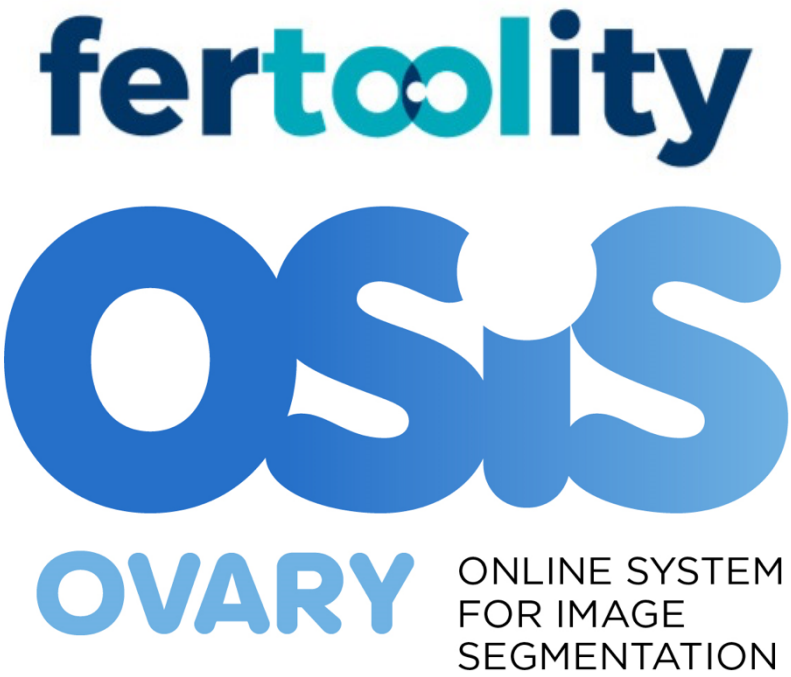
ENGLISH



Instructions for Use

Version of the instructions for Use: 6.0
Review date: 11/02/2026
Version of OSIS Ovary: 2.0

OSIS Ovary

Online System for Image Segmentation

Instructions for use are provided electronically.

MD

This is a medical software for exclusive use in clinics.

INTENDED PURPOSE

Online Ultrasound Image Segmentation System (OSIS) Ovary is a web-based online platform that uses Artificial Intelligence (Deep Learning) to provide objective anatomical measurements of the different ovarian follicles (folliculometry) from three-dimensional (3D) transvaginal ultrasound. The software runs on a centralized server and its results can be accessed via a standard "off-the-shelf" computer browser. OSIS Ovary can be used to perform automatic segmentation, 3D rendering of segmentation, quantification of ovarian follicles and provide quantitative measurements of ovarian follicles. Healthcare professionals can use this information to control the follicle monitoring of controlled ovarian stimulation (COS) patients (adult women) during any in vitro fertilization (IVF), oocyte vitrification or artificial insemination (AI) cycles. It is not indicated for pediatric use.

SN 2.0.0

UDI (01)8437024165026(21)V020000(11)260204

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Revision log

AUTHORISATION				
	Name	**Position**	**Signature**	**Date**
Developed by:	José Enrique Romero Gómez	Responsible for software design and development/production		11/02/2026
Developed by:	Belén Fos Guarinos	Technical Manager, Quality Manager, PRRC		11/02/2026
Reviewed by:	Belén Fos Guarinos	Technical Manager, Quality Manager, PRRC		11/02/2026
Approved by:	Marcos Alepuz Requena	Managing Director		11/02/2026

MODIFICATIONS LOG				
Date	**Name of the person making the change**	**Version**	**Details of the correction**	**Reason for the modification**
27/10/2022	José Enrique Romero Gómez	1.0	New document	N/A
10/10/2023	José Enrique Romero Gómez	2.0	The different sections of the previous IFUs are adapted to include the new software requirements in version 1.1.	Adaptation of the Instructions for Use to OSIS Ovary version 1.1
31/05/2024	José Enrique Romero Gómez Belén Fos Guarinos	3.0	Intended purpose that includes the effect of the medical device and for aligning it with the rest of OSIS Ovary's technical documentation (section 1.1). Intended users clarified (section 1.2) Rest of sections of the Introduction (section 1) aligned with the CER information (there was a discrepancy in some words due to translation) The content of the contradictions is updated according to risk management. Example: RCM 25.2 (section 1.8) Limitations section (1.9) included The residual risks section (1.9) is removed Section 1.11 is added that was not available in previous versions regarding warnings and precautions according to question 7g) and the evidence of GSPR 23.4 s, annex I of MDR 2017/745. The content of this section was included in Security notes section. OSIS Ovary label is modified as well for including the intended purpose, as the UDI-DI and UDI-PI. All COS (Controlled Ovarian Stimulation) references were unified, instead of COH (Controlled Ovarian Hyperstimulation)	OSIS Ovary's Instructions for Use have been modified following the first round of questions after the technical review by BSI (Review Questions MDR 791921 Technical Round 1 - SMO 30001004, by Louis Tsui, Technical Specialist & Clinical Reviewer). This version 3 has been created to address questions such as the change in Intended Purpose (question 2), the inclusion of limitations (question 4), address questions 1 regarding Manual adjustment (section 6.10), compliance with some GSPR which evidence was not clear (question 7)

			Typos are corrected throughout the document. Section 9.1 Performance is modified according to question 7.c) in accordance with GSPR 23.4e, of Annex I of MDR 2017/745	
07/03/2025	José Enrique Romero Gómez Belén Fos Guarinos	4.0	Change Fertoolity SLU to Fertoolity SL The Notified Body number 2797, assigned to BSI, is added, as we have now obtained the CE Marking. Consequently, the XXXX placeholders in the DRAFT label template are replaced with the official number. Update the label of OSIS Ovary v1.1.2 Replace the screenshot referring to the product changelog on the OSIS Ovary platform Additionally, the UDI-DI and UDI-PI are updated, along with all relevant dates, to reflect the date of this change.	In July 2024, our company transitioned from being a single-member limited liability company (Fertoolity SLU) to a standard limited liability company (Fertoolity SL). The company name remains the same—Fertoolity—the team is unchanged, and the tax ID (CIF) also remains the same. However, the legal designation has changed, and we are now officially registered as Fertoolity SL instead of Fertoolity SLU. The Notified Body number 2797, assigned to BSI, is added, as the company has obtained the CE Marking. Consequently, the XXXX placeholders in the DRAFT label template are replaced with the official number.
24/06/2025	José Enrique Romero Gómez Belén Fos Guarinos	5.0	Update the label of OSIS Ovary v2.0.0. Input format changes to DICOM via PACS making the platform multivendor. Steps for sending data to OSIS Ovary have been updated in section 4 WORKFLOW. Integration with IVIRMA management software SIVIS has been generalized to include any client management software (ERP).	This update reflects the changes introduced in OSIS Ovary version 2.0.0, which includes multiple improvements to ensure compatibility with a broader range of clinical environments and enhance software robustness. In particular, this version incorporates: - A new functionality for DICOM file integration via PACS, enabling compatibility with different acquisition systems and improving interoperability. - The removal of specific references to the SIVIS software, allowing the solution to be used independently from a single ERP system and thus supporting its use with multiple client management platforms. - Update of screenshots and workflow descriptions to align with the new software interface and processing steps in version 2.0.0. - Alignment with the updated labelling, including UDI-DI and UDI-PI information for traceability and compliance with MDR requirements.

				These changes are part of the scope described in Change Request Notification MDF 4900 (MDF 4900 for T0089156 - Change Notification Transition of OSIS Ovary from version 1.1 to version 2.0 (cloud-based)) and are intended to support the continued CE compliance of the product under Regulation (EU) 2017/745 (MDR).
11/02/2026	Belén Fos Guarinos	6.0	OSIS Ovary has been validated with General Electric scanners that are compatible with DICOM and PACS.	All compatibility tests with DICOM and PACS have been carried out for General Electric ultrasound scanners. No validation tests have been carried out for other ultrasound equipment manufacturers.

Contents

1. INTRODUCTION

1.1. Intended purpose

Online Ultrasound Image Segmentation System (OSIS) Ovary is a web-based online platform that uses Artificial Intelligence (Deep Learning) to provide objective anatomical measurements of the different ovarian follicles (folliculometry) from three-dimensional (3D) transvaginal ultrasound. The software runs on a centralized server, and its results can be accessed via a standard "off-the-shelf" computer browser. OSIS Ovary can be used to perform automatic segmentation, 3D rendering of segmentation, quantification of ovarian follicles and provide quantitative measurements of ovarian follicles. Healthcare professionals can use this information to control the follicle monitoring of controlled ovarian stimulation (COS) patients (adult women) during any in vitro fertilization (IVF), oocyte vitrification or artificial insemination (AI) cycles. It is not indicated for paediatric use.

1.2. Intended user

OSIS Ovary is intended for use by healthcare professionals in the area of assisted reproduction, i.e., only by personnel assigned to the patient (gynaecologists, nurses and imaging technicians) qualified in the use of 3D gynaecological ultrasound with transvaginal probe. Not intended for home use or non-professional users.

1.3. Medical condition

The way to follow up the controlled ovarian stimulation and estimate when the follicles are mature for follicular puncture is through hormonal analysis and periodic transvaginal ultrasounds in which the number of follicles that are mature and their sizes can be appreciated to predict the date of the ovarian puncture when there are several (3 or more) follicles that reach a certain size (usually larger than 16-17 mm) in mean diameter (folliculometry).

This is an arduous task that requires a medical specialist (gynecologist) to dedicate a great deal of time to, in addition to the subjectivity and errors involved, in manual measurement directly on transvaginal ultrasound. Furthermore, it must be considered that in each session both ovaries are analyzed and that during each stimulation treatment between 3 and 6 ultrasound scans are performed per patient, which leads to a high number of daily ultrasound scans.

OSIS Ovary is indicated for follow-up treatment of adult women, primarily women undergoing controlled ovarian stimulation (COS) cycles, as a tool to perform folliculometry (provide objective anatomical measurements of the different ovarian follicles) from any three-dimensional (3D) transvaginal ultrasound machine, during the cycle, from the beginning to the collection of oocytes to be fertilized in vitro. It is not

indicated for pediatric use. OSIS Ovary provides the number and size of the follicles at different patient visits.

Many times, even if mature follicles are extracted, they do not contain an oocyte inside. In this case, the whole process must be repeated again with the patient from the beginning. In case OSIS Ovary would give an error, the physician could avoid it by measuring manually himself/herself and basing his/her decision on his expertise and the other clinical values external to OSIS Ovary to provide the correct guidelines for the next steps of the process. In the worst case, no harm could be done to the patient other than lengthening the time to become pregnant and repeating again the same process carried out from the beginning.

1.4. Clinical benefits

The clinical benefits of this software as a medical device are indirect. In other words, the device itself does not directly have a positive impact on patients, but it allows a procedure to be performed. The indirect clinical benefits of OSIS Ovary are the following:

- OSIS Ovary improves the patient's quality of life as it improves the practitioner's clinical management of the patient by providing objective and accurate quantitative measurements of the patient's follicles and streamlining the treatment process.
- It objectively quantifies the number and size (relaxed diameter or d(V) and volume) of follicles, with the precision of a gynecologist, present in women's ovaries throughout the controlled ovarian stimulation (COS) cycle. These measurements are used in current clinical practice during the cycle to adjust, along with the patient's other clinical information, the treatment administered to the woman and to schedule folliculometry.
- OSIS Ovary performs the intended function (implying that there is a clinical benefit in doing so).

In summary, the clinical benefits of OSIS Ovary are the positive impact related to its function intended to facilitate and expedite the practitioner's management of the patient from 3D transvaginal ultrasound in the folliculometry process to continue with the process.

1.5. Target patient population

Adult women, mainly women undergoing controlled ovarian stimulation (COS) cycles.

1.6. Technical product claims

OSIS Ovary is an independent stand-alone Medical Device Software (MDSW) intended to:

- Allow automatic segmentation of ovarian follicles that are present in women 3D-transvaginal ultrasound scans using an Artificial Intelligence (AI) algorithm.
- Allow 2D and 3D segmentation visualization.
- Objectively quantify the number and size (relaxed diameter or d(V) and volume) of follicles, with the accuracy of a gynecologist, present in women's ovaries throughout the controlled ovarian stimulation (COS) cycle. These measurements are used in current clinical practice during the cycle to adjust the treatment given to the woman and to schedule folliculometry.
- Allow the professional to perform quality control to validate the results or discard incorrect results once reviewed, as well as correction of the measurements provided, after measuring manually with a ruler in the various 2D planes as it is currently done in current clinical practice.

1.7. Indications

- This device is indicated for follow-up treatment of adult women, primarily women undergoing controlled ovarian stimulation (COS) cycles, as a tool to perform folliculometry during the cycle, from the beginning to the pick-up of the oocytes.
- It is indicated for patients who have acquired 3D transvaginal ultrasound images that include the complete region of both ovaries.
- OSIS Ovary must be used with 3D transvaginal ultrasound acquired in DICOM format with PACS protocol compatible scanner. Images must follow the image quality criteria provided in the instructions for use for a correct output of OSIS Ovary.

1.8. Contraindications

- The device is contraindicated to any other medical purpose that is not stated in the intended purpose of the device.
- Not for use in pediatric patients.
- Not for use on 3D transvaginal ultrasound in another format than DICOM.
- Not for use in 2D ultrasound images.
- Excluded patients: fat or bowel loops, bladder with urine, patient's surgery, missing ovary. Patient with bladder including urine is required to empty his/her bladder.

After wide preclinical research on possible contraindications on the use of the device, no known contraindications to OSIS Ovary were identified, as well as no undesirable side effects from its use.

1.9. Limitations

LIMITATIONS OF OSIS OVARY

- Not for use in 2D ultrasound images. Only for use in 3D ultrasound images of the ovaries of a patient who meets the requirements for use.

- Developing image processing software is a constant fight against image quality. The ability to deal with poor quality images is a serious limitation in terms of applicability in retrospective studies that gathers images from considerably old ultrasound equipment. Only images that comply with the recommendations provided in section 1.14 of these IFUs are accepted.
- Regarding the ultrasound equipment, OSIS Ovary can work only with DICOM and PACS compatible General Electric scanners. Not for use on 3D transvaginal ultrasound acquired with different image formats or protocols.
- Regarding the format only DICOM format can be read by OSIS Ovary (no screenshots nor video exported from user's ultrasound machine).
- OSIS Ovary should only be used in combination with equipment that meets the defined and detailed minimum system requirements (section 1.14 of the IFUs): browser, screen, resolution, computer characteristics…
- The correct functioning of all the features of the platform when used from a mobile device (smartphone, tablet, etc.) is not guaranteed. It is always recommended to use the platform from a computer (requirements in section 1.14 of these IFUs).

LIMITATIONS IN PERFORMANCE

- Future works may develop the capabilities of OSIS Ovary to process volumes from different formats, scanners and accept images with low resolution or high noise levels.

1.10. Any undesirable side effects

OSIS Ovary does not have any undesirable side effects.

1.11. Warnings and precautions

- It is intended for use exclusively in clinic environments by experienced professionals (doctors, nurses, or technicians) in the use of 3D gynecological ultrasound with transvaginal probe.
- Read and understand the instructions for use before attempting to use OSIS Ovary.
- It requires specific training in the use of ultrasound equipment.
- The images obtained with transvaginal ultrasound equipment must have an adequate quality, that is, contain the desired anatomy in its entirety, show contrast (brightness differences between tissues) and not be affected by high levels of noise or artifacts. Fertoolity provides the requirements that guarantee the quality of the input images (provided by the user) in the Instructions for Use. Otherwise, the algorithm of OSIS Ovary may fail because of issues concerning image quality: signal to noise ratio, artifacts, spatial resolution, and contrast resolution. The user must, therefore, follow the requirements of the input images as suggested by Fertoolity to obtain reliable results.

- OSIS Ovary does not guarantee the quality, accuracy, or legality of the medical images (provided by the user) based on which the software calculates parameters. The user must, therefore, use caution when using the software.
- The final evaluation should always be supervised by a physician with competence in the area of fertility. The software is intended to assist gynecologists and cannot fully substitute their clinical judgement.
- This tool has been developed for non-pediatric patients. This decision support tool should not be used for patients below this age group.
- The software should only be used in combination with equipment meeting the defined minimum system requirements detailed in the instruction for use.

All warnings and precautions for the use of this device are included in the documentation accompanying the device.

1.12. About these instructions for use

- Please read and understand these instructions for use provided with the software before attempting to use OSIS Ovary.
- Please check that the version of the instructions for use matches the version of OSIS Ovary you wish to use.
- The instructions for use are available in Help option of OSIS Ovary's platform, as well as on OSIS Ovary's About tab page. Instructions for use are also available on Fertoolity's website: https://fertoolity.com/es/manuales-usuario.
- The instructions for use are only available in PDF. They can be consulted using the free reader available at: https://get.adobe.com/uk/reader/.
- These instructions for use are only provided in electronic format. If you need them in paper format, please contact Fertoolity's team at info@fertoolity.com or (+34) 96 317 36 10 and request the instructions in hard copy. To do so, you will need to provide a Full Name associated with an OSIS Ovary user, a telephone number, an email address and a physical address where you would like to receive the paper instructions for use. The user will receive the paper instructions for use, at no additional cost, within 7 working days of receipt of the request. If you do not receive it or encounter any issues related to the request, please contact the same number Fertoolity's team at info@fertoolity.com or (+34) 96 317 36 10.
- It is recommended that the user keeps these instructions for use together with the product for future reference.
- The images in these instructions for use are provided for helping the user's understanding only. In some cases, they may differ slightly from what you see on the screen.
- All references to regulations and standards and their revisions are valid at the time of publication of these instructions for use.

1.13. Declaration of Conformity

This product conforms to the following regulations and standards:

- MDR 2017/745: Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.
- EN ISO 13485:2016+A11:2021 - Medical devices. Quality management systems. Requirements for regulatory purposes
- EN 62304:2006+A1:2015 - Medical devices software - Software lifecycle processes
- EN 82304-1:2017 - Healthcare software. Part 1: General requirements for product safety.
- EN 62366-1:2015+AC:2015+AC:2016+AC:2016+A1:2020 - Medical devices - Application of usability engineering to medical devices
- EN ISO 14971:2019+A11:2021 - Medical devices - Application of risk management to medical devices - Risk management application to medical devices
- ISO/TR 24971:2020 - Medical devices. Guidance on the application of ISO 14971.
- EN ISO 15223-1:2021 - Medical devices. Symbols to be used with information to be supplied by the manufacturer. Part 1: General requirements
- EN ISO 20417:2021 - Medical devices. Information supplied by the manufacturer.
- IEC/TR 80002-1 Medical device software - Part 1: Guidance on the application of ISO 14971 to medical device software
- ISO/IEC/IEEE 12207:2017 Systems and software engineering. Software life cycle processes.

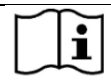
1.14. Security Notes

- The OSIS Ovary platform is a diagnostic and treatment monitoring tool. It in no way presents, predicts, suggests, or forecasts the patient's diagnosis.
- The final diagnosis of the study is the sole responsibility of the professional, so the results provided by the platform must be verified before finalising the analysis of the cases. A case should not be automatically closed or concluded without first checking that the results provided by the platform are correct. The software is intended to assist the clinician and cannot completely replace their clinical judgement.
- Do not include personal patient information during data export from the ultrasound machine that could compromise the patient's identity.
- Before exporting images to OSIS Ovary from your ultrasound machine, make sure that these images correspond to the patient whose identifier you have entered in the ultrasound machine.
- The images to be exported must be 3D volumes of the ovaries of a patient who meets the requirements for use.
- Do not attempt to export screenshots or video from your ultrasound machine.
- The browser supported by the platform is Google Chrome version 138.0.7204.101 (and later).
- For the correct representation of the results in OSIS Ovary, a screen of at least 14 inches with a minimum resolution of 1920 x 1080 pixels is required.
- OSIS Ovary is not a real-time service. Images exported from your ultrasound machine will be queued for processing on the server. Please note that the delay you experience when exporting images will depend on the internet speed at your centre.

- In order for the platform to function correctly, the user is recommended to use a computer with the following minimum characteristics:
    - i3 processor or similar
    - 8 GB RAM
- OSIS Ovary should only be used in combination with equipment that meets the defined and detailed minimum system requirements.
- The correct functioning of all the features of the platform when used from a mobile device (smartphone, tablet, etc.) is not guaranteed. It is always recommended to use the platform from a computer with the aforementioned features.
- The user should always verify that the information in the reports generated by the platform matches the corresponding case information displayed on the platform.
- The platform is intended exclusively for clinical use by professionals (doctors, nurses, or technicians) experienced in the use of 3D gynaecological ultrasound with transvaginal probe.
- The use of OSIS Ovary requires specific training in the use of ultrasound equipment.
- Pay close attention when using OSIS Ovary, especially when interpreting the results. Any distraction may cause a misinterpretation of OSIS Ovary results and lead to a wrong decision about possible diagnoses, treatment follow-up or interpretations.
- Images obtained with transvaginal ultrasound equipment must be of adequate quality, i.e., contain the whole of the desired anatomy, show contrast in the different parts of the anatomy, and not be affected by high levels of noise or artefacts.
- OSIS Ovary does not guarantee the quality, accuracy or legality of the medical images (provided by the user) from which the software calculates the parameters. Therefore, the user should exercise caution when using the software.
- The final evaluation of the OSIS Ovary results should always be supervised by a physician with expertise in the area of fertility.
- In the event of any eventuality, problem or query, the user should contact the Fertoolity Technical Service via email: info@fertoolity.com.
- The user should report any serious incident related to the product to Fertoolity (info@fertoolity.com) as well as to the competent health authority, in this case the AEMPS.

1.15. Symbols

Symbol	Meaning	Reference
	Manufacturer	EN ISO 15223-1 ISO 20417
	Date of manufacture	EN ISO 15223-1 ISO 20417
	See instructions for use	EN ISO 15223-1

		ISO 20417
	Electronic instructions for use to indicate on the product or on its packaging that information relevant to the use of the product is available in electronic format instead of, or in addition to, printed on paper.	ISO 7000 - 3500
	Medical device	EN ISO 15223-1 ISO 20417
	Serial Number In the case of OSIS Ovary, the version of the software platform is provided.	EN ISO 15223-1 ISO 20417
	Unique Device Identifier or Unique Product Identifier	EN ISO 15223-1 ISO 20417
	The CE marking indicates compliance with the MDR 2017/745 medical device regulation in Europe. It is accompanied by the Notified Body number (BSI 2797).	MDR 2017/745

1.16. Nomenclature

- **2D:** 2 dimensions
- **3D:** 3 dimensions
- **AEMPS:** Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products).
- **HTTPS:** Hypertext Transfer Protocol Secure
- **COS:** Controlled ovarian stimulation.
- **AI:** Artificial Intelligence
- **AI:** Artificial Insemination
- **IVI RMA:** Instituto Valenciano de Infertilidad - Reproductive Medicine Associates
- **IP:** Internet Protocol
- **IVF:** In Vitro Fertilisation
- **LMP:** Last Menstrual Period
- **MDR:** Medical Device Regulation 2017/745
- **MDSW:** Medical Device Software
- **MRN:** Medical Record Number
- **OSIS:** Online System for Image Segmentation
- **OTS:** Off-the-shelf software
- **ERP:** Enterprise Resource Planning

- **SOUP:** Software of Unknown Provenance
- **UDI:** Unique Device Identifier
- **DICOM:** Digital Imaging and Communications in Medicine.
- **PACS:** Picture Archiving and Communication System.

1.17. OSIS Ovary Identification

- **BASIC UDI-ID:** 8437024165OSIS7J
- **UDI-DI:** (01)8437024165026
- **UDI-PI:** (21)V020000 (11)260204
- **GMDN:** 40873 → Ultrasound imaging system application software → An individual software program or group of programs, routines or algorithms that add specific image processing and/or analysis capabilities to a diagnostic ultrasound system configuration. A basic set of applications programs and routines are included with such computer-controlled imaging systems, and they can be upgraded to correct programming errors or to add new system capabilities. Some applications software programs or program packages must be combined with specific hardware or firmware configurations in order to function as intended. Applications program packages are typically identified by a proprietary name and "version" or "upgrade" number.
- **EMDN**: Z11049092 → Various ultrasound instruments – Medical Device Software.
- **MDR CODE**: MDA 0315 Software.
- **PRODUCT CLASS:**
    - According to annex VIII of MDR 2017/745, class IIa active medical device (rule 11).
    - According to EN 62304 for being a Medical Device Software, class B.

1.18. Information about the manufacturer

Fertoolity S.L.
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https://fertoolity.com/es/

2. GENERAL DESCRIPTION

OSIS Ovary is an online web platform for use in clinics specialized in reproductive medicine, which provides segmentation and objective anatomical measurements of the different ovarian follicles (folliculometry) based on the reception of ultrasound volumes (3D) of the ovaries, so that healthcare professionals can use this information to control the monitoring of controlled ovarian stimulation (COS) of patients during in vitro fertilization (IVF), oocyte vitrification or artificial insemination (AI) cycles, making folliculometry processes in clinics more flexible, as well as making clinical decisions.

Folliculometry is a procedure that involves periodic transvaginal ultrasound scans to monitor the growth of follicles in the ovary, measuring follicular size to monitor COS. It is a simple and routine procedure, performed 2-6 times during each ovarian stimulation cycle. Currently, manual folliculometry is performed by the gynecologist in order to count the number of follicles per ovary and measure the diameter of the follicles, one by one (manual follicle measurement). This technique is considered the Gold-Standard in clinical practice.

OSIS Ovary enables the automation of ovarian follicle measurements (number and size), significantly reducing the hours spent by clinicians in processing and analyzing these images, providing repeatable anatomical measurements of the different ovarian follicles in an objective way, and it can be used from any 3D ultrasound machine no matter where it is located.

The automatic segmentation of ovarian follicles is carried out using an Artificial Intelligence (Deep Learning) model. From this segmentation, OSIS Ovary calculates the number of follicles detected in an ovary and their relaxed diameter.

OSIS Ovary is hosted at Microsoft Azure's cloud services and is designed to remotely receive (via Fertoolity PACS) Cartesian volumes in DICOM format captured with the 3D endocavity probes - ultrasound machines, via encrypted IP connection with Ethernet network cable. The OSIS Ovary platform can be accessed via the web browser of any standard "off-the-shelf" computer connected to the site's network and requires no installation on the user's computer. The user simply needs to have a username and password associated with a clinic and center.

When a new license to use OSIS Ovary is created for a center and a clinic, Fertoolity's IT team configures the platform to receive inputs from the 3D ultrasound machines in those clinics: the acquisition of the right and left ovary by a technician using a 3D transvaginal ultrasound machine. All acquisitions made with those ultrasound machines that meet the criteria defined during setup will be sent to OSIS Ovary and analyzed.

The user exports the volumes from the ultrasound machine to the OSIS Ovary server, which automatically processes the files received and performs follicle segmentation and quantification. Finally, users can access the OSIS Ovary web platform to view the reports, manually correct follicle quantification if necessary, and validate the report.

OSIS Ovary incorporates an alert logging system, which triggers alarm messages to the user when the ultrasound volume has not been correctly received, determining the specific cause detected and thus facilitating correction or resolution of the problem.

OSIS Ovary is equipped with a manual quality control system, which allows the healthcare professionals to verify that the ultrasound volumes received are properly assessed, and to report and manually correct those that have not been processed correctly.

OSIS Ovary is designed to work with ultrasound Cartesian volumes in DICOM. A copy of each volume exported to OSIS Ovary will also be stored on the OSIS Ovary system. This will enable subsequent remote reviews of the ultrasound data by the user or by Fertoolity Technical Support, if necessary.

OSIS Ovary treats the patient's data (3D transvaginal ultrasound) independently of the patient or the user, being a calculation and visualization tool. The information provided by OSIS Ovary is used for follicular monitoring during controlled ovarian stimulation cycles. However, the entire clinical process and the decisions involved are the responsibility of the gynecologist, not only depending on the information provided by OSIS Ovary but also on other clinical parameters obtained from the patient in other ways.

OSIS Ovary does not make decisions or provide diagnoses but instead allows the gynecologist to visualize and analyze 3D transvaginal ultrasound images with the possibility of verifying the quality and editing the output of each step of the process being able to correct the information provided. Therefore, it does not carry any risk for the patient.

The process of controlled ovarian stimulation is produced by gonadotropins and is assessed with serial ultrasound exams by measuring ovarian follicle-growth tracking (intended use) by nurses and doctors up to schedule oocyte recovery, previously to an in vitro fertilization, oocyte vitrification or artificial insemination indistinctly. OSIS Ovary is specifically used for this intended use in all cases.

The user can save or discard the obtained results provided by OSIS Ovary as well as manually correct them in case of errors by using a ruler over the viewer. In case of modification/correction, the last results manually entered by the user are saved and they are highlighted as being edited by the user, so that they can be identified later.

OSIS Ovary provides the size of the follicles at different patient visits. In current clinical practice, this is measured manually by the gynecologist, directly on transvaginal ultrasound. When there are several (3 or more) follicles that reach a certain size (usually larger than 16-17 mm) the patient is scheduled for folliculometry to extract the mature follicles. This decision is not only based on the size of the follicles, but also on many other clinical values, hormones (all of them external to OSIS Ovary). Many times, even if mature follicles are extracted, they do not contain an oocyte inside. In this case, the whole process must be repeated again with the patient from the beginning. In case OSIS Ovary would give an error, the physician could avoid it by measuring manually himself/herself and basing his/her decision on his expertise and the other clinical values external to OSIS Ovary to provide the correct guidelines for the next steps of the process.

In the worst case, no harm could be done to the patient other than lengthening the time to become pregnant and repeating again the same process carried out from the beginning.

All the details of OSIS Ovary can be found in: FERTOOLITY-TF001-2.02 User Manual - OSIS Ovary.

2.1. Expected lifetime

Hardware parts can rust, degrade, fatigue, any kind of ageing phenomenon... However, nothing rusts or degrades in software. Degradations of performance can be seen more as bugs than ageing. E.g.: if a software slows down, it's because the memory or hard drive are full. It can be corrected by maintenance (emptying the HD) or by bug fix (fixing the memory leak).

Lifetime of software shall then be based on the context of use: when this context changes, the software turns out to be unusable.

Medical Device Software (MDSW) runs on hardware. When this hardware is obsolete, namely when the hardware manufacturer ceases its support, the software running on this hardware cannot be used any more. In this case, the obsolescence can be estimated, based on hardware generation lifetime. E.g.: the technical characteristics of a PC of today can still be found in a PC in five years' time.

The expected lifetime that can be defined for a MDSW depends on the technology used:

- MDSW running on a Windows PC could have a lifetime of 3 to 5 years.

Software as a medical device needs SOUP/OTS to run. When the versions of the SOUP/OTS used by the software as a medical device become obsolete, Fertoolity can no longer maintain this software as a medical device. This is especially the case for security problems that are not fixed by the supplier of the SOUP/OTS. The software as a medical device can function with an obsolete version of a SOUP/OTS as long as there are no critical issues published in this SOUP/OTS. However, when that SOUP/OTS is an operating system or a browser, it is almost impossible to continue using the software as a medical device on a new major version of the operating system/browser, without revalidating the software as a medical device.

OSIS Ovary is a cloud software program and expected lifetime is still a requirement for cloud software. Cloud software needs to be updated periodically to keep up to date with the continuous changes in the underlying cloud infrastructure. The software is only implemented in the cloud by Fertoolity's IT team and is therefore accessible to its customers. Customers are not required to install anything. This ensures that they always have access to the latest version of the software.

The only solution is to define a major version release, a milestone in the cloud software lifecycle. All subsequent versions will be minor changes, until a new major version is released. The reliability of each version will be followed according to the methodology

described in the software development plan of OSIS Ovary, that complies with the applicable technical standards: EN 62304, EN 82304, ISO/TR 80002 and ISO 14971.

Lifetime and release versions aren't equal. The lifetime starts when a major version is released. Then, we can have several minor release versions within the lifetime of the Medical Device Software.

Defining a lifetime compatible with medical device regulation requires monitoring SOUP/OTS software, their updates, their obsolescence, in order to assess if SOUP/OTS software changes trigger major MDSW updates and revalidation.

Therefore, with all the above information, the defined expected lifetime for OSIS Ovary according to the state of the art is 5 years, provided that the user follows the intended purpose of the product and the Instructions for Use provided. Before this time, a new major version of the software will be released and during this time the obsolescence of the SOUP/OTS (including the operating system and web browsers) and the obsolescence of the hardware will be monitored. If for these reasons a major version has to be released earlier (due to post-commercial information), this will be duly justified, and the defined theoretical expected lifetime of OSIS Ovary will be updated.

Sources:

- https://www.johner-institute.com/articles/regulatory-affairs/and-more/what-constitutes-the-lifetime-of-a-medical-device-in-the-eu/#:~:text=The%20lifetime%20of%20a%20medical%20device%20is%20the%20period%20during,performance%20are%20no%20longer%20guaranteed.
- https://www.johner-institut.de/blog/iec-62304-medizinische-software/lebensdauer-von-software/?__hstc=101363102.1d01e92c50a720bbf93cb200022919c0.1688916547636.1688916547636.1688916547636.1&__hssc=101363102.1.1688916547636&__hsfp=2272596688
- https://blog.cm-dm.com/post/2022/02/25/Medical-Device-lifetime-and-SaMD
- and MDR Annex I, Chapter I GSPR No. 6

2.2. Duration of use

When we talk about continuous use of a medical device, it is considered as the concept of duration such as transient, short term and long term are defined in terms of continuous use. Continuous use must be understood as an uninterrupted actual use for the intended purpose.

OSIS Ovary is a software that will be used by the gynecologist on a transient basis for each patient he/she reviews (less than 60 minutes) on a continuous use. Therefore, we can consider the continued use of the product to be transient. However, the gynecologist uses the software in several follow-up sessions for the same patient during the entire cycle is ovarian stimulation, until ovarian retrieval occurs.

The information available in the software for the same patient could be consulted multiple times (by the gynecologist) in the software in subsequent uses. As the software will be used for multiple patients, we can justify that it is a medical device for long-term use, even if its continued use for the same patient in a single use case is transient.

Therefore, the length of follow-up should be justified based on how long the treatment effective is expected to last and what would be required to demonstrate a positive benefit-risk conclusion in comparison to other SOTA treatment options.

We can consider the continued use of the product to be transitory. However, the practitioner uses the software in several follow-up sessions for the same patient during the patient's entire treatment process, which may take several sessions.

3. INSTALLATION

OSIS Ovary is distributed as a web platform and does not require installation by users on their computers. Likewise, uninstalling is not required. If you wish to stop using OSIS Ovary and have your data deleted, please contact the Fertoolity team by sending an email to info@fertoolity.com.

OSIS Ovary service and storage is deployed in Microsoft Azures's cloud servers. The user interface and the software required to process the ultrasound scans sent to OSIS Ovary from the ultrasound machines are installed on the server. This allows users (who are authorised) to access remotely at any time and from anywhere as long as they are using a computer with the minimum requirements. This means patient data is kept anonymous and stored in a secure environment.

The Fertoolity team will take care of deploying OSIS Ovary at your centre so that all users will always have access to the latest version of the software, without having to worry about software updates.

The Fertoolity team will also take care of the maintenance of OSIS Ovary. The team will notify all users of each update by email with all changes and a link to the user manual.

In addition, as software as a medical device, there are no consumable or expendable items that must be used with the product.

3.1. Requirements

To be able to use OSIS Ovary, at least the following is required:

- A DICOM image format and PACS compatible ultrasound machine
- A PC with a screen size of at least 14 inches and a resolution of at least 1920 x 1080 pixels with an Intel i3 processor or higher and at least 8 GB of RAM.

- A browser and an Internet connection.
- All the aforementioned equipment must have authorised access to OSIS Ovary system.

Once the medical staff has been registered by Fertoolity's Technical Service, they will receive an email notification to access the online web system. In this email the user will be provided with a link to select their secure password before accessing the platform. This ensures that no one else has access to each user's credentials at any time.

Users will be able to access the OSIS Ovary platform from within their company ERP without having to generate another password. However, they need to be authorised to access OSIS Ovary by Fertoolity Technical Support.

Fertoolity's Technical Service will configure your clinic's ultrasound machine(s) to obtain correct connection and export of ultrasound volumes to the OSIS Ovary platform.

Fertoolity team is not responsible for the regular maintenance of ultrasound machines, probes, computer equipment and network connections. Furthermore, to ensure a correct result of the ultrasound volumes processed in OSIS Ovary, the clinic staff authorised to perform ultrasound scans (doctors, nurses, or imaging technicians) must be familiar with the technique of capturing and handling the export of ultrasound volumes and may request additional training specifically for this purpose from Fertoolity.

3.2. How to start

To start using OSIS Ovary you will need the Fertoolity technical team to configure your ultrasound machines so that you can export volumes to the platform.

Likewise, the Fertoolity team will register a username with which you will be able to access the platform. To do this, you must provide the Fertoolity team with a valid email address to which a link will be sent so that you can enter a password before accessing the platform.

4. WORKFLOW

The workflow in OSIS Ovary starts with the ultrasound machine. The equipment needs to be configured to send data to OSIS Ovary in DICOM format via the Fertoolity PACS. Fertoolity will provide the necessary support to properly configure the ultrasound machines and stablish a secure connection with the Fertoolity PACS.

Once this configuration is done, the steps to process a case with OSIS Ovary are the following:

1. Introduce patient ID and last menstrual period (LMP

Users must introduce the patient ID and LMP. This information can be introduced manually in the ultrasound machine or can be managed by worklist. The configuration and management of worklist is not provided by Fertoolity.

2. Acquire left and right ovarian 3D volumes

Ovarian volumes must be acquired in the correct order, first the right ovary and then the left ovary so OSIS Ovary can properly identify them as right or left. It is required to put special effort in acquire good quality images as detailed in this manual, so OSIS Ovary produces optimal results. We strongly recommend storing volumes in the ultrasound machine after acquisition. This would enable Fertoolity to help in case of any issue the user may have.

3. Send data to OSIS Ovary

Depending on ultrasound machine brand and model, the buttons and controls to navigate through menu options may be different. Fertoolity will provide assistance to stablish a proper workflow and data acquisition/exportation procedure. In general terms. Once the volumes are acquired, users may access the ultrasound machine archive, select the desired patient, select both right and left ovary volumes and send them as DICOM. The ultrasound machine will be configured so the data is sent to Fertoolity PACS to be received by OSIS Ovary.

5. LOGIN

There are two ways for the user to access the OSIS Ovary platform:

1) Logging in from the Login screen (Figure 10): http://osis.ivi.org
2) In case of integration, users will be able to access from client ERP.

In both cases, your username must be registered on the platform. To register it, you can contact the person in charge at your centre or the Fertoolity team.

In this view it is possible to change the language (English, Spanish) before logging in as a user. After logging in, it will maintain the language selected by the user in the last session.

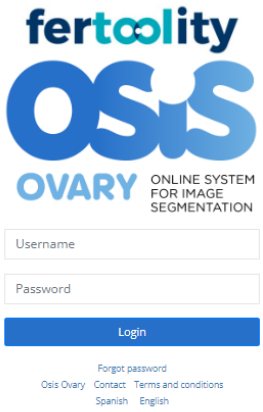

Figure 1. OSIS Ovary.

6. ACTIONS YOU CAN TAKE WITH OSIS OVARY

6.1. Consult and/or accept the terms and conditions

You can access the terms and conditions before logging in by clicking on the "Terms and Conditions" link on the login screen (Figure 10).

Once you have logged in as a user, if you are a first-time user, the platform will direct you to the OSIS Ovary terms and conditions of use screen (Figures 11 and 12) where you must read and accept the terms and conditions in order to use the platform. You will not be able to use any of the platform's functions if you have not accepted the terms and conditions. In the event that these terms and conditions change, you will need to read and accept them again in order to use the platform.

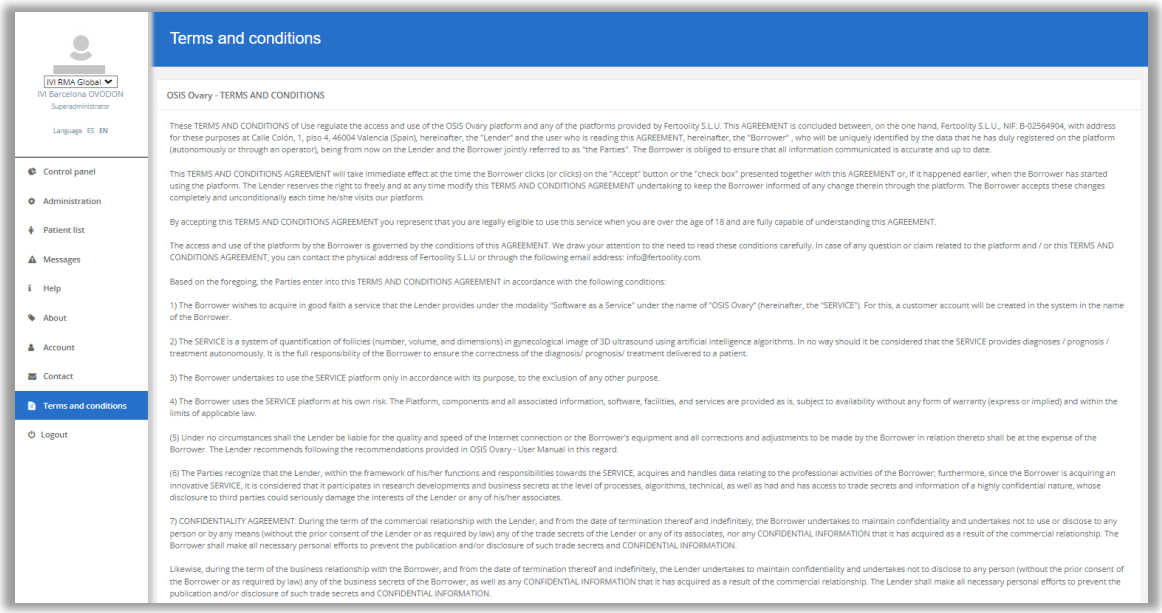

Figure 2. OSIS Ovary terms and conditions of use screen.

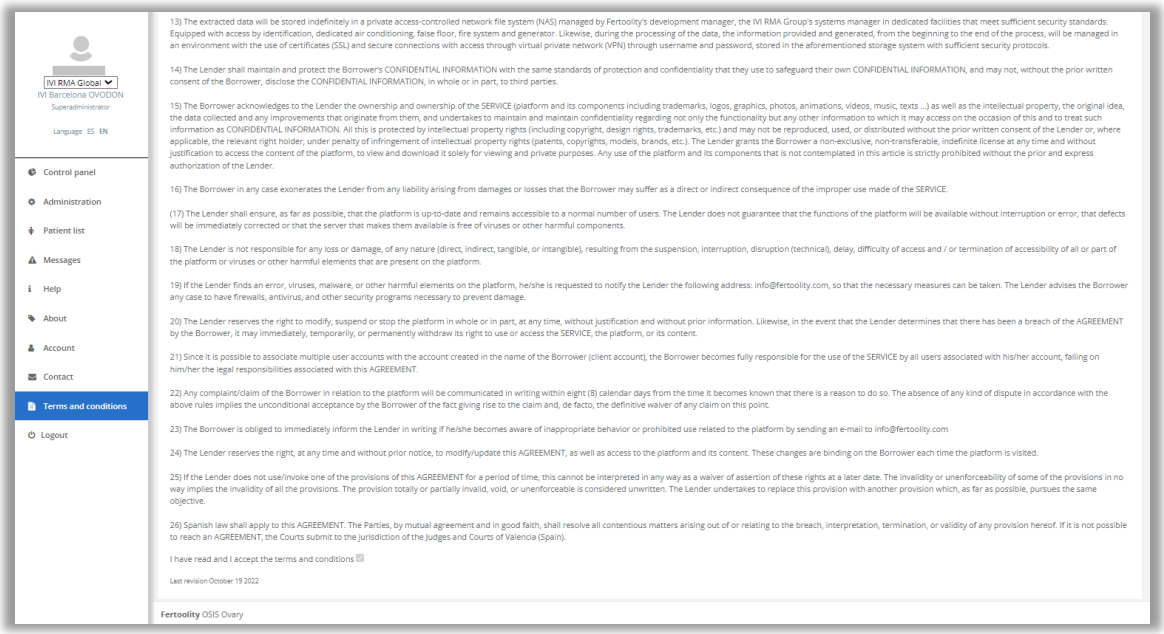

Figure 3. OSIS Ovary terms and conditions of use screen (acceptance box).

You can access the terms and conditions screen at any time by clicking on the side menu option (Figure 13) "Terms and Conditions". The terms and conditions are available in English and Spanish.

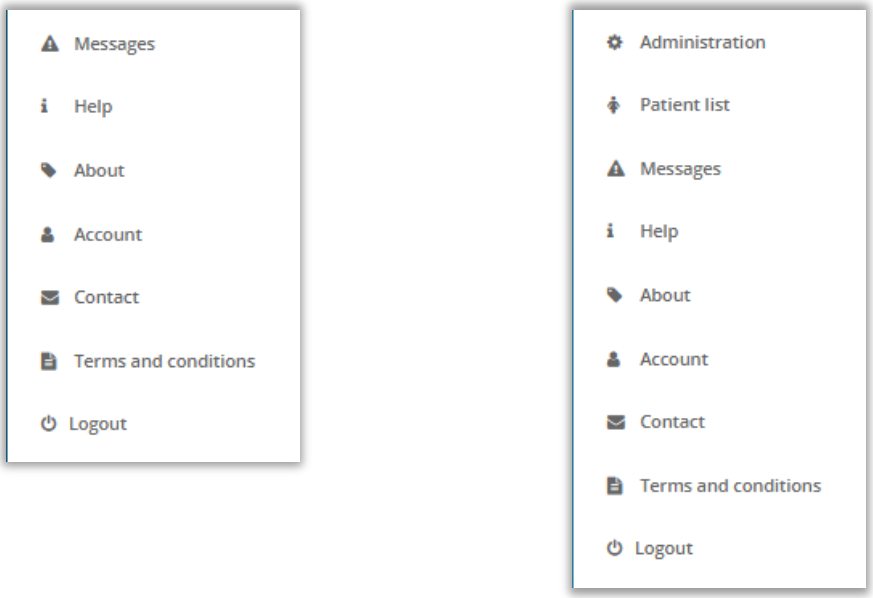

Figure 4. Side menu, on the left the basic user's menu, on the right the site manager's menu.

6.2. See product label

You can view the product label (Figure 14) before logging in as a user from the login screen (Figure 10) by clicking on the "OSIS Ovary" link.

The elements that appear on the label are detailed in the Symbols section (section 1.7).

In addition, you can find:

- the UDI, which is a medical device traceability number and identifies this particular software with its UDI-DI (01), and UDI-PI (11) and (21).
- a link to the latest version of the OSIS Ovary user manual.

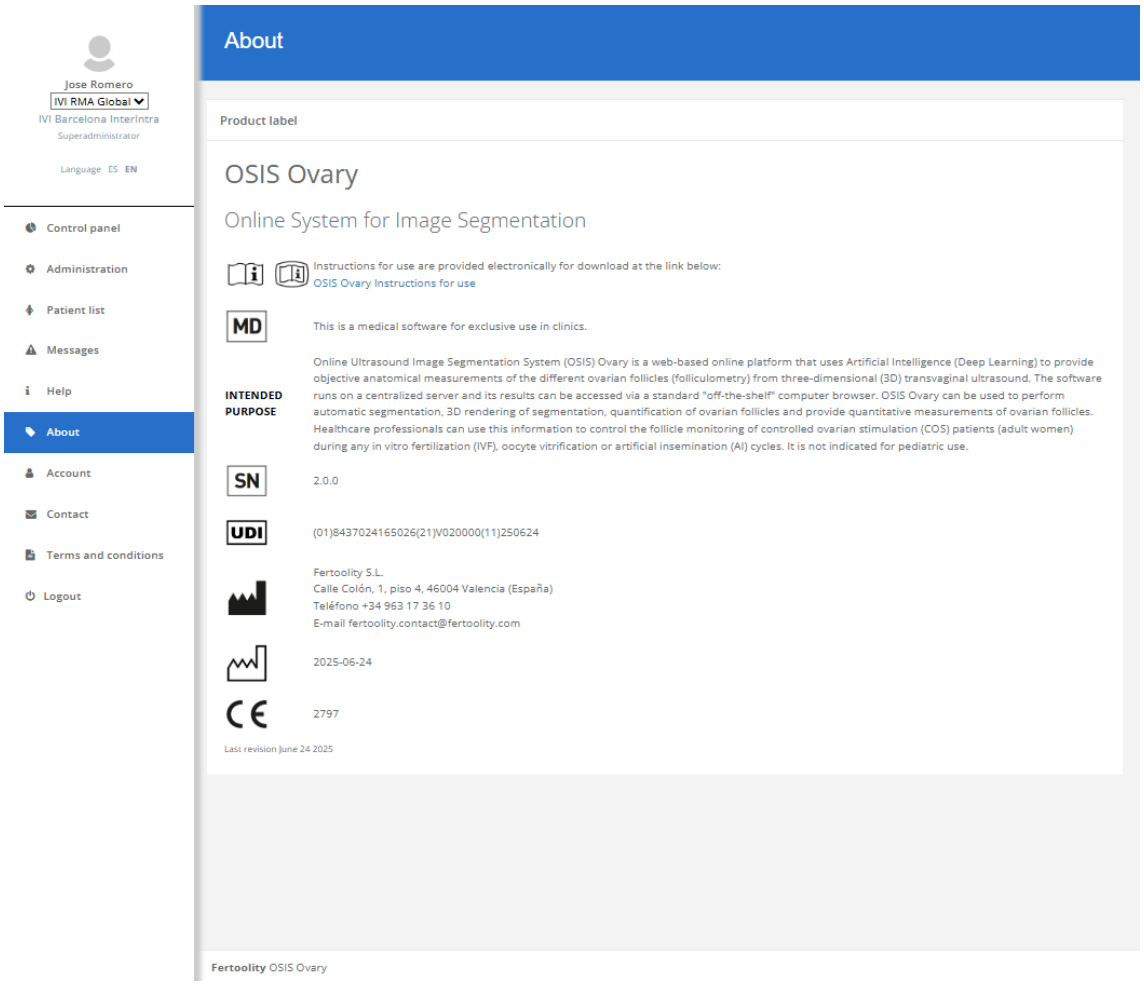

Figure 5. OSIS Ovary product label screen.

Once you are logged in as a user, you can access this screen by clicking on the side menu option (Figure 14) "About".

6.3. Contact the OSIS Ovary Team

You can contact the OSIS Ovary team by sending an email to info@fertoolity.com. You can easily access this email address by clicking on the "Contact" link on the login screen (Figure 10) or the "Contact" menu option on the side menu (Figure 13).

6.4. Download the user manual

You can download the user manual once you have logged in from the Help (Figure 15) or Product Label (Figure 14) screens which can be accessed from the side menu options (Figure 13) "Help" and "About" respectively.

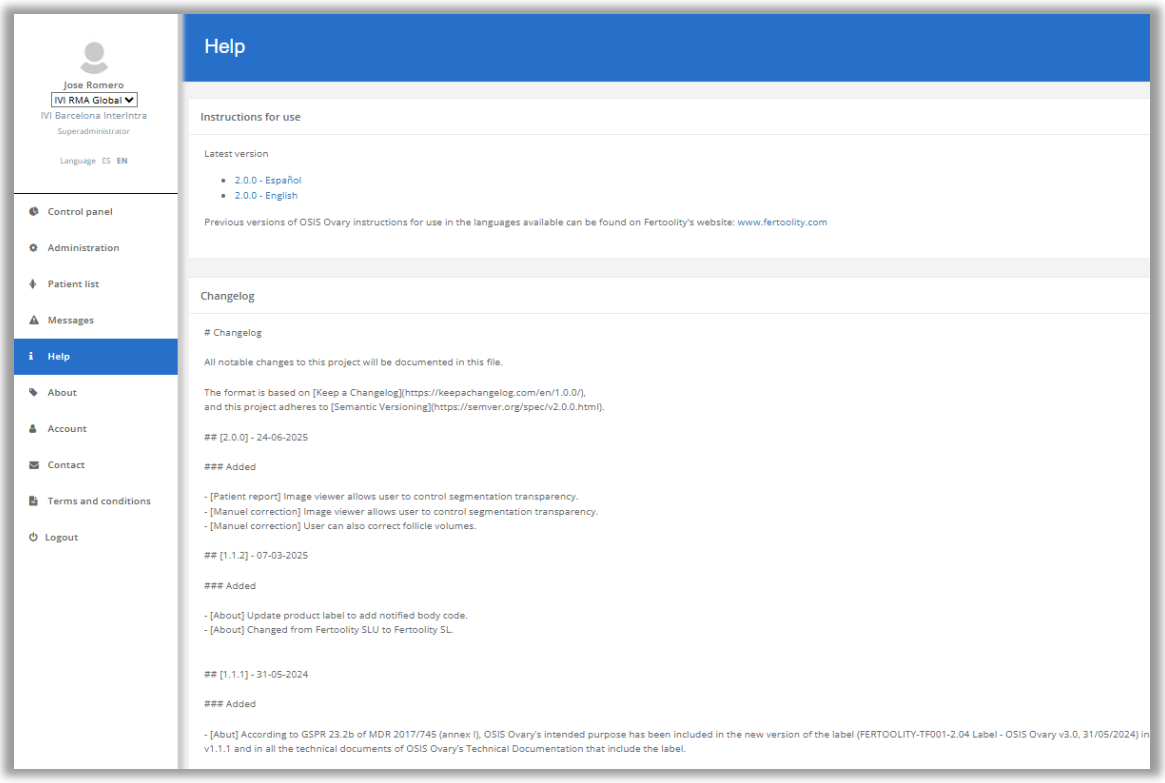

Figure 6. OSIS Ovary help screen.

6.5. Change your password and view account information

You can change your password from the Account screen (Figure 16), in the "Change password" section. You can access from the side menu option (Figure 13) "Account".

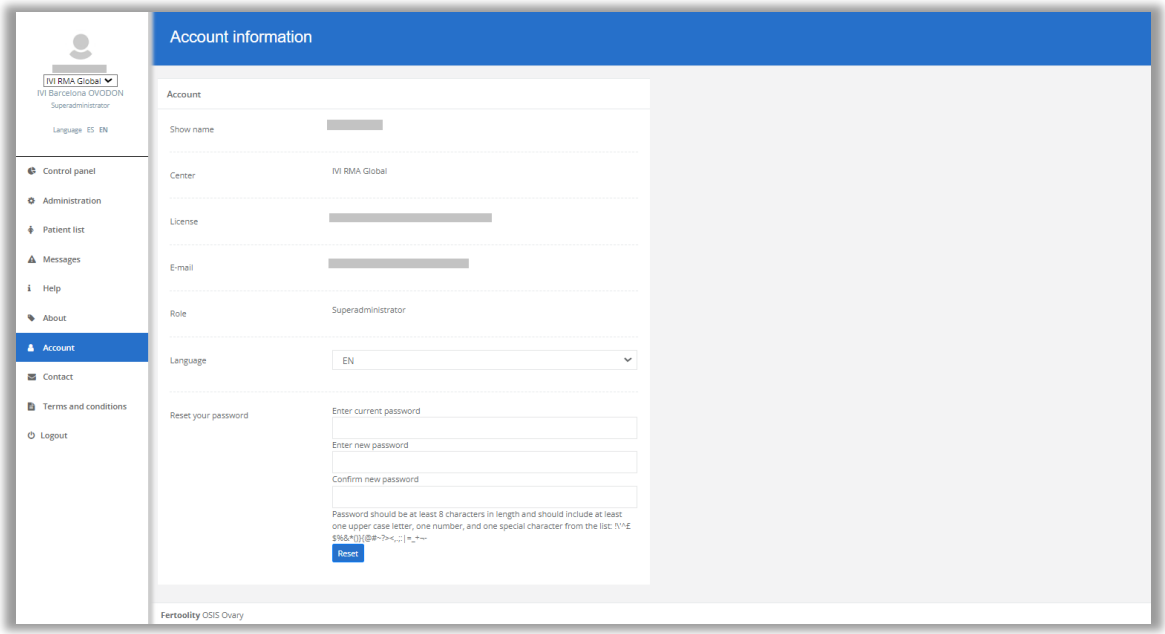

Figure 7. OSIS Ovary user account information screen.

In addition, on this screen, the user can consult the e-mail they are using to access the platform (e-mail), the centre where they are been registered (Centre), the licence through which they are accessing the service and its status (Licence), the level of privileges of their username (Role) and the current language selected and change it (Language).

6.6. Recover your password

If you have forgotten your password, you can set a new one by clicking on the "Forgot your password" link on the login screen (Figure 10). The platform will take you to a new screen to enter the email account you use to log in to the system (Figure 17).

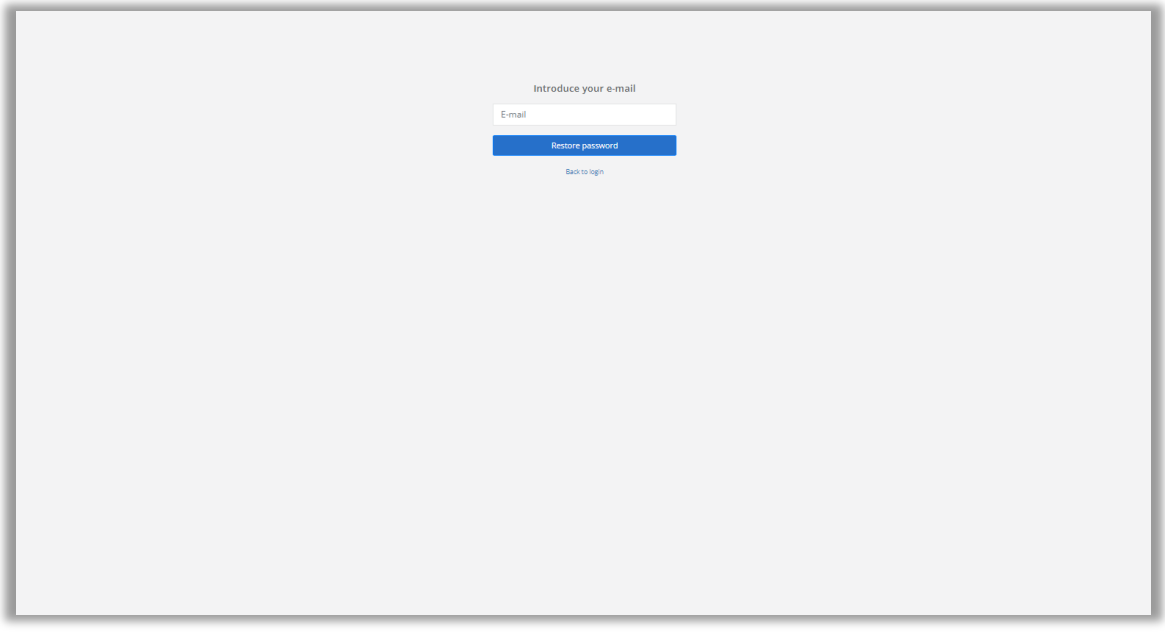

Figure 8. Screen to start the OSIS Ovary login password recovery process.

Enter your email address and click on the "Reset password" button. You will receive an e-mail with a link to access the screen where you can enter a new password (Figure 18). Please note that this link will only be valid for 15 minutes. After this time, you will have to re-request a password reset by clicking on "Forgot your password".

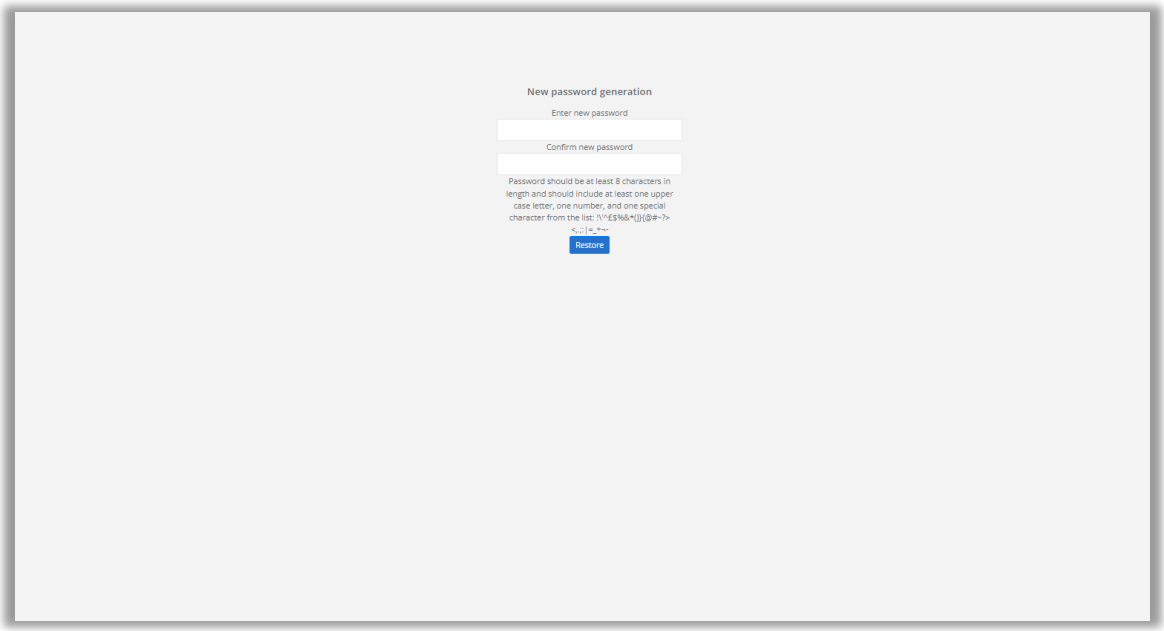

Figure 9. OSIS Ovary access password reset screen.

6.7. Processing a case

To process a case, you must follow the steps described in section 4 (WORKFLOW).

6.8. View the results of a case

If you do not have a user profile with site manager privileges, you will only be able to access a patient report from your company ERP. If you need assistance with this matter, you will need to open an incident on the IVI Group's incident platform (https://ivirma.cloud.invgate.net/portal) to request technical assistance.

If you are a site manager, you can access the list of patients (Figure 19) by clicking on "List of patients".

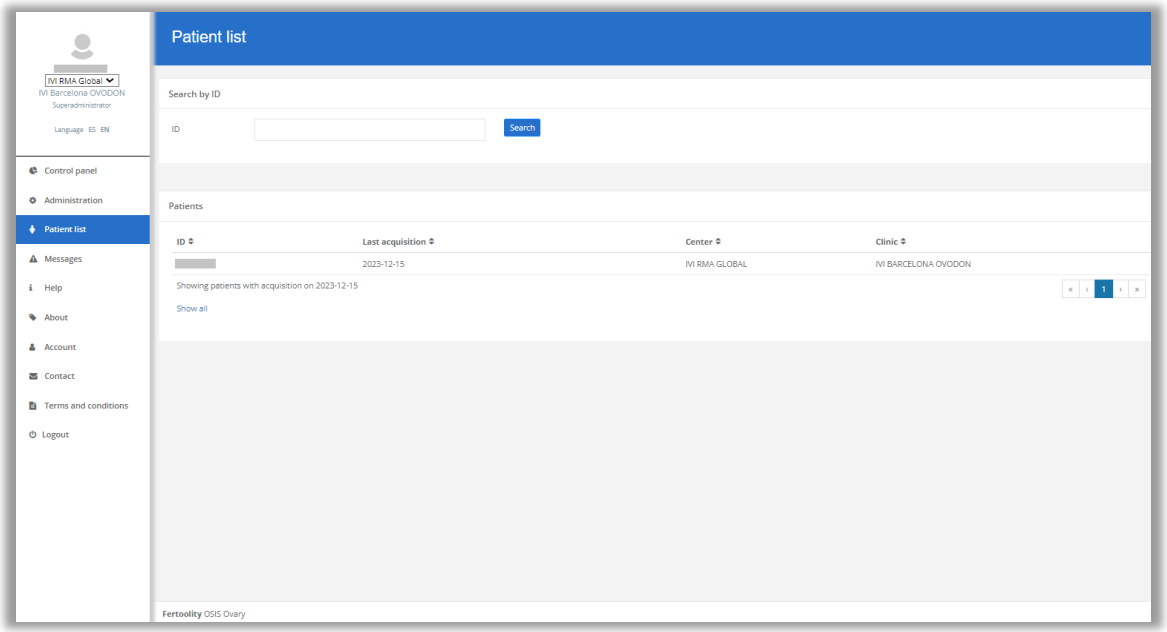

Figure 10. List of patients.

From this screen you can browse the patient table to find the MRN of the patient you wish to consult or enter the MRN in the "Search by ID" box and click on the "Search" button.

You can enter the patient's full MRN (8 digits) or enter a partial number for the platform to search for all MRNs starting with the digits entered in the box.

Once you have located the patient, click on their MRN to access the patient report screen (Figure 20).

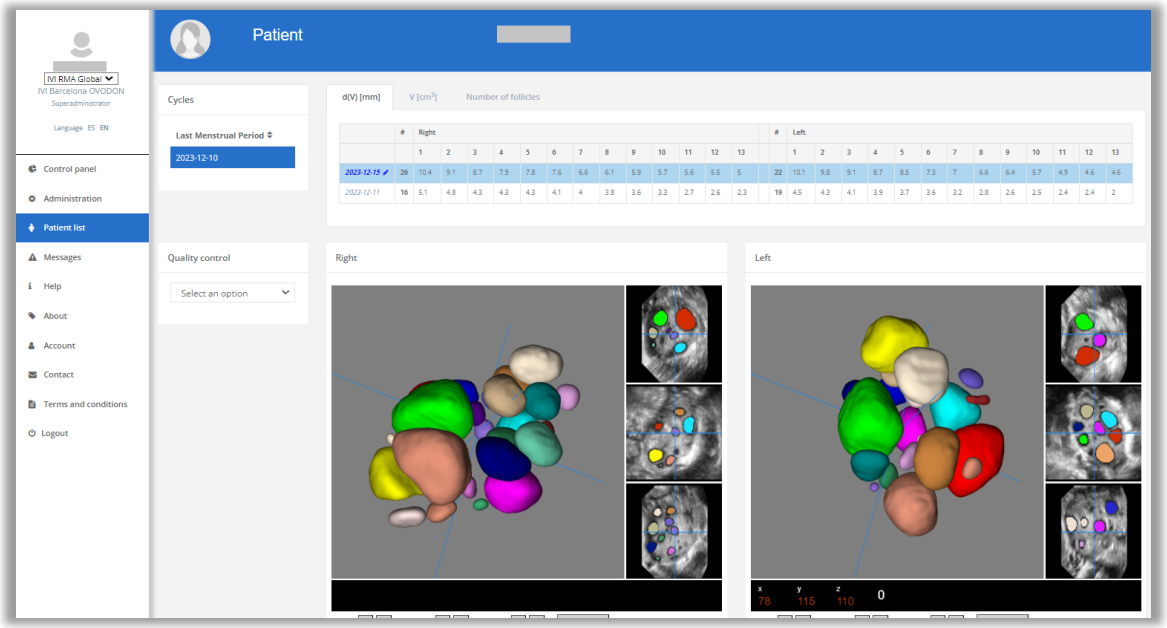

Figure 11. Patient information screen.

On the patient report screen, you can select a stimulation cycle (if there is more than one) in the top left box labelled "Cycle" by clicking on the Last Menstrual Period (Figure 21).

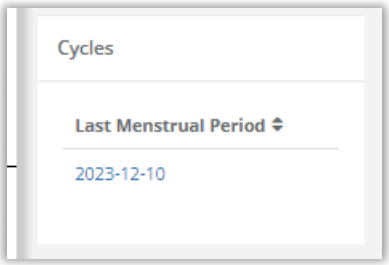

Figure 12. Stimulation cycle table.

Once the stimulation cycle has been selected, a table with follicular diameter d(V), follicular volume and number of follicles will be displayed in different tabs. The rows of the table give access to the different acquisitions (ultrasound scans) that have been performed on the patient during the cycle to date. On this table, each row corresponds to an acquisition in which the above-mentioned information is displayed. The "Right" column corresponds to the right ovary, the "Left" column corresponds to the left ovary and the "#" column indicates the number of follicles detected in that ovary, from highest to lowest (from left to right).

You can click on the acquisition date (Figure 22) to select the one you wish to view (the system selects the latest by default). Once selected, the system highlights the row in blue and displays the automatic segmentation of the patient's follicles in the lower "Right" and "Left" boxes, corresponding to the patient's two ovaries.

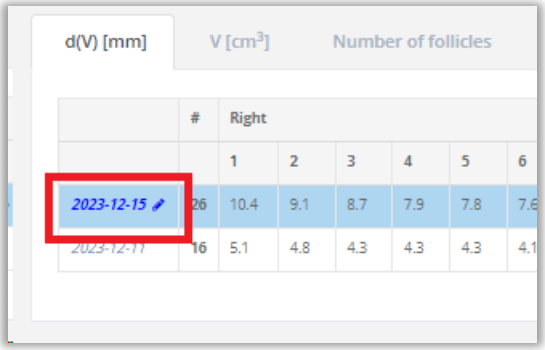

Figure 13. Selected acquisition date.

The main view of the multiplanar reconstruction viewer (Figure 23) displays the 3D representation of the automatic segmentation of the follicles present in each ovary (you can move it by clicking and dragging the mouse over the 3D representation). In addition, it shows you the 3 acquisition planes, Sagittal, Coronal and Axial with the automatic segmentation superimposed. You can swap these planes in the main view (which is the largest square) by clicking on the "Swap view" button in the viewer.

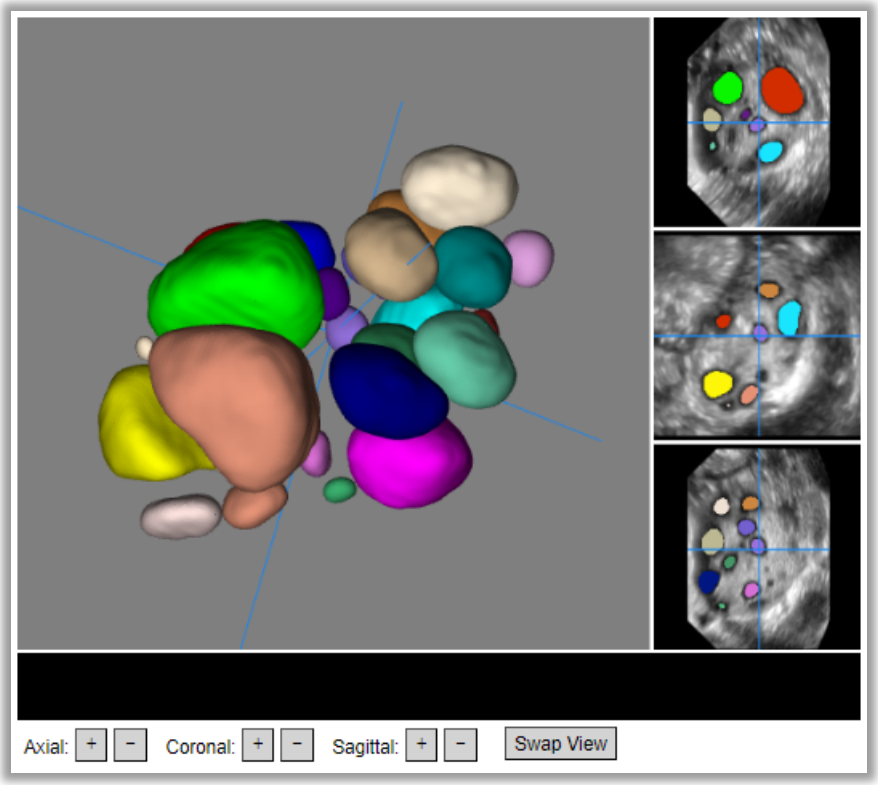

Figure 14. OSIS Ovary multiplanar viewer.

With the mouse over one of the three acquisition planes, you can use the mouse wheel to scroll through the volume slices. You can also scroll through the planes using the "+" and "-" buttons on the viewer (Figure 23) when an acquisition plane is displayed in the main view. The blue axes superimposed on the acquisition planes and represented in the 3D view show the same pixel so that the user can compare the corresponding area between the 4 views.

6.9. Performing quality control of a case

On the patient report screen (Figure 20), after selecting a stimulation cycle in the "Cycle" box and an acquisition (ultrasound) in the "Mean Follicular Diameter" table, you can select one of the options in the lower left box "Quality Control" (Figure 24) referring to the quality of the ultrasound images and results. Once you have clicked on "Save" and confirmed the operation, you will no longer be able to modify the selection. If you have reviewer, administrator or super administrator permissions, you can revert the quality control selection by pressing the "Undo" button.

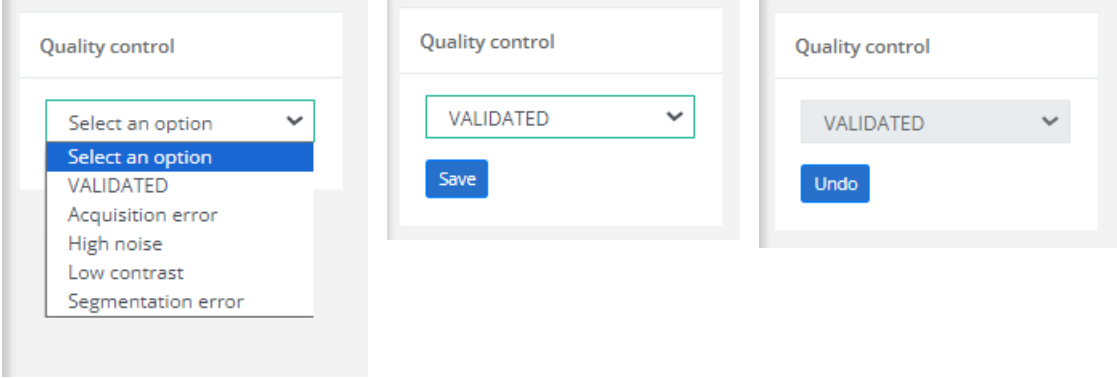

Figure 15. Quality control options.

If you conclude that the images (ultrasound scans) are of sufficient quality, the automatic follicle segmentation is correct and the mean diameter values are adequate, you can select the VALIDATED option in the quality control menu.

If, on the other hand, you consider that the results are not correct due to poor image quality, you can select one of the following options in the quality control menu to state the reason. Figure 25 shows examples of images of insufficient quality:

- VALIDATED: Both segmentation and diameter values are correct.
- Acquisition error: If any of the images (ultrasound scans) do not contain an ovary.
- Excessive noise: If any of the images (ultrasound scans) present too much noise to be able to distinguish the follicles.
- Low contrast: If any of the images do not show enough contrast to distinguish the follicles.
- Segmentation error: If the quality of the images is adequate but the automatic segmentation is incorrect, you can consider a manual correction of the values in the table (explained in the following section).

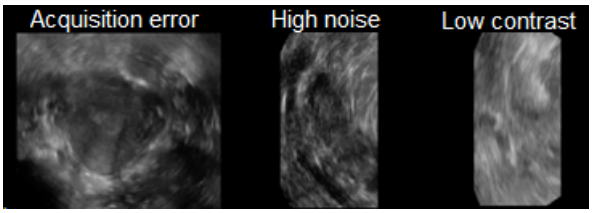

Figure 16. Example of poor-quality images. From left to right, image of a uterus, image with too much noise, image with too low contrast.

6.10. Manually correcting the folliculometry of a case

If the values generated by OSIS Ovary are not sufficient, you can consider a manual correction of these values.

To do this, first select the acquisition you wish to modify (make sure it is highlighted in blue as shown in Figure 20). The acquisition date will appear in bold with a pencil icon next to it indicating that the values can be edited (Figure 22).

Click again on the acquisition date and you will be taken to the manual correction screen (Figure 26).

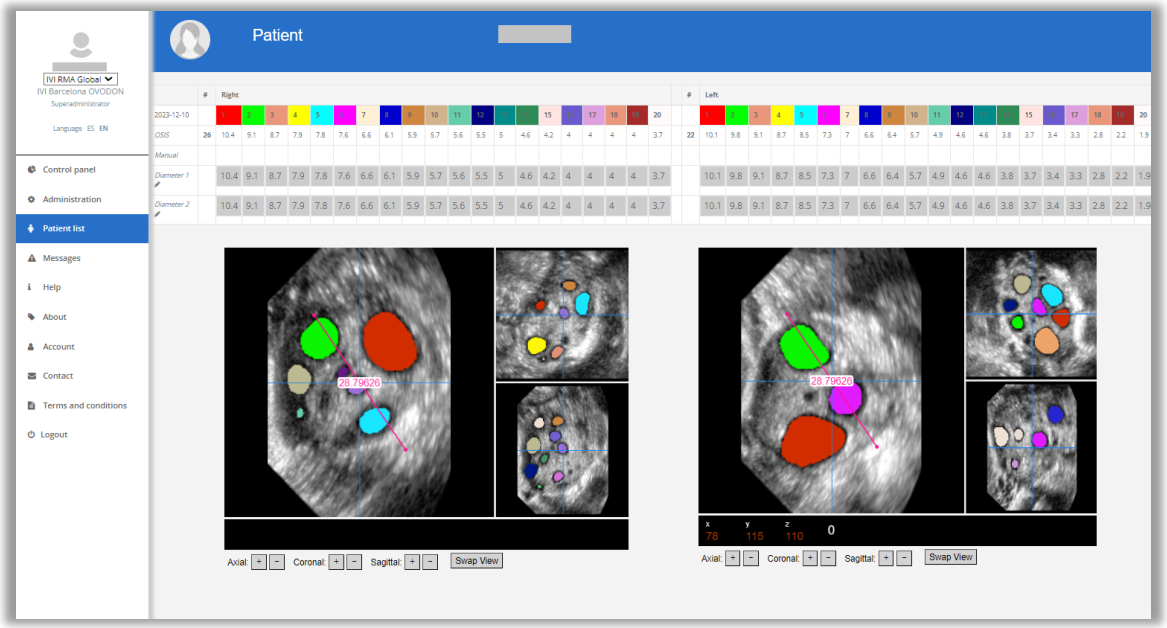

Figure 17. Manual folliculometry correction screen.

The screen is similar to the patient results report, but this time in the upper table where the d(V)'s are displayed, each follicle is assigned a colour that matches that of the segmentation of that follicle in the multiplanar representation below showing the three acquisition planes (axial, sagittal and coronal) with the segmentation superimposed and a ruler with two adjustment points (the ends of the ruler).

The table of diameters has five rows. The first row indicates each follicle's number and its colour. The other rows indicate the following information:

- OSIS: It displays the diameters obtained automatically by OSIS Ovary.
- Manual: It displays the values of the last manual correction if any. When you access the editor again after saving your manual correction, you will be reminded of the result in this row.
- Diameter 1 and Diameter 2: These are editable boxes which, when the screen is opened, they show the automatic values obtained by OSIS Ovary to facilitate the task. In these boxes the diameters measured with the ruler tool on the multiplanar viewer will be entered.

On this screen you can take diameter measurements manually. The steps are the following:

1. Identify the colour of the follicle you need to correct (e.g., orange).
2. Navigate the display until the follicle to be measured is located (Figure 27).
3. Select a slice where the diameter can be clearly measured (Figure 27). Note that for the measurement to be representative, you should select two planes where the diameter is at its maximum.
4. Adjust the ends of the ruler by dragging them to the contour of the follicle to be measured (Figure 27). Click on the circular point in one of the ends of the ruler, keep it pressed and drag it to one of the ends of the diameter of the follicle that you want to measure. When you are in the edge of the follicle, please release. Do the same with the other end of the ruler. The ruler will measure the distance between both ends and provide the value.
5. Write the value provided by the ruler in the Diameter 1 box of the follicle to be corrected. If you are measuring a follicle that has already been detected, you should overwrite its previous value in the box. If, on the other hand, you are measuring an undetected follicle in order to add it, enter it in one of the empty boxes.
6. You must enter two measurements for each follicle you wish to correct. Repeat steps 3, 4 and 5 to obtain another measurement **in the orthogonal plane** of Diameter 1 to be entered in the Diameter 2 box of the follicle to be corrected.
7. When you have noted down the measurements for all the follicles you wish to correct, click on the "Save" button at the bottom (Figure 29).

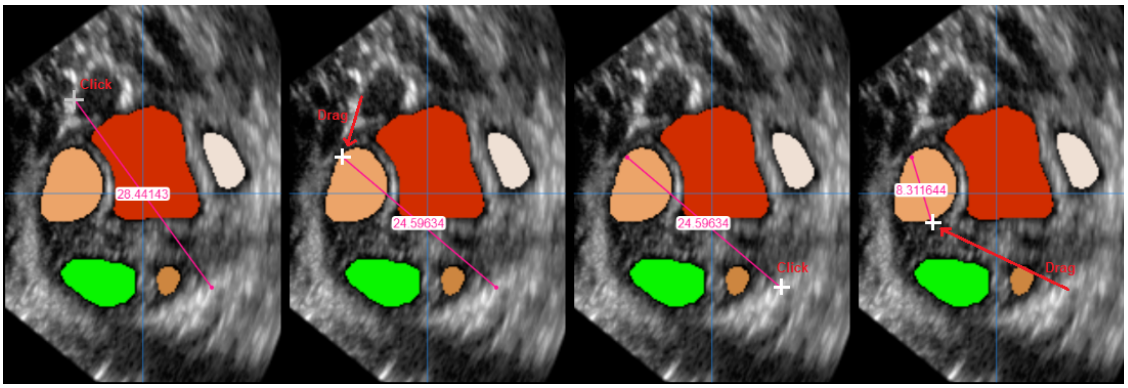

Figure 18. Manual correction process: Adjusting the ruler ends by click and drag.

Make sure you take two measurements in orthogonal planes. If a measurement has been missed, the system will remind you with an error message next to the "Save" button with the text "You must enter two values per follicle". From these two measurements, the system will calculate the average and save it.

If you want to remove a follicle (e.g., the green one), leave its Diameter 1 and Diameter 2 boxes blank as shown in Figure 28.

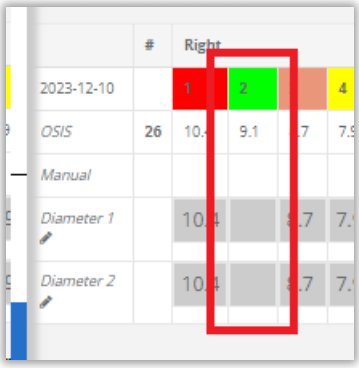

Figure 19. Blank boxes to delete a follicle.

When you click on save, the system will:

- read the data entered in Diameter 1 and Diameter 2 boxes
- compute the mean value for each follicle by calculating the average of the two diameters entered (formula 1)
- and store it for display in the patient report.

$$Mean\ diameter = \frac{Diameter\ 1 + Diameter\ 2}{2} \quad (1)$$

After the manual corrections the user will obtain the mean diameter instead of the relaxed diameter provided by OSIS Ovary, since it has been manually modified by the clinician and recalculated from the two orthogonal measurements.

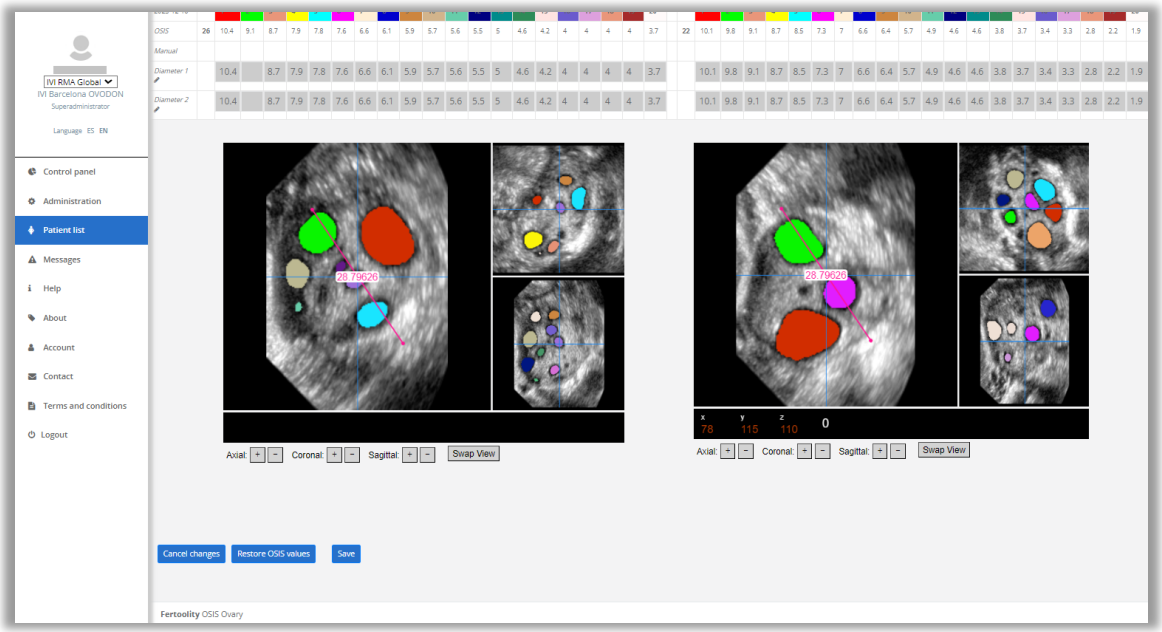

Figure 20. Manual folliculometry correction screen (buttons).

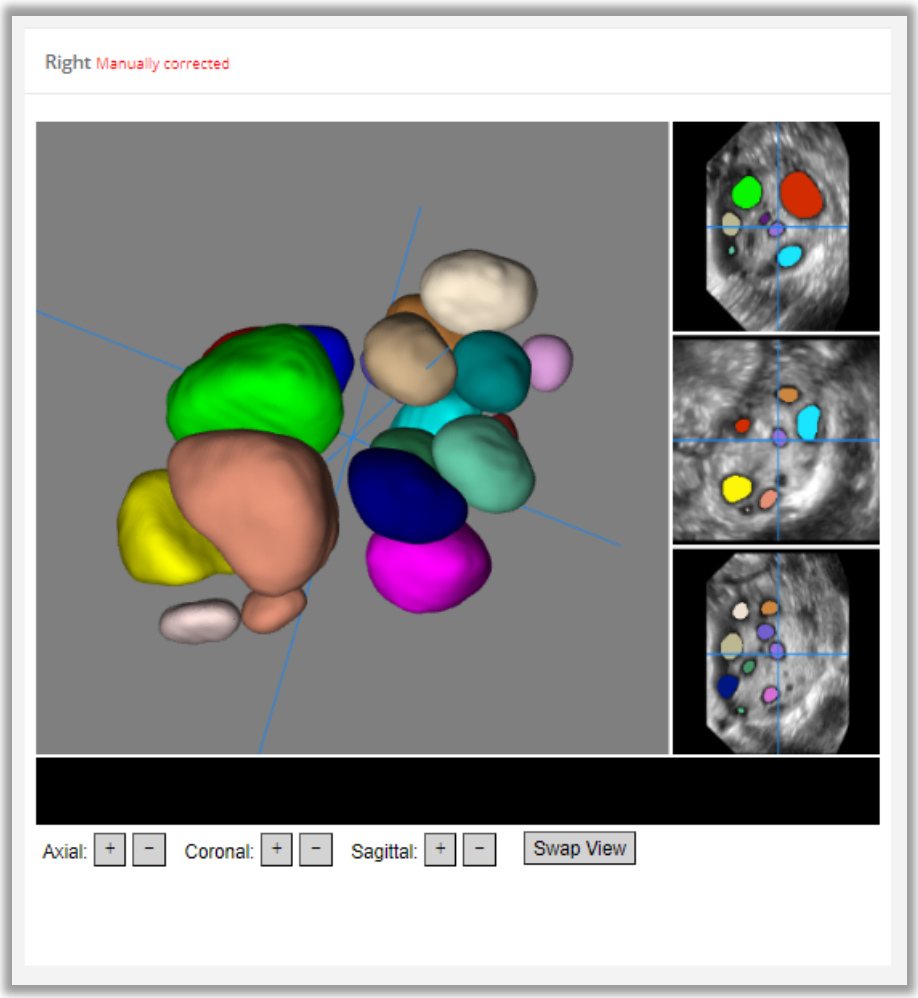

Figure 21. Multiplanar display in the patient report after manual correction.

If, during the correction process, you want to discard the changes made and return to the patient report, click on "Cancel changes" button.

If you wish to revert the values of a manual correction that has already been saved and restore the automatic OSIS Ovary's values (the values before the manual correction were performed) click on the "Restore OSIS values" button.

6.11. Manage clinics and centre users (Administrator)

If you are an administrator, a new option will appear in the side menu (Figure 13) under the name "Administration" (Figure 31) where you can consult the licence contracted by your centre in the upper table "Licence", the ultrasound equipment registered in the system in the table "List of clinics", and the users who have been given access to the platform in the table "List of users".

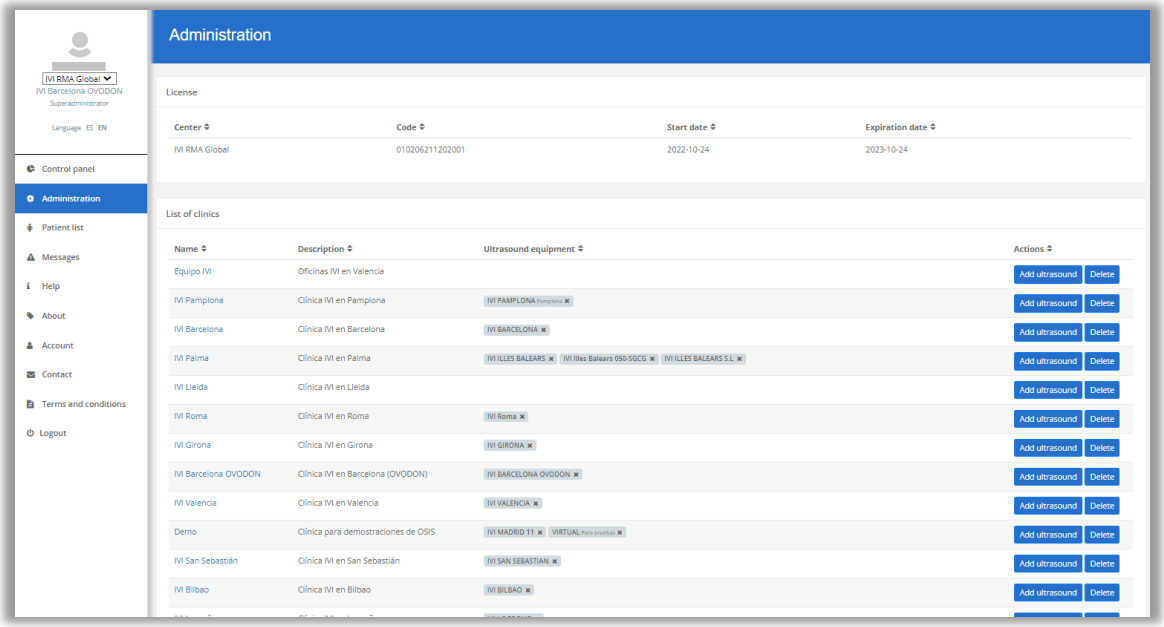

Figure 22. Administration screen.

Consulting licences:

In the "Licences" table you can check the licence status of your centre. This includes the licence code, the start date and the end date of the licence.

Administration of clinics and ultrasound machines:

In the table "List of clinics" you will find a list by rows of all the clinics registered to your centre identified by name and description as shown in Figure 31.

The "Ultrasound equipment" column contains a list of ultrasound machines associated to each clinic and displayed as labels with the name and description (if any) of each registered ultrasound equipment, as well as an "X" which you can click to delete the corresponding ultrasound equipment, in the event you wish to deconfigure it.

In the "Actions" column you will find two buttons associated to each clinic: the first one, "Add ultrasound equipment" will allow you to open a dialogue to enter a new ultrasound equipment for the corresponding clinic by entering the machine's identifier and a description (see Figure 32). This identifier corresponds to the HOSPITAL parameter of your ultrasound equipment. Contact the technician at your centre or clinic to access this configuration or our technicians by sending an email to info@fertoolity.com.

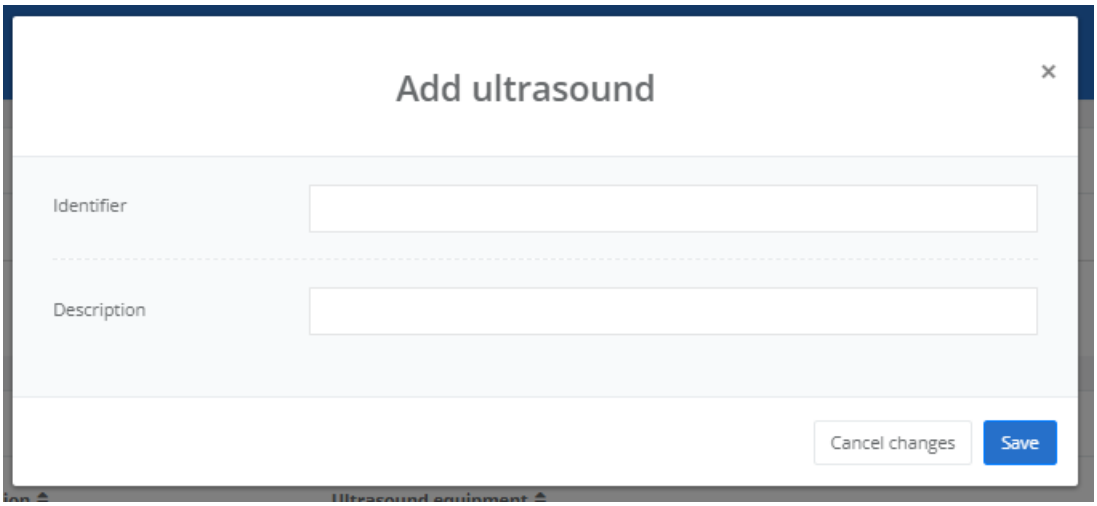

Figure 23. Dialogue to add an ultrasound equipment to a clinic.

The second button you will find in the "Actions" column is the "Delete" button, which will allow you to delete a clinic after confirming the action in a dialogue. Please note that the application will not allow you to delete clinics that have users or patients registered in them for security reasons.

User administration (Administrators):

In the "List of users" table you will find a list of all the users registered at your centre identified by the columns "Name", "Surname" and "E-mail" (Figure 33).

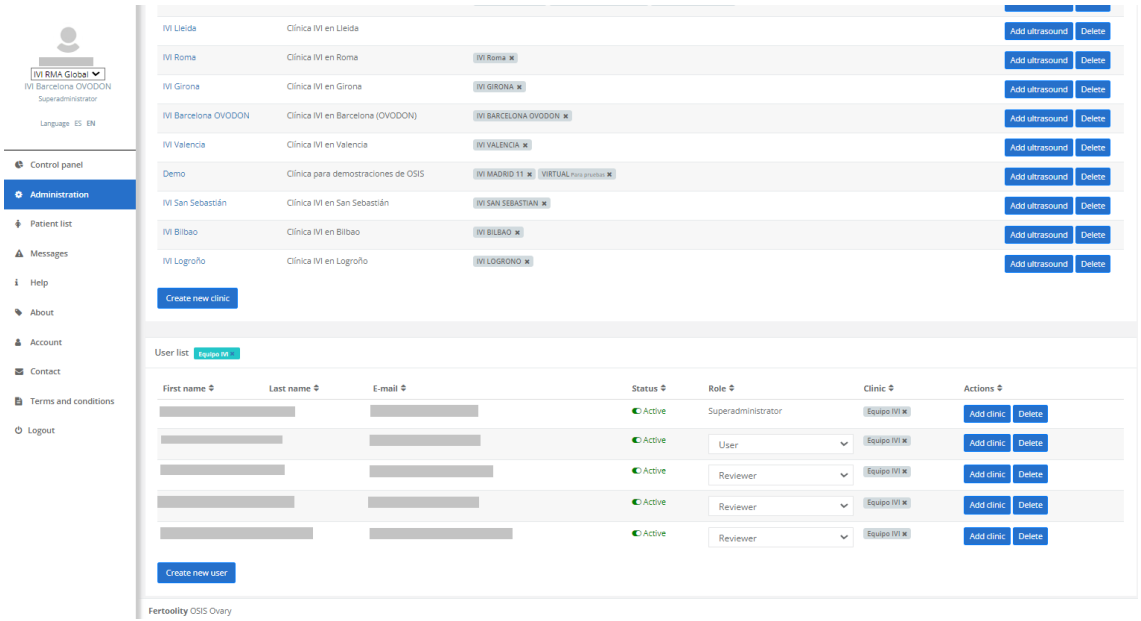

Figure 24. List of users.

In the "Status" column you will see an indicator with two possible positions, "Active" when the user can access the platform or "Blocked" when the user is not allowed to access the platform. By clicking on the status, you can toggle between Active and Blocked. In addition, when a user enters their password incorrectly too many times, the platform blocks their access for security reasons.

In the "Role" column, the user's role or privilege level will appear. As long as the user is not a Super Administrator, the role can be modified by clicking on the drop-down menu and selecting a new value.

The "Clinics" column shows a list of all the clinics to which the user is linked. This link allows you to view patients from that clinic. Each clinic appears as a label with the name of the clinic and an "X" that will allow you to disconnect the user from that clinic. Please note that the application will not allow you to delete a user's last clinic.

Finally, in the "Actions" column you will find two buttons: The "Add clinic" button will allow you to link the user to a new clinic. By clicking on the button, a dialogue will open with a drop-down menu where you can select the clinic (Figure 34). Finally, the "Delete" button will allow you to remove the user from the list.

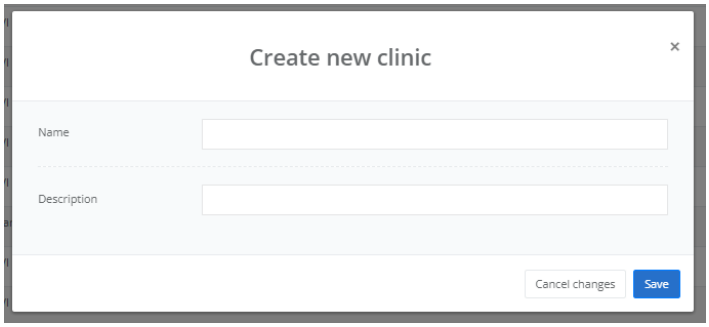

Figure 25. Dialogue to link user to clinic.

If you need to assign Super Administrator privileges to one or more users you can contact the Fertoolity team by sending an email to info@fertoolity.com.

At the bottom of the table, you will find the "Create new user" button which will open a dialogue to create a new user account as shown in Figure 35. In this dialogue you will have to enter a valid e-mail address belonging to the new user to which a confirmation e-mail will be sent for them to set their password. You will also need to enter the user's first name and surname, assign a role (privileges) and select a clinic to which the user will be linked to start with.

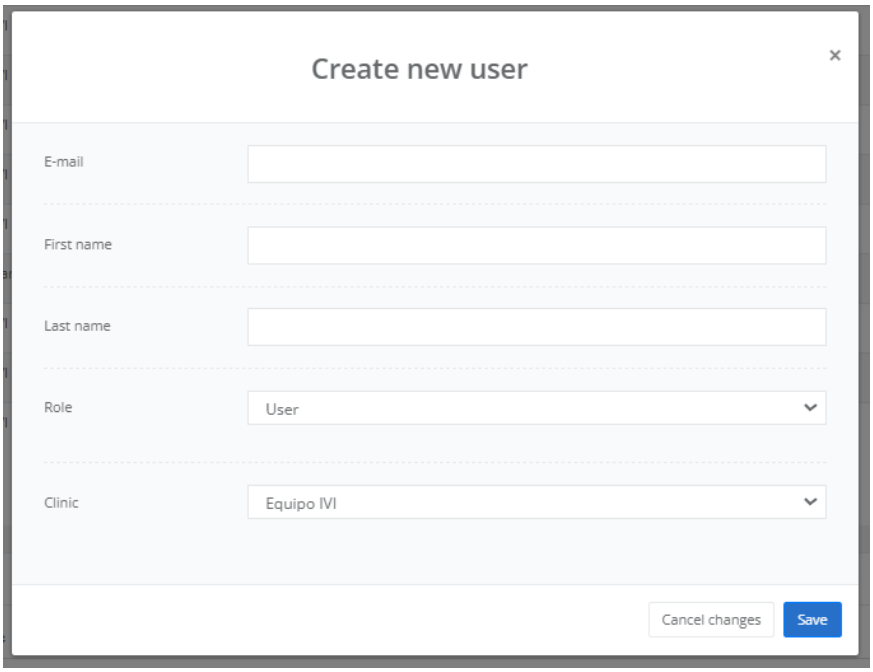

Figure 26. User creation dialogue.

6.12. Log out

To log out, click on the "Log out" button on the side menu (Figure 13). We strongly recommend that you do not leave your workstation without logging out of the active session on the platform.

This option is valid whether you are logged in from your company ERP or directly from the Login screen.

7. POSSIBLE ERRORS

It is possible that an error may occur during the process of exporting or generating results. Whenever it is possible to retrieve the information, the system will display an error message in the "Messages" section. If you submit a case to OSIS Ovary and after some time it does not appear in the list of patients, please contact the technician at your centre or clinic or contact us at info@fertoolity.com to identify the cause of the problem.

OSIS Ovary will log these errors with as much information as possible and display them to the user on the platform in the "Messages" section (Figure 36) available on the side menu (Figure 13).

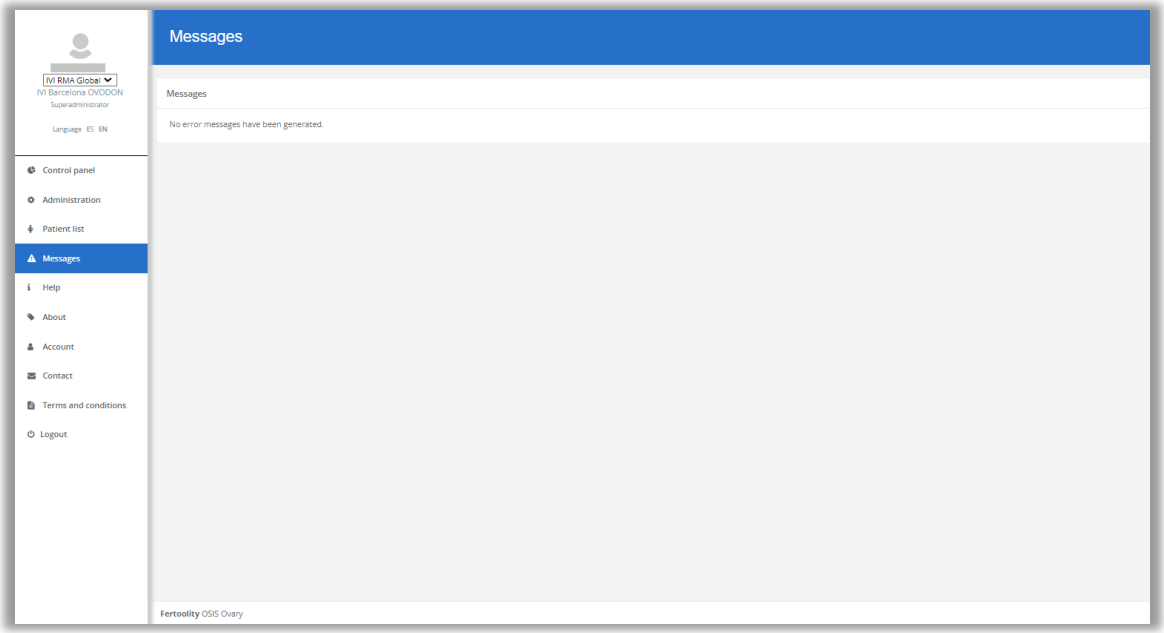

Figure 27. Error message screen.

When OSIS Ovary detects an error, the icon in the "Messages" section will appear in red. Click on the "Messages" option to access and read any errors that may have occurred.

In the "Messages" table, a list of the last unread error messages will be displayed. Once read, when you exit the screen, they will not appear again and the icon in the side menu will change from red to grey.

For each error we observe the following fields:

- Date: Date on which the error was generated.
- MRN: MRN of the patient whose case generated the error (if it was possible to retrieve it).
- File: Name of the file that generated the error.
- Message: Description of the error and a recommendation to fix the problem. The error description appears in red the first time it is read.

After following the recommendations, if the error persists, please contact the Fertoolity team by sending an email to info@fertoolity.com indicating all the details of the error listed in the table.

The following are the possible errors that OSIS Ovary is able to detect, with a brief description of each and the actions to be taken by the user:

1. **File cannot be processed**: OSIS Ovary has received a file in a format that it cannot process. The user will have to re-export the case from the ultrasound machine following the instructions in section 4 of this manual, Workflow.

2. **Incorrect MRN for the file received**: The system reports the reception of a volume with an incorrect MRN (without the eight digits it should contain). In these cases, it is therefore impossible to identify the patient. The way to solve this is to re-edit the volume in the ultrasound machine, and re-enter the correct MRN and export the volume (previously saved) from the ultrasound machine again.
3. **No valid images found (images must be 3D volumes)**: The system reports the incorrect format of processable files for OSIS Ovary. In these cases, the user must export the ultrasound volumes again making sure they are exported as DICOM.
4. **No acquisitions found**: No ultrasound file has arrived in the OSIS Ovary system, but the associated data has arrived. This may be due to two causes: either the Internet connection failed for a few seconds (and therefore the file is incomplete or corrupted and not received) or the option "create patient/examination folders" was not selected prior to export, or the file did arrive at OSIS Ovary, but it is located in the server's bin, and therefore is not indexable, and is not detectable. In these cases, the user should export the ultrasound volumes again as explained in section 4 (Workflow) of this manual, as well as contact the clinic's IT maintenance services to check that the network connections are working properly.
5. **Patient data not included in the export**: Patient data have not arrived with the exported image. In this case, the user must export the ultrasound volumes again as explained above.
6. **Incorrect image name**: The images that have arrived at OSIS Ovary are not named correctly and, therefore, it is not possible to identify which one corresponds to the right ovary and which one to the left. You should contact your centre manager or the Fertoolity team to solve this problem.
7. **An error occurred during image analysis**: Fault in the file handling process and/or automatic analysis. Contact the Fertoolity team for a thorough review.
8. **Ultrasound identifier received is not registered**: OSIS Ovary has not registered the identifier under which your ultrasound machine sends cases to the platform. This may be because your ultrasound machine's configuration has been changed or your centre's manager has not registered your ultrasound machine. Please contact the Fertoolity team so that they can review your case carefully.

It is possible that neither the exported ultrasound volume file nor the accompanying data will reach OSIS Ovary. In this case, OSIS Ovary will obviously not be able to report this fault to the user. If this happens, contact the Fertoolity team to identify the cause of the problem.

8. OSIS OVARY SECURITY MEASURES

8.1. Authentication options

OSIS Ovary supports token-validated registration by email. Emails are checked to prevent re-use, spam or malware emails, and other security issues.

8.2. Secure storage of credentials

OSIS Ovary follows secure credential storage best practices by never storing regular passwords, and only irreversible hashes using SHA3 are stored. Fertoolity employees cannot access credentials even in the event of a data breach.

8.3. Secure credential policies

Each OSIS Ovary user sets their own password according to the following password policies:

- At least 8 characters in length.
- At least one lower case character.
- At least one upper case character.
- At least one number
- At least one special character

All credentials are only stored as a hash and it is not possible to access the full password.

8.4. Security and authentication

Users are authenticated by their username (which is their e-mail address) and password. The password is transferred encrypted from the user's computer to the server making it impossible to recover in case of interception of the transfer.

8.5. Security vulnerabilities

Security issues such as the OWASP (Open Worldwide Application Security Project) top 10 vulnerability issues are covered by our use of security frameworks and measures such as same-origin policies and SQL (Structured Query Language) injection protectors.

8.6. Additional product security features

8.6.1. Access privileges and roles

Access to data within OSIS Ovary is governed by access rights and can be configured to define access privileges. OSIS Ovary has several permission roles: User, Reviewer, Administrator and Super Administrator. Table 1 lists the functionality each role has access to.

Table 1: Access to OSIS Ovary functionalities by user role

User role	Functionalities
User	1. Change language 2. Messages: Access to error messages

	3. Help: Access to these instructions for use and change log 4. About: Access to the product label 5. Account: Accessing account information, language change and password change 6. Contact: Contact link by e-mail. 7. Terms and conditions: Consulting the platform's terms and conditions of use. 8. Logout: Close the open user session. 9. Access to patient report via company ERP 10. Access to make manual corrections to a patient report. 11. Access to select an option in quality control.
Reviewer	1. All accesses of the "User" role 2. List of patients: Consulting and searching for patients on the platform. 3. Possibility to revert a saved quality control on a patient report.
Administrator	1. All accesses of the "User" and "Reviewer" roles. 2. Administration: Access to clinic creation and ultrasound machine management. Access to the creation of user accounts and administration of their access and user role. Access to the contracted licence.
Super administrator	1. All access for the "User", "Reviewer" and "Administrator" roles. 2. Change of centre. 3. Control panel: Access to the current server utilisation percentage and free storage space. Access to a summary of the centres registered on the platform. Access to the UDI code and the possibility of modifying it to generate a new one. Access to the user access log.

8.6.2. User provisioning

Adding and editing users can be carried out manually by the Fertoolity team.

8.6.3. Transmission security

All communications with OSIS Ovary's service provider servers are encrypted using industry standard HTTPS (HyperText Transfer Protocol Secure). This ensures that all traffic between you and OSIS Ovary is secure in transit.

OSIS Ovary is designed to be integrated into Microsoft Azire's cloud services that implement state of the art cybersecurity. OSIS Ovary cloud infrastructure is managed by IVIRMA IT department. Therefore, in addition to the measures described above, the IVI RMA Group implements protection mechanisms so that OSIS Ovary is not affected by security problems. These mechanisms are as follows:

1. Vulnerability analysis
2. 24-h network monitoring
3. Troubleshooting
4. Accident response
5. Desktop support
6. Alert system
7. Protection with Azure Sentinel

In addition to these measures, the health sector good practices recommended by the European Union are complied with:

1. General Data Protection Regulation (GDPR)
2. Network and Information Security Directive (NIS Directive)
3. European Union Cybersecurity Act

A Perimeter Protection System, which protects OSIS Ovary, is also implemented at IVI RMA:

1. Cisco Umbrella
2. Fortinet firewalls
3. Windows Defender
4. Multi-factor authentication.

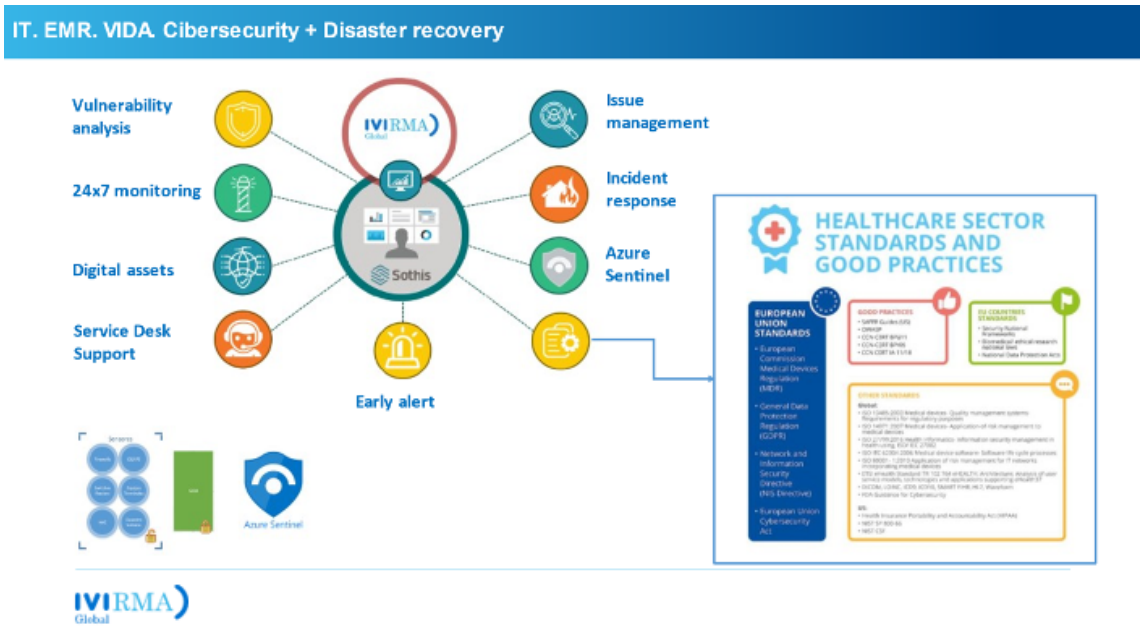

Figure 28. Outline of Cybersecurity measures implemented by IVI RMA Global at OSIS Ovary.

9. PERFORMANCE OSIS OVARY

9.1. Performance

TECHNICAL PERFORMANCE WITH MANUAL SEGMENTATIONS

The database of manually segmented images generated from a total of 100 3D transvaginal ultrasound images was used for the development of the segmentation algorithm. The model was trained following a 10-fold manner (10 rounds of 90 cases for training and 10 for test) to increase the robustness of the results by using all the cases for train and test. Inside the training step, the 90 cases were split in 80 for training and 10 for validation. Based on the analysis of the state-of-the-art, the best fitting architecture to the system is a volumetric convolutional neural network.

To evaluate the degree of agreement between two different follicle segmentation (manual versus automatic) we used the well-known DICE index (Zijdenbos et al., 1992) used in thousands of publications in the field of medical image segmentation.

The result (DICE Index) for automatic segmentation with 80 training cases, 10 validation and 10 test cases was 0.91. Regarding the volumetric results, the correlation obtained in the test was almost total (0.99). The correlation with the number of objects detected was 0.96.

TECHNICAL PERFORMANCE WITH DIGITAL REFERENCE OBJECT (DRO)

We analyzed the automatic segmentation of OSIS Ovary for the seven DROs created with artificial follicles to obtain the measurement error of OSIS Ovary.

The analysis of the seven DROs consisted of 61 artificial follicles compared resulting in a mean follicle measurement error of 4.8% being the minimum error detected of 0.18% and the maximum equal to 10.5%, which is within the limits of acceptance criteria. Acceptance criteria:

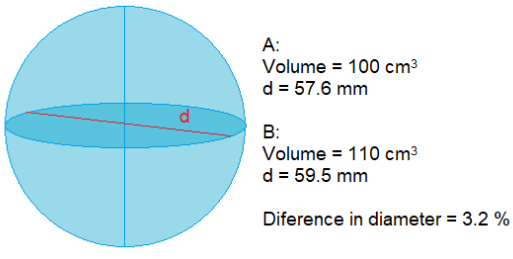

Figure 38. Illustration of the volume variation impact in diameter. In the example, a volume variation of 10% produces a diameter variation of 3.5%.

In current clinical practice, follicle growth and maturation are evaluated by manually measuring follicle mean diameter. Being this a method with high variability variability (2 mm in average [*Baris Ata, Ayse Seyhan, et al. Comparison of automated and manual follicle monitoring in an unrestricted population of 100 women undergoing controlled ovarian stimulation for IVF. Human Reproduction, Vol.26, No.1 pp. 127–133, 2011*] which is far larger than the 10.5%), the tolerance of the follicle tracking process to size variations is considerable. We consider that a 10.5% of volume measurement error has no impact in follicle quantification as the variation of diameter produced by a volume variation of such order of magnitude is depreciable (figure 38).

CLINICAL PERFORMANCE

In this study, we compared the measurement of ovarian follicles by 3D ultrasound imaging obtained by the automatic method OSIS Ovary with Manual measurement performed in the current clinical practice.

Manual follicle measurement stands for Gold Standard in the actual clinical practice. By establishing concordance between manual practice and OSIS Ovary we have demonstrated that OSIS Ovary is a reliable tool suitable for clinical use.

To prove OSIS Ovary to manual method correlation, we have conducted a comparison by calculating Pearson correlation, Intra-class correlation (ICC) and Bland-Altman assessment using results from a 626 images dataset of ovary 3D ultrasound volumes.

Having the 626 volumes passed an exhaustive quality control we can rely con correlation results between OSIS Ovary and manual method outputs. The main values showed a high ICC (> 0.7) for ongoing follicles and all measures. Also, mature follicles show a moderate to high ICC (> 0.6). These two follicle groups are representative of the evolution of follicle in patients, especially the ongoing one which is not affected by early oocyte extraction.

After all the comparison, we can state that, under medical supervision, OSIS Ovary consists of a reliable tool for clinical usage, reducing the inter-operator variability from the manual measurement, providing a more objective measurement of the follicles. These findings need to be correlated with clinical outcomes and be tested with a greater number of operators, in posterior studies, to obtain advanced metrics and to refine the performance in future versions.

The benefit of using OSIS Ovary consists of an increase in measurement accuracy and reproducibility by using a deterministic automated method that produces reliable follicle segmentation. Also, a sensitive reduction in the time required to conduct a patient evaluation via 3D sound is achieved as the measurement task is now detached from the acquisition.

In addition, the software allows to perform fast and reliable quality control. This offers a huge advantage compared to manual methods as it makes possible to build large

datasets to conduct studies aimed to improve the system performance itself, patient satisfaction and COS optimization.
Performance claim is evaluated and quantified with the outcome parameters explained in

- FERTOOLITY-TF001-6.06.02 Technical Performance - OSIS Ovary
- FERTOOLITY-TF001-6.06.03 Clinical Performance - OSIS Ovary
- FERTOOLITY-TF001-3.20 Artificial Intelligence algorithm - OSIS Ovary
- FERTOOLITY-TF001-3.12 Software V&V report - OSIS Ovary

9.2. Quantification

OSIS Ovary calculates the number and size of follicles in each ovary by automatically segmenting them using an artificial intelligence algorithm. This measurement process is called quantification and is carried out as follows:

- **Number of follicles**: number of independent segmented elements in the ovary calculated from the grouping of pixels corresponding to the interior of a follicle that are adjacent to each other.

- **Follicular volume**: For each follicle, the voxels that make up the follicle are counted. This count is multiplied by the volume in cubic centimetres of each voxel, which is given by the image resolution (obtained from the image analysed).

- **d(V) or Relaxed sphere diameter:** The diameter corresponding to a perfect sphere is calculated with the volume measured for each follicle. The following formula is used for this purpose:

$$d(V) = \sqrt[3]{\frac{6 * volume}{\pi}}$$