

# Instruction for Use (IFU) of the EDS.



Version 2.0

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Keunen Medical BV  
The Netherlands

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## Label info

- a. Product: The Emboli Detection System or EDS
- b. Manufactured by Keunen Medical BV, Bloemcamplaan 17, 2244 EA Wassenaar, The Netherlands.
- c. Developed by R.W.M Keunen & R. Hoogenboezem
- d. Website R.W.M. Keunen, MD PhD: [www.strokeprevention.nl](http://www.strokeprevention.nl)
- e. The EDS is a software application for transcranial Doppler ultrasound systems. The EDS has been developed to detect micro-embolic in the bloodstream which are indicative for unstable vascular lesions and are associated with an increased stroke risk.
- f. The EDS is 'packaged' on a USB Flash drive; by clicking on the EDS.exe on the USB the EDS opens up.
- g. The EDS has a CE certificate (Class I)

## Table of contents IFU

1. Label info
2. Disclaimers
3. How to install the EDS on existing ultrasound systems.
  - a. How to install the EDS
  - b. How to calibrate the EDS
  - c. How to check if the EDS is properly installed and can operate correctly and safely
  - d. Maintenance of the EDS
4. Performances of the EDS.
  - a. Introduction
  - b. Process specification
  - c. Graphical User Interface
    - i. Patient info screen
    - ii. Monitoring screen
    - iii. Verification screen
5. Instruction Info.
  - a. Introduction
  - b. How to fix a TCD monitoring probe
  - c. Specific instruction
    - i. How to start and finish an exam
    - ii. How to verify a MES or artefact
    - iii. How to verify rapidly large numbers of MES or artifacts
    - iv. How to import a wave file
    - v. How to export a EDS file
    - vi. How to produce a report
    - vii. How to finish the EDS
6. Instructions to prevent undesirable side effects
  - a. Prevention of disk overloading
  - b. Prevention of inappropriate calibration
  - c. Prevention the use of the EDS network as a 100 % reliable classifier
7. The accuracy of the EDS to identify MES.

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## 2. Disclaimers

- a. Limitation of the EDS: the EDS cannot replace the human expert

The EDS system has been developed by Keunen Medical Software BV, without the use of intellectual property of any other party. The EDS has been validated against human experts and tested under clinical conditions and published in peer review magazines [1] [2]. All specifications of the EDS are listed in this user manual. The product information of the EDS will reveal that embolus detection by the EDS is able to detect all intensity transients above a preset intensity setting; the ability to discriminate embolus and artifacts depends on the function of a neural network based classifier. The accuracy of the neural network is high but - inherently to neural networks classifiers - not 100 %. Emboli below the intensity threshold may flow to the brain undetected and false embol counts may result from external sources such as patients movements or by artificial very short periodic transients in the Doppler speckle itself. Therefore: the results of the EDS measurement must always be validated by human experts! The human experts can use the verification program included within the EDS. In other words: the EDS can help, but not replace, the human expert. Recent publications by Leunissen et al 2017 scientifically backed up the EDS disclaimers [3].

- b. Statement regarding the responsibility to act on EDS results

The responsibility of acting medically on the presence of active cerebral embolism always lies by the physician(s) responsibility for the wellbeing of the patient. The EDS is not intended to substitute proper medical diagnosis, care or treatment.

### References

- [1] Keunen RWM, et al. Introduction of an embolus detection system based on the analysis of transcranial Doppler audio-signal. Journal of Medical Engineering and Technology. 2008 Jul-Aug;32(4):296-304.
- [2] Keunen RWM, et al. Exploration of a zero-tolerance regime on cerebral embolism in symptomatic carotid artery disease. Perspectives in Medicine (2012), doi:10.1016/j.permed.2012.02.064

[3] Leunissen T, et al. Validation of the automated electronic Microemboli Detection Systems in patients undergoing carotid endarterectomy. *Ultraschall in der Medizin* 2017. Apr 6. doi: 10.1055/s-0043-106737.

### 3. How to install the EDS on existing ultrasound systems.

#### a. How to install the EDS

The EDS is sometimes integrated into a TCD system; then the user does not have to install or calibrate the EDS. The integrated version allows bilateral MCA monitoring. In case the EDS is not integrated into a TCD systems the EDS can only monitor one MCA at a time (unilateral MCA monitoring).

There are two options possible to run the EDS if the EDS is not integrated into a TCD system. Option one is connect the laptop with the EDS and the TCD machine by an audio-cable. Most TCD systems have a headphone in-jack which can be used for this purpose. Option two is to upload the EDS in the PC of the TCD machine and use the windows stereo-mixer for sampling the audio. In case of option two it is essential that only the stereomixer has been activated. All other audio-entrances such as microphones and line-in should be switched off. Check by making a noise (clapping of the hands) that the EDS does not have input from unwanted external sources.

For optimal control it is possible to switch from the EDS and the TCD displays and vice versa by using the Alt-Tab combination of the keyboard.

#### b. How to calibrate the EDS

When the EDS has been executed, the following steps are essential for optimal monitoring results:

Step1. When the audio-signal is sampled from the headphone-in-jack, the PC has to use the line-in entrance ( if not available use the microphone in-jack). *If the PC uses the line- in jack all other audio-entrances of the PC should be switched off .*

Step 2. It is essential to know the sample frequency of the TCD machine. If an exam is started one has to fill in the sample-frequency. If the wrong frequency is used the EDS will not function properly. One can check this in the velocity display because in case of a mismatch of real sample frequency and the EDS sample frequency *the blood flow velocities of the TCD machine will not match with the velocities of the EDS velocity display.*

Step 3. temper both the volume of the TCD audio output as well as the audio input of the PC or laptop. High audio output increases the intensity of the audio signal which may lead to distortion of sound and in extreme cases to improper functioning of the EDS. The reason for this is that low intensity MES will not be detected if the intensity

of the background speckle of the TCD signal is more intense than the intensity of the MES.

#### c. How to check if the EDS is properly installed and can operate correctly and safely

If the blood flow velocities of the TCD equipment and the blood flow velocities of the EDS velocity display show the same values and if the algorithm for MES detection has been activated (which one can check by either the fact that in the annotation list the annotation 'start algorithm' appears or by the fact that the list of emboli and artifacts starts to fill-up) one can be sure that the EDS is properly installed and operates correctly.

#### d. Maintenance of EDS

Once the EDS has been properly installed it will not need any maintenance. From time to time Keunen Medical will issue new EDS versions which can be uploaded.

## **4. Performances of the EDS.**

### **a. Introduction**

The Embolus Detection System or EDS is a developed for the detection of cerebral emboli. It analyses the audio-output of TCD equipment and searches for transients in the signal that have the characteristics of an embolus. The software has been developed to detect emboli in TIA and Stroke patients. In these patients the emboli frequency and intensity can be extremely low so the software must be very sensitive to detect these events. The current software has been tested and validated clinically and the accuracy has been published in a peer reviewed magazine. The EDS is intended to use as a tool which may reduce the recurrent stroke rate in patients who recently experienced a TIA or Stroke. Advances of the EDS are: easy to use, reliable, adjustable on any TCD machine, validated and high accuracy. The current manual highlights embolus detection by TCD in general with emphasis on the safe use of the EDS system.

### **b. Process specification**

The EDS is a software application for existing hardware transcranial Doppler ultrasound systems. The EDS uses the audio output of the TCD system by importing this signal from the audio stereo-mixer.

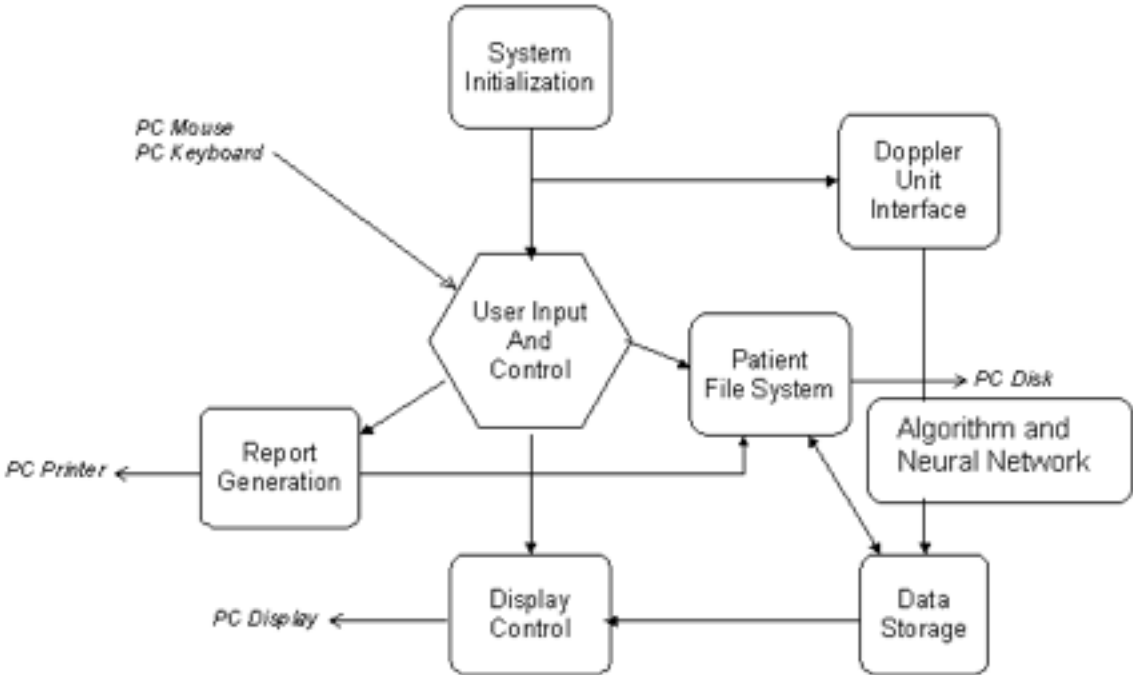
The EDS reconstruct from this signal a velocity display which shows realtime the bloodstream velocities. If an intensity increase occurs within the audio-signal the EDS calculates from every event the duration, intensity and certain audio-dynamics which characterize that particular signal. All the latter calculations are input for a neural network or 'classifier' which has been taught to classify the observed events in two classes: embolus or artifact. The EDS list both emboli and artifacts.

The EDS allows to verify each listed event by looking at the velocity display and look and listening to audio-signal. This allows the human observer to determine if the classification by the EDS was correct or wrong. This verification is of utmost performance because the final responsibility of the diagnosis of the presence of emboli in the time-series lies in the hands of the human observer. The EDS facilitates the human observer to perform such a otherwise tedious and time consuming task.

To facilitate verification process the EDS has built in zoom and order functions. Zoom functions allow to visually analyze the audio-signal at different timescale; the order function ranks every event according a likelihood-score how certain the neural network was that the event under study was a true embolus or true artifact. This order functions allow a rapid review of all the listed emboli and artifacts which is a big

timesaver when a time-series has for instance just a few emboli but hundreds of artifacts which must be verified.

Graph 1 shows the process specification of the EDS. The input of the EDS is the audio output of the TCD system. After initialization (box: system initialization) of the EDS system it contacts the Doppler Unit interfaces and samples the audio-signal which is processed by the classifier (box: algorithm and neural network). Now the monitoring can begin; all data are stored (box: data-storage) and can be online displayed (box: display control). This allows verification by a human observer if the classifier was right or wrong in labeling the event as a MES or artifact (box: user input and control). After the monitoring session has been finished the clinician can generate a report (box: report generation) which can be printed or transferred by internet to the physician that requested the examination.

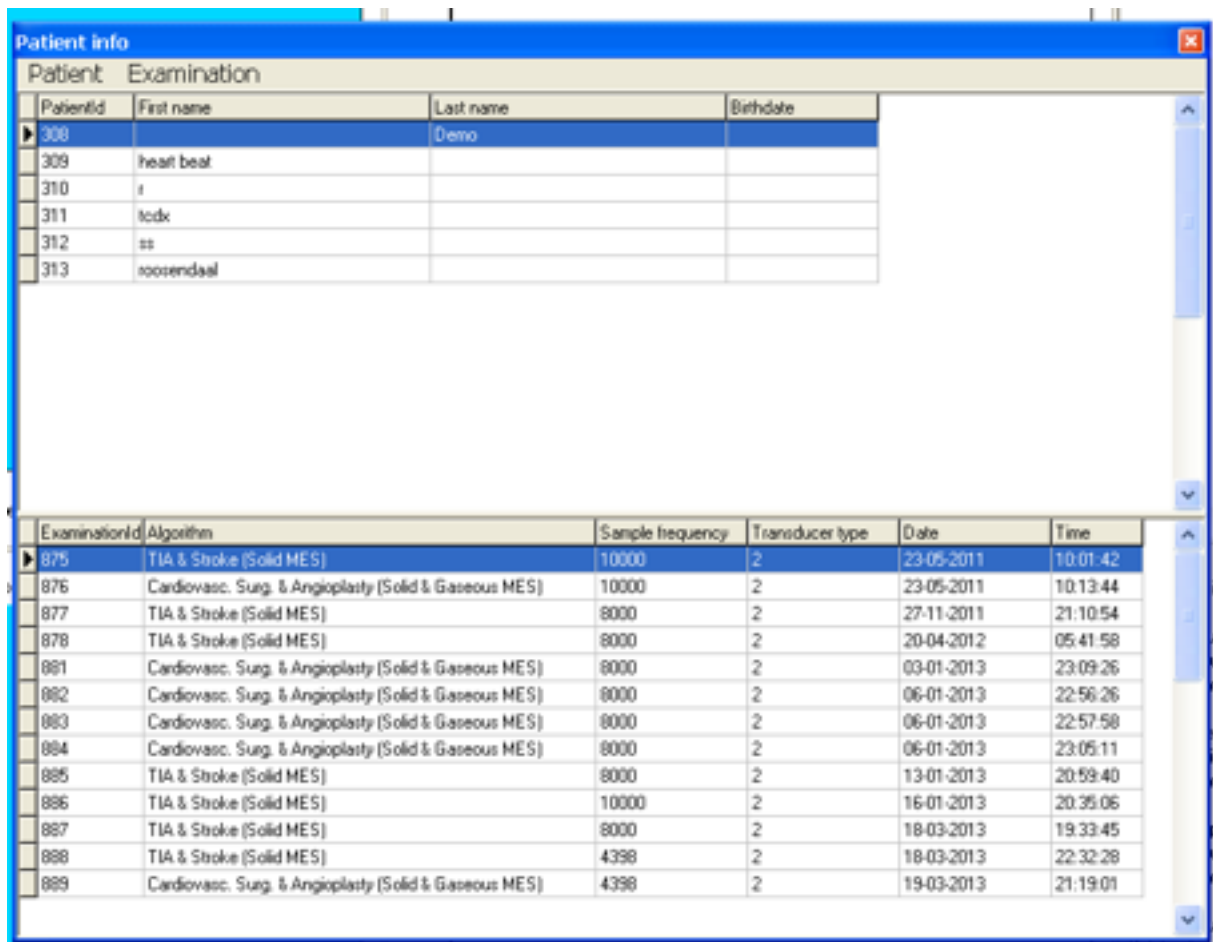


Graph 1 shows the process specification of the EDS (for info see text).

## c. Graphical user interface

### i Patient info screen

The patient info screen (see screenshot below) shows in the upper screen all patients who has been monitored and allows to add new patients for new monitoring sessions. The lower screen shows of each patient a single or multiple examinations. One can add new exams to the list as well for new monitoring sessions.



The screenshot displays a software window titled "Patient info" with two data tables. The top table, "Patient", lists patient details. The bottom table, "Examination", lists monitoring sessions for each patient.

PatientId	First name	Last name	Birthdate
▶ 308		Demo	
309	heart beat		
310	i		
311	icdx		
312	ss		
313	roozendaal		

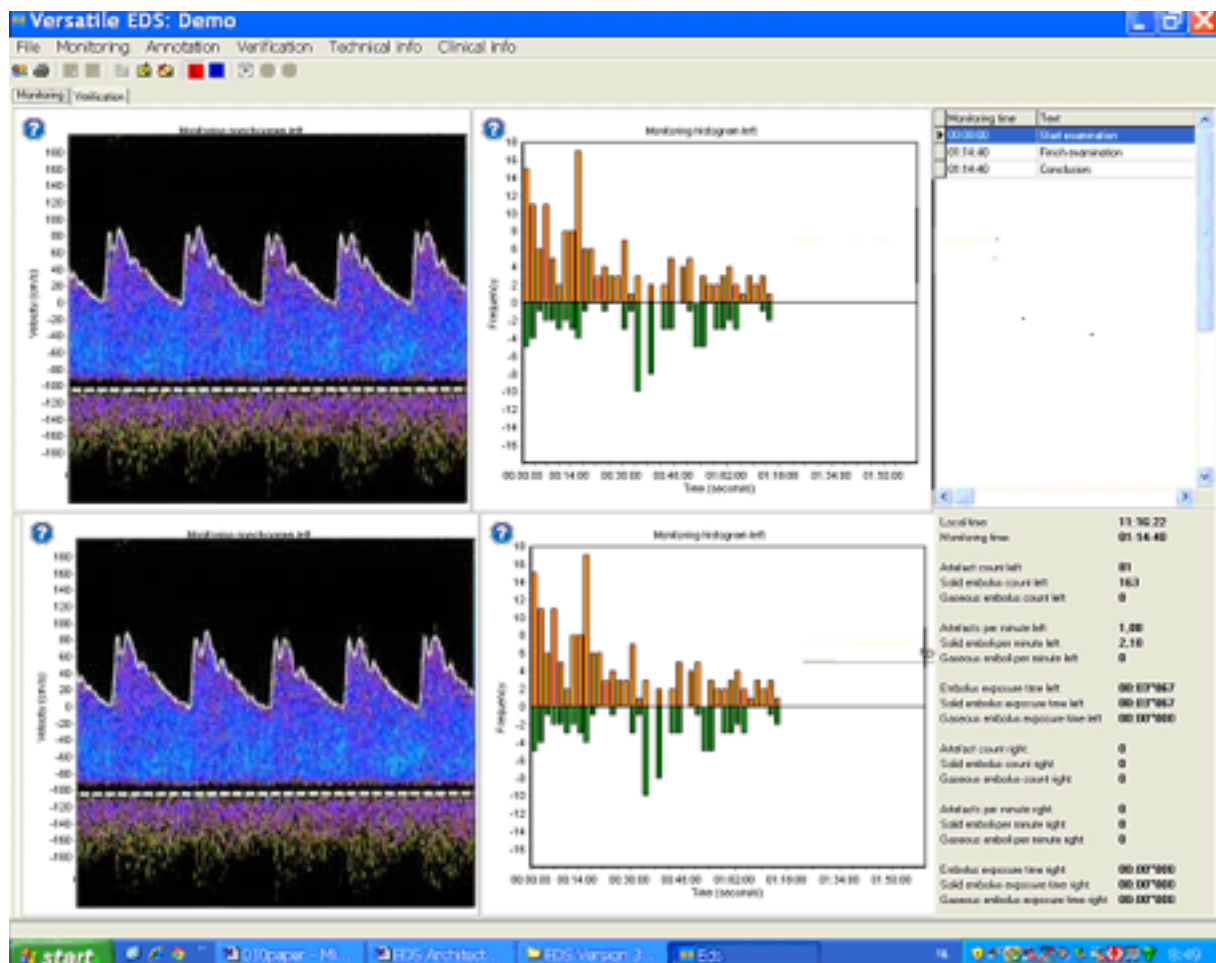
ExaminationId	Algorithm	Sample frequency	Transducer type	Date	Time
▶ 875	TIA & Stroke (Solid MES)	10000	2	23-05-2011	10:01:42
876	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	10000	2	23-05-2011	10:13:44
877	TIA & Stroke (Solid MES)	8000	2	27-11-2011	21:10:54
878	TIA & Stroke (Solid MES)	8000	2	20-04-2012	05:41:58
881	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	8000	2	03-01-2013	23:09:26
882	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	8000	2	06-01-2013	22:56:26
883	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	8000	2	06-01-2013	22:57:58
884	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	8000	2	06-01-2013	23:05:11
885	TIA & Stroke (Solid MES)	8000	2	13-01-2013	20:59:40
886	TIA & Stroke (Solid MES)	10000	2	16-01-2013	20:35:06
887	TIA & Stroke (Solid MES)	8000	2	18-03-2013	19:33:45
888	TIA & Stroke (Solid MES)	4398	2	18-03-2013	22:32:28
889	Cardiovasc. Surg. & Angioplasty (Solid & Gaseous MES)	4398	2	19-03-2013	21:19:01

Screenshot of the patient info screen: for details see text.



## ii Monitoring screen

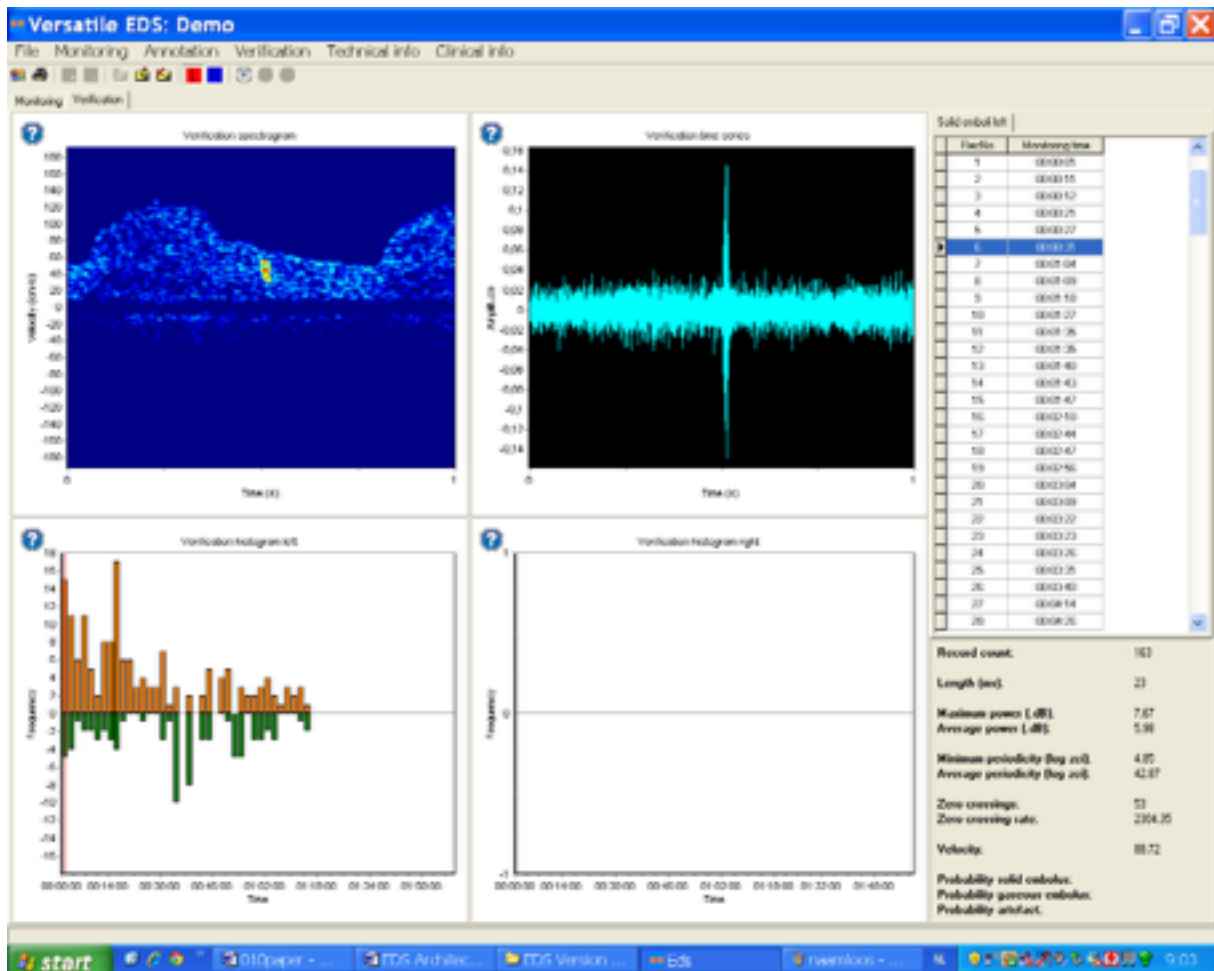
The monitoring screen shows from right to left both the velocity display and histograms of the left and right middle cerebral arteries. The velocity display shows the waveforms of the bloodstream during a monitoring session; the histogram shows over time the number of observed emboli (orange bars) and the artifacts (blue bars). Moreover this screen shows in the left upper corner a logbook of all relevant events that the technologist has observed during the monitoring session and gives a numerical summary of all data in the lower left corner.



Screenshot of the monitoring screen: for details see text.

### iii Verification screen

The verification screen shows on the left side a list of all emboli or artifact with subsequent details such as record number, time of appearance, intensity, duration, velocity and some other parameters. By clicking on an embolus in the list one can listen to that event and look at the same time to the velocity screen and audio signal of this event under verification. Zoom en order functions facilitate fast and accurate verification. If the technician judges that the embolus or artifact has been misclassified by the EDS classifier one can transport the misclassified event in the correct list.



Screen shot of the verification screen: for details see text.

## 5.

## Instruction Info

### a. Introduction

Once can use the EDS for monitoring, verification and producing a conclusion, report or export/import of a wave.file. In order to do so one must click on the right icons. Within the GUI one can see several '?' icons which provide the requested information. In this subchapter the user manual provides the steps necessary to perform monitoring and verification by simple rules. For ease of instruction the following symbols are used

- > click once
- >> double click
- => go to and open
- UB Upper Bar

Before giving specific info about monitoring will will briefly review 'how to fix a TCD probe for optimal monitoring

### b. How to fix a TCD monitoring probe

For long-time embolus detection a fixed probe is necessary to obtain an optimal monitoring result. Most of the probes are fixed to the head with a headband or spectacles. Some newer devices allow the patient to move around. However for a 30-60 minutes monitoring within a clinical setting the next advices will be of value:

1. inform the patient before the exam starts about the headband and the monitoring goals and the time of TCD monitoring. Instruct the patient that is not allowed to talk or to touch the headband.
2. Before fixing the headband, exam the temporal bone if a proper window exists by a hand-held probe.
3. If a temporal window exist, fix the headband so it cannot move.
4. Then fix the probe holder in the correct position.
5. Aim the probe at the right spot and if - the signal is located - do not fix the probe but leave the probe untouched for a moment and see what happens. If the probe goes out the target area, aim the probe again until the probe stays in the right position without application of external forces.
6. If the probe shows no drift outside the sample volume area anymore then fix the probe gently but firm and start the monitoring session.

## c. Specific Info

### i. How to start and finish an exam.

To open a new patient file use the following pathways in the openings screen

> Patient (UB) => New Patient and fill in boxes => OK

[Note it is important to fill in the correct sample frequency and probe frequency of the TCD system and the required intensity threshold]

> Examination (UB) => New Examination (options are Delica, wave file, DPY file, Windows mixer audio) => and fill in boxes => OK

Now the monitoring screen will show the TCD blood flow velocities

> Monitoring => Start monitoring

Now the algorithm for TIA and Stroke starts to run; one can check this by the fact that in the annotation list the annotation 'start monitoring' appears. To finish the exam on

> Monitoring => Stop monitoring

Now the monitoring session stops and the latest annotation with 'Conclusion:' appears, which gives the clinician the possibility to type a conclusion in the textbox. This conclusion will appear in the monitoring Report.

### ii. How to verify a MES or artefact.

Go to the verification screen.

Go to the list of emboli; standard the display shows 'solid emboli left'

- > with the right paddle for display options
- > for instance on record number, maximum power and minimum periodicity
- > choose for instance to by maximum power.

After each choice the EDS list chose the required options.

Now you can scroll in the list to the required record number.

To activate this number you need to click on the item on the top of the list in this case the item is 'solid emboli'

Note if only one event appears in the list you need to activate the list by using the scroll up and down tab while you put the cursor on item on the top of the list.

By activating the '?' you can zoom in and out in both the audio-display and the velocity display. If the clinician decides that the MES is an artifact or vice versa he/she can place the item in the correct list by

- > 'solid embolus' with the right paddle => place selected embolus in artifact list.

### iii. How to verify rapid a large number of MES or artefacts

In order to verify rapidly a large number of MES or artifacts one should order them according to a feature that is very sensitive between discriminating MES and artifacts. When one chooses as order function the minimum periodicity (= lowest ZCI values) one can list the MES and artifacts according to a very sensitive discriminator. The advantage of this is that the MES list will show 100 % real MES in the area with the lowest minimum periodicity values while in the areas with the relatively high minimum periodicity one will find misclassified events. The opposite is true for the artifact list. Here one will find misclassified MES in the area of the list with the lowest minimum periodicity and the 100 % true artifact in the area with the highest minimum periodicity. This feature of order function allows very rapid verification of large data sets.

### iv. How to import a wave file

- patient => examination => New examination (playback wave file)

Now the EDS allow to open up a file on the computer; in case of a wave-file the correct sample frequency is incorporated into the wave-file so the sample frequency is always automatically correct.

### v. How to export a file

Monitoring data of the EDS are stored on the hard disk in a data-map. It includes the annotation list, list of emboli and artifacts, and the whole audio-signal. The audio-signal is located in the of the EDS data-folder in so-called SIG files and mbd files. If consecutive monitoring leads to a limitation of the storage capacity of the hard disk data load can be reduced either by deleting the patient in the EDS entry screen. However, if patients are deleted in this way all information is lost. If the the options of deleting is not feasible the whole data set including SIG files and mbd files can be archived to a specified folder (for instance on a USB stick, DVD or CD). To copy the data the EDS must not be activated. The whole data set can be copied by clicking on the data-map. By the use of the right mouse button the copy option can be chosen and the map is copied to an appropriate folder. Now the content of the original data-map can be deleted by use of the entry screen of the EDS; all patients, settings and examinations can now be deleted. After this procedure, the empty EDS is ready to store new files. We advise to make and check multiple copies before the original data files are deleted. If the copies are re-installed at the data-map the original patients can again be found in the entry screen of the EDS. *Note that re-installation can only be done safely the data-map is completely empty.* If new files are installed after removal of the original files; reinstallation results in overwriting of existing data.

### vi. How to produce a report

- > Patient => Report =>

### vii. How to finish the EDS.

- > Patient => Exit



## 5. Instructions to prevent undesirable side-effects.

### a. Prevention of Disk overloading

To prevent disk overload check the reserve capacity of the disk; in case of a reduced capacity store the EDS files on other storage medium (USB, DVD, CD); see in IFU: how to export EDS files.

### b. Prevention of inappropriate calibration

Always use the correct sample frequency and probe of the TCD instrument for optimal EDS results; see IFU: how to install the EDS.

### c. Prevention the use of the EDS neural network as a 100 % reliable classifier.

Read carefully the IFU disclaimers: the EDS is a help for human experts but cannot replace human experts

## 6. The accuracy of the EDS to identify MES.

The accuracy of the EDS has been determined for the the algorithm for 'TIA and Stroke Services'. The overall accuracy is around 96 % and has been published in the Journal of Med. Engineering & Technology 2008. Given that the EDS had detected a transient signal over 3 dB in intensity, human experts agreed with the EDS classification for 98% of signals classified as emboli, and 95% of signals classified as artifacts. Adopting the human experts' decision as a gold standard, the EDS had a 93% probability of correctly classifying emboli and a 98% probability for correctly classifying artifacts.