AIRAscore 2.3.0

# Instructions for Use

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**AIRAmed GmbH**
Konrad-Adenauer-Str. 13, 72072 Tübingen, Germany
service@airamed.de, www.airamed.de
Phone: +49 7071 53 933 40

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# 1 Customer Information

Dear customers,

The software AIRAscore is a certified medical device with CE mark according to council directive (EU) 93/42/EEC, which is placed on the market in accordance with transitional provision of regulation (EU) 2017/745 on medical devices. AIRAmed has established a quality management system according to ISO 13485 and is certified therefor.

This customer information applies as instructions for use, describes the basic features of our evaluation report and provides information on the correct use of AIRAscore. It describes the correct indication, the appropriate reference set, and basic warnings that must be followed. The customer information is intended for all physicians with knowledge of MR anatomy of the brain who use the AIRAscore report to check segmentations and place the output measurements in the clinical context (primary users).

All users and administrators of the software who use the software or install and maintain it must have access to these instructions for use and be familiar with their contents.

If you have any questions beyond this customer information, please do not hesitate to contact us:

service@airamed.de
https://www.airamed.de
phone number: +49 7071 53 933 40

**AIRAmed GmbH**
Konrad-Adenauer-Str. 13, 72072 Tübingen, Germany
service@airamed.de, www.airamed.de
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# 2 General Customer Information

## 2.1 General Specifications

It is your responsibility as the user to inform the patient of the service and the associated transfer of image data to AIRAmed and to take appropriate local protective measures to prevent unauthorized third parties from accessing AIRAmed's service and patient data.

### 2.1.1 Intended Purpose

AIRAscore is intended for automatic labeling, visualization and volumetric quantification of segmentable brain structures from a set of MR images. This software is intended to automate the current manual process of identifying, labeling and quantifying the volume of segmentable brain structures identified on MR images.

### 2.1.2 Indication

The software AIRAscore is intended to be used for MR image data of patients between the ages of 18 and 85 for which a physician requires a volume quantification of brain structures.

### 2.1.3 Contraindications

The device is not intended to be used for segmentation of brains with structural abnormalities (e.g., tumor, arachnoid cyst, postoperative-, posttraumatic-, postischemic-, or posthemorrhagic defects, brain development disorders and neuronal migration disorders).

### 2.1.4 Availability

AIRAscore is usually available 24 hours a day and operates fully automated.

We usually perform scheduled maintenance Monday through Friday from 0:00 to 4:00 (CET) or all day on weekends. Scheduled maintenance is announced at least 24 hours in advance. Unscheduled maintenance can be performed at any time without notice if the security of the system is affected.
We keep downtime as low as possible.

If you have any questions, our support is available Monday through Friday from 9:00am to 4:00pm (CET) by phone or email.

### 2.1.5 Avoidable Misuse and Abnormal Use

> ⚠ • AIRAscore is not suitable for evaluating image data that is not based on a T1 data set.
> • Image datasets after administration of contrast agents are not suitable for evaluation and may lead to erroneous findings.
> • Any mass lesion (e.g., tumor, hemorrhage, arachnoid cyst) or any lesion that is characterized by a defect of the brain tissue (e.g., defects after trauma, ischemia) may lead to severe missegmentation and also cannot be evaluated against the reference set.
> Corresponding patient image data must NOT be evaluated with AIRAscore!

> ⚠ Age and natural sex of the patients are essential for a correct classification of the volumes. Changes to the DICOM metadata should therefore be avoided, since AIRAmed has no possibility to check the correctness of the DICOM data. In the case of anonymized data or research data, it is therefore essential to ensure that age, sex and the interval between examination date and date of birth are correctly preserved in the DICOM data.

> ⚠ Reports of the same patient are only comparable with regards to the progression if they were acquired with the same scanner and the same sequence. Even minor changes in scan parameters can lead to strong contrast changes and discrete shifts in the gray-white boundary, which make segmentation comparability impossible. Information on measurement inaccuracy due to rounding can be found in the customer note of each evaluation report on the last page.

> ⚠ The automated quantitative evaluation of brain structures can only support the assessment by a qualified physician (specialist), and by no means replaces it.

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## 2.1.6 Ordering AIRAscore MS

In order to add the multiple sclerosis analysis to the general AIRAscore structure report, we need a T2-FLAIR dataset in addition to a T1 dataset. After installing our software (see AIRAscore Client Installation Instructions), two new PACS nodes will be available, the names of which will be determined by the person performing the installation. The node for the AIRAscore structure report will only accept T1 datasets and will start processing immediately if a valid dataset is found. The node for AIRAscore MS expects a T1 dataset as well as a T2-FLAIR dataset that meet the requirements listed in the next paragraph. You can send the datasets in any order, but there should be no more than two hours between the two datasets, otherwise the order will be discarded.

> (i) AIRAscore MS is not intended for diagnosis of multiple sclerosis, but rather is a tool for quantitative analysis of MR images in patients with existing diagnosis of MS.

## 2.1.7 Technical Requirements for the Dataset

To process your image data, AIRAscore structure requires datasets with the following properties:

- T1 dataset, native, DICOM format: *MR Image IOD*
- Clear gray-white contrast between gray and white matter and, if possible, hypointense representation of cerebrospinal fluid (CSF)
- 3D dataset
- Device manufacturer: GE, Philips or Siemens
- Field strength: 1.5 or 3 Tesla
- Resolution of image data in each spatial direction < 2mm and voxel size ≤ 2.4mm$^3$
- The head must be completely captured
- The head should not be captured tilted if possible
- No pronounced artifacts should be visible in the image (motion, folding, etc.)

If you decide to use AIRAscore MS, we require a corresponding T2-FLAIR dataset with the following properties in addition to each T1 dataset:

- T2-FLAIR dataset, DICOM format: *MR Image IOD*
- 2D or 3D dataset
- Device manufacturer: GE, Philips or Siemens
- Field strength: 1.5 or 3 Tesla
- Resolution of image data ≤ 1.5mm in x and y direction and ≤ 6mm in slice direction
- The head must be completely captured
- The head should not be captured tilted if possible
- No pronounced artifacts should be visible in the image (motion, folding, etc.)

For a detailed list of all requirements for DICOM data, please refer to the separate DICOM Conformance Statement.

## 2.1.8 Automated Control of Image Data and Accountability of the Requesting Physician

All image data are automatically checked after being received by AIRAmed. For this purpose, in addition to the actual image data, the technical data of the sequence, the age and the gender of the patient from the DICOM header are transferred. Other patient-related data, such as the name, are not transmitted to AIRAmed and remain locally and encrypted on your system. The majority of possible technical errors are detected automatically. However, this does not exclude the residual risk that datasets for which the technical requirements are not met or datasets of patients with contraindications are nevertheless processed. Also, despite all due care, incorrect segmentation may occur in rare cases.

> ⚠ All reports must be **checked** for plausibility and accuracy by a **qualified physician** (specialist) with sufficient knowledge of neuroanatomy and MR imaging of the head. The identity of the patient should also be checked.

The original images are overlaid with the results of the segmentations performed by AIRAscore structure. These are displayed in the report for verification purposes. If you have ordered AIRAscore MS, the segmentation of lesions and

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their categorization into juxtacortical, periventricular and infratentorial will be presented in a similar way. In addition, the segmentations are provided in the PACS. The hippocampus is reported as a distinct structure. The hippocampus and cingulate gyrus are not included in the frontal or parietal lobes.

For viewing you need a PACS and a connected DICOM viewer including a monitor that can display the DICOM formats *Encapsulated PDF IOD* as well as *Secondary Capture Image IOD* in color and is approved for reporting.

Usually, you will receive the results within a few minutes, although the actual time also depends on your internet connection. If you do not receive an evaluation within one hour after sending the data, please contact us directly. In rare cases, datasets may not be sent to us, or may not be sent completely, and thus processing may not take place.
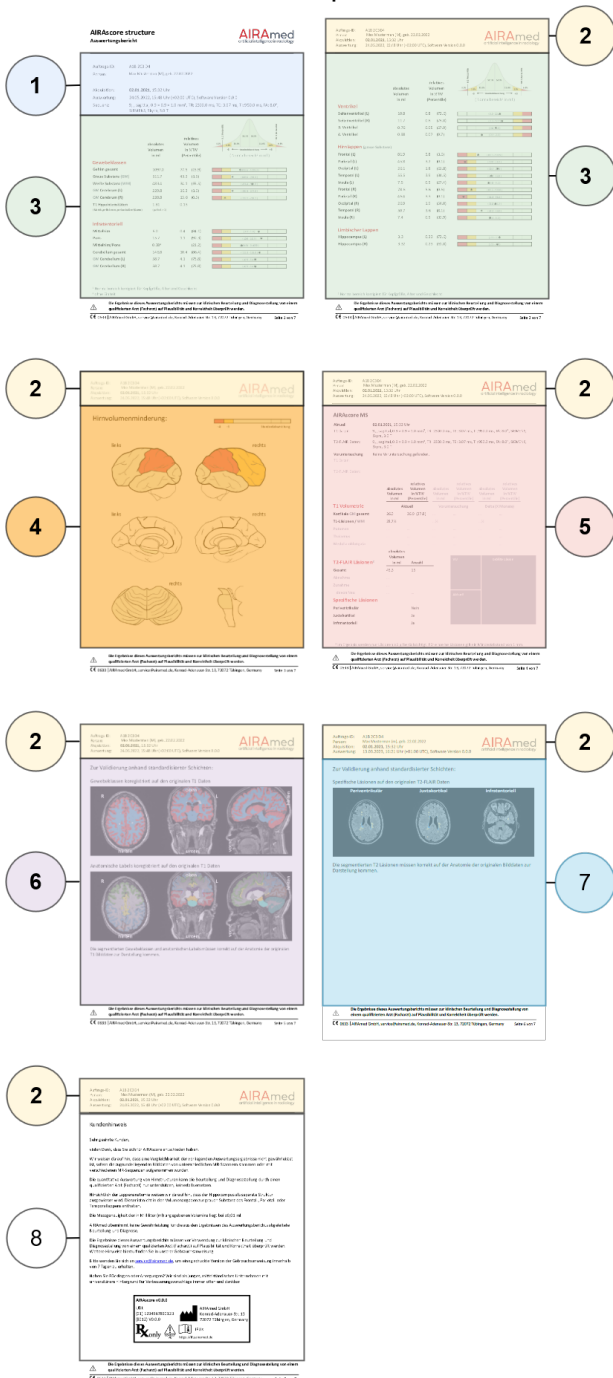
If you are of the opinion that there is a safety-relevant malfunction in the product, please contact our customer service immediately.

> (i) AIRAmed does not assume any warranty for assessments or diagnoses derived from the evaluation results of the evaluation report and cannot be held liable for this.

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## 2.1.9 Structure of the Report



The AIRAscore structure report has 5 pages, and 7 pages with AIRAscore MS. The respective page number is listed on the bottom right.

The individual sections of the report are described below:

① Examination Summary:
Contains the order ID*, personal data of the patient and the sequence on which the report is based.

② Headers:
The headers also list the most important identification parameters and relevant data again.

③ Volume Report:
Contains the volume evaluation for each segmented anatomical area - the absolute volume in ml, the relative volume (absolute volume normalized by the total intracranial volume), and the percentile for the patient compared to the reference set**.

④ Schematic Overview of Reference Comparison:
Quick overview of z-scores for brain areas. For values smaller than two or three standard deviations compared to the reference set, areas are shown in yellow or red, respectively**.

⑤ MS Report:
This page is optional and is only issued to customers requesting AIRAscore MS. It shows the number and volume of lesions and their categorization. Grayed-out elements represent functionality not included in this version.

⑥ Quality Control Images:
The quality control images are used for the traceable validation of our segmentation results. These quality control images must always be checked for plausibility. In the event of discrepancies or inexplicable volume data, the plausibility of the overlays provided in the PACS should also be checked.

⑦ MS Control Images:
This page is optional and is only issued to customers requesting AIRAscore MS. It displays slices with the largest juxtacortical, periventricular and infratentorial lesions for reference.

⑧ Customer Notices:
The customer notices contain information on the use of the report, the accuracy of the results and contact options for AIRAmed GmbH.

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(i) * The individual order ID allows us to make a reliable assignment if required. Apart from the pseudonymized order ID and the pure image data as well as age and gender for the assignment of the correct reference values, AIRAmed does not store any personal data in the image archive. Without individual order ID of your patients, no assignment of image data in the long-term archive or in our log files is possible. All our processes meet the requirements of the GDPR.
** If the patient age is not between 18 and 85, no comparison to the reference set will be performed and the percentile will not be shown in the report. The page "Schematic Overview of Reference Comparison" will be omitted. Furthermore, a watermark "Not released for clinical evaluation" will be shown in the report, if the patient is younger than 18 years.

## 2.1.10 Color-Coded Segmentation Results

Several DICOM series are also available for visual control. All customers receive the two DICOM series Anatomy Map and Tissue Map. Customers requesting AIRAscore MS receive an additional DICOM series T2-Lesion Map. All available series can be found in the same study as the PDF report. If there are several segmentations, you can identify the correct assignment via the name of the initial series.

The segmentation results are displayed as colors overlaid on top of the original input image. See the used colors below:

**Anatomical Regions**
Anatomy Map

- Midbrain
- Pons
- Superior cerebellar peduncle *
- Cerebellum
- Ventricle
- Hippocampus
- Cingulate gyrus *

- Frontal lobe
- Parietal lobe
- Occipital lobe
- Temporal lobe
- Insula
- Deep gray matter *

**Tissue Classes**
Tissue Map

- Gray matter
- White matter
- T1 Hypointensities

**Lesion Categories**
T2-Lesion Map

- Periventricular
- Juxtacortical
- Infratentorial
- Unspecific

(i) *) Volume of this structure is not reported.

## 2.1.11 Reported Structures and Their Definitions

This section describes all structures reported in the report.

### 2.1.11.1 AIRAscore structure: Reported Structures

| Reported Structure | | Definition of Structure |
|---|---|---|
| **Tissue Type** | | |
| Total brain volume | | Summed volume of white matter, gray matter and T1 hypointensities based on the Tissue map |
| Gray matter (GM) | | Volume of gray matter based on the Tissue map |
| | GM cerebrum (L)/(R) | Summed GM volume of left or right hemisphere of temporal, frontal, occipital, parietal, and insula lobes, cingulate gyrus, and hippocampus based on the Anatomy map |

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| Reported Structure | Definition of Structure |
|---|---|
| White matter (WM) | Volume of white matter based on the Tissue map |
| T1 hypointense lesions | Volume of T1 hypointensities based on the Tissue map |
| **Infratentorial** | |
| Midbrain | WM volume of midbrain based on the Anatomy map |
| Pons | WM volume of pons based on the Anatomy map |
| Midbrain / Pons | Ratio of midbrain to pons |
| Total cerebellum | Summed GM and WM volumes of left and right hemisphere cerebellum based on the Anatomy map |
|     GM cerebellum (L)/(R) | GM volume of left or right hemisphere cerebellum based on the Anatomy map |
| **Ventricles** | |
| Lateral ventricle (L)/(R) | Cerebrospinal fluid (CSF) volume of left or right hemisphere lateral ventricle based on the Anatomy map |
| Third ventricle | CSF volume of third ventricle based on the Anatomy map |
| Fourth ventricle | CSF volume of fourth ventricle based on the Anatomy map |
| **Brain Lobes (Gray Matter)** | |
| Frontal (L)/(R) * | GM volume of left or right hemisphere frontal lobe based on the Anatomy map |
| Parietal (L)/(R) * | GM volume of left or right hemisphere parietal lobe based on the Anatomy map |
| Occipital (L)/(R) | GM volume of left or right hemisphere occipital lobe based on the Anatomy map |
| Temporal (L)/(R) | GM volume of left or right hemisphere temporal lobe based on the Anatomy map |
| Insula (L)/(R) | GM volume of left or right hemisphere insula lobe based on the Anatomy map |
| **Limbic Structures** | |
| Hippocampus (L)/(R) * | GM volume of left or right hemisphere hippocampus based on the Anatomy map |

(i) * The hippocampus is not included in the volume of the temporal lobe. The cingulate gyrus is not included in the volume of the frontal lobe or parietal lobe.

*2.1.11.2  AIRAscore MS: Reported Structures*

| Reported Structure | Definition of Structure |
|---|---|
| **T1 Volumetry** | |
| Total cortical GM | Summed volume of GM cerebrum (L) and GM cerebrum (R) |

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| T2 Lesions | |
|---|---|
| Total absolute volume and count | Summed volume of voxels segmented as lesions independent of their location in the brain. Only lesions ≥5 µl are taken into account in the total absolute volume and count. A minimum distance of 1 mm applies to all individual lesions. |
| Periventricular lesion | Voxels of a lesion that borders the ventricles |
| Juxtacortical lesion | Voxels of a lesion that borders the cerebral cortex |
| Infratentorial lesion | Voxels of a lesion with an infratentorial position |

### 2.1.12  Volume Comparison to the Reference Set

If the patient age is between 18 and 85, a comparison to an age- and sex-specific reference set is performed. We calculate the following metrics for the reported structures:

| Metric | Definition |
|---|---|
| Z-score | A value that represents how many standard deviations the computed relative volume falls below or above the reference mean. |
| Normal range lower limit | The 5th percentile of the reference set volume converted to absolute volume in ml using the patient's total intracranial volume. |
| Normal range upper limit | The 95th percentile of the reference set volume converted to absolute volume in ml using the patient's total intracranial volume. |
| Percentile | Percentage of values from the reference set that fall below the computed z-score assuming a normal distribution. |

## 2.2  Precision and Accuracy

Metrics used for the precision and accuracy calculations include the intraclass correlation coefficient (ICC), 95% confidence interval (CI95%), 90th percentile (p90), median, sensitivity, and precision. All metrics were calculated in milliliter.

### 2.2.1  Precision

Precision of AIRAscore structure was calculated through the evaluation of a Test-Retest dataset consisting of 804 samples. Across all anatomy and tissue regions the median ICC(2,1) is 0.99 and P90 ICC(2,1) is 0.99. Graphics processing unit-induced random effects can lead to minor differences in volumes for the same image. These differences are smaller or equal to the 10th percentile of Test-Retest differences for all regions.

The precision of lesion segmentations with AIRAscore MS was calculated using a dataset of 19 Test-Retest samples. ICC(2,1) and ICC(2,1) CI95% for total lesion volume is 0.9996 and [0.99898, 0.99986] respectively, for lesion count 0.9957 and [0.98907, 0.99835] respectively. P90 for total lesion volume is 0.252 and for lesion count 3.0.

### 2.2.2  Accuracy

The accuracy of AIRAscore structure was evaluated by comparison with 18 samples that were manually segmented by experts. The average ICC(3,1) between AIRAscore structure segmentations and manual segmentations across all anatomy and tissue region volumes is 0.852 with a CI95% of [0.725, 0.905].

Accuracy metrics for AIRAscore MS were calculated by comparison to manual segmentation by experts of 10 samples from patients with MS. The sensitivity and precision of the total lesion count is 70% and 72%, respectively. The median absolute volume deviation is 1.04 milliliter with a CI95% of [0.150, 4.430].

## 2.3  AIRAscore Client Installation

AIRAmed provides you, the customer, with the AIRAscore Client software. The AIRAscore Client operates as the interface to AIRAmed's servers. For instructions how to install AIRAscore Client, please refer to the AIRAscore Client Installation Instructions, which will be provided to you by AIRAmed.

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## 2.4 AIRAscore Client Configuration

The AIRAscore Client can be configured as follows.

### 2.4.1 Report Language

The report can be returned in one of the languages listed below. To change the configured language, please refer to AIRAscore Client Installation Instructions, section "Country Code".

The formatting of the following information in the report is affected by the configured country code:

| Country Code | Language | Patient Name Format | Date Format | Time Format |
|---|---|---|---|---|
| en_US | English | First_Name Last_Name | Mon dd, yyyy | AM/PM |
| de_DE | German | Last_Name, First_Name | dd.mm.yyyy | 24-hour clock (military time) |

### 2.4.2 Error Reports

Problems may occur during processing of datasets by AIRAmed. In such a case, we will send a DICOM Secondary Capture image containing the error reason to your PACS. If you do not wish to receive error reports, we are happy to deactivate this feature for you. Please contact the AIRAmed support in that case.

### 2.4.3 DICOM Structured Reports

The AIRAscore client supports the DICOM Structured Reporting feature. We provide the option to send the following DICOM Structured Reports to your PACS:

- Order confirmations
- AIRAscore reports
- Error reports

By default, no DICOM Structured Reports are sent to your PACS. If you wish to receive them, we are happy to activate this feature for you. Please contact the AIRAmed support in that case.

> ⚠ The DICOM Structured Report is only an add-on to the AIRAscore report and must not be used on its own.

## 2.5 Known Problems

The DICOM PatientOrientation field is set as an empty field for the segmentation results. However, the ImageOrientation (Patient) [0020,0037] and ImagePosition (Patient) [0020,0032] fields contain the relevant information.

The DICOM field IssuerOfPatientID contains the value *None* if it was not set in the input data.

## 2.6 Obligation to Report (Only for EU-Countries)

Please report all serious incidents (harms, injuries, etc) related to this medical device to the manufacturer and the responsible authority of the EU member state, that you are established in.

In Germany the responsible authority is the BfArM. The latest contact information can be obtained from the BfArM website at: https://www.bfarm.de.

## 2.7 Querying the UDI

The Unique Device Identification (UDI) for AIRAscore can be obtained by accessing the following URL: https://api.airamed.de/v1_0/udi. The response will include the UDI-DI (Device Identifier) as well as the UDI-PI (Production Identifier).

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## 3 Glossary

| Symbol | Symbol Title | Explanatory Text |
|---|---|---|
| CE | CE-Marking | This product complies with the applicable requirements set out in the European Union harmonization legislation on their affixing. |
| [Manufacturer symbol] | Manufacturer | Indicates the medical device manufacturer. |
| [Consult IFU symbol] | Consult instructions for use | Indicates the need for the user to consult the instructions for use. |
| Rx only | Prescription only | Caution: US federal law restricts this device to sale by or on the order of a physician. |
| ⚠ | Caution | Indicates that the current situation requires the user's attention to avoid undesirable consequences. |
| MD | Medical Device | Indicates that the item is a medical device. |
| LOT | Batch code/Lot number | Indicates the manufacturer's batch code or lot number. |
| UDI | Unique Device Identification | Indicates the Unique Device Identification information. |
| (i) | Indication | Alerts the user to helpful information. |

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## 4  About AIRAscore Client

AIRAscore Client is used to connect to the AIRAscore software and is developed by AIRAmed GmbH. All rights reserved.

AIRAscore Client uses the Requests library, Copyright 2019 Kenneth Reitz, in version 2.26.0.

AIRAscore Client uses Watchtower, Copyright 2021 Simon Aronsson, in version 1.3.0.

AIRAscore Client uses the fpdf2 library, Copyright 2013 Lucas Cimon, in version 2.5.1.

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