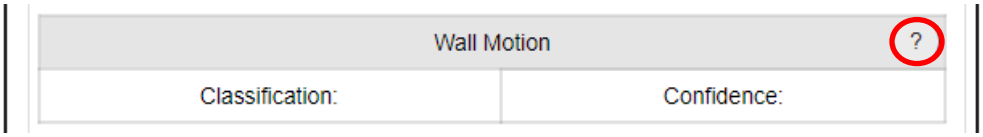
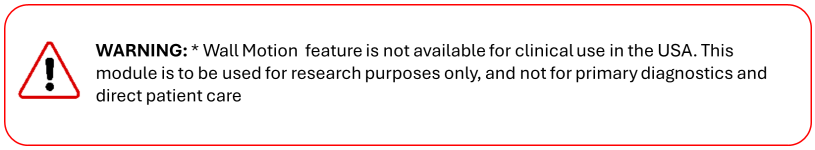


Figure 15. Confidence disclaimer button example.



Feedback button

This button can be used to redirect the User to a feedback webpage, email software, present a mobile number or any other communication way that might fit the task of providing feedback or requesting assistance. The plugin team can also include (or prefill) the message to be sent so that possible problems are easier to track.

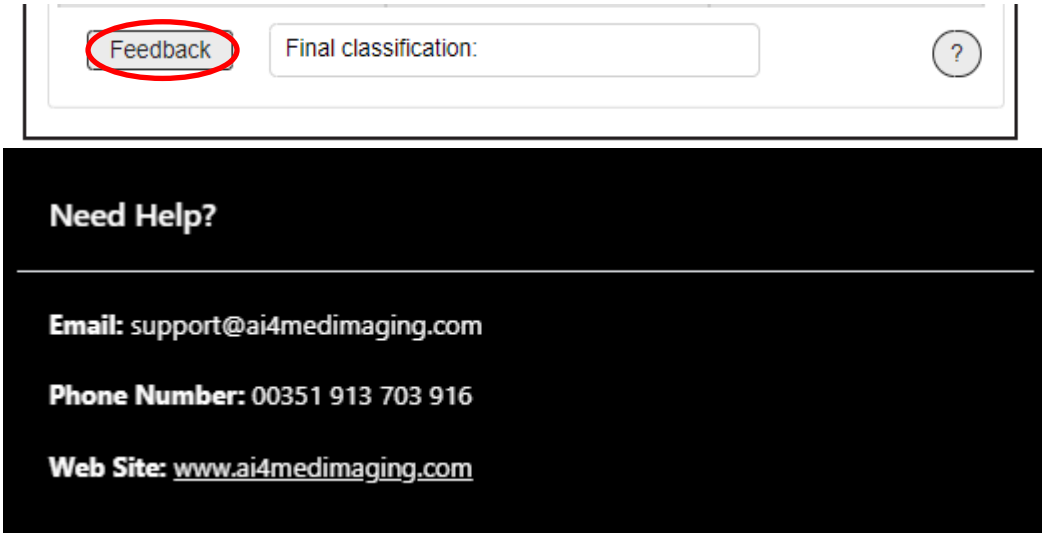


Figure 16. Feedback button example.

4 User account handling

The AI4CMR provides a user account handling page, that allows each user to change their personal information and credentials. To access this functionality, the user should use the following link via the Google Chrome browser (minimum recommended version: 97) or the Safari browser (minimum recommended version: 14.1):

- https://auth.ai4medimaging.com/auth/realms/srerealm/account

4.1 Authentication

To access the account, the user should provide the assigned username or email and password.
Note: the authentication/login window depends on the third-party plugin integration.

Figure 17. User account login page.

After successful authentication the user handling page will be presented, 18.

4.2 User information handling

After logging in, on the separator “Account” the user can change the email, first name and last name by filling the respective field and clicking on “Save”. If these values already exist, they will be presented in the respective field.

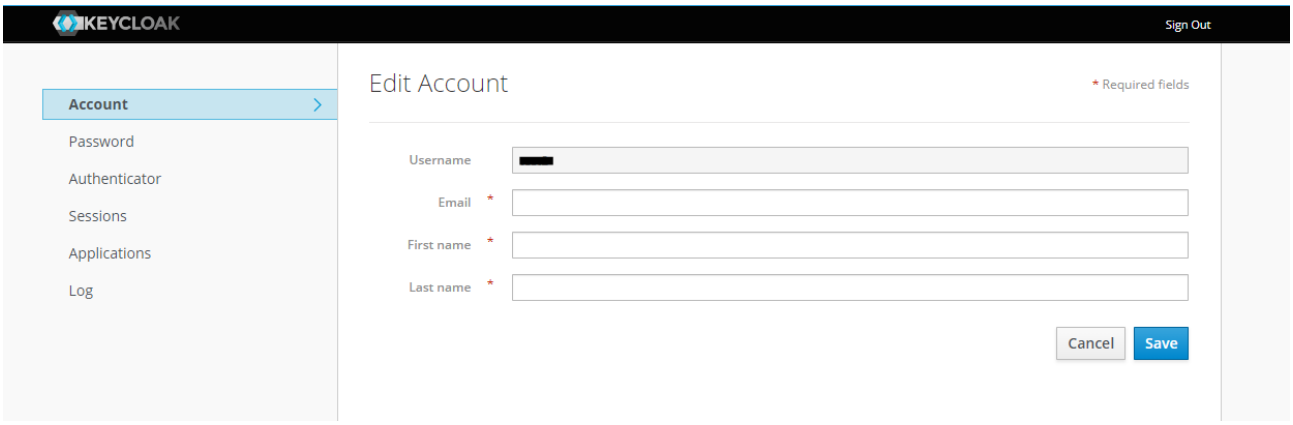


Figure 18. User account personal information edit page.

4.3 Password handling

To change the password, the user should log in first and change to the “Password” separator, provide the current password on the “Password” field and the new password on the “New Password” and “Confirmation” fields. After clicking on “Save” the password will be updated.

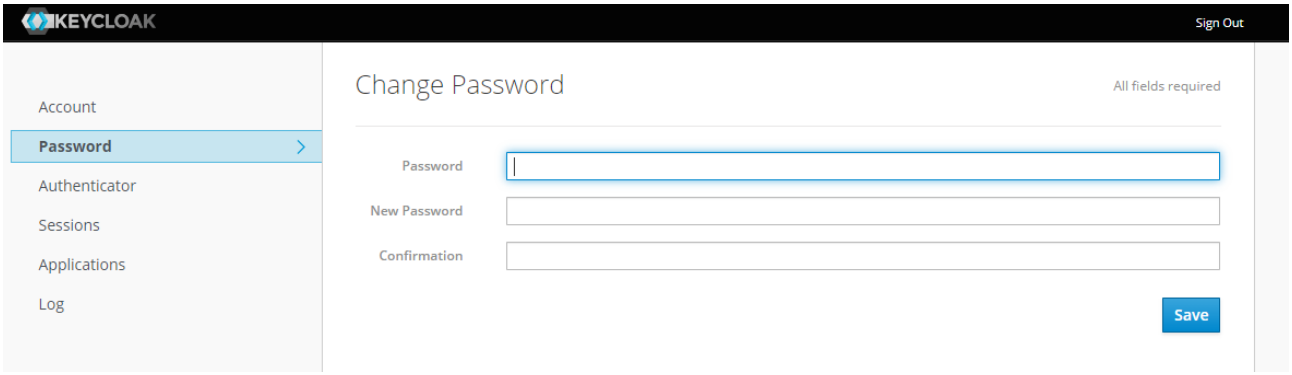


Figure 19. User account password edit page.

In case of password loss or account compromised, the IT Manager of the User’s Institution should contact the AI4MedImaging’s Technical Support (see section 5 for details).

4.4 Open sessions

The user has the option to monitor all open sessions associated with his account. That information is accessible in the “Sessions” separator. If any of the sessions open is considered suspect, the user has the option to close it using the “Log out all sessions” button.

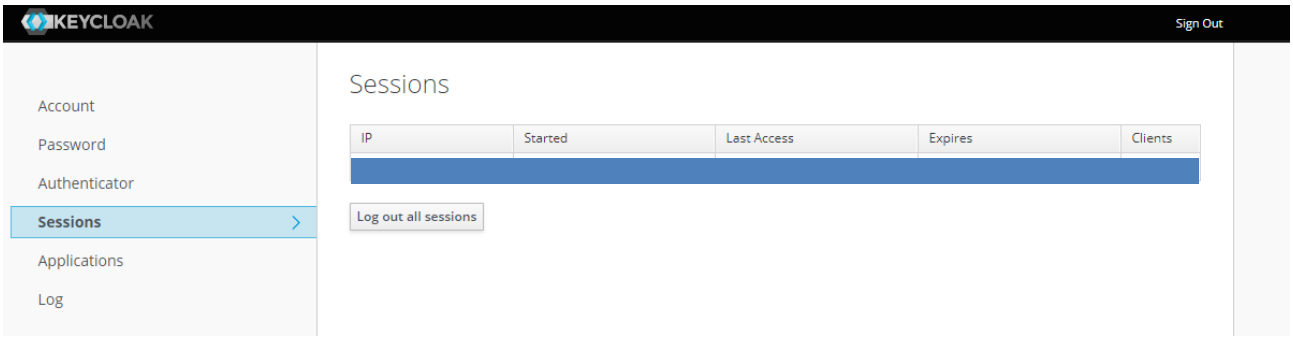


Figure 20. User account open sessions page.

4.5 Logging info

In addition to the open sessions, the user has the option to see all logging events that happen using his account. This information can be accessed on the “Log” separator.

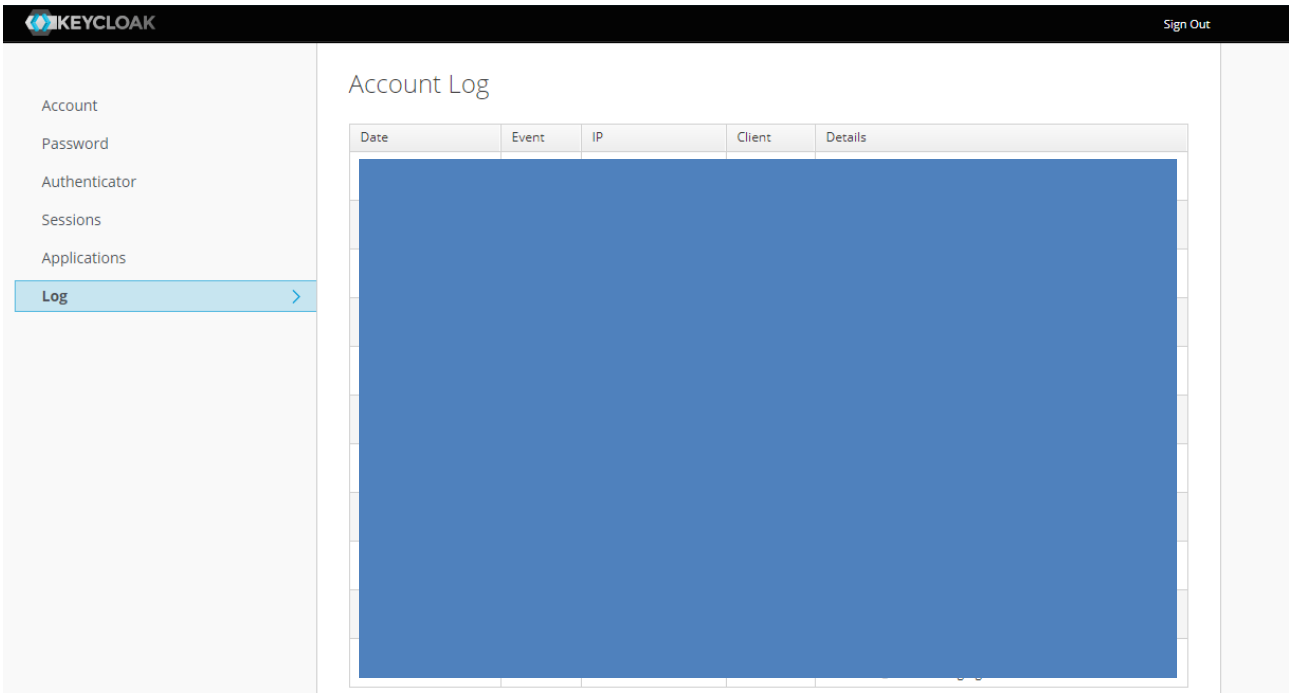


Figure 21. User account access log page.

5 Technical Support

For technical questions, to report a problem, or to request individual/group training or demos, please contact our team by e-mail or website:

AI4MedImaging Medical Solutions S.A.

Pólo de Negócios de Braga
Avenida Dom João II, nº 404, 1º andar, sala 12
4715-275 Braga
Portugal

Website: https://ai4cmr.com/

E-mail: support@ai4cmr.com

Appendix 1 - Information About the Artificial Intelligence (AI) Components of the Software

1. Overview

AI4CMR uses deep learning–based algorithms to assist with the automatic segmentation of cardiac structures on cardiac MRI images. These AI components support the user by generating quantitative measurements of cardiac morphology and function.

2. Role of AI in the Software

The AI modules perform the following functions:

- Automatic segmentation of the left ventricle (LV) myocardium and right ventricle (RV) bloodpool in Cine short-axis images.
- Segmentation of cardiac vessels on 2D Phase-Contrast Flow images occurs after user-provided seed point that labels the cardiac vessel.

All quantification measurements derived from segmentations are calculated using deterministic, physics-based methods.

A supervised deep learning model (UNet-based architecture) is used for automatic vessel segmentation in 2D Phase-Contrast Flow images. This machine learning component generates vessel contours after the user provides an initial seed point. The subsequent 2D flow quantification is fully deterministic and does not use machine learning. The model is locked and only updated when a new software version is released.

3. Intended Use of AI Outputs

The AI-generated measurements are intended to support qualified healthcare professionals in reviewing and analyzing cardiac MRI studies.

They do not provide diagnostic interpretation or clinical conclusions.

All outputs must be reviewed and verified by the user.

4. Inputs and Outputs

Inputs:

- Cine CMR images (DICOM format).

- 2D Phase-Contrast Flow images (DICOM format)

AI Outputs:

- Segmentation contours of cardiac chambers in Cine short-axis images.
- Segmentation contours of cardiac vessels in 2D Phase-Contrast Flow images

5. Limitations of the AI Component

- Not validated on pediatric patients under 18 years
- Not designed for 4D flow MRI
- Not validated on congenital anomalies with extreme structural distortion

The performance of the AI algorithms may be affected by:

- Low image quality or motion artifacts
- Non-standard acquisition protocols
- Anatomical anomalies not well represented in training data
- Severe pathology altering cardiac geometry
- Incomplete or corrupted DICOM metadata

The user should verify the automatic segmentations and adjust contours when necessary.

6. User Responsibilities

- Review and confirm AI-generated contours and measurements.
- Modify or re-run analysis if data quality is inadequate.
- Interpret all quantitative results in the context of the full clinical evaluation.

7. Data Quality and Error Handling

If the image data does not meet minimum quality requirements, the software may produce warnings or be unable to generate results.

Common causes include incorrect slice orientation, low signal-to-noise ratio, or incompatible sequence metadata.

8. Model Update Policy

The AI models in AI4CMR are “locked” and are only updated when a new version of the software is released following the manufacturer’s-controlled development and validation processes. The software does not perform automatic, adaptive or continuous learning updates in the field.

9. Models overview

Model Name: Cine SA – LV segmentation
Version: 1.0.0
Developer / Manufacturer: AI4CMR
Model Category: Convolutional Neural Network (U-Net architecture)
Primary Function: Automated segmentation of left ventricle myocardium in Cine short-axis CMR images.
Regulatory Classification: Class II, System, Image Processing, Radiological

Short Description:

The model uses a U-Net convolutional neural network to generate pixel-wise segmentation masks of left ventricle (LV) myocardium on Cine short-axis images. The segmentation supports calculation of cardiac function measurements**.**

Model Summary:

AI4CMR uses a deep-learning–based segmentation model to outline the LV endocardial and epicardial borders on Cine short-axis images. Contours are displayed to the user and can be manually refined. The model is “locked” and does not update its parameters during clinical use.

Performance Summary:

Segmentation Performance

- Dice: 0.93
- Precision: 0.93
- Recall: 0.94

Clinical Measurement Agreement

Comparison against expert manual contours across multi-center datasets showed high agreement:

Measurement	ICC
• LV End-Diastolic Volume (EDV)	0.99
• LV End-Systolic Volume (ESV)	0.83
• LV Stroke Volume (SV)	0.96
• LV Ejection Fraction (EF)	0.96
• LV Mass	0.97

External Reference Dataset Evaluation

The model was additionally evaluated using the SCMR Cardiac Atlas Project reference dataset, demonstrating consistency with consensus expert contours

Model Name: Cine SA – RV segmentation
Version: 1.0.0
Developer / Manufacturer: AI4CMR
Model Category: Convolutional Neural Network (U-Net architecture)
Primary Function: Automated segmentation of right ventricle bloodpool in Cine short-axis CMR images.
Regulatory Classification: Class II, System, Image Processing, Radiological

Short Description:

The model uses a U-Net convolutional neural network to generate pixel-wise segmentation masks of right ventricle (RV) bloodpool on Cine short-axis images. The segmentation supports calculation of cardiac function measurements.

Model Summary:

AI4CMR uses a deep-learning–based segmentation model to generate RV bloodpool contours. These contours are displayed to the user and may be manually edited. The model is “locked” and does not change with new clinical data.

Performance Summary:

Segmentation Performance:

- Dice: 0.88
- Precision: 0.88
- Recall: 0.89

Clinical Measurement Agreement

Comparison against expert manual contours across multi-center datasets showed high agreement:

Measurement	ICC
• RV End-Diastolic Volume (EDV)	0.97
• RV End-Systolic Volume (ESV)	0.94
• RV Stroke Volume (SV)	0.80
• RV Ejection Fraction (EF)	0.82

Model Name: 2D Flow Segmentation
Version: 1.0.0
Developer / Manufacturer: AI4CMR
Model Category: Convolutional Neural Network (U-Net architecture)
Primary Function: Automated segmentation of major cardiac vessels on 2D flow CMR (PC-MRI) images.
Regulatory Classification: Class II, System, Image Processing, Radiological
Short Description:
The model uses a U-Net convolutional neural network to generate pixel-wise segmentation masks of cardiac vessels (aorta, pulmonary artery) on phase-contrast MRI images. The segmentation supports calculation of flow and velocity profiles and quantification.

Model Summary:

AI4CMR uses a convolutional neural network–based segmentation model to outline vascular structures on magnitude and phase images. A user-selected seed point localizes the vessel, and generated contours may be manually edited by the clinician.
The model is “locked,” meaning it does not adapt or change with new input data.

Performance Summary:

Performance was evaluated using internally validated datasets and independent multi-center data.

Segmentation Performance:

- Dice: 0.95
- Precision: 0.96
- Recall: 0.95

Agreement With Predicate/Reference Measurements:
(In multi-vendor, multi-center evaluation)

- Total Forward Volume (TFV): ICC 0.95
- Total Backward Volume (TBV): ICC 0.82
- Maximum Velocity (Vmax): ICC 0.95

Appendix 2 - Cybersecurity Labeling, Secure Use Requirements, and User Responsibilities

1. System Interfaces, Connectivity Dependencies and Communication Protocols

AI4CMR is accessed only through a third-party DICOM viewer plugin in a networked environment. Communication is initiated by the local client system and processed remotely over secure encrypted channels.

- AI4CMR is hosted in a cloud environment and does not run locally at the customer site.
- Users interact exclusively through authenticated sessions managed via login credentials.
- AI4CMR does not provide a local user interface; all interaction occurs via the third-party plugin.

Communication between the plugin and AI4CMR uses encrypted HTTPS-based APIs over standard network protocols. No other communication channels are available at device level.

2. Cybersecurity-Related Responsibilities of Users and Healthcare Institutions

The following responsibilities apply to users and institutions deploying AI4CMR:

- Ensure that only authorized individuals have access credentials to AI4CMR.
- Operate systems communicating with AI4CMR over secure, hospital-managed networks with appropriate access controls (e.g., network segmentation, firewalls, VPNs as applicable).
- Ensure that patient data is anonymized or de-identified before transmission to AI4CMR, in accordance with the User Manual and applicable regulations.
- Maintain up-to-date endpoint protection software (e.g., anti-virus/anti-malware) on local systems that interact with AI4CMR.
- Implement periodic secure backups of local systems to reduce the risk of data loss in case of cyber incidents or system failures.

Failure to implement these measures may increase cybersecurity risk and could impact the confidentiality, integrity or availability of data and services

3. Shared Cybersecurity Responsibilities

Cybersecurity is a shared responsibility between AI4MedImaging and customer institutions:

AI4MedImaging responsibilities include:

- Implementing and maintaining appropriate security controls within the AI4CMR cloud environment (e.g., hardening, network protections, logging, monitoring).
- Applying security updates and patches to AI4CMR cloud components and underlying infrastructure within a controlled quality management system.
- Operating vulnerability management and incident response processes for the cloud-hosted service.
-

Healthcare institution responsibilities include:

- Securing local systems and networks that interface with AI4CMR (viewers, plugins, workstations, local servers).
- Managing user accounts and access credentials (creation, removal, password policies).
- Detecting, investigating and responding to local cybersecurity events (e.g., compromised workstations, unauthorized access to hospital networks).

4. Software Maintenance and Updates

All AI4CMR software and service maintenance is performed remotely by AI4MedImaging:

- Users are not required to install local updates for AI4CMR itself.
- Changes to third-party plugins and local components remain under the responsibility of the institution and/or plugin vendor.

Any changes to the third-party plugin that may affect communication with AI4CMR must be communicated to AI4MedImaging. Depending on the nature of the changes, re-validation of the integration may be required before resuming routine clinical use.

5. Authentication, Session Management, and Logging

AI4CMR uses authenticated sessions based on user credentials:

- Users access their account information and session management through the AI4MedImaging account portal, as described in the User Manual (e.g., via https://auth.ai4medimaging.com/...).

- Users can view a list of open sessions associated with their account and terminate them if suspicious activity is detected.

- Users can review log history related to authentication and access attempts for their account.

Users must keep their credentials confidential and follow institutional policies for password management and account use.
.

6. User Actions in Case of Security Related Events

If suspicious login activity, unusual behavior, or a potential cybersecurity event is detected (for example, unexpected active sessions, repeated authentication failures, or abnormal plugin behavior), users should:

1. **Immediately terminate active sessions** using the available “log out all sessions” function or equivalent.
2. Notify the institution’s **IT/security team** as soon as possible.
3. Collect and preserve relevant information (e.g., screenshots, time of occurrence, error messages).
4. Contact AI4MedImaging Support using the channels described in the User Manual (e-mail or website).
5. Users must avoid submitting additional patient cases until the situation has been assessed and cleared by IT/security and AI4MedImaging.

7. Cybersecurity Documentation Available to Customers

The following cybersecurity-related documentation is maintained by AI4MedImaging and can be made available to healthcare institutions upon request (subject to confidentiality and regulatory considerations):

- Cybersecurity Risk Management Report for AI4CMR.
- Cybersecurity Management Plan (post-market cybersecurity management).
- Secure Deployment and Network Configuration guidelines / Communication and Deployment Specifications.

Requests for these documents should be directed to: **support@ai4cmr.com** or the contact channels specified in this User Manual.

8. Additional Technical Information on Interfaces and Off-the-Shelf Components

Explicit Interface Declaration

AI4CMR communicates only via secure HTTPS-based communication channels, using encrypted API requests between the third-party plugin and the AI4CMR cloud environment.

- No additional communication interfaces are available at device level.
- In particular, AI4CMR does not expose USB, Bluetooth, Wi-Fi, serial ports or local LAN server-side interfaces on customer premises.

Presence of Interfaces Not in Use

The device does not expose any unused or disabled communication ports beyond the HTTPS channel required for its operation. No additional physical or logical interfaces are available for user access or configuration.

Off-the-Shelf Components Clarification

AI4CMR does not install, run, or depend on locally maintained third-party operating software, runtime frameworks or libraries on customer-side systems:

- All execution of the AI4CMR medical device occurs in the cloud environment maintained by AI4MedImaging.
- Any off-the-shelf software used within that cloud environment (e.g., operating systems, libraries, databases) is managed, patched and controlled by AI4MedImaging under its quality management and cybersecurity processes.

No off-the-shelf components require updating by the customer as part of AI4CMR itself.

9. Detectable Security-Related Events and User Actions

The following events may occur during use and are communicated to the user through the plugin interface or via the account management portal:

Detectable Event	User Notification	Required User Action
Authentication failure	Login error message	Verify credentials; reset password or contact local IT
Unexpected active session	Visible under “Sessions” interface	Terminate suspicious session(s) immediately
Submission failure due to missing metadata	Error message in plugin	Correct missing fields and resubmit
Connectivity interruption / timeout	Processing blocked and/or status message	Verify hospital network connectivity and retry

Users must follow institutional procedures if these events are suspected to be related to cybersecurity issues.

10. Incident Response Instructions

If a cybersecurity concern or unauthorized access is suspected, users and institutions shall:

1. **Stop submitting cases** to AI4CMR immediately.
2. Terminate active sessions using the **“log out all sessions”** option or equivalent.
3. Contact the institution’s **IT/security team** to initiate local incident response.
4. Preserve available evidence, such as logs, error screens or screenshots.

5. Notify AI4MedImaging at **support@ai4cmr.com** (or as specified in the User Manual) with a description of the issue, affected systems and approximate time of occurrence.

Operational use of AI4CMR should not resume until the incident has been investigated, and both the institution and AI4MedImaging have confirmed that it is safe to do so.

11. Required Supporting Documentation

The following documents are provided to FDA and available to customer institutions upon request:

- US-AI4CMR-RM-Cybersecurity Risk Management Report
- Cybersecurity Management Plan
- Secure Deployment and Network Configuration Document

Note: This appendix is intended to satisfy the cybersecurity labeling requirements of FD&C Act Section 524B(b)(2)