Clinical Evaluation Report for Universal IVF Medium Version C

Technical Documentation TD033

The content of this report has been evaluated and agreed:

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Revision History		
CER Revision	**Date Issued**	**Change Description**
A	2021.May.20	Initial CER for Universal IVF Medium
B	2023.Jul.05	Regular CER update for Universal IVF Medium
C	2025.May.06	Regular CER update for Universal IVF Medium

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1 List of Abbreviations and Definitions

Abbreviation	Written Out	Explanation
2PN	2 pronuclei	Once fertilized, the oocytes normally contain two haploid pronuclei; one derived from the fertilizing sperm and the other from the oocyte
ART	Assisted Reproductive Technology	Part of reproductive medicine which deals with means of conception other than normal coitus
ASRM	American Society for Reproductive Medicine	A multidisciplinary organization dedicated to the advancement of the science and practice of reproductive medicine. The Society accomplishes its mission through the pursuit of excellence in education and research and through advocacy on behalf of patients, physicians, and affiliated health care providers.
CAPA	Corrective and Preventive Actions	Corrective action(s) taken to eliminate the cause(s) of the identified nonconformity by identifying and removing the root cause(s) of the quality issue in order to prevent recurrence. Preventive action(s) taken to identify and eliminate the probable cause of a potential nonconformity. These actions are taken to prevent occurrence of a potential nonconformity prior to an actual incident.
CEP	Clinical Evaluation Plan	A plan describing the scope and methodology of the clinical evaluation
CER	Clinical Evaluation Report	A report with analysis of all available performance and safety data for product documentation according to General Safety and Performance Requirements within the EU.
COS	Controlled ovarian stimulation	Pharmacological treatment with the intention of inducing the development of ovarian follicles
EBSS	Earls Balanced Salts Solution	An isotonic solution of salts used as the basis for many ART culture media.
EDTA	Ethylenediamine-tetra acetic acid	Chelating agent
EMDN	European Medical Device Nomenclature code	The nomenclature of use by manufacturers when registering their medical devices in the EUDAMED database.
ESHRE	European Society of Human Reproduction and Embryology	A society to improve clinical practice through organizing teaching and training activities, developing- and maintaining data registries, and providing guidance to improve safety and quality assurance in clinical and laboratory procedures
FDA	Food and Drug Administration	A federal agency of the Department of Health and Human Services in the United States, responsible for regulatory approval of drugs, biological products, medical devices, animal drugs and food additives on the US market.
FSCA	Field safety corrective action	An action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market

Abbreviation	Written Out	Explanation
GMDN	Global Medical Device Nomenclature	A system of internationally agreed generic descriptors used to identify all medical device products at a global level, as identified in the Global Harmonization Task Force (GHTF).
GMN	Global Model Number	The Basic UDI-DI is a new identifier that has been introduced by the MDR (EU) 2017/745. The Global Model Number (GMN) is a new key developed by GS1 to support the implementation of the Basic UDI-DI.
GSPR	General Safety and Performance Requirements	Requirements for safety and performance a device must meet to be CE marked; Annex I of the EU MDR regulation
HAS	Human Albumin Solution	A solution derived from human blood constituents. Main component being human serum albumin (HSA), which is a major constituent of the oviductal fluid. Acts as stabilizer by buffering pH and regulating osmolality. Functions as carrier of other substances, scavenger, surfactant, and nutrient
HTF	Human Tubal Fluid	An IVF formula which mimics the *in vivo* environment to which the oocyte/embryo is exposed. The formulation was based on the known chemical composition of the fluids in human fallopian tubes as known at the time of development (1985). This medium is based on a simple balanced salt solution without amino acids.
ICSI	Intracytoplasmic sperm injection	Injection of a single spermatozoon into the cytoplasm of the oocyte
IFU	Instructions for use	Guidance on how to use the product, which is included in the package insert
IUI	Intrauterine insemination	A procedure in which laboratory processed sperm are placed in the uterus to attempt a pregnancy
IVF	*In vitro* fertilization	Fertilization of oocytes in a dish in a laboratory
KPI	Key performance indicator	An objective measurable value for systematic monitoring and evaluating the clinical laboratory contribution to patient care
MAUDE	Manufacturer and User Facility Device Experience Database	FDA provided database of reports of adverse events involving medical devices
MII	Metaphase II	The developmental stage of mature oocytes with successful completion of meiosis I
MDD	Medical Devices Directive	European Union Medical Device Directive 93/42/EEC
MDR	Medical Device Regulation	The Medical Device Regulation (MDR) (EU) 2017/745 of the European Parliament and of the council, amending Directive 200183/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, repealing Council Directive 93/42/EEC
MEDDEV	European Medical Device Vigilance System	The present MEDDEV is part of a set of guidelines relating to questions of application of EU Directives on medical devices. This MEDDEV contains guidance for the application of the classification

Abbreviation	Written Out	Explanation
		rules for medical devices as set out in Annex IX of Directive 93/42/EEC1, as amended.
MHRA	Medicines & Healthcare products Regulatory Agency	The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK.
NPESU	National Perinatal Epidemiology and Statistics Unit	NPESU provides information and statistics in reproductive and perinatal health in Australia and New Zealand.
PCOS	Polycystic ovarian syndrome	A condition requiring the presence of two of three criteria: 1) oligo-ovulation or anovulation, 2) hyperandrogenism, 3) polycystic ovaries (more than 24 total antral follicles 2-9mm in size across both ovaries)
PICO	Population Intervention Comparator Outcomes	A model used in evidence-based practice to frame and answer a clinical or health care related question
PGT	Preimplantation Genetic Testing	A test performed to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA typing or for determining genetic abnormalities. These include: PGT-A for aneuploidy; PGT-M for monogenic/single gene defects; and PGT-SR for chromosomal structural rearrangements. *NB: The nomenclature was introduced by ICMART (the International Committee for Monitoring Assisted Reproductive Technologies) in 2017. Previously referred to as PGD/PGS (Preimplantation Genetic Diagnosis/Screening).*
PMCF	Post Market Clinical Follow-up	A continuous process should be in place to update the clinical evaluation of the device and shall be addressed in the PMS plan. When conducting PMCF, clinical data from the use of the device in or on humans shall proactively be collected and evaluated for CE-marked devices that are placed on the market within their intended purpose. This is done to confirm the safety and performance of the device throughout its expected lifetime, ensuring the continued acceptability of identified risks, detecting emerging risks on basis of factual evidence, and identifying possible systematic misuse or off-label use of the device with a view to verify that the intended purpose is correct. The clinical data can be collected as clinical experience data or through a clinical study or trial.
PMCF study	Post Market Clinical Follow-up study	A follow-up study conducted following the CE marking of a medical device, to assess specific issues related to the safety and performance of the product
PMS	Post Market Surveillance	The continuous safety monitoring of a medical device after it has been released on the market. Incl. information from customer complaints, incident reporting, field safety corrective actions, customer feedback and field visit reports as well as scientific publications.
ROS	Reactive Oxygen Species	Derivatives of oxygen which are more reactive than molecular oxygen, and if in excess, can damage DNA, protein, and lipids of cells
SSCP	Summary of safety and clinical performance	An executive summary of the technical documentation for a CE-marked medical device, to be made public available via the European database on medical devices (Eudamed).

Abbreviation	Written Out	Explanation
SSR®	Synthetic Serum Replacement	A synthetic substitute for human serum in the media
TESA/TESE	Testicular sperm aspiration/ extraction	A surgical procedure involving one or more testicular biopsies or needle aspirations to obtain sperm for use in IVF and/or ICSI.
WHO	World Health Organization	A specialized agency of the United Nations that is concerned with international public health

Definitions:

Benchmark device: Alternative treatment option (from own company product or competitor product) used as standard for the same procedure (state of the art). For Universal IVF Medium, this is CE-marked commercially available Human Tubal Fluid (HTF) media.

Cleavage rate: Percent of zygotes developing into ≥2-cell embryos on day 2 of culture. The cleavage stage embryos are beginning with the 2-cell stage and up to, but not including, the morula stage.

Clinical experience data: Routine clinical data provided by a clinic as summary data without reference to identifiable subject data, being used either for PMCF or for marketing purposes. This type of data is only collected for medical devices with regulatory market approval being used routinely in the healthcare environment.

Clinical performance: The ability of a medical device to achieve its intended purpose as claimed by the manufacturer; behavior of a medical device or response of the subject(s) to that medical device in relation to its intended use[1], when correctly applied to appropriate subject(s).

Clinical pregnancy rate: Percent of women with an embryo transfer who have a clinical pregnancy detected around gestational week 6 - 8. The diagnosis is based on ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intra-uterine pregnancy, it includes a clinically documented ectopic pregnancy.

Clinical safety: The absence of unacceptable clinical risks, when using the device according to the manufacturer's instructions for use.

Embryo: The biological organism resulting from the development of the zygote, until eight completed weeks after fertilization, equivalent to 10 weeks of gestational age.

Embryo transfer: Placement into the uterus of one or more embryos at any embryonic stage from day 1 to day 7 after IVF or ICSI.

Fertilization rate: Percent of oocytes exposed to sperm either by injection (ICSI) or by standard *in vitro* fertilization (IVF) that develop into pronuclei stage. Fertilization is a sequence of biological processes initiated by entry of a spermatozoon into a mature oocyte followed by formation of the pronuclei (2PN).

Gamete: The reproductive haploid cells whose union is necessary in sexual reproduction to initiate the development of a new individual. Also referred to as oocyte or spermatozoon.

[1] As per MDCG 2020-6 'intended use' should be considered to have the same meaning as 'intended purpose'

Implantation rate: Percent of transferred embryos that result in a gestational sac (with or without fetal heartbeat). The diagnosis is based on ultrasonographic visualization, usually around gestational week 6 – 8. An implantation is defined by the attachment and subsequent penetration by a zona-free blastocyst into the endometrium, but when it relates to an ectopic pregnancy, into tissue outside the uterine cavity.

***In vitro*:** In a test tube, culture dish, or other controlled experimental environment outside a living organism.

Live birth delivery rate: Percent of women with an embryo transfer who end up with delivery of at least one live birth. A live birth is defined as the complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heartbeat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A birth weight of 500 grams or more can be used if gestational age is unknown. Live births refer to the individual newborn; for example, a twin delivery represents two live births.

Miscarriage rate: Percent of clinical pregnancies ending in a spontaneous loss before 22 completed weeks of gestational age. A pregnancy loss is where the implanted embryo(s) or fetus(es) are nonviable and expelled from the uterus, with fetal loss defined as early fetal death between 10 and 22 weeks of gestational age. Still birth is when the fetal death takes place after 28 weeks of gestational age.

Sibling oocytes: These are oocytes collected from the same woman in the same ART treatment, and therefore originating from the same cohort of oocytes.

State of the Art[2]**:** Current technology and practice accepted as good and with high level of safety in the medical field concerned. State of the Art is defined by applicable standards and guidance documents, ESHRE and NPESU reports, review and meta-analysis of publications and literature relating to clinical performance and safety of the same type of devices.

Zygote: A single cell (also referred to as 2PN) resulting from fertilization of a mature oocyte by a spermatozoon and before completion of the first mitotic division.

[2] State of the Art embodies what is currently and generally accepted as good practice in technology and medicine. This does not necessarily imply the most technologically advanced solution and is sometimes referred to as the “generally acknowledged state of the art” (MDCG 2020-6)

2 Executive Summary

This Clinical Evaluation Report (CER) is written in conformance with Article 61 and Part A of Annex XIV of the Europe's Medical Device Regulation (MDR) (EU) 2017/745 and MEDDEV 2.7/1 revision 4, providing a documented critical evaluation of clinical data as it relates to the Universal IVF Medium product family, for the purpose of demonstrating conformity of this device with Annex XIV and Annex XV of MDR. The clinical evaluation has been performed in accordance with the manufacturer's Clinical Evaluation Procedure, BSR-QAR-021.

It is a scheduled regulatory update that constitutes a routine review of content to identify any new clinical evidence, and review associated risks related to Universal IVF Medium (also known as "subject devices"). There have been no new risks identified for Universal IVF Medium through Post Market Surveillance (PMS) activities or risk management, since the previous version of the CER (CE033R Version B). According to the outlined equivalence definition in MDR Annex XIV Part A (3) and MDCG 2020-5, there is no claim of equivalence.

Universal IVF Medium (1031 [with phenol red], 1030 [without phenol red]) is classified as a Class III non-invasive medical device according to EU MDR 2017/745 Rule 2, Rule 3 second indent, Rule 5 (when used for embryo transfer), Rule 14, and Rule 18. Rule 2 as the device is designed for storage of human gametes in ART procedures. Rule 3 as the device is intended to be used *in vitro* in direct contact with human cells, tissues or organs taken from the human body or used *in vitro* with human embryos before their implantation or administration into the body. Rule 5 as the device may be introduced back into the body during embryo transfer. Rules 14 and 18 as the Universal IVF Medium contains ancillary medicinal substances (Human Albumin Solution (HAS), gentamicin, and Human Insulin Recombinant), which if used separately, have pharmaceutical indications independent of the Universal IVF Medium and the device also utilizes HAS, which is derived from human blood. Furthermore, Rule 18 also applies due to the presence of gentamicin, which has risks related to fish peptone used during production of the gentamicin.

Universal IVF Medium is an *in vitro* fertilization culture medium applied in Assisted Reproductive Technology (ART) in treatment of infertility, intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer. Universal IVF Medium is well-established technology (WET), containing well-known components present in similar ART media with the same intended purpose, and has been used by ART clinics in Europe since 1988. The product was CE-marked in 2009, after a first step towards regulation of ART media as medical devices in Europe was published May 2008; US FDA 510(k) cleared in 2000.

Objectives of this CER are to:

- Summarize the assessment and evaluation of clinical data pertaining to the subject device to demonstrate its clinical safety and performance
- Verify performance of the device in accordance with the claimed intended purpose
- Evaluate the clinical benefits, and specifically the acceptability of the benefit/risk ratio, associated with the intended purpose of the finished device

- Provide a conclusion of the clinical safety of the device and supporting requirements for not conducting or conducting proactive Post Market Clinical Follow-up (PMCF) activities managed through PMS.

The clinical evaluation is based on documentation related to clinical performance and safety of Universal IVF Medium. All data are benchmarked against state of the art (as defined in section 1), as well as available data on benchmark or similar devices, especially data from comparison studies with head-to-head comparison of Universal IVF Medium versus benchmark devices (CE-marked commercially available Human Tubal Fluid (HTF) media with similar composition and intended purpose). The evaluation of safety includes customer complaints and product recalls related to the actual device, as well as any adverse event reports, serious incidents, and product recalls for the actual device, benchmark and similar devices published in public safety databases. Clinical data covers the period of June 2011 through December 2024, including total 27 data reports (25 publications and two (2) data-sets on file at CooperSurgical) on the actual device.

Because Universal IVF Medium and all other ART media are considered WET[3], the focus of this CER is to ensure continued state of the art clinical performance and safety of the device, without any critical trends or reported issues concerning subject device, benchmark, or similar devices. Any problems or concerns with the device or device type are expected to be published in peer reviewed journals. However, for a thorough evaluation, this CER includes both posters, abstracts and full-text publications. Clinical experience with ART media is generally considered of low scientific value, difficult to get accepted for publications in peer-reviewed journals. Consequently, most experience with ART media is shared among ART professionals as posters and abstracts presented at congresses/conferences. Although posters and abstracts often include limited information on patient population, ART results are affected by a number of confounding factors other than the ART medium, which can be even more important than the patient population. Most of these are unmeasurable or not described in any publications (e.g. staff skills and quality/calibration of equipment used). Moreover, study design and sample size is considered more important than format of the publication (poster/abstract or full-text) with cohort studies including prospective randomized sibling oocytes/2PN zygotes (derived from the same patient) and split sperm samples (the same ejaculate split into two or more parts) being the most optimal study design for this type of device, when evaluating performance and safety based on embryology parameters in comparison to benchmark or similar devices. Therefore, both peer reviewed publications as well as posters and abstracts are included.

The most recent literature search presented in Appendix 2 (covering the period 2023.Jan.01 – 2024.Dec.31) identified three (3) publications relating to the actual device, supported with four (4) publications with state of the art information. No (0) publications relating to benchmark and/or similar devices were identified. There were no (0) data-sets on file on the actual device from

[3] characterized by stable designs with little evolution, claims according to state of the art (incl. clinical performance and safety), and no special requirements for protocol compared to state of the art.

PMCF activities performed since last update of the CER, and complaints and vigilance reports covering the PMS period 2023.Jan.01 – 2024.Dec.31.

This document will be revised during a defined period to include PMS data, additional clinical evidence, and any changes to the benefit-risk profile. In addition, clinical investigations, and PMCF studies, according to Annex XIV of EU MDR and MEDDEV 2.12/2, have also been considered and discussed in the analysis sections contained in this report.

Clinical Safety and Performance:

Universal IVF Medium belongs to a first generation of ART media, characterized as simple balanced salts solutions with energy sources (carbohydrates), bicarbonate buffer, antibiotics, and Human Albumin Solution (HAS), and therefore without amino acids and vitamins.

Clinical safety and performance of the Universal IVF Medium product family has been documented through clinical use for >37 years.

The only change that has been made to Universal IVF Medium product family, is replacement of streptomycin and penicillin G sodium with gentamicin (10 µg/ml) in connection to a change performed for all devices with antibiotics in the ORIGIO brand, back in 2009. Gentamicin is a broad-spectrum antibiotic with activity against many gram-positive as well as most gram-negative bacteria, and superior to penicillin/streptomycin in aspects of eliminating bacterial strains. Moreover, gentamicin has been used for many years as standard antibiotic in commercially available media for ART procedures. When ORIGIO a/s (a.k.a. MediCult a/s) made the general change to gentamicin back in 2009, this was already the preferred antibiotic used by other media manufacturers. There are no reports of any effects of gentamicin on embryo quality, live birth rates or health of babies born, nor are there any reports of allergic reactions to gentamicin when used in media in contact with the human body. In conclusion, the supplement of 10 µg/ml Gentamicin sulphate to Universal IVF Medium is safe and without any negative impact on clinical performance.

Apart from the change of antibiotics, there have been no changes made to the design, material, or indications for use of the subject devices.

Clinical results after ART treatments vary depending on numbers of confounding factors, including but not limited to intrinsic quality of the gametes (e.g. female/male -age, -health, -fertility, environmental exposures), and ex vivo manipulations (handling, skills, procedures, equipment). The risk of introducing confounding factors, possibly affecting the results, increases with time (from obtaining the gametes to birth of a healthy child). This means that data recorded just after the intended purpose of the device in question best reflect possible effects of the device with a minimum of contributing confounding factors. Therefore, when evaluating performance of devices involved in ART treatments, this must always be considered. Evaluation of clinical performance of a culture medium intended for fertilization and culture until the 2-8 cell stage is primary based on fertilization, cleavage and implantation rates. Oocytes can be fertilized by two different procedures: IVF or ICSI. During the IVF process spermatozoa are left to fertilize the oocyte in a dish/well, while in ICSI one spermatozoon is injected into the oocyte by the aid of a micromanipulator and therefore more dependent on technician skills. Therefore, IVF fertilization

rates are preferable when assessing clinical performance of a fertilization medium. Data published or available after use of Universal IVF Medium show fertilization rates of 61-77% for IVF, 41.7-89.6% for ICSI, and 59.3 -100% for IVF/ICSI. Cleavage rates were 76.6-98.2%, blastocyst rates were 50-66.6%, implantation rates were 10-100%, clinical pregnancy rates were 0-68.6%, live birth rates were 16.6-100%, and miscarriage rates were 0-53%. There were no data published after standard IVF/ICSI treatment using benchmark or similar devices.

Based on this, there are no trends of any negative effects of Universal IVF Medium on clinical outcome, and the device is performing according to state of the art, as well as benchmark and similar devices.

There are no reports (reviews or meta-analysis) of any safety issues related to the subject device, benchmark, or similar devices. Five (5) publications reported data on safety parameters after use of the actual device. No (0) publications using benchmark devices reported data on safety parameters.

Vigilance Data:

During the post-market surveillance reporting period of 2023.Jan.01 – 2024.Dec.31, there were no (0) reports of adverse events, product recalls or other product related problems identified through public safety databases (UK, USA, and Australia). Over the period between (January 01, 2023, to December 31, 2024), two (2) product complaints were collected internally, and evaluated per the Adverse Event Reporting (AER) Procedure, BSR-QAR-043. No Adverse Event Report (AER) or Medical Device Report (MDR) was identified. No new risks were identified based on the clinical evaluation of Universal IVF Medium. The complaint analysis did not reveal any trends of clinical performance or safety related issues through the product-related complaints, with an overall complaint ratio of 0.01 – 1.79%. (19,967 units sold). Data supports a well-recognized safety profile related to the type of device.

In summary, no new risks were identified based on this clinical evaluation, and no trends of clinical performance or safety issues were identified.

Conclusion:

This CER supports the continued CE-marking of the devices in the Universal IVF Medium product family (listed in Section 4.2) The clinical evaluation demonstrates compliance with the General Safety and Performance Requirements (GSPRs) 1, 2, 6 and 8 of the Medical Device Regulation (EU) 2017/745 Annex I and, with clinical evidence documenting state-of-the-art clinical safety and performance, as well as a positive benefit-risk profile for Universal IVF Medium product family, when used as intended by professionals within ART. Long-term safety and performance has been demonstrated through clinical use for >37 years. However, after request from the British Standards Institution (BSI) to perform proactive PMCF for all Class III devices, proactive PMCF is performed on a continuous basis. As this device is part of a product family where not all data have been collected at the time of this report, this CER is including proactive PMCF according to PMCF033P, version B, with inclusion of all collected data at the

time of the CER which will also be included in the final PMCF report (PMCF033R, version B) according to the schedule (PMCF033P, version B).

3 Reference Documents

Document Number	Document Title	Version
BSR-ENG-007	Procedure for Risk Management (RM)	See MasterControl
BSR-QAR-042	Post Market Surveillance (PMS) Procedure	See MasterControl
BSR-QAR-021	Clinical Evaluation Procedure	See MasterControl
TD033	Technical Documentation File for Universal IVF Medium	See MasterControl
DIOVV033	Design Input/Output Verification/Validation for Universal IVF Medium	See MasterControl
Rep1.02.07.43	Biological evaluation of Universal IVF Medium (1030/1031)	See MasterControl
CE033P	Clinical Evaluation Plan for Universal IVF Medium	See MasterControl
GSPR033	General Safety and Performance Requirements Matrix for Universal IVF Medium	See MasterControl
RMF0108-RMR	Risk Management Report for Universal IVF Medium	See MasterControl
PMS033P[4]	Post Market Surveillance Plan for Universal IVF Medium	See MasterControl
PSUR033	Periodic Safety Update Report for Universal IVF Medium	See MasterControl
CLP4274554	Instructions for Use for Universal IVF Medium	See MasterControl
See attachment in the MasterControl infocard TD033	Justification for implemented changes during final IFU remediation for MDR	See MasterControl

[4] Please refer to section 7.1.2 in CE033R ver. C, which indicates the PSUR/PMSP version.

4 Scope and Objective

4.1 Clinical Evaluation Plan

A Clinical Evaluation Plan (CEP) outlining the requirements associated with scoping, responsibilities, data appraisal methods, and data evaluation for the Universal IVF Medium product family is presented in the CEP listed in section 3.

This is a scheduled regulatory update of the Clinical Evaluation Report (CER), as no new risks have been identified for Universal IVF Medium through Post Market Surveillance (PMS) or risk management, since the previous version of the CER (CE033R Version B).

Pursuant to equivalence requirements in MDR Annex XIV Part A (3) and MDCG 2020-5, there are no claims of equivalence.

Universal IVF Medium (1031 [with phenol red], 1030 [without phenol red]) is classified as a Class III non-invasive medical device according to EU MDR 2017/745 Rule 2, Rule 3 second indent, Rule 5 (when used for embryo transfer), Rule 14, and Rule 18. Rule 2 as the device is designed for storage of human gametes in ART procedures. Rule 3 as the device is intended to be used *in vitro* in direct contact with human cells, tissues or organs taken from the human body or used *in vitro* with human embryos before their implantation or administration into the body. Rule 5 as the device may be introduced back into the body during embryo transfer. Rules 14 and 18 as the Universal IVF Medium contains ancillary medicinal substances (Human Albumin Solution (HAS), gentamicin, and Human Insulin Recombinant), which if used separately, have pharmaceutical indications independent of the Universal IVF Medium and the device also utilizes HAS, which is derived from human blood. Furthermore, Rule 18 also applies due to the presence of gentamicin, which has risks related to fish peptone used during production of the gentamicin. The device is based on existing technology and only contains well-known components present in similar Assisted Reproductive Technology (ART) media with the same intended purpose. Universal IVF Medium has been available and used by ART clinics in Europe since 1988, when it was first introduced to the market.

The scope of the clinical evaluation is to ensure sufficient clinical evidence to confirm compliance with General Safety and Performance Requirements (GSPRs) 1, 2, 6 and 8 of the Medical Device Regulation (EU) 2017/745 Annex I. This includes documentation of state-of-the-art clinical performance and a positive benefit-risk profile for the Universal IVF Medium, including the oocyte, resultant embryos and babies, as well as the mother/patient and user handling the devices according to the instructions for use (IFU). This is done by evaluating clinical data on the devices under evaluation, as well as clinical data and market experience on benchmark devices.

4.2 Model or Version of Device

General Information					
Device name/Product family name	Universal IVF Medium / Universal IVF Medium				
Proprietary trade name(s)	Universal IVF Medium				
Catalogue number	1031 (with phenol red), 1030 (without phenol red)				
GMDN/EMDN Code	44046/ U08020502				
GMDN/EMDN Name	*In vitro* fertilization culture medium/ Materials/solutions for preparation/handling for assisted reproduction				
Basic UDI-DI number and GMN Number	0888893TD033ZJ				
Manufactured by	CooperMedical, SRL Parque Industrial Zona Franca Coyol, Edificio Nº B49, 51 Ave 0, La Garita, Alajuela Province, Coyol, Costa Rica				
Legal manufacturer and Single Registration Number (SRN)	CooperSurgical, Inc. Corporate Drive Campus Trumbull, CT, 06611 USA	US-MF-000002607			
EU Authorized Representative and Single Registration Number (SRN)	CooperSurgical Distribution BV Celsiusweg 35 5928 PR Venlo, The Netherlands	NL-AR-0000000059			
Notified Body (NB) Information and Number	BSI Group The Netherlands B.V. Say Building, John M. Keynesplein 9, 1066 EP, Amsterdam The Netherlands	2797			
Governing Regulation	European Union Medical Device Regulation (EU) 2017/745				
Medical Device Classification	**EU Class**	**I / Is**	**IIa**	**IIb**	**III**
					X
	FDA Class	**I**	**II**		**III**
			X		

General Information			
First launch	Universal IVF Medium has been available, and used for fertilization of oocytes and culture through to cleavage stage, and embryo transfer, since 1988, when it was first introduced to the market.		
Regulatory approvals	**Authority**	**First Approved**	**Cert. No**
	CE-Mark	12.Jun.2009	DGM 633 CE 733560
	FDA	20.Jul.2000	K991279

The following devices are covered by this clinical evaluation.

Table 1: Product order codes

Product Name	Part Number	Product Description
Universal IVF Medium, with phenol red	10311010	Package of 10X10 ml bottles of Universal IVF Medium, with phenol red
Universal IVF Medium, with phenol red	10310060	Package of 1x60 ml bottle of Universal IVF Medium, with phenol red
Universal IVF Medium, with phenol red	10315060	Package of 5x60 ml bottles of Universal IVF Medium, with phenol red
Universal IVF Medium, without phenol red	10301010	Package of 10X10 ml bottles of Universal IVF Medium, without phenol red
Universal IVF Medium, without phenol red	10300060	Package of 1x60 ml bottle of Universal IVF Medium, without phenol red
Universal IVF Medium, without phenol red	10305060	Package of 5x60 ml bottles of Universal IVF Medium, without phenol red

4.3 Device Description

Intended Purpose of the Device
Universal IVF Medium is intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer.
Device description

The product is provided in standard design (plastic bottles with a screw cap, containing a non-viscous clear or red colored liquid depending on content of Phenol Red), in standard packaging (cardboard boxes), with instructions for use (IFU) provided in clear and plain language in the package insert. Further, the label on the product is marked with symbols stating to consult the IFU.

The device incorporates human albumin solution (HAS), gentamicin sulphate (antibiotic), and recombinant human insulin, all considered as ancillary medicinal substances.

HAS is derived from human blood constituents.

Gentamicin sulphate is produced via fermentation using, among others, fish peptone. Fish peptone is the only animal-derived material used in the production of gentamicin sulphate.

Description of Accessories

Universal IVF Medium is not supplied with any accessories. Universal IVF Medium is used with typical materials and equipment found in an ART clinical laboratory setting.

Description of Connected Devices

Universal IVF Medium is not to be connected to any other device or dependent on the operation of another device.

Indication(s)

Universal IVF Medium is intended for patients undergoing Assisted Reproductive Technology (ART) treatment, whether the cause of infertility is male or female.

Patients are all persons/couples who have been assessed suitable by a gynecologist to undergo IVF.

Disease/Condition To Be Treated

Universal IVF Medium is used in the treatment of infertility (male and/or female), a disease defined by the World Health Organization (WHO) as a failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse (Zegers-Hochschild et al. 2017).

One in six couples experience some form of infertility during their reproductive lifetime, due to female factors, male factors, problems in both partners, as well as cases where no cause is found (unexplained/idiopathic infertility). Increasing age in the female partner is one of the most common explanations for infertility, but age of the male partner, as well as lifestyle factors such as smoking, bodyweight, and stress also influence ART success rates (Eisenberg and Meldrum 2017; ESHRE 2018). In women, infertility is commonly caused by ovulatory dysfunction, tubal obstructions and/or endometriosis. Whereas in men, infertility is a result of abnormalities in sperm production and function, or sperm duct blockages (Nardelli et al. 2014). When lifestyle changes alone are not sufficient, treatment mainly falls into three categories (NCC-WCH 2013):

- Medical treatment to restore fertility (e.g. drugs for ovulation induction)
- Surgical treatment to restore fertility (e.g. laparoscopy for ablation of endometriosis)
- ART treatment, including all kinds of conception other than normal coitus, involving a large variety of techniques for in vitro handling of gametes and embryos (incl. intrauterine insemination (IUI)/artificial insemination, in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI).

Intended User

The product should only be used by professionals trained in ART procedures, such as embryologists, gynecologists, and laboratory technicians.

Patient Population

Universal IVF Medium can be used for all persons/couples assessed suitable for ART treatment by a gynecologist.

Type of Contact	
Contact with oocytes/zygotes and resultant embryos in a prolonged* period during culture (>24h), corresponding to short term contact (>60 minutes) according to the EU MDR. *NOTE : According to FDA Biocompatibility guidance, 2020, and ISO 10993-1:2020	X
Contact with mother/patient in connection to the procedure when used for embryo transfer is limited* (<24h), corresponding to transient contact (<60 minutes) according to the EU MDR. *NOTE : According to FDA Biocompatibility guidance, 2020, and ISO 10993-1:2020	X

Contraindications

There are no contraindications.

Warning and Cautions

Precautions and warnings

1. Do not use the product if:

- Product packaging appears damaged or if the seal is broken.
- Expiry date has been exceeded.
- The product becomes discolored, cloudy, turbid, or shows any evidence of microbial contamination.

2. This product contains:

- Human serum albumin (HSA) 5 mg/mL.
- Recombinant human insulin
- Gentamicin sulphate 10 µg/mL.

Note: This product contains human serum albumin (HSA), a derivative of human blood.

Caution: All blood products should be treated as potentially infectious. **The source material used to manufacture this product is fulfilling all regulatory requirements (Ph.Eur., USP), including screening of plasma donors for prior exposure to certain viruses, testing for presence of certain current virus infections (e.g., hepatitis, HIV, and parvovirus), and inactivating certain viruses by pasteurization. No known test methods can offer assurances that products derived from human blood will not transmit infectious agents. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is considered extremely remote, with no cases of transmission of viral diseases or CJD ever identified for human serum albumin.**

CautionThis product contains Gentamicin and should not be used on patients that have known allergy to Gentamicin or similar antibiotics.

Note: To avoid contamination CooperSurgical strongly recommends that product/bottle should be opened and used only with aseptic technique.

Note: Please note the need for traceability of this product. In addition, national legal requirements for this field may exist in your country.

Note: Only to be used in combination with other products intended for the same purpose.

Note: Dispose of the product in accordance with local regulations for disposal of medical devices.

Note: Universal IVF Medium is a medium that supports viability of oocyte together with sperm function necessary for successful fertilization in vitro. In addition, it supports embryo development through the cleavage stages.

Clinical benefit is derived from the provision of a suitable milieu that supports fertilization and maintains viability of oocytes, zygotes, and embryos as shown by rates of normal fertilization, embryo development and clinical pregnancy.

SSCP: https://webgate.ec.europa.eu/eudamed/landing-page#/

Until EUDAMED is fully implemented, the Summary of Safety and Clinical Performance (SSCP) is available upon request by contacting CooperSurgical customer service or the local distributor.

Note: Any serious incident that has occurred in relation to the product should be reported to the manufacturer and the Competent Authority of the member state in which the user is established.

4.4 Principle of Operation

The intended purpose is achieved by the Universal IVF Medium formulation providing a liquid environment with physiological osmolality and pH, and energy components supporting biological function of gametes and embryos during *in vitro* fertilization, *in vitro* culture and embryo transfer.

ART media are generally categorized into simple balanced salt solutions with energy sources, or more complex mixtures of inorganic salts, energy sources, amino acids, vitamins, and other substances. Common for all ART media used for fertilization of oocytes and culture through to cleavage stage, as well as for embryo transfer, is the inclusion of:

- Physiological salts to maintain a physiological osmolality and regulation of cell volume.
- Energy components to support gamete and embryo metabolism.
- Antibiotics to decrease the risk of bacterial contamination in the culture dish, from bacteria in the uterus/vagina collected during oocyte pick-up, and from collection of the sperm sample.
- Macromolecules to protect gametes and embryos from physical stress during handling and avoid adhesion of these to plastic consumables used in the procedures (e.g. culture dish, pipettes and transfer catheter); generally, in the form of HAS. Apart from this, HAS is also functioning as a source of amino acids, energy (lipids, carbohydrates/citrate), hormones, steroids, and small ionic molecules, as well as mopping up hydrophobic contaminants and providing a weak buffer capacity (Leese 1988; Blake et al. 2002; Meintjes et al. 2009).

Universal IVF Medium is a simple balanced salt solution consisting of:

- Earle's Balanced Salts Solution (EBSS)
- Energy components (glucose and pyruvate)
- Bicarbonate buffer
- Antibiotics (10 µg/ml gentamicin sulphate)
- HAS
- SSR®
- Phenol Red (only included in 1031)

SSR® is an ORIGIO based technology, which is a metal ion buffer containing a balanced mixture of iron and trace metals to support embryo metabolism through its content of insulin (promoting absorption of glucose) and prevents the *in vitro* formation of ROS through its content of chelating agent EDTA working as an antioxidant.

Phenol Red is a pH indicator used as a standard component in ART media for customers with preference for visual pH monitoring during the procedure.

4.5 Market History of Device

Universal IVF Medium has been available and used by ART clinics in Europe since 1988, where it was first introduced to the market.

Apart from a long history on the market, Universal IVF Medium forms part of a group of devices characterized by common and stable designs with little evolution, and well-known safety without any safety issues in the past and with well-known clinical performance characteristics.

In May 2008, a first step towards regulation of ART media as medical devices in Europe was published (Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices (version 1.1, 06-05-2008)), which was the beginning of a CE-marking process for all ART media. The same year, ORIGIO a/s (a.k.a. MediCult a/s) was one of the first companies receiving CE-mark approval of the complete ART media portfolio (March 2008).

4.6 Claims or Intended Claims

Claims	Specific claims	Evidence Support	Source
pH 7.3 -7.5	pH tested to ensure pH 7.3 - 7.5	• Stability Report 1030/1031 Universal IVF (Rep4.01.05.01) • Stability Study Report. 9587 Flushing w/ Heparin. Insourcing of Earle's Balanced Salt Ingredients. (Rep4.01.02.02) • Stability Report: 9529 BlastAssist with Gentamicin (Rep:4.01.07.01) • QC Test records (Navision) • Validation report: 1030 IVF Medium without phenol red (Rep4.02.06.01.11) • Validation report: 1031 IVF Medium (Rep4.02.06.01.12)	DIOVV033
Osmolality 277 -293 mOsm/kg	Osmolality tested (Ph.Eur., USP)		
Endotoxin level ≤0.1 EU/mL	Endotoxin tested ≤0.1 EU/mL (Ph. Eur., USP)		

Claims	Specific claims	Evidence Support	Source
Sterile	• Sterile tested (Ph.Eur., USP) • The product is aseptically processed and supplied sterile	• Sterility test justification after change from pencillin/streptomicin to gentamicin (Rep4.02.09.01.01) • Stability Report 1030/1031 Universal IVF. (Rep4.01.05.01) • Stability Study Report. 9587 Flushing w/ Heparin. Insourcing of Earle's Balanced Salt Ingredients. (Rep4.01.02.02) • Stability Report: 9529 BlastAssist with Gentamicin (Rep:4.01.07.01) • Verification of Containers' Ingress Barrier after Real as well as Simulated Transportation. Rep6.26.01	DIOVV033
Supports fertilization, and cleavage stage embryos	For fertilization and culture until 2-8 cell stage and can also be used for embryo transfer.	• Literature is reporting state-of-the-art fertilization,cleavage and implantation rates, as well as clinical outcome • There are no reports of any performance or safety issues through literature or PMS.	CE033R PSUR033
Stable for at least 25 weeks after production	When stored as directed by the manufacturer the product is stable until the expire date shown on the label.	Stability study shows stability for 24 weeks + 7 days after opening	Stability Study Report (Rep4.01.05.01)
Suitable for use up to seven days after opening	The product is to be used within 7 days after opening	Stability study shows that the bottles can be used for seven days after opening	Stability Study Report (Rep4.01.05.01)
Product lifetime	Product lifetime for the Universal IVF Medium is short term, as one of the intended use procedures takes >60 minutes. Each procedure is performed in freshly equilibrated aliquots, with longest exposure being embryos cultured up to 72 hours.	• There are no reports of any performance or safety issues through literature or PMS	DIOVV033 PSUR033

Claims	Specific claims	Evidence Support	Source
Ready-to-use	Contains: • Human albumin solution (HAS) • Recombinant insulin • Gentamicin sulphate 10 µg/mL • High glucose concentration for fertilization Designed for use inside and outside the incubator.	DIOVV033	DIOVV033
With Human Serum Albumin (HSA) that reduces adhesion, acts as an antioxidant, scavenger of excess ions and reservoir for cholesterols, fatty acids and vitamins	Contain HSA to reduce adhesion and protect the gametes and embryos during handling	(Leese 1988)	(Leese 1988)
Safe in use	• Optimal conditions for gamete fusion • Consistent, high fertilization rates for more than a decade • EDTA chelates heavy metals, especially iron, which thereby reduce Reactive Oxygen Species (ROS)	• There are no reports of any performance or safety issues through literature or PMS. • The complaint analysis shows no trends of performance or safety related issues and a low complaint rate • There are no reports of safety issues related to the subject device, benchmark, or similar devices.	CE033R PSUR033

4.7 Clinical Benefits

Universal IVF Medium is a medium that supports viability of oocyte together with sperm function necessary for successful fertilization *in vitro*. In addition, it supports embryo development through the cleavage stages. Clinical benefit is derived from the provision of a suitable milieu that supports fertilization and maintains viability of oocytes, zygotes, and embryos as shown by rates of normal fertilization, embryo development and clinical pregnancy.

Clinical Benefit	Reference
Safe throughout more than 37 years of use (within IVF laboratories):	Literature: (Ajayi, Parsons, and Bolton 2003;

1) No risk of cytotoxicity for the oocytes. 2) No risk of mutagenicity, oncogenicity, teratogenicity or carcinogenicity for the oocytes, resultant embryos and babies, as well as mother/patient and users handling the device according to the IFU. 3) No risk of allergenic and irritancy for the mother/patient or user handling the device.	Laursen, Andersen, and Hindkj 2003; Sills et al. 2009; C. De Geyter et al. 2006; Eskild, Monkerud, and Tanbo 2013) CooperSurgical Post Market Surveillance during all years
1) Universal IVF Medium is supporting the intended purpose of the device: fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer, resulting in: • Fertilization rate: IVF: 61-77%, ICSI: 41.7-89.6%, IVF/ICSI: 59.3-100% • Cleavage rate: 76.6-98.2% • Blastocyst rate: 50-66.6% • Implantation rate: 10-100% • Clinical Pregnancy Rate: 0-68.6% • Live Birth Rate: 16.6-100% • Miscarriage Rate: 0-53% in line with ESHRE (2017) KPI values and general ART records from Europe (Smeenk et al. 2023), Australia/New Zealand (Newman, Repon C Paul, and Georgina M Chambers 2023) 2) Compatible with the current techniques, used in reproductive laboratories.	Literature: (Monks et al. 1993; Ajayi, Parsons, and Bolton 2003; Barak et al. 1998; Bekzatova and Shishimorova 2021; Coskun et al. 2000; Ferraretto et al. 2021; Frydman et al. 2004; Hambiliki et al. 2011; Hatakeyama et al. 2024; Ş. Hatirnaz et al. 2024; S. Hatirnaz et al. 2024; Holst et al. 1990; Jaroudi 2004; Karaki, Lahloub, and Ibrahim 2002; Karamalegos and Bolton 1999; Kattera and Chen 2003; Kidera et al. 2022; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Sills et al. 2009; Staessen et al. 1998; Uppangala et al. 2020; Xella et al. 2010) Data on file: Erb et al. 2004, ORIGIO A/S 2006
Perform as stated by the manufacturer until the end of lifetime of the device	DIOVV033 PSUR033

4.8 Qualifications

Conducting clinical evaluation is a multi-faceted approach requiring input from different sources that are identified by roles and responsibilities.

Individuals must have documented qualifications and experience related to their role and responsibilities concerning the device, use of device, clinical safety, clinical performance, risks, and other aspects of the device. These are identified by positions within or external to the organization for development, review, expert opinion, and approval of the clinical evaluation report. As part of scope, planning, and updates, these positions may be adjusted, or responsibilities changed depending on organizational needs. The Subject Matter Expert must have hands-on experience with the type of device and clinical aspect, and the Medical Writer must have post-graduate experience in a relevant science or in medicine, training and experience in medical writing, systematic review, and clinical data appraisal. In total, the team must have 5 years of documented professional experience in the respective fields.

Qualifications and experience of the author, and individuals responsible for review or approval of the CER must be supported by Curriculum Vitae (CV), or resume, as well as a Declaration of Conflict. This includes all involved employees of the company, and any contractors and parties that are external to CooperSurgical.

Please refer to **Appendix 4**.

5 Clinical Background, Current Knowledge, and State of the Art

5.1 Overview of Clinical Application

The techniques involving ART media include:

- artificial insemination or intrauterine insemination (IUI) using sperm from homologue male partner (IUI-H) or donor semen (IUI-D)
- *in-vitro* fertilization (IVF), involving:
    - oocyte collection and washing (with or without follicle flushing)
    - sperm collection, preparation, and selection
    - oocyte insemination/fertilization:
        - standard *in vitro* fertilization (IVF), or
        - intracytoplasmic sperm injection (ICSI)
    - embryo culture (until 2-8 cell stage or blastocyst)
    - oocyte or embryo biopsy with pre-implantation genetic testing (PGT), if applicable
    - assisted hatching (AHA), if applicable
    - embryo transfer.
- Cryopreservation (freezing) of ovarian and testicular tissue, oocytes, semen samples and any extra embryos remaining after embryo transfer for future use/transfer.

Procedures performed in ambient air (outside a CO_2 incubator):

IUI, oocyte collection and washing, sperm collection and preparation, sperm selection and ICSI, ovarian and testicular tissue preparation, change of culture medium (from fertilization to culture medium, as well as when changing to freshly incubated culture medium or transfer medium), PGT, AHA, loading of the embryo transfer catheter, embryo transfer, and cryopreservation of ovarian- or testicular tissues, gametes and embryos.

Procedures performed inside a CO_2 incubator:

Oocyte insemination/fertilization by IVF and embryo culture.

Currently, there are no recommendations regarding culture systems, except that the type and number of CO_2 incubators should be appropriate to the workload, and embryos should be cultured individually with oil overlay for traceability and to minimize temperature, pH, and osmolality fluctuations (Labs et al. 2016).

More detailed descriptions of the procedures are published by the ASRM (ASRM Booklet for patients 2018), ESHRE (Labs et al. 2016), and the World Health Organization (WHO) (World Health Organization 2010).

5.2 Historical Background and Process

Traditional IVF involves controlled ovarian stimulation (COS) and extracting the woman's oocytes for fertilization outside the body in a petri dish, either by incubation with a high number of progressive motile spermatozoa (IVF) or by injection of a single spermatozoon into the oocyte (ICSI). This is followed by culture to cleavage stage (Day 2/3) or blastocyst stage (Day 5/6), and transfer into the woman's uterus or cryopreservation for later use. Today nearly 70% of all *in vitro* fertilization is performed by ICSI (Calhaz-Jorge et al. 2017; Fitzgerald et al. 2017). Alternatively, where there are no obvious reasons for performing IVF/ICSI, patients are treated by IUI, injecting the prepared sperm sample into the woman's uterus at the time of ovulation, and making the fertilization happen inside the fallopian tube rather than in a dish.

Since introduction of ART techniques in the 1970s, no other medical field has integrated new knowledge into daily practice more quickly than ART (Kamel 2013). Apart from clinical improvements (e.g. better-quality drugs for individualized COS) the ART laboratory has continuously improved as well as expanded the treatment options. During the period 1997–2016, the numbers of recorded ART treatments increased considerably (5.3-fold in Europe, 4.6-fold in the USA, 3.0-fold in Australia and New Zealand), while the number of registered treatment modalities rose from 3 to 7 in Europe, from 4 to 10 in the USA and from 5 to 8 in Australia and New Zealand, as published by EIM, CDC and ANZARD registries, respectively (Ch De Geyter et al. 2020). Today ART includes a wide variety of original (e.g. IUI, IVF/ICSI), improved (e.g. gamete selection using high resolution microscopy, as well as embryo selection using time-lapse systems for kinetic measures, and/or embryo biopsy for preimplantation genetic testing (PGT), and new treatment options, making it possible to help infertile couples previously considered completely infertile. Moreover, the ART treatment of today includes alternative options for patients who for various reasons do not want a standard treatment (e.g. avoiding COS by *in vitro* maturation of oocytes, although resulting in compromised success rates) (Cohen et al. 2005; Nagy, Varghese, and Agarwal 2012; Tilia et al. 2016; Kamel 2013). The mix of ART procedures depends on religion, national regulations, skills/preferences, workload, cost effectiveness and/or investments. Therefore, despite introduced refined methods for gamete and embryo selection, only a limited number of clinics have invested in the necessary equipment and/or devices, and the use of PGT is limited by national regulations. Another example is cryopreservation of gametes and embryos, where both vitrification (rapid cooling to produce a 'glass like' state preventing ice crystal formation) and the original slow-freezing method (using a programmable freezing machine) are used, in spite of generally better survival rates after vitrification. The vitrification procedure is very dependent on laboratory skills and is a time-consuming process for the embryologist when handling larger amounts of samples, while the slow-freezing method is using a full-automatic programmable machine (Rienzi et al. 2016). Moreover, slow-freezing is still part of recommended procedures for pronuclear and cleavage-

stage embryos (Labs et al. 2016). However, while both vitrification and slow-freezing are still in use at many clinics, recent years have shown a significant increase in the availability of vitrification; a three-fold increase in the number of frozen embryo transfers reported in Australia is likely to have been caused by an increasing number of clinics changing their procedures to include a greater number of vitrified embryos and the introduction of 'freeze-all' cycles (Choi et al. 2022).

ART media are characterized as liquids with physiological pH and osmolality to sustain viability of gametes and embryos during different ART techniques. The first culture media used for human *in vitro* fertilization (IVF), e.g. Ham's F-10 and Earle's Balanced Salt Solution, were constructed to support the development of somatic cells and cell lines in culture. Other media, such as Tyrode's T6 and Whitten's WM1, have been used for IVF and embryo culture in laboratory animals. One of the first media specifically designed for human IVF was HTF. Until the 1980s, fertility clinics prepared their own media in-house based on animal embryo culture media (Youssef et al. 2015). IVF culture media can generally be categorized into either the simple balanced salt solutions containing energy sources or the more complex mixtures of inorganic salts, energy sources, amino acids, vitamins, and other substances. During the past 40 years, developments within ART media have primarily been incremental adjustments based on a 'back to nature' strategy, trying to mimic the in vivo environment in the reproductive system as well as adjusting for negative effects of the *in vitro* environment (Chronopoulou and Harper 2015). This includes changing the protein source from animal/patient serum to pharmaceutical grade HAS; introduction of commercial ART media undergoing quality control; inclusion of antioxidants to avoid formation of detrimental Reactive Oxygen Species (ROS) caused by the *in vitro* oxygen and light exposure; inclusion of components found in vivo in the reproductive tract (e.g. amino acids, the cytokine GM-CSF, and the macromolecule hyaluronic acid (HA)); and inclusion of extracellular buffers (e.g. HEPES and MOPS) for improved pH stability when handling gametes and embryos outside the CO_2 incubator (Chronopoulou and Harper 2015; Swain 2010; Swain and Wilding 2012). Developments within ART media used for other indications than embryo culture have mainly focused on buffer systems to ensure pH stability in ambient air, antioxidants for limited ROS formation, and cryoprotectants for controlled de-/re-hydration of gametes and embryos in the case of cryopreservation.

ART media are characterized by having supportive and not therapeutic functions, and as described below (section 5.3) a number of confounding factors influence clinical data and are limiting factors when it comes to ART media development and testing. As a result, a variety of ART media compositions are available for the same procedures, and so far, there are no documented differences in clinical performance and safety relating to ART media (Sfontouris et al. 2016; Swain et al. 2016; Youssef et al. 2015). Therefore, generally all ART media introduced are still being used. For example, PVP is more widely used for slowing down the spermatozoa when selected for ICSI, instead of physiological alternatives using HA (e.g. SpermSlow, SpermCatch or PICSI); and animal derived hyaluronidase enzyme (bovine or ovine) for oocyte denudation before ICSI is preferred instead of the more expensive recombinant human hyaluronidase (ICSI Cumulase) (Simopoulou et al. 2016). Moreover, although special embryo transfer media containing the adhesion molecule HA have become available (e.g. EmbryoGlue

and UTM) most clinics are still using culture medium for both culture and transfer, as the documentation of HA as an adhesion molecule is of moderate quality (Bontekoe et al. 2015).

Certain emphasis should be placed on the Registry data, which are a valuable adjunct to randomized studies and to meta-analyses, as they have the potential to demonstrate ongoing changes under real-life conditions based on data sets arising from large cohorts. However, the quality of the recorded data must be optimized, particularly in Europe with its very fragmented political and legal landscape. In 1999, ESHRE created the European IVF-monitoring Consortium (EIM) and published in 2001 the first data set of the European survey on ART, performed in 1997. Since then, annual reports have appeared with data sets that have become increasingly more complete over time. The comparison of the EIM reports (2001-2020) with those of the USA and Australia/New Zealand, published by CDC and ANZARD registries respectively, reveals several differences among the three registries, including uptake of new treatment modalities over time, reported number of initiated treatment cycles (underreporting in Europe), and some adverse events such as maternal death, ovarian hyperstimulation syndrome, hemorrhage and infections (only recorded by EIM and ANZARD) (Ch De Geyter et al. 2020). Hence, as the current trend towards a higher diversity in treatment modalities and the rising impact of cryostorage require an efficient surveillance organization, the present comparison must stimulate to optimize surveillance and data quality assurance in ART.

In May 2008, a first step towards regulation of ART media as medical devices in Europe was published (Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices (version 1.1, 06-05-2008)), which was the beginning of a CE-marking process for all ART media. The same year, ORIGIO a/s (back then MediCult a/s) was one of the first companies receiving CE-mark approval of the complete ART media portfolio (March 2008).

5.3 Factors Affecting Device

Clinical data are influenced by numbers of confounding factors. For ART treatments, these include but are not limited to: intrinsic quality of the gametes (e.g. female/male -age, -health, -fertility, environmental exposures), and ex vivo manipulations (handling, skills, procedures, equipment) (Zhang et al. 2010; Logsdon et al. 2022) as well as external influences such as socioeconomic and demographic factors affecting the type of ART treatments available to patients (Choi et al. 2022).

The evaluation of ART media is very much dependent on other laboratory devices and equipment (e.g. culture dishes, paraffin oil for media covering, incubator control of temperature, CO_2 and O_2 level, and heating stages for handling the oocytes/embryos outside the incubator), as well as the laboratory set-up and environmental conditions (e.g. transport distances for the culture dish, light, air quality, humidity) (Sifer et al. 2009; ESHRE 2017). Therefore, when evaluating clinical data for ART media effects on embryology parameters in comparison to benchmark or similar devices, cohort studies with prospective randomized sibling oocytes/2PN zygotes (derived from the same patient) are generally the most optimal study design. Examples of exceptions to this are ART media used for oocyte retrieval/follicle flushing (as it is difficult/

time-consuming to perform oocyte retrieval, and impossible to perform follicle flushing of the same ovary, using more than one oocyte retrieval/flushing medium) and ART media for cryopreservation (as not all specimens are being thawed/warmed and used at the same time).

Moreover, when evaluating ART media with regard to clinical outcome, implantation/clinical pregnancy and live birth delivery rates, these data are additionally dependent on patient demographics (incl. endometrial receptivity, woman age, cause of infertility etc.), and also on a number of confounding factors involved in the embryo transfer procedure including but not limited to potential trauma in connection to the transfer procedure, transfer time and temperature control during the procedure, developmental stage and number of embryos transferred (Schoolcraft 2016). Replacement of more embryos does not necessarily increase the chance of a pregnancy, but often results in low implantation rates due to replacement of low-quality embryos which do not implant and potentially harm implantation of other embryos (Berkhout et al. 2017). Similarly, retrieval of immature oocytes may not increase the chances of pregnancy despite increasing the number of available embryos, as higher numbers of immature oocytes obtained from a retrieval procedure are associated with higher rates of abnormal development and longer times to each developmental stage. However, the use of time-lapse incubators may limit the impact of this factor due to the ability to monitor embryos and select for normal development (Setti et al. 2022).

Environmental factors may also impact clinical outcomes; while *in vitro* culture protects embryos from environmental factors due to the controlled conditions, environmental exposure to pollutants during ovarian stimulation and after embryo transfer can have a negative impact on clinical outcomes (Liu et al. 2022). In addition, there are confounding factors specific to the environment within the female reproductive tract; a 2022 cohort study found that for ART patients who had previous deliveries by caesarean section, the rates of clinical pregnancy and live birth deliveries after initial transfer of cultured embryos were significantly lower than those reported for patients with previous vaginal delivery (Gale et al. 2022). While the precise reason for this difference remains unconfirmed, several explanations have been suggested, including both direct effects (e.g. scar defects in the uterus/endometrium affecting likelihood of implantation) and indirect effects (e.g. anatomical issues or medical conditions such as endometriosis, which may affect fertility and also the safety of any resulting pregnancy and delivery). Subgroup analyses performed by Gale et al. show that the reduction in live birth delivery rate was identified specifically for patients whose previous caesarean section had been carried out during active labor, which may suggest at least some influence of indirect factors affecting the chances of both successful pregnancy and safe delivery. Furthermore, there is evidence suggesting that the microbiome within the uterus may affect clinical outcomes. A prospective cohort study examining clinical outcomes of ART treatment in patients with recurrent pregnancy loss found that within this patient population, an endometrial microbiome with relative dominance of Ureaplasma bacterial species was associated with higher rates of miscarriage and preterm delivery in comparison with the more common Lactobacillus-dominant microbiome type (Shi et al. 2022).

In the ART laboratory, key performance indicators (KPIs) are important surveillance tools for systematically monitoring and evaluating the laboratory contributions to patient care. KPIs are

used as benchmarks to compare results over time (ESHRE 2017). However, due to the high number of confounding factors, ART results vary between clinics as well as countries. As stated in the (ESHRE 2017) report, the accumulated KPIs are related to possible poor reliable sperm motility data, variability in sperm preparation method used, and differences in oocyte quality depending on the ovarian stimulation as well as the patient population. The suggested KPI values are mainly based on expert opinions and derived relative to cycles that meet the criteria for a 'reference population' (female < 40 years old, ejaculated spermatozoa (fresh or frozen), no PGT, all insemination performed by routine IVF/ICSI), including high benchmark values with regard to quality of the oocytes (derived from 80-95% of follicles and including 70-90% mature (MII) oocytes at ICSI) as well as a competence value for the sperm sample for IVF and IUI (≥90% sperm motility post-preparation). Therefore, it is recommended that each indicator value is read in association with the summary for each indicator, and that each laboratory develops its own set of KPIs, possibly subdivided into specific patient groups based on clinical practices, laboratory organization and processes. The fact that ART success rates are dependent on population and applied techniques is also emphasized in the Australian Code of Practice for ART units. Here it is recommended that the values are adjusted according to age, fresh/frozen embryo transfer, IVF, ICSI, PGT, body weight, and cause of infertility (Fertility Society of Australia and Reproductive Technology Accreditation Committee (RTAC) 2017).

Worldwide trends within ART suggest that clinical outcome is improved through investments in new equipment and optimized quality control (Alper 2013; Swain 2014). In Europe, the EU Directive 2004/23/EC and guidelines for good practice in IVF laboratories published by the European Society of Human Reproduction and Embryology (ESHRE) were introduced. In Australia this information was provided by the Code of Practice for ART units (first issued in 1987) and introduction of the Reproductive Technology Accreditation Committee (RTAC) Certification Scheme issued October 2010. Focus on quality control and awareness of staff skills as a high impact factor on clinical outcome has increased attention on how and by whom procedures are being performed (Fertility Society of Australia and Reproductive Technology Accreditation Committee (RTAC) 2017; Labs et al. 2016; Schoolcraft 2016).

Two publications are available with retrospective analysis of IVF/ICSI treatment in Europe (1997-2011) and Australia/New Zealand (2002-2013) respectively, showing shared trends with regard to increasing maternal age, increased proportion of ICSI cycles, and a clear trend towards transferring fewer embryos resulting in a decreasing number of multiple pregnancies. During these same periods, the number of frozen embryo replacements (FER) has increased in Europe while remaining stable in Australia/New Zealand (Ferraretti et al. 2017; Chambers et al. 2016), although data from the period 2009-2017 does demonstrate an overall threefold increase in frozen embryo transfers taking place in Australia, suggesting that trends in ART treatment continue to share similarities (Choi et al. 2022). Data are further supported by a systematic review of worldwide trends in ART from 2004 till 2013, demonstrating increasing utilization of IVF/ICSI, single embryo transfer (SET), and FER, with considerable variations between regions (Kushnir et al. 2017). Consequently, results after IVF/ICSI in Europe increased until year 2007, after which the figures steadied (Ferraretti et al. 2017); a trend confirmed through the yearly ESHRE reporting on European IVF/ICSI results comparing against previous years. Further,

worldwide results are showing stable success rates after fresh embryo transfer, and increasing success rates after FER (Kushnir et al. 2017; Wyns et al. 2022). In Australia/New Zealand, effectiveness of both fresh and frozen cycles has continued to increase by moving to blastocyst transfer. For the first time in 2016, the ESHRE data collection allowed for separate analysis of blastocyst and cleavage stage embryo transfers, showing majority of embryos being transferred at blastocyst stage (41.9% for fresh IVF + ICSI and 62.2% for FER), and confirming higher clinical pregnancy rates per FER of blastocysts versus cleavage stage embryos (39.7% versus 28.3%) (Wyns et al. 2020). Although clinical pregnancy and live birth delivery rates are higher after blastocyst transfer, such a strategy is also associated with a higher risk of the patient ending up with no embryos surviving to blastocyst stage, thereby reducing the number of cycles with transfer and cryopreservation (Smeenk et al. 2023). During the period 2002-2013, the proportion of transfer cycles relative to initiated cycles as well as the number of FER cycles remained constant (Chambers et al. 2016), while latest data reported for Europe and Australia are showing trends towards lower number of transfer cycles per initiated IVF/ICSI cycles and increasing numbers of FER cycles (incl. freeze-all cycles) (Smeenk et al. 2023).

5.4 Development of Universal IVF Medium

Universal IVF Medium belongs to a first generation of ART media, characterized as simple balanced salts solutions with energy sources (carbohydrates), bicarbonate buffer, antibiotics, and Human Albumin Solution (HAS), and therefore without amino acids and vitamins.

Clinical safety and performance of the Universal IVF Medium product family has been documented through clinical use for >37 years.

The only change that has been made to Universal IVF Medium product family, is replacement of streptomycin and penicillin G sodium with gentamicin (10 µg/ml) in connection to a change performed for all devices with antibiotics in the ORIGIO brand, back in 2009. Gentamicin is a broad-spectrum antibiotic with activity against many gram-positive as well as most gram-negative bacteria, and superior to penicillin/streptomycin in aspects of eliminating bacterial strains. Moreover, gentamicin has been used for many years as standard antibiotic in commercially available media for ART procedures. When ORIGIO a/s (a.k.a. MediCult a/s) made the general change to gentamicin back in 2009, this was already the preferred antibiotic used by other media manufacturers. There are no reports of any effects of gentamicin on embryo quality, live birth rates or health of babies born, nor are there any reports of allergic reactions to gentamicin when used in media in contact with the human body. In conclusion, the supplement of 10 µg/ml Gentamicin sulphate to Universal IVF Medium is safe and without any negative impact on clinical performance.

Apart from the change of antibiotics, there have been no changes made to the design, material, or indications for use of the subject devices.

5.5 Materials

Universal IVF Medium is based on Earle's Balanced Salts Solution (EBSS) and forms part of the first generation of ART media provided by ORIGIO a/s (a.k.a. MediCult a/s); all developed by Professor Bertheussen and characterized by inclusion of Synthetic Serum Replacement (SSR®).

SSR® is an ORIGIO based technology, which is a metal ion buffer containing a balanced mixture of iron and trace metals to support embryo metabolism through its content of insulin (promoting absorption of glucose) and prevents the *in vitro* formation of ROS through its content of chelating agent EDTA working as an antioxidant (Bertheussen 1993).

Composition:

- Earle's Balanced Salts Solution (EBSS)
- Energy components (glucose and pyruvate)
- Bicarbonate buffer
- Antibiotics (10 µg/ml gentamicin sulphate)
- HAS
- SSR®
- Phenol Red (only included in 1031)

The product is provided in standard design (plastic bottles with a screw cap, containing a non-viscous clear (Ref# 1030) or red colored (Ref# 1031) liquid depending on content of Phenol Red), in standard packaging (carboard boxes), with a package insert (IFU) in clear and plain language and aligned with all requirements of MDR Annex I, Chapter III, focusing only on how to use the actual device and not on how to perform the related ART procedures where user will need to follow own standard operation procedures. Further, the label on the product is marked with symbols stating to consult the IFU.

The device incorporates HAS, gentamicin sulphate (antibiotic), and recombinant human insulin (as part of the SSR®), all considered as ancillary medicinal substances.

HAS is derived from human blood constituents.

Gentamicin sulphate is produced via fermentation using, among others, fish peptone. Fish peptone is the only animal-derived material used in the production of gentamicin sulphate.

The product is manufactured aseptically and supplied as a sterile and ready-to-use liquid.

5.6 Benefit-Risk Analysis

5.6.1 Benefits Related to Universal IVF Medium

Universal IVF Medium is a medium that supports viability of oocyte together with sperm function necessary for successful fertilization *in vitro*. In addition, it supports embryo development through the cleavage stages. Clinical benefit is derived from the provision of a suitable milieu that supports fertilization and maintains viability of oocytes, zygotes, and embryos as shown by rates of normal fertilization, embryo development and clinical pregnancy.

Although more complex ART media including amino acids, vitamins and other substances not included in Universal IVF Medium are now available, this device is still used as an all-round ART medium providing customers with the possibility of only having to keep one ART medium in stock for fertilization, embryo culture and transfer.

Universal IVF Medium is still performing well in many laboratories, and a Cochrane review of published data on available culture media for human pre-implantation embryos concluded that there is no evidence to support or refute the use of any specific culture medium (Youssef et al. 2015).

Like other ART media for fertilization, embryo culture and transfer, Universal IVF Medium provides a physiological environment including:

- Physiological salts to maintain a physiological osmolality and regulation of cell volume.
- Energy components to support gamete and embryo metabolism.
- Bicarbonate buffer to maintain a physiological pH during use in a CO_2 incubator.
- Antibiotics to decrease the risk of bacterial contamination in the culture dish, from bacteria in the uterus/vagina collected during oocyte pick-up, and from the collection of the sperm sample.
- Macromolecules to protect gametes and embryos from physical stress during handling and avoid adhesion of these to plastic consumables used in the procedures (e.g. culture dish, pipettes and transfer catheter); generally, in the form of HAS. Apart from this, HAS also functions as a source of amino acids, energy (lipids, carbohydrates/citrate), hormones, steroids, and small ionic molecules, as well as mopping up hydrophobic contaminants and providing a weak buffer capacity (Leese 1988).

5.6.2 Risks Related to Universal IVF Medium

A risk analysis has been performed for the Universal IVF Medium product family. All risks associated with the products have been reduced to an acceptable level when weighed against the benefits for the patient and constitute no recognized risks for the mother/patient or user, when used as intended and by professionals within ART (RMF0108-RMR).

Universal IVF Medium contains Ph. Eur. (European Pharmacopoeia)/USP (United States Pharmacopeia) grade HAS, resulting in two (2) residual risks which have been evaluated and deemed acceptable:

1) Exposure to transmissible diseases / viral contamination from infected HAS (patient).
2) Viral contamination during disposal (ART technician).

HAS, which is of biological origin from human blood, introduces a theoretical risk of viral contamination, which cannot be excluded, and is thus ranked with a higher severity. Due to Risk Control Measures (RCM) incorporated, the occurrence of a viral transmission from HAS is judged to be very low. However, if HAS does contain a virus, it cannot be detected in the final media. Clear warnings have been incorporated within the Instructions for Use regarding the risks of blood products, and their treatment as potentially infectious. However, the risk is considered to be reduced as far as possible. The benefits of adding albumin proteins to the medium are greater than the associated risks, and as such the risk has been accepted.

Pharmaceutical grade HAS is a standard component of ART media, which is also included in other CE-marked media used for ART treatments. Besides HAS, the Universal IVF Medium only contains other well-known components also present in other ART media with the same intended purpose, and which do not cause any concern regarding genotoxicity, carcinogenicity, or reproductive and developmental toxicity (please refer to Biological Evaluation (Rep1.02.07.43, version 3).

Apart from this, there are a number of risks associated with ART. Women who undergo ART procedures are at risk of developing ovarian hyper stimulation syndrome (OHSS) following the drug treatment for ovarian stimulation; they can be injured either during laparoscopic evaluation for female factors or the oocyte retrieval process; and are more likely to deliver multiple-birth infants which introduce substantial risks to both mother and babies (incl. pregnancy complications, preterm delivery, and low birthweight). Moreover, meta-analysis and retrospective cohort analysis are showing ART singletons with compromised health including higher incidence of low birth weight, preterm birth, small for gestational age (SGA), and birth defects when compared to natural conception. However, all of these observations might as well be related to parental characteristics, underlying infertility etiology, and/or ART procedures themselves (incl. the ovarian stimulation, transfer of >1 embryo, and insemination by ICSI) (Li et al. 2014; Luke et al. 2017; Davies S. et al. 2018; Hansen and Bower 2014; Chambers et al. 2016). A recent pilot follow-up study investigating buccal smears from 7-8 years old children born, found that ART singleton children compared to naturally conceived singletons were characterized by changes in DNA methylation levels. No differences were found between culture media used, and the authors concluded that it is still unclear whether observed differences were due to specific ART procedures and/or to parental infertility (Barberet et al. 2021). Contrary to analysis showing higher incidence of low birth weight, there are concerns about large for gestational-age (LGA) infants born after frozen/thawed embryo transfer, though reported data go back to before 2012 (Hansen and Bower 2014). Finally, a recent registry-based cohort study using data from 4 Nordic countries (Denmark, Finland, Norway and Sweden) incl. 171,774 children born after use of ART and 7,772,474 children born after spontaneous conception, found

no increased risk of childhood cancer in children born after use of ART, but a higher risk of childhood cancer in children born after frozen embryo transfer (FET) compared with children born after fresh embryo transfer and spontaneous conception (Sargisian et al. 2022).

5.7 Medical Alternatives Related to Universal IVF Medium

Where there are no obvious reasons for performing IVF/ICSI, patients are treated by IUI, injecting the prepared sperm sample into the woman's uterus at the time of ovulation, and allowing fertilization and embryo development to happen inside the fallopian tube rather than in a dish. Where IVF/ICSI is required, various ART media are available for the intended purpose of fertilization, embryo culture and transfer. These are generally categorized into simple balanced salt solutions containing energy sources (e.g. Universal IVF Medium and HTF from FUJIFILM, Irvine Scientific), and more complex mixtures of inorganic salts, energy sources, amino acids, vitamins, and other substances.

5.8 Current State of the Art

Universal IVF Medium forms part of a group of devices (*in vitro* fertilization culture medium) characterized by common and stable designs with little evolution, and well-known clinical safety and performance characteristics. The device is intended for fertilization of oocytes and culture through to cleavage stage, and for embryo transfer. Various meta-analyses and reviews have been performed on issues related to these procedures, but evidence for one procedure or medium being superior to another is yet to be established:

- A systematic review by Heymann et al. (2020) initially identified some evidence for improvements in clinical pregnancy, live birth, and miscarriage rates when using ART media containing hyaluronic acid for embryo transfer. However, this evidence was of mixed quality, and when including only the evidence at low risk of bias, no effects remained (Heymann et al. 2020).
- Two systematic reviews compared clinical outcomes after fresh and frozen embryo transfers (Zaat et al. 2021; Gaume et al. 2021). No clear differences were found between fresh and frozen transfer when comparing live birth delivery rates, miscarriage rates, ongoing pregnancy rates, or neonatal outcomes. Gaume et al. (2021) suggested a link between frozen embryo transfer and larger babies, however, there was minimal evidence to support this claim.
- A third systematic review comparing fresh and frozen embryo transfers did identify increased live birth delivery rates and decreased miscarriage rates when frozen embryo transfer was used (Chang et al. 2022). This review is focused on patients undergoing ART due to endometriosis; results may be less applicable to the wider ART patient population.
- Paffoni et al. (2021) found that a combination of rescue ICSI and cryopreservation of resulting embryos can result in a relatively high clinical pregnancy rate of 37%. The authors also state that this may be due to the combination of procedures and note that

conventional ICSI alone does not always improve clinical outcomes, depending on other confounding factors such as the indication for ART (e.g. ICSI is primarily intended for use in cases of male infertility) (Paffoni et al. 2021).

- A systematic review by Glujovsky et al. (2022) found low-to-moderate-quality evidence in favour of improvements in clinical pregnancy and live birth delivery rate for blastocyst-stage embryo transfer compared with cleavage-stage transfer (Glujovsky et al. 2022). However, many confounding factors remain, and as yet there has been little assessment of any differences seen in poor prognosis patients.

Additionally, Fancsovits et al. (2022) examined three randomized controlled trials and found that embryo culture in low-oxygen environments resulted in higher live birth delivery rates in comparison with culture environments with oxygen levels closer to ambient air (Fancsovits et al. 2022).

6 Identification of Clinical Evaluation Data

6.1 Literature Data Pertaining to Device

ART media are considered WET[5], and therefore clinical experience with this type of devices is generally considered of low scientific value, difficult to get accepted for publications in peer-reviewed journals. Consequently, most experience with ART media is shared among ART professionals as posters and abstracts presented at congresses/conferences. Although posters and abstracts often include limited information on patient population, ART results are affected by a number of confounding factors other than the ART medium, which can be even more important than the patient population. Most of these are unmeasurable or not described in any publications (e.g. staff skills and quality/calibration of equipment used). Moreover, study design and sample size, is considered more important than format of the publication (poster/abstract or full-text) with cohort studies including prospective randomized sibling oocytes/2PN zygotes (derived from the same patient) and split sperm samples (the same ejaculate split into two mor more parts) being the most optimal study design for this type of device, when evaluating performance and safety based on embryology parameters in comparison to benchmark or similar devices. Therefore, for a thorough evaluation of clinical performance and safety in various clinical settings, all types of publications and study designs are included.

Different sources of posters/abstracts and peer-reviewed scientific literature are used for the assessment of clinical evaluation including a search strategy defined in the following steps and according to the clinical evaluation plan and contained in **Appendix 2: Literature Search Results**. This involves searching several scientific, medical, and healthcare databases previously listed, including published scientific literature, peer-reviewed literature, and non-published scientific literature that may be related to the subject device and/or similar devices.

[5] characterized by stable designs with little evolution, claims according to state of the art (incl. clinical performance and safety), and no special requirements for protocol compared to state of the art.

Review of peer-reviewed scientific literature is clearly indicated through a ranking process, including relationship to the subject device, benchmark or similar device(s).

Three (3) publications from the current search have been found relevant for inclusion in the clinical evaluation for assessment of safety and performance of the subject device. Please refer to **Table 6-1** for an overview of number of in- and exclusions.

Table 6-1: Overview of data related to Subject Device included in the CER

Data From:	Number of Results from Search	Not Relevant and Screened from Review	Excluded During Detailed Appraisal (Full Text)	Included in the Clinical Evaluation
Subject device	3	0	0	3
Benchmark or similar device	0	0	0	0
Clinical Investigations	0	0	0	0
Total	**3**	**0**	**0**	**3**

A detailed appraisal of literature from the latest search is presented in **Appendix 3: Literature Search Appraisal**.

Literature included from the previous version of the CER (CE033R, Version B) has been reviewed and assessed for suitability for use by reading through the already assembled literature information, non-clinical data, and post market information.

6.2 Literature Review Summary of Clinical Data

Altogether, the previous and current literature searches for the Universal IVF Medium family of devices resulted in total 27 data reports or publications (25 publications and two (2) data-sets on file at CooperSurgical) on the actual device, relevant for the evaluation of clinical performance and safety examining subject device against benchmark or similar devices. Data extracted from the appraised literature are presented in **Table 6-2**. In cases where none of the represented parameters are included in the publication, a short summary is given instead.

Reports with original clinical data relating to Universal IVF Medium, are evaluated according to its/their contribution with data relating to performance and/or safety, and further appraised according to suitability criteria and data quality. Data regarding safety are considered most important and are listed in the top of the table. Data from the literature regarding performance and comparability on the device in question are listed below according to the described criteria, and, when data are considered equally important, the data are listed according to sample size. Data related to benchmark device(s) are listed beneath data on the actual device and weighted in the listed order and according to the device in question.

State of the art publications which do not include new data (reviews and meta-analyses) are not ranked (neither are safety notices), however, they are discussed in the relevant sections. Please refer to section 7.3.

Table 6-2: Clinical Safety and Performance Data on Subject Device

Data are presented as mean ± standard deviation. Uplifted lowercase letters indicate statistically significant differences ($p < 0.05$).

ART = Assisted Reproductive Technology; COS = controlled ovarian stimulation; EBSS = Earl's Balanced Salts Solution; ET = embryo transfer; HTF = Human Tubal Fluid medium; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; PCOS = polycystic ovarian syndrome; TESA = testicular sperm aspiration

Reference	Procedure	Study Groups	No. of Cycles/ Patients	ART Indications	Mean Age, Years	Mean Number of Embryos Transferred	Embryological/ Clinical parameters						
							Fertilization Rate (%)	Cleavage Rate per 2PN (%)	Blastocyst Rate (%)	Implantation Rate (%)	Clinical Pregnancy Rate per ET (%)	Live Birth Rate (%)	Miscarriage Rate (%)
Ajayi et al. (2003)	Fertilization and culture in Universal IVF Medium	ICSI	2	Tubal factor Azoospermia (TESE)	-	-	-	-	-	3/3 (100) 1/2 (50)	-	2/2 (100)	-
Barak et al. (1998)	Fertilization and culture until confirmed fertilization and in new media till day 2 or 3 in	P1 (Irvine Scientific)	IVF: 12 ICSI: 25	IVF: infertility ICSI: male factor infertility (<5×10^6 spermatozoa /ml)	33.6 ± 6.0	3.7 ± 1.0	222/315 (70.5)[a,b,c]	16/23 (69.6)[g]	-	-	7/37 (18.1)[h,i,j]	-	-
		HTF (Irvine Scientific)	IVF: 8 ICSI: 14		34.0 ± 5.2	3.5 ± 1.4	138/225 (61.3)[a,d]	-	-	-	7/22 (31.8)[h]	-	-

	one of the study groups → transfer	M3	IVF: 21 ICSI: 33		31.7 ± 5.0	3.7 ± 1.2	250/447 (55.9)[b,e]	81/88 (92.0)[f,g]	-	-	18/54 (33.3)[i]	-	-
		Universal IVF Medium	IVF: 29 ICSI: 40		32.5 ± 4.8	3.9 ± 0.9	452/578 (78.2)[c,d,e]	57/73 (78.1)[f]	-	-	32/69 (46.4)[j]	-	-
Bekzatova & Shishimorova (2021)	Fertilization in Universal IVF Medium	Natural IVF cycles	324	Maternal age ≥ 35 years	36.3	-	-	-	-	-	28.1	-	-
		Oocyte accum. in poor responders	46		37.6	-	-	-	-	-	20	-	-
Coskun et al. (2000)	Fertilization and culture until day 3 in Universal IVF Medium → transfer	Universal IVF Medium, ET Day 3	101 patients ICSI/IVF	Male factor, tubal, unexplained, PCOS, endometriosis others	30.7 ± 5.4	2.3 ± 0.6	68	-	-	21	39	-	13.2
	Fertilization in Universal IVF Medium, culture in G1 & G2 media → transfer	Sequential media, ET Day 5	100 patients ICSI/IVF		30.4 ± 4.9	2.2 ± 0.5	67	-	-	24	39	-	7.9
De Geyter et al. (2006)	Embryo culture in Universal IVF Medium	-	203	**Short summary:** De Geyter et al. (2006) retrospectively studied the birth weight of singletons born after ART and natural conception in (previously) infertile couples. In the period between August 1996 and March 2004, a total of 203 deliveries after IVF/ICSI was recorded. Mean birthweight after ICSI and IVF was 3237 and 3266 g, respectively.									

Eskild et al. (2013)	Culture in Universal IVF Medium, ISM1, or G-1 Plus	-	2435	**Short summary:** Eskild et al. (2013) report a retrospective analysis of singleton births from the University Hospital in Oslo (Norway) during a period of fourteen years, divided into three periods depending on culture medium used: Universal IVF Medium (1999 through 2007, n= 1584), ISM1 (2008 until September 2009, n= 402) and G-1 PLUS (September 2009 through 2011), n= 449). In singleton offspring from IVF the mean birthweight was 3447.6 g with MediCult Universal, 3351.7 g with MediCult ISM1 and 3441.4 g with Vitrolife G-1 PLUS (p<0.05).									
Ferraretto et al. (2021)	Fertilization (IVF and ICSI) in Universal IVF Medium	-	250/318	Female and male infertility	34.7	2.04	61.7	-	-	-	38.4 (cumulative)	26.4 (cumulative)	-
Frydman et al. (2004)	Fertilization (IVF and ICSI) in Universal IVF Medium, followed by culture in ISM1/ISM2	IVF	239	Classical IVF, male infertility, endocrinology abnormalities, viral serologic discordant	33	2.5-2.8	(71)	-	-	(21)	98/239 (41)[6]	83/239 (34.7)[7]	9/98 (9.2)
		ICSI	218		34	2.3-2.8	(63.5)	-	-	(23.5)	84/218 (38.5)[6]	74/218 (33.9)[8]	9/84 (10.7)
Hambiliki et at. (2011)	Fertilization in Universal IVF → and culture in EmbryoAssist → transfer	Universal IVF Medium	110 patients ICSI/IVF	Male factor, tubal, unexplained, endometriosis anovulation, others	33.9 ± 3.8	-	315/469 (67.2)[a]	174/315 (55.2)[9]	-	9/24 (37.5)	8/22 (36.4)	8/22 (36.4)	(0)

[6] Per oocyte retrieval
[7] Nine miscarriages, 5 ectopic pregnancies, one reduction due to trisomy 18
[8] Nine miscarriage, one ectopic pregnancy
[9] Only including good quality embryos.

	Fertilization in G-IVF Plus and culture in G-1 Plus v5 → transfer	G-IVF Plus (VitroLife)				-	382/520 (73.5)[a]	233/382 (61.0)[9]	-	36/88 (40.9)	32/69 (46.4)	24/69 (34.8)	8/32 (25.0)
Hatakeyama et al. 2024	Assisted Sperm Fusion Insemination (ASFI)	ASFI	83 oocytes	-	40.1 ± 3.2	-	73 (88.0%)	-	39 (63.9%)	-	-	-	-
	Conventional ICSI (C-ICSI)	C-ICSI	114 oocytes		40.1 ± 3.2	-	80 (70.2%)	-	44 (62.0%)	-	-	-	-
Hatirnaz, Safak, et al. 2024a	In-vitro maturation (IVM), intracytoplasmic sperm injection (ICSI) Universal IVF medium (MediCult)	Group 1 (IVM primed with FSH-HCG) Fresh embryo transfer	75 women	Women with oocyte maturation abnormalities	31.00 ± 4.50	-	41.7 ± 34.4[a]	-	-	-	-	-	-
		Group 2 (IVM primed with letrozole-HCG) Frozen embryo transfer	52 women		32.30 ± 4.60	-	64.3 ± 29.1[a]	-	-	-	37.5[a]	28.6	7.1
Hatirnaz, Safak, et al. 2024b	*In vitro* maturation (IVM),	Follicular phase IVM (Group 1)	27 (44 cycles)	Women with oocyte maturation abnormalities	31.93 ± 4.85	-	65.8 ± 32.3	-	-	-	20	20	-

	Intracytoplasmic sperm injection (ICSI), vitrification, fresh and frozen embryo transfer Universal IVF medium (MediCult)	Luteal phase IVM (Group 2)	15 (23 cycles)		33.17 ± 2.77	-	70.0 ± 29.2	-	-	-	50	33.3	16.7
		Duostim IVM follicular phase	5 (9 cycles)		34.56 ± 4.41	-	70.0 ± 29.8	-	-	-	-	-	-
		Duostim IVM luteal phase	5 (9 cycles)		34.56 ± 4.41	-	78.6 ± 30.7	-	-	-	-	-	-
Holst et al. (1990)	Insemination, culture and transfer in Universal IVF or Ham´s F10 + patient serum	Universal IVF Medium	110	Tubal factor, endometriosis, unexplained	31.6	3.0	563/949 (59.3)	547/563 (97.2)	-	47/326 (14.4)	30/105 (34)	-	6/36 (17)
		Ham´s F10 + Patient serum	110		32.2	3.1	498/867 (57.4)	480/498 (96.4)	-	34/310 (11.0)	36/105 (29)	-	9/30 (30)
Jaroudi et al. (2004)	Fertilization in Universal IVF Medium → transfer	Zygote transfer	IVF: 19 ICSI: 97 IVF/ICSI: 7	Male factor, tubal, unexplained, others	31.12	1.85	66	-	-	39/227 (17.2)[a]	34/123 (27.64)[b]	-	7/34 (20.59)

	Fertilization and culture until day 3 in Universal IVF Medium → transfer	Day 3 embryo transfer	IVF: 23 ICSI: 104 IVF/ICSI: 7		31.52	1.91	66	-	-	64/251 (25.5)[a]	55/131 (41.98)[b]	-	13/55 (23.64)
Karaki et al. (2002)	Fertilization and culture in Universal IVF Medium → transfer	Day 3 embryo transfer	82	Male factor, tubal, unexplained, endometriosis, PCOS, others	29.2 ± 5	3.5 ± 0.63 [a]	-	-	-	13[b]	26	-	-
	Fertilization in Universal IVF Medium, culture in G1 & G2 media → transfer	Day 5 embryo transfer	80		30 ± 4.5	2.0 ± 0.1[a]	-	-	-	26[b]	29	-	-
Karamalegos and Bolton (1999)	Gametes and embryos handled and cultured in Universal IVF Medium or EBSS	Universal IVF Medium	230	All IVF patients less than 38 years old	33	2.1	(70.7)	-	-	71/442 (16.1)	59/214 (27.6)	-	-
		EBSS	218		33	2.2	(71.4)	-	-	51/441 (11.6)	38/205 (18.5)	-	-
Kattera and Chen (2003)	Fertilization and culture until day 3 in Universal	Oocytes and spermatozoa co-incubated for 2 hours	130 IVF	Tubal, unexplained, PCOS, endometriosis	35.4 ± 4.1[10]	3.0	838/1105 (75.8)	-	-	96/390 (24.6)[a]	63/130 (48.5)[b]	-	-

[10] Mean ± standard error of mean

	IVF Medium → transfer	Oocytes and spermatozoa co-incubated for 20 hours		129 IVF		35.1 ± 3.9[10]	3.0	924/1200 (77.0)	-	-	47/387 (12.1)[a]	37/129 (28.7)[b]	-	-
Kidera et al. (2022)	Fertilization in Universal IVF Medium	Maternal age <35	A	338	Infertility with normal sperm parameters	31	-	77.7	-	66.6	-	68.6	58.4	13.1[b]
			B	156		33	-	75.9	-	66.6	-	67.1	61.8	7.8[b]
			C	41		33	-	80	-	66.6	-	68.1	45.4	33.3[b]
		Maternal age 35-39	A	108		36	-	100[a]	-	66.6	-	48.9	38.7	20.8
			B	383		37	-	71.4[a]	-	60	-	58.2	44.7	22.2
			C	221		38	-	77.7[a]	-	66.6	-	60.3	45.2	23.4
		Maternal age ≥40	A	36		41	-	100	-	50	-	25	16.6	33.3
			B	93		41	-	100	-	50	-	34.2	25.7	25
			C	281		41	-	75	-	50	-	46.6	21.9	53
Kovačič et al. (2002)	Fertilization and culture until day 2 in Universal IVF Medium → transfer	Day 2 embryo transfer		131 ET of 133 cycles: IVF 46 ICSI 79 TESA + ICSI 8	Female, male (including azoospermia), combined, unexplained	36.1 ± 5.1	1.5 ± 0.6	204/524 (38.9)	-	-	36/202 (17.8)[a]	30/131 (22.9)[b]	24/131 (18.3) Single-tons:19 Twins: 3	6/30 (20.0)
Laursen et al. (2003)	Fertilization (IVF or ICSI) and culture until day 2 in	Sperm Filter		329	Tubal factor, male factor, idiopathic, PCOS, and other cause	31.5	1.89	69.8	-	-	21	33.8	20.4	16

	Universal IVF Medium → culture in M3 medium for 24 hrs. → transfer	Pure sperm	266		31.4	1.89	70.6	-	-	19.8	32.9	21.4	8.8
Monks et al. (1993)	Gametes and embryos handled and cultured in four different media	Universal IVF Medium	34	Infertile patients treated by natural cycle IVF	33.1	-	-	-	-	-	4/34 (11.8)	2/34 (5.9)	-
		B2	57		-	-	-	-	-	-	5/59 (8.5)	5/59 (8.5)	-
		HTF-WFI	36		-	-	-	-	-	-	4/37 (10.8)	3/37 (8.1)	-
		HTF-UHP	63		-	-	-	-	-	-	9/63 (14.3)	6/63 (9.5)	-
Sills et al. (2009)	Universal IVF Medium used for fertilization (IVF or ICSI) and equilibration after thawing blastocysts	-	14	IVF patients with transfer of dual frozen-thawed embryos	32.7	2.1	-	-	-	-	-	5/14 (35.7)	-
Staessen et al. (1998)	Fertilization (IVF) and culture in Universal IVF or B2 medium	Universal IVF Medium	57	Patients undergoing conventional IVF treatment	32.0	2.1	61.0	76.6	-	13.8	22.8	11/57 (19.3)	1/12 (8.3)
		B2	60		33.2	2.1	62.9	77.7	-	21.5	36.7	17/60 (28.3)	4/21 (19)
		Mix	261		33.0	2.9	-	-	-	18.8	35.6	65/261 (24.9)	17/82 (20.7)
Uppangala et al. (2020)	COS followed by ICSI fertilization in	Normal responders	10	Infertility without identified pathology	30.2 ± 1.09	-	68.5	-	-	-	-	-	-
		Poor responders	10		31.6 ± 0.99	-	60	-	-	-	-	-	-

	Universal IVF Medium	Hyper-responders	10		31.5 ± 1.09	-	64.2	-	-	-	-	-	-
Xella et al. (2010)	Fertilization (ICSI) in Universal IVF, culture until day 3 in Universal IVF or ISM1™	Universal IVF Medium	323	Tubal factor, male factor, anovulation and idiopathic	35.7	2.43	1873/2091 (89.6)[11]	784/798 (98.2)	-	80/778 (10)[a]	67/323 (21)[b]	-	10/67 (15)[12]
		ISM1™	403		35.8	2.64		1065/1075 (99.1)	-	166/1075 (15)[a]	125/403 (31)[b]	-	14/125 (11)[12]
Erb et al. 2004 (Data on file)	Fertilization and culture until day 2. IVF/ICSI Sibling oocytes	Universal IVF Medium	216	Tubal factor, male factor, anovulation, endometriosis unexplained	31.8	1.5	68.3	-	-	35/100 (35)	29/68 (42.6)	-	-
		ISM1™				1.6	63.5	-	-	36/131 (27.5)	31/84 (36.9)	-	-
ORIGIO A/S 2006 (Data on file)	Fertilization and culture until day 2 → transfer	Universal IVF Medium	94: IVF 46 ICSI 48	Male, tubal, endocrine abnormalities, PCOS, endometriosis, idiopathic	31.6 ± 4.0	1.7 ± 0.5	50.8 ± 30.2	-	-	10/35 (28.6)	9/21 (42.9)	-	-
		Embryo Assist				1.6 ± 0.5	54.7 ± 32.8	-	-	16/50 (32.0)	12/32 (37.5)	-	-

[11] All oocytes in both study groups were fertilized in Universal IVF Medium
[12] Abortions in first trimester

6.3 Determination of Equivalent Device

Pursuant to the outlined equivalence definition in MDR Annex XIV Part A (3) and MDCG 2020-5, there is no claim of equivalence.

6.4 Post Market Surveillance

PMS data are collected and analyzed on a regular basis by CooperSurgical per BSR-QAR-042.

This CER includes PMS covering the period 2023.Jan.01 – 2024.Dec.31, with searches performed according to the PMS plan (PMS033P). Results include a summary of complaints, vigilance, adverse event reports and recalls, field corrective actions and CAPAs, and any proactive PMS data sources collected. The PMS data are presented in Section 7.1.2 where they are analyzed for trending and relevant updates to the risk management process.

6.5 Data Pertaining to State of the Art

Alternative state of the art treatment and procedures are described in section 5.7 and 5.8.

Different sources of peer-reviewed scientific literature are used for the assessment of clinical evaluation, including a search strategy defined in the following steps and according to the clinical evaluation plan, and contained in **Appendix 2: Literature Search Results**. This involves searching several scientific, medical, and healthcare databases previously listed, including applicable standards and guidance documents, ESHRE and NPESU reports, review and meta-analysis of publications and literature relating to clinical performance and safety of the same type of devices.

Four (4) new publications from the current search have been found relevant for inclusion in the clinical evaluation for assessment of state of the art. Please refer to **Table 6-3** for an overview of number of in- and exclusions.

Table 6-3: Overview of data related to state-of-the-art included in the CER

Data From:	Number of Resulting Articles	Screened Out as Not Relating to Procedure / Intended Purpose (Abstract)	Excluded During Detailed Appraisal (Full Text)	Included in the Clinical Evaluation
Subject of state of the art	51	36	11	4
Total	**51**	**36**	**11**	**4**

6.6 Additional Supporting Literature

State of the art clinical safety and performance is defined by KPI values published in the ESHRE consensus report (ESHRE 2017), as well as ART results collected from 39 European registers by ESHRE (Smeenk et al. 2023) and the Australian register including data from fertility centers in Australia and New Zealand (Newman, Repon C Paul, and Georgina M Chambers 2023).

Apart from this, various other literature has been included as supportive information (e.g. for the clinical background and device description). Please refer to section 11 for a complete list of references used for this CER.

6.7 Appraisal of Clinical Data

Clinical data found suitable for inclusion was appraised according to the principles outlined as part of clinical planning. The evaluation has been thorough and objective with no systematic exclusion of clinical data. Hence, the included clinical data consider both favorable and unfavorable results, appraised in Appendix 3, with the intention of demonstrating valid clinical evidence of the clinical performance and safety of the device under evaluation.

Appraisal and suitability criteria are described in **Appendix 3: Literature Search Appraisal**.

6.8 Clinical Investigation and PMCF

Universal IVF Medium was lawfully placed on the market in accordance with Directive 93/42/EEC and with the clinical evaluation fulfilling requirements for the legacy devices described in MDR Article 61(6a).

- The device is well-established technology, only containing components present in similar devices
- There have been no significant changes to the device or its intended purpose
- The device does not contain any high-risk components other than human derived components like HAS
- The device has been marketed for more than 37 years without safety or performance related issues emerging from PMS or risk analysis. Long-term clinical safety and performance have been demonstrated through literature review and PMS data collection since the device was first introduced to the market in 1988
- No new risks have been identified from the literature or other data sources for benchmark or similar devices.

In summary, there are no trends of general safety and performance issues for the actual device, benchmark or similar devices.

Based on the above, no clinical investigations, Post Market Clinical Follow-up (PMCF) studies or other proactive PMCF activities have been performed since the last update of the CER, as there was no additional need for clinical evidence to support clinical safety or clinical performance, with current data sources including clinical literature, market history, and post market surveillance data. However, after request from the British Standards Institution (BSI) to perform proactive PMCF for all Class III devices on a continuous basis, clinical experience data after routine use of Universal IVF Medium in a routine setting have been collected according to plan (PMCF033P, version B), including data from at least one clinic where they have been using Universal IVF Medium for fertilization of oocytes and culture through to cleavage stage, for a minimum of 50 patients.

7 Data Analysis

The clinical evaluation is based on documentation related to clinical performance and safety of Universal IVF Medium. All data are benchmarked against state of the art (as defined in section 1), as well as available data on benchmark or similar devices, especially data from comparison studies with head-to-head comparison of Universal IVF Medium versus benchmark devices, or benchmark versus benchmark devices (CE-marked commercially available Human Tubal Fluid (HTF) media, with similar intended purpose).

7.1 Clinical safety

7.1.1 Clinical Safety Related to Subject Device

Primary function of Universal IVF Medium is to support the biological function of gametes and embryos during *in vitro* fertilization, *in vitro* culture and embryo transfer. Due to a high number of confounding factors affecting ART results in general, no unintended events related to the use of Universal IVF Medium has been identified as the primary special requirement for evaluation of clinical safety, supported by no trends of negatively affected health of children born.

There are no reports (reviews or meta-analysis) of any safety issues related to the subject device, benchmark, or similar devices. Five (5) publications reported data on safety parameters after use of the actual device. No (0) publications using benchmark devices reported data on safety parameters.

Actual device:

Health of Children Born

Two (2) larger studies report birth weight after use of Universal IVF Medium:

- Eskild et al. (2013) report a retrospective analysis of singleton births from the University Hospital in Oslo (Norway) during a period of fourteen years, divided into three periods depending on culture medium used: Universal IVF Medium (1999 through 2007, n= 1584), ISM1 (2008 until September 2009, n= 402) and G-1 PLUS (September 2009 through 2011), n= 449). When adjusted for maternal age, previous deliveries and gestational age at birth compared with spontaneous pregnancies, results showed a statistically significant difference in birthweight in favor of G-1 PLUS (P=0.01). However, although Eskild et al. (2013) performed a grouped difference-in-difference statistical analysis comparing births after IVF and spontaneous conception during an equivalent period, as well as adjusting for maternal age at delivery (years), previous deliveries (0 or ≥1) and gestational age at birth (days), the analysis was limited by missing adjustment for confounding factors like maternal BMI, number of embryos transferred, and other clinical/laboratory changes during the fourteen years. In Norway, as well as other Nordic countries, there has been a trend towards an increased amount of elective single embryo transfers in order to lower the twin rate, which has not been accounted for in the study by Eskild et al. (2013). The authors state that “during our study period there was a gradual decrease in transfer of two embryos or more”. Several studies have investigated obstetric outcomes of singleton births resulting from twin

pregnancies where one of the twins is lost spontaneously (also referred to as vanishing twin). In spite of contradicting reports, there might be an effect of vanishing twins on gestational age and birth weight on the remaining fetus (Sun et al., 2017). Further, there is evidence that maternal BMI influences the risk of pregnancy complications as well as birth weight of singleton babies (Elfeky et al., 2017; Wallace et al., 2012).

- De Geyter et al. (2006) retrospectively studied the birth weight of singletons born after ART and natural conception in (previously) infertile couples. In the period between August 1996 and March 2004, a total of 203 deliveries after IVF/ICSI were recorded. Universal IVF Medium was used as the culture medium. Although lower than for the spontaneously conceived babies, mean birthweight after ICSI and IVF was within the normal range (3237 and 3266 g, respectively, normal range: 2.5 – 4.5kg). Information as to whether the malformations reported had occurred in the spontaneous or ART group is not provided. However, even if all seven were to be found among the two hundred and thirty-five deliveries which were the result of ART, this amounts to a malformation rate of only 2.9% (De Geyter et al., 2006). The risk of malformation after ART is generally higher compared to spontaneous pregnancies, which has been confirmed in a meta-analysis of 45 cohort studies (Hansen et al., 2013). Based on the included studies, the malformation rate after ART was in the range 1.5 – 12.0%. There is a growing evidence that subfertility on its own increases the risk of birth defects (Hansen et al., 2013).

Supporting Data:

In support of this, one (1) clinical study and two (2) case-reports describe delivery of live and healthy children after use of Universal IVF Medium:

- Laursen et al. (2003) compared two study groups with different sperm preparation media (Laursen, Andersen, and Hindkj 2003). Fertilization was carried out in Universal IVF Medium for both groups. There were no malformations in any of the children born, however there was a neonatal death in each of the PureSperm and Sperm Filter groups.
- Sills et al. (2009) carried out scrutiny of 14 cases of dual freeze-thaw sequences. Oocytes were fertilized in Universal IVF Medium and frozen in Embryo Freezing Pack at the 2PN stage. Next, embryos were thawed in Embryo Thawing Pack and cultured in BlastAssist System until the blastocyst stage. Then, blastocysts were frozen-thawed in BlastFreeze-BlastThaw. Finally, blastocysts were washed and equilibrated in Universal IVF Medium until transfer. Fourteen women had a transfer and five gave birth to live children. There were no malformation or developmental anomalies among offspring.
- Ajayi et al. (2003) reported two cases of ICSI where Universal IVF Medium was used for fertilization and culture of oocytes/embryos. In the first case, the woman was pregnant with triplets. However, one fetus died at 19 weeks gestation (with no evidence for this being related to the culture medium). The other two fetuses were born alive and well. In the second case, the woman was pregnant with a singleton. The baby was born alive and well (Ajayi et al., 2003).

In summary, none of the publications are reporting any safety issues related to Universal IVF Medium, benchmark, or similar devices; nor are there any general safety issues related to the procedure (e.g. IVF, ICSI).

7.1.2 Post Market Surveillance Data Analysis

A review of PMS data for Universal IVF Medium is presented below, including:

1. Complaints received during the period 2023.Jan.01 – 2024.Dec.31
2. Field corrective actions and CAPAs reported in the CooperSurgical QMS system, covering the period 2023.Jan.01 – 2024.Dec.31
3. Vigilance, adverse event reports, recalls and field corrective actions published during the period 2023.Jan.01 – 2024.Dec.31.

7.1.2.1 Complaints

During the Surveillance period (2023.Jan.01 – 2024.Dec.31), 10,472 (2023.Jan.01 – 2023.Dec.31) and 9495 (2024.Jan.01 – 2024.Dec.31) units of Universal IVF Medium were sold globally, respectively. One (1) (2023.Jan.01 – 2023.Dec.31) and 170* (2024.Jan.01 – 2024.Dec.31) complaints were reported during the surveillance period, therefore, the overall rate of complaints to the sales is 0.01 – 1.79%.
Additionally, there were no adverse events or serious incidents during this surveillance period and no corrective actions were initiated.

Please, refer to the PSUR033 ver. C and PSUR033 ver. E for more details.
*156 complaints of the 170 total could not be confirmed and are considered “alleged complaints”.

7.1.2.2 Reportable adverse events

Over the period between (January 01, 2023, to December 31, 2024), two (2) product complaints were collected internally, and evaluated per the Adverse Event Reporting (AER) Procedure, BSR-QAR-043. No Adverse Event Report (AER) or Medical Device Report (MDR) was identified. No new adverse event category was detected throughout the aforementioned time frame.

7.1.2.3 Serious Incident Reporting

Adverse event reports involving serious incidents relating to Universal IVF Medium were identified through public databases using the following terms:

- Product code MQL[13]
- *In vitro* fertilization culture medium[14]
- *In vitro* fertilization culture medium kit[2]

Adverse event reports relating to subject device, benchmark or similar devices or relevant general notifications identified through public databases retrieved for further assessment are listed in Table 7-1 and discussed below.

[13] The Product Code ”MQL” covers all media within reproduction and associated supplements
[14] The GMDN Product Code’s ”*In vitro* fertilization culture medium” and ”*In vitro* fertilization culture medium kit” covers all media within reproduction and associated supplements

Table 7-1: Adverse Event Reports

Searches	Number of Events
Search dates: 2023.Jan.01 – 2024.Dec.31	
FDA Manufacturer and User Facility Device (MAUDE): The Manufacturer and User Facility Device was searched for Product code: MQL.	N/A
Medicines and Healthcare products Regulatory Agency (MHRA): The Medicines and Healthcare products Regulatory Agency (MHRA) database was searched for 1) *In vitro* fertilization culture medium 2) *In vitro* fertilization culture medium kit	N/A
Database of Adverse Event Notification (DAEN)*: The Database of Adverse Event Notification) DAEN was searched for 1) *In vitro* fertilization culture medium 2) *In vitro* fertilization culture medium kit	N/A

*DAEN search allowed search dates from 01-Jan-24 to 02-Oct-2024

7.1.2.4 Field Safety Corrective Actions (FSCA)

For the reporting period 2023.Jan.01 – 2024.Dec.31, there have been no (0) FSCAs for the Universal IVF Medium products.

FSCAs, otherwise known as recalls, relating to Universal IVF Medium were identified through the CooperSurgical internal tracking system. Apart from this, FSCAs relating to subject device, benchmark or similar devices, or relevant general notifications, identified through public databases were retrieved for further assessment.

The following terms were used:

- Product code MQL
- *In vitro* fertilization culture medium
- *In vitro* fertilization culture medium kit

Recalls relating to subject device, benchmark or similar devices or relevant general notifications identified through public databases retrieved for further assessment are listed in Table 7-2 and discussed below.

Table 7-2: Recalls

Searches	Number of Events
Search dates: 2023.Jan.01 – 2024.Dec.31	
Medical Device Recall Database: The Manufacturer and User Facility Device was searched for Product code: MQL.	N/A
Medicines and Healthcare products Regulatory Agency (MHRA): The Medicines and Healthcare products Regulatory Agency (MHRA) database was searched for 1) *In vitro* fertilization culture medium 2) *In vitro* fertilization culture medium kit	N/A

Searches	Number of Events
System for Australian Recall Actions (SARA): The System for Australian Recall Actions SARA was searched for 1) *In vitro* fertilization culture medium 2) *In vitro* fertilization culture medium kit	N/A

7.1.3 Overall Conclusion of Clinical Safety

In summary, based on current knowledge, including literature and PMS data, Universal IVF Medium is safe when used by professionals within ART and as intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer. The complaint analysis showed no trends of performance or safety related issues, and an overall complaint ratio of 0.01 – 1.79% based on 19,967 units sold. Data supports a well-recognized safety profile related to the type of device. However, after request from the British Standards Institution (BSI) to perform proactive PMCF for all Class III devices, proactive PMCF is performed on a continuous basis. The data to be collected are clinical experience data from at least one (1) clinic where they have been using Universal IVF Medium for a minimum of 50 patients. According to the current PMCF plan (PMCF033P, version B), final signed data summaries must be available and included in an updated version of the CERs by Q2 2025. However, as this device is part of a product family where not all data have been collected at the time of this report, the CER will include proactive PMCF according to PMCF033P, version B , with inclusion of all collected data available at the time of the CER which will also be included in the final PMCF report (PMCF033R, version B) according to the schedule (PMCF033P, version B).

7.2 Clinical Performance

A total of 25 data reports (23 publications and two (2) data-sets on file at CooperSurgical) are available with clinical performance data related to the subject device. No (0) publications using benchmark devices reported data on performance parameters. These are further supported by PMS data presented in section 7.1.2, including a thorough analysis of customer complaints.

7.2.1 Clinical Performance Related to Subject Device

Performance of Universal IVF Medium is evaluated based on several parameters. However, these are all affected by several external factors which contribute to the outcome. Factors include but are not limited to intrinsic quality of the gametes (e.g. female/male -age, -health, -fertility, environmental exposures), and ex vivo manipulations (handling, skills, procedures, equipment). Moreover, the risk of introducing confounding factors, possibly affecting the results, increases with time (from obtaining the gametes to birth of a healthy child). This means that data recorded just after the intended purpose of the device in question best reflect possible effects of the device with a minimum of contributing confounding factors. Primary function of Universal IVF Medium is to support the biological function of gametes and embryos during *in vitro* fertilization, *in vitro* culture and embryo transfer. Therefore, the embryology parameters (fertilization, cleavage, and blastocyst rates) are most closely related to

performance of Universal IVF Medium. Oocytes can be fertilized by two different procedures: IVF or ICSI. During the IVF process spermatozoa are left to fertilize the oocyte in a dish/well, while in ICSI one spermatozoon is injected into the oocyte by the aid of a micromanipulator. In both cases, results are very dependent on gamete quality and operator skills. Patients undergoing IVF insemination are characterized by normal sperm quality and oocyte maturation (ESHRE 2017). Therefore, when assessing performance of a fertilization medium, the IVF fertilization rates are considered the best indicator.

Cohort studies with prospective randomized sibling oocytes/2PN zygotes (derived from the same patient) and split sperm samples (the same ejaculate split into two or more parts) are the most optimal study designs for comparison of these performance parameters. However, even if sibling oocytes are more comparable than oocytes from different patients, evaluation of a culture medium based on randomized sibling oocytes include a risk of unequal randomization of different oocyte qualities resulting in unequal fertilization rates. Moreover, comparison of an unequal number and/or quality of 2PN/zygotes can result in unequal embryo development caused by factors other than the culture media. The risk of bias introduced through oocyte or 2PN/zygote randomization increases the lower the number of patients included, and the lower the number of good quality oocytes/zygotes available per patient.

The confounding factors are increasingly important, the lower the sample size, and therefore case stories, retrospective analysis or comparison of individual studies often reflect more than just the performance of the applied culture medium. However, the evaluation is supported by comparison to KPIs published in the ESHRE 2017 consensus report, as well as data on clinical pregnancy rates collected from 39 European registers by ESHRE (Smeenk et al. 2023).

Implantation and clinical pregnancy rates are even more dependent on patient-related factors (incl. endometrial receptivity, age, cause of infertility), and on the number of embryos transferred, with decreasing implantation rates and increasing pregnancy rates the higher the number of embryos replaced. Further, many of the publications dealing with fertilization and culture until 2-8 cell stage as well as embryo transfer are limited by study design and sample size as well as reported results, and often do not provide sufficient information on confounding factors. Therefore, implantation/clinical pregnancy, live birth, and miscarriage rates are only considered as supportive data on performance for Universal IVF Medium.

Please refer to **Table 7-3**, for an overview of clinical performance data in comparison to state of the art. For more detailed information on the individual publications, please refer to **Table 6-2**, section 6.2.

Actual device:

Fertilization, Cleavage, and Blastocyst Rates

A total of 17 publications and two (2) data reports on file reported on fertilization rate. The overall fertilization rate ranges were 61-77% for IVF, 41.7-89.6% for ICSI, and 59.3[15]-100% for IVF/ICSI

[15] Excluding ORIGIO a/s 2006, where rates were low in both groups (54.7% in the control), and Kovacic et al. (2002), where fertilization rates were very low (38.9%).

(Barak et al. 1998; Coskun et al. 2000; Ferraretto et al. 2021; Frydman et al. 2004; Hambiliki et al. 2011; Hatakeyama et al. 2024; Ş. Hatirnaz et al. 2024; S. Hatirnaz et al. 2024; Holst et al. 1990; Jaroudi 2004; Karamalegos and Bolton 1999; Kattera and Chen 2003; Kidera et al. 2022; Laursen, Andersen, and Hindkj 2003; Staessen et al. 1998; Uppangala et al. 2020; Xella et al. 2010). Five (5) publications reported an overall cleavage rate range of 76.6[16]-98.2% (Barak et al. 1998; Holst et al. 1990; Staessen et al. 1998; Xella et al. 2010). Two (2) publications reported blastocyst rates between 50-66.6% (Kidera et al. 2022; Hatakeyama et al. 2024).

Four (4) studies are available with comparison data based on cohort studies with prospective randomized sibling oocytes:

- Staessen et al. performed 416 consecutive oocyte retrieval cycles in patients undergoing infertility treatment by IVF, including a total of 4812 oocytes divided into two groups and cultured in parallel in Universal IVF medium (2435 oocytes) and Ménézo B2 medium (2377 oocytes). The study showed no statistically significant differences in fertilization and cleavage rates after insemination by IVF. Fertilization rates were in line with the ESHRE KPI value of ≥60% for IVF (Staessen et al. 1998).
- Hambiliki et al. carried out 110 oocyte retrieval cycles in patients undergoing IVF or ICSI, including a total of 1206 oocytes divided into two groups and cultured in parallel: A) cultured in G-IVF Plus for 18-20 hours followed by G-1 Plus v.5 until 46 - 70 hours post-insemination (622 oocytes) and B) cultured in Universal IVF Medium for 18-20 hours followed by EmbryoAssist™ until 46 – 70 hours post-insemination (584 oocytes). Results showed similar fertilization rates of 67.2% in Universal IVF Medium and 73.5% in G-IVF Plus, and there were 'good cleavage' rates of 55.2% and 61% in these respective groups. All fertilization rates in both study groups were above ESHRE KPI values for IVF (Hambiliki et al. 2011).
- Erb 2004 (data on file) included data from 3 clinics with a total of 216 oocyte retrieval cycles from patients undergoing IVF or ICSI, and oocytes were randomized between Universal IVF Medium and ISM1™. Data showed similar fertilization rate in Universal IVF Medium versus ISM1™ (68.3% versus 63.5%), but a statistically significant higher rate of good quality embryo development in ISM1™ (69.4% versus 56.0% in Universal IVF Medium, $p < 0.0001$). The assessors in the study were blinded, but number of sibling oocytes available for randomization per woman was varying with a standard deviation of 5.1 and 4.3 for the two largest clinics, including patients with down to 5 oocytes. Moreover, some of the patients ended up having no embryos available after culture, indicating low oocyte quality. The combination of patients with down to 5 oocytes and low oocyte quality, introduces a risk of uneven randomization of the various oocyte qualities, which could explain the observed difference in embryo quality between the two study groups. This is further supported by large variations in overall fertilization rates between the 3 clinics (60.8% to 76.2%).
- ORIGIO a/s (2006) included data from 94 oocyte retrieval cycles from patients undergoing IVF or ICSI, and oocytes were randomized between Universal IVF Medium and EmbryoAssist™. Data showed similar fertilization rate in Universal IVF medium versus

[16] The lowest rates are due to publications before year 2000 (Staessen et al. 1998 and Barak et al. 1998), all showing similar rates in the control groups, and excluding Hambikili et al. (2011) which only provides 'good cleavage' rates. When excluding these publications, the cleavage rates are 96.4 - 98.2%

EmbryoAssist™ (50.8% versus 54.7%), but a statistically significant higher rate of good quality embryo development in EmbryoAssist™ (20.7% versus 45.9%, p<0.0001). Although the sample size was low, the clinical outcome was similar in the two groups.

Apart from the above, four (4) comparison studies are available with data after fertilization/culture in Universal IVF Medium compared to similar devices.

- Karamalegos and Bolton carried out a prospective, randomized study, including a total of 448 oocyte retrieval cycles where patients were randomized between Universal IVF Medium (n=230) and Earle's balanced salt solution (EBSS) (n=218). All women included were less than 38 years old with oocyte fertilization by standard IVF. Results showed no differences in fertilization rate (70.7% in Universal IVF Medium versus 71.4% in EBSS) (Karamalegos and Bolton 1999).
- Holst et al. investigated ART outcome after fertilization by IVF and culture in Universal IVF Medium or Ham's F10 supplemented with patient serum. 220 consecutive cycles were analyzed, with 110 cycles assigned to fertilization with each device. Fertilization (59.3% in Universal IVF Medium versus 57.4% in Ham's F10 + serum) and cleavage rates (97.2% in Universal IVF Medium versus 96.4% in Ham's F10 + serum) were similar in the two groups. The sample size is small, but the results do not indicate that a replacement of patient serum with HAS and SSR® negatively impact embryological outcomes (Holst et al. 1990).
- Xella et al. retrospectively investigated IVF and ICSI treatment of 726 women with all oocytes fertilized in Universal IVF Medium, followed by culture in Universal IVF medium or ISM1 from fertilization check until day 3. Data showed an overall fertilization rate of 89.6%, and cleavage rates of 98.3% in Universal IVF Medium versus 99.1% in ISM1™, with no significant differences in cleavage rate between the two devices. The two media were tested during different time periods, introducing a risk of other factors impacting the outcome (technicians experience and knowledge, fluctuations in culture conditions, other ART media or equipment changed etc.) (Xella et al. 2010).
- Barak et al. (1998) compared fertilization and culture to day 2-3 in Universal IVF Medium versus three competitor devices (P1 (Irvine Scientific), HTF (Irvine Scientific), and M3). Fertilization rates were significantly higher in the Universal IVF Medium group (78.2%) in comparison with competitors (55.9-70.5%). Cleavage rates for Universal IVF Medium were significantly lower than those reported for M3 medium (78.1% versus 92%), however, this did not have an impact on clinical outcomes (Barak et al. 1998).

Additionally, 12 publications reported data for Universal IVF Medium without comparison to other devices:

- Kidera et al. (2022) compared the impact of paternal age on fertilization rate achieved in female patients in the age groups <35 years, 35-39 years, and ≥40 years (Kidera et al. 2022). Paternal age had a significant effect only for the patients with maternal age 35-39 years, with paternal age <35 years resulting in a significantly higher fertilization rate (100%) compared with paternal age 35-39 years (71.4%) and ≥40 years (77.7%). However, all fertilization rates reported in this study were greater than the ESHRE KPIs for fertilization, with overall reported rates of 75-100%. In addition, the overall blastocyst rate range was 50-66.6%, greater than

the ESHRE KPIs. In each group with maternal age <35 years and ≥40 years, there was no significant difference in high-quality blastocyst rates.

- Coskun et al. (2000) compared fertilization rates after fertilization in Universal IVF Medium, followed by either culture in Universal IVF Medium until embryo transfer on Day 3 or culture in sequential media until transfer on Day 5 (Coskun et al. 2000). As expected, fertilization rates recorded in the two groups were comparable (68% and 67%) as this outcome was recorded at a point where all oocytes had been exposed to Universal IVF Medium only.
- Laursen et al. (2003) compared two study groups with different sperm preparation media (Laursen, Andersen, and Hindkj 2003). Fertilization was carried out in Universal IVF Medium for both groups, and there was no significant difference in fertilization rates, which were 69.8% in the Sperm Filter group and 70.6% in the PureSperm group.
- Frydman et al. (2004) fertilized oocytes from a total of 457 cycles in Universal IVF Medium (Frydman et al. 2004). On comparing the fertilization rates for IVF and ICSI fertilization, results were slightly higher for the IVF group (71%) compared with the ICSI group (63.5%), though this difference was not statistically significant. It is possible that the conditions requiring the use of ICSI are confounding factors in this study, as these conditions may also affect overall outcome.
- Ferraretto et al. (2021) recorded fertilization rates of 61.7% in a mixed group of ICSI and IVF patients, with results reported for 250 cycles. Although these results do not meet the ESHRE KPI value of ≥65% for ICSI fertilization, they are comparable with the KPI value of ≥60% for conventional IVF (Ferraretto et al. 2021).
- Kovacic et al. (2002) reported a fertilization rate of 38.9% after fertilization and culture to Day 2 in Universal IVF Medium (Kovačič et al. 2002).
- Jaroudi et al. (2004) compared embryological and clinical outcomes in two groups: both groups underwent fertilization in Universal IVF medium with subsequent culture in the same medium, with one group transferred at the zygote stage of development and the other group transferred at Day 3 (Jaroudi 2004). As expected, since both study groups included oocytes fertilized in Universal IVF Medium, there was no difference in the fertilization rates recorded, which were 66% in both groups.
- Karaki et al. (2002) compared Day 3 embryo transfer after fertilization and culture in Universal IVF Medium with Day 5 embryo transfer after fertilization in Universal IVF Medium and culture in sequential media (Karaki, Lahloub, and Ibrahim 2002).
- Kattera and Chen (2003) compared the fertilization rates of oocytes co-incubated with sperm for 2 hours versus oocytes co-incubated with sperm for 20 hours. Fertilization was carried out in Universal IVF Medium in both groups. There were no significant differences in fertilization rate, with rates of 75.8% in the 2 hour co-incubation group and 77% in the 20 hour group (Kattera and Chen 2003).
- Uppangala et al. (2020) compared the fertilization rates achieved after controlled ovarian stimulation and ICSI in patients with normal, poor, and hyper-response to stimulation (Uppangala et al. 2020). Although fertilization rates in the poor responders were lower than normal and hyper-responders (60% versus 68.5% and 64.2%) there were no statistically significant differences between groups.

- Hatirnaz, Safak, et al. (2024a) compared the efficacy of in-vitro maturation primed with either FSH-HCG using fresh embryo transfer (Group 1) or letrozole-HCG using frozen embryo transfer (Group 2) in women with oocyte maturation abnormalities (OMAs) (S. Hatirnaz et al. 2024). Fertilization was carried out in Universal IVF Medium for both groups. Results showed that Group 1 had a significantly lower fertilization rate than Group 2 (Group 1: 41.7% ± 34.4%, Group 2: 64.3% ± 29.1%, p = 0.027). The significantly lower fertilization rate in Group 1 did not meet the ESHRE KPIs for fertilization, and may be a result of a significantly higher endometrial thickness and serum estradiol concentration in this group (both $p < 0.001$).
- In another study, Hatirnaz, Safak, et al. (2024b) compared the effectiveness of Follicular Phase IVM with Luteal Phase IVM in women experiencing OMAs. (Ş. Hatirnaz et al. 2024). Fertilization was carried out in Universal IVF Medium for both groups, and there was no significant difference in fertilization rates, which were 65.8% ± 32.3% in the Follicular Phase IVM group and 70.0% ± 29.2% in the Luteal Phase IVM group. An additional study was performed on nine (9) women who underwent a Duostim protocol (both follicular and luteal phase IVM within the same cycle). Similar outcomes were observed, with no significant difference in fertilization rates (Follicular Phase Duostim IVM: 70.0% ± 29.8%, Luteal Phase Duostim IVM: 78.6% ± 30.7%).
- Hatakeyama et al. (2024) compared the impact on fertilization and embryonic development of assisted sperm fusion insemination (ASFI), against conventional intracytoplasmic sperm injection (C-ICSI) (Hatakeyama et al. 2024). The mean maternal age was 40.1± 3.2 years, and paternal age was 43.3 ± 5.5 years. The fertilization rate was significantly higher in the ASFI group (88.0%, 73/83) than in the C-ICSI group (70.2%, 80/114). In addition, there were no statistically significant differences in the rates of blastocyst formation (ASFI group: 63.9% (39/61); and C-ICSI group: 62.0% (44/71), p=0.858). The overall fertilization rate range was 88.0-70.2% and the blastocyst rate range was 62-63.9%, which are both greater than the ESHRE KPIs.

Supporting Data:

Implantation, Clinical Pregnancy, Live Birth, and Miscarriage Rates

Thirteen (13) publications reported implantation rates between 10-100% (Ajayi, Parsons, and Bolton 2003; Coskun et al. 2000; Frydman et al. 2004; Hambiliki et al. 2011; Holst et al. 1990; Jaroudi 2004; Karaki, Lahloub, and Ibrahim 2002; Karamalegos and Bolton 1999; Kattera and Chen 2003; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Staessen et al. 1998; Xella et al. 2010). A total of 19 publications reported clinical pregnancy rates between 0-68.6%[17] (Barak et al. 1998; Bekzatova and Shishimorova 2021; Coskun et al. 2000; Ferraretto et al. 2021; Frydman et al. 2004; Hambiliki et al. 2011; Ş. Hatirnaz et al. 2024; S. Hatirnaz et al. 2024; Holst et al. 1990; Jaroudi 2004; Karaki, Lahloub, and Ibrahim 2002; Karamalegos and Bolton 1999; Kattera and Chen 2003; Kidera et al. 2022; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Staessen et al. 1998; Xella et al. 2010). Twelve (12) publications reported live birth rate range of 16.6-100% (Ajayi, Parsons, and Bolton 2003; Ferraretto et al. 2021; Frydman et al. 2004; Hambiliki et al. 2011; Ş. Hatirnaz et al.

[17] Excluding Monks et al. (1993) which reported unusually low clinical pregnancy and live birth rates due to use of natural cycle IVF

2024; S. Hatirnaz et al. 2024; Kidera et al. 2022; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Sills et al. 2009; Staessen et al. 1998). A total of 12 publications reported miscarriage rates between 0-53% (Coskun et al. 2000; Frydman et al. 2004; Hambiliki et al. 2011; Ş. Hatirnaz et al. 2024; S. Hatirnaz et al. 2024; Holst et al. 1990; Jaroudi 2004; Kidera et al. 2022; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Staessen et al. 1998; Xella et al. 2010).

Four (4) studies are available with comparison data based on cohort studies with prospective randomized sibling oocytes.

- Staessen et al. performed 416 consecutive oocyte retrieval cycles from patients undergoing infertility treatment by IVF, including total 4812 oocytes divided into two groups and cultured in parallel in Universal IVF medium (2435 oocytes) and Ménézo B2 medium (2377 oocytes). Fifty-seven embryo transfers were performed in the Universal IVF Medium group, resulting in an implantation rate of 13.8%, compared with an implantation rate of 21.5% in a group of 60 patients after use of B2 medium and an implantation rate of 18.8% in a large mixed group. While reported implantation rates were below the ESHRE KPI value of ≥35%, there were no statistically significant differences between study groups. There was a clinical pregnancy rate of 22.8%, a live birth delivery rate of 19.3% and a miscarriage rate of 8.3%. Sixty women had oocytes replaced from the B2 group, resulting in a clinical pregnancy rate of 36.7%, live birth delivery rate of 28.3% and a miscarriage rate of 19%. Finally, a large mixed group reported clinical pregnancy rates of 35.6%, live birth delivery rates of 24.9% and miscarriage rates of 20.7%. There were no statistically significant differences between study groups (Staessen et al. 1998).
- Hambiliki et al. carried out 110 oocyte retrieval cycles from patients undergoing IVF or ICSI, including total 1206 oocytes divided into two groups and cultured in parallel in two groups: A) cultured in G-IVF Plus for 18-20 hours followed by G-1 Plus v.5 until 46 - 70 hours post-insemination (622 oocytes) and B) cultured in Universal IVF Medium for 18-20 hours followed by EmbryoAssist™ until 46 – 70 hours post-insemination (584 oocytes). Implantation rates were similar for the two groups, with rates of 37.5% for Universal IVF Medium and 40.9% for G-IVF Plus. All implantation rates in both study groups were above ESHRE KPI values for IVF. Clinical pregnancy rates were slightly higher in the G-IVF Plus group, at 46.4% versus 36.4%, but this was not statistically significant. Live birth rates were similar in the two groups (36.4% for Universal IVF Medium versus 34.8% for G-IVF Plus) and miscarriage rates were 0% (Universal IVF Medium/EmbryoAssist™) versus 25% (G-IVF Plus/G-1 Plus) (Hambiliki et al. 2011).
- Erb 2004 data on file included data from 3 clinics with total 216 oocyte retrieval cycles from patients undergoing IVF or ICSI, and oocytes randomized between Universal IVF Medium and ISM1™. Clinical outcomes were similar in the two groups, with implantation rates of 35.0% versus 27.5% and clinical pregnancy rates of 42.6% versus 36.9% in Universal IVF Medium versus the ISM1™ group.
- ORIGIO a/s (2006) included data from 94 oocytes retrieval cycles from patients undergoing IVF or ICSI, and oocytes randomized between Universal IVF Medium and EmbryoAssist™. Although the sample size was low, clinical outcome was similar in the two groups, with implantation rates of 28.6% versus 32.0% and clinical pregnancy rates of 42.9% versus 37.5%.

Apart from the above, five (5) comparison studies are available with supporting data after fertilization/culture in Universal IVF Medium compared to similar devices:

- Karamalegos and Bolton did a prospective, randomized study, including a total of 448 oocyte retrieval cycles where patients were randomized between Universal IVF Medium (n=230) and Earle's balanced salt solution (EBSS) (n=218). Implantation rates were slightly higher with Universal IVF Medium (16.1%) versus EBSS (11.6%), though this difference was not statistically significant. Clinical pregnancy rates were similar, although there was a tendency to a higher rate in the Universal IVF Medium group (27.6% versus 18.5% in EBSS) (Karamalegos and Bolton 1999).
- Holst et al. investigated ART outcome after fertilization by IVF and culture in Universal IVF Medium or Ham's F10 supplemented with patient serum. 220 consecutive cycles were analyzed, in the first 110 Ham's F10 + serum was used, followed by 110 cycles with Universal IVF Medium. Implantation rates were comparable in the two groups, with rates of 14.4% for Universal IVF Medium and 11% for Ham's F10. Clinical pregnancy rates were also comparable in the two groups, with rates of 34% for Universal IVF Medium and 29% for Ham's F10. Miscarriage rates were 17% (Universal IVF) and 29% (Ham's F10 + serum) (Holst et al. 1990). The sample size is small, but the results do not indicate that a replacement of patient serum with HAS and SSR® negatively impact ART outcome.
- Xella et al. retrospectively investigated IVF and ICSI treatment of 726 women with all oocytes fertilized in Universal IVF Medium, followed by culture in Universal IVF medium or ISM1™ from fertilization check until day 3. Data showed that implantation rates were significantly lower in the Universal IVF Medium group (10%) versus the ISM1 group (15%). The two media were tested during different time periods, introducing a risk of other factors impacting the outcome (technicians experience and knowledge, fluctuations in culture conditions, other ART media or equipment changed etc.). This may explain why the implantation rate of the Universal IVF Medium group, which was reported first, is statistically significantly different from that in the ISM1 group. Clinical pregnancy rates were lower for the Universal IVF Medium group, with a rate of 21% versus 31% in the ISM1 group. However, there was no significant difference in miscarriage rates, which were 15% for the Universal IVF Medium group and 11% for the ISM1 group (Xella et al. 2010). The two media were tested during different time periods, introducing a risk of other factors impacting the outcome (technicians experience and knowledge, fluctuations in culture conditions, other ART media or equipment changed etc.). This may explain why the results of the Universal IVF Medium group, which were reported first, are statistically significantly different from those in the ISM1 group.
- Barak et al. (1998) compared fertilization and culture to day 2-3 in Universal IVF Medium versus three competitor devices (P1 (Irvine Scientific), HTF (Irvine Scientific), and M3). Clinical pregnancy rates were significantly higher after the use of Universal IVF Medium (46.4%) compared with competitor devices (clinical pregnancy rates of 18.1-33.3%).
- Monks et al. (1993) compared Universal IVF Medium with three competitor devices (B2, HTF-WFI, and HTF-UHP) in natural cycle IVF (Monks et al. 1993). There were no significant differences between Universal IVF and competitor devices for clinical pregnancy rate (11.8% versus 8.5-14.3%) or live birth delivery rate (5.9% versus 8.1-9.5%).

Further to this, there are 14 additional publications including supporting data for Universal IVF Medium:

- Kidera et al. (2022) compared the impact of paternal age on clinical outcomes for female patients in the age groups <35 years, 35-39 years, and ≥40 years (Kidera et al. 2022). Overall, clinical pregnancy rates were 25-68.6% and live birth delivery rates were 16.6-61.8%, with more successful outcomes in younger female patients, and paternal age did not affect these results. Miscarriage rates showed a similar pattern overall, with rates of 7.8-53% dependent on maternal age. However, paternal age had a significant effect on miscarriage rate in female patients <35 years, with paternal age ≥40 years resulting in higher miscarriage rates (33.3%) in comparison with paternal age <35 years (13.1%) and 35-39 years (7.8%).
- Coskun et al. (2000) compared implantation, clinical pregnancy, and miscarriage rates after fertilization in Universal IVF Medium, followed by either culture in Universal IVF Medium until embryo transfer on Day 3 or culture in sequential media until transfer on Day 5 (Coskun et al. 2000). There were no significant differences between the two study groups.
- Laursen et al. (2003) compared two study groups with different sperm preparation media (Laursen, Andersen, and Hindkj 2003). Fertilization was carried out in Universal IVF Medium for both groups. Implantation rates were comparable, at 21% in the Sperm Filter group and 19.8% in the PureSperm group. There were no significant differences between those groups for clinical pregnancy, live birth delivery rate, or miscarriage rate.
- Frydman et al. (2004) fertilized oocytes from a total of 457 cycles in Universal IVF Medium (Frydman et al. 2004). On comparing clinical outcomes for IVF and ICSI fertilization, there were no significant differences between these groups for implantation, clinical pregnancy, live birth delivery, or miscarriage rates.
- Bekzatova and Shishimorova (2021) compared natural IVF and oocyte accumulation in known poor responders (Bekzatova and Shishimorova 2021). Oocytes in both groups were fertilized in Universal IVF Medium. Clinical pregnancy rate was higher in the natural IVF group (28.1%) compared with the oocyte accumulation group (20%); however, this difference was not statistically significant.
- Ferraretto et al. (2021) recorded a cumulative clinical pregnancy rate of 38.4% and a cumulative live birth delivery rate of 26.4%.
- Kovacic et al. (2002) reported an implantation rate of 17.8%, a clinical pregnancy rate of 22.9%, a live birth delivery rate of 18.3%, and a miscarriage rate of 20% after fertilization and culture to Day 2 in Universal IVF Medium (Kovačič et al. 2002).
- Sills et al. (2009) reported a live birth delivery rate of 35.7% after the use of Universal IVF Medium for fertilization of oocytes resulting in the eventual transfer of frozen-thawed blastocysts (Sills et al. 2009).
- Ajayi et al. (2003) reported the results of two ICSI cycles using Universal IVF Medium for fertilization. Both cycles resulted in live births.
- Jaroudi et al. (2004) compared embryological and clinical outcomes in two groups: both groups underwent fertilization in Universal IVF medium with subsequent culture in the same medium, with one group transferred at the zygote stage of development and the other group transferred at Day 3 (Jaroudi 2004). Implantation rates were significantly higher in the Day 3 group (25.5%) versus the zygote transfer group (17.2%). Clinical pregnancy rates were

significantly higher in the Day 3 group (41.98%) versus the zygote transfer group (27.64%). However, there was no significant difference in miscarriage rate.

- Karaki et al. (2002) compared Day 3 embryo transfer after fertilization and culture in Universal IVF Medium with Day 5 embryo transfer after fertilization in Universal IVF Medium and culture in sequential media (Karaki, Lahloub, and Ibrahim 2002). Although implantation rates were significantly higher on Day 5 (26% versus 13% for Day 3 transfer), there was no significant difference in clinical pregnancy rate (29% in Day 5 patients versus 26% in Day 3 patients).
- Kattera and Chen (2003) compared the clinical outcomes of oocytes co-incubated with sperm for 2 hours versus oocytes co-incubated with sperm for 20 hours. Fertilization was carried out in Universal IVF Medium in both groups. Implantation rates were significantly higher in the 2 hour incubation group (24.6%) compared with the 20 hour incubation group (12.1%). Clinical pregnancy rates were significantly higher in the 2 hour incubation group compared with the 20 hour incubation group (Kattera and Chen 2003).
- Hatirnaz, Safak, et al. (2024a) compared the efficacy of in-vitro maturation primed with either FSH-HCG using fresh embryo transfer (Group 1) or letrozole-HCG using frozen embryo transfer (Group 2) in women with oocyte maturation abnormalities (OMAs) (S. Hatirnaz et al. 2024). Fertilization was carried out in Universal IVF Medium for both groups. Results showed that Group 1 had a significantly lower clinical pregnancy rate than Group 2 (Group 1: 0%, Group 2: 37.5%, $p = 0.042$). Of the pregnancies that resulted in Group 2, the live birth rate was 28.6% and miscarriage rate was 7.1%.
- In another study, Hatirnaz, Safak, et al. (2024b) compared the effectiveness of Follicular Phase IVM with Luteal Phase IVM in women experiencing OMAs. (Ş. Hatirnaz et al. 2024). Fertilization was carried out in Universal IVF Medium for both groups. On comparing clinical outcomes, clinical pregnancy, live birth delivery, and miscarriage rates were higher for Group 2, though these differences were not statistically significant.

Table 7-3: Summary of Clinical Performance

	Fertilization Rate (%)	Cleavage Rate (%)	Blastocyst Rate (%)	Implantation Rate (%)	Clinical Pregnancy Rate (%)	Live Birth Rate (%)	Miscarriage Rate (%)	References
Universal IVF Medium	IVF: 61-77 ICSI: 41.7-89.6 IVF/ICSI: 59.3[18]-100	76.6[19]-98.2	50-66.6	10-100	0-68.6[20]	16.6-100[20]	0-53	Literature: (Monks et al. 1993; Ajayi, Parsons, and Bolton 2003; Barak et al. 1998; Bekzatova and Shishimorova 2021; Coskun et al. 2000; Ferraretto et al. 2021; Frydman et al. 2004; Hambiliki et al. 2011; Hatakeyama et al. 2024; Ş. Hatirnaz et al. 2024; S. Hatirnaz et al. 2024; Holst et al. 1990; Jaroudi 2004; Karaki, Lahloub, and Ibrahim 2002; Karamalegos and Bolton 1999; Kattera and Chen 2003; Kidera et al. 2022; Kovačič et al. 2002; Laursen, Andersen, and Hindkj 2003; Sills et al. 2009; Staessen et al. 1998; Uppangala et al. 2020; Xella et al. 2010) Data on file: Erb et al. 2004, ORIGIO A/S 2006

[18] Excluding ORIGIO a/s 2006, where rates were low in both groups (54.7% in the control), and Kovacic et al. (2002), where fertilization rates were very low (38.9%).

[19] The lowest rates are due to publications before year 2000 (Staessen et al. 1998 and Barak et al. 1998), all showing similar rates in the control groups, and excluding Hambikili et al. (2011) which only provides 'good cleavage' rates. When excluding these publications, the cleavage rates are 96.4 - 98.2%

[20] Excluding Monks et al. (1993) which reported unusually low clinical pregnancy and live birth rates due to use of natural cycle IVF

	Fertilization Rate (%)	Cleavage Rate (%)	Blastocyst Rate (%)	Implantation Rate (%)	Clinical Pregnancy Rate (%)	Live Birth Rate (%)	Miscarriage Rate (%)	References
Data on benchmark/similar devices and state of the art for comparison								
ESHRE KPI's	IVF: ≥ 60 ICSI: ≥ 65	≥ 95	≥40	≥35	-	-	-	(ESHRE 2017)
State of the art (Europe)	-	-	-	-	IVF: 34.6 (27.4-63)[21] ICSI: 33.5 (29.5-52.1)	IVF: 25.3 (17.9-43.5) ICSI: 24.1 (17.7-39.2)	-	(Smeenk et al. 2023)
State of the art (Australia)	-	-	-	-	32.5 (20.2-35.1)	25.3 (14.5-27.5)	-	(Newman, Repon C Paul, and Georgina M Chambers 2023)

[21] (Mean, range)

Summary of clinical performance:

Clinical results after ART treatments vary depending on numbers of confounding factors, including but not limited to intrinsic quality of the gametes (e.g. female/male -age, -health, -fertility, environmental exposures), and ex vivo manipulations (handling, skills, procedures, equipment). The risk of introducing confounding factors, possibly affecting the results, increases with time (from obtaining the gametes to birth of a healthy child). This means that data recorded just after the intended purpose of the device in question best reflect possible effects of the device with a minimum of contributing confounding factors. Therefore, when evaluating performance of devices involved in ART treatments, this must always be considered. Evaluation of clinical performance of a culture medium intended for fertilization and culture until the 2-8 cell stage is primary based on fertilization, cleavage and implantation rates. Oocytes can be fertilized by two different procedures: IVF or ICSI. During the IVF process spermatozoa are left to fertilize the oocyte in a dish/well, while in ICSI one spermatozoon is injected into the oocyte by the aid of a micromanipulator and therefore more dependent on technician skills. Therefore, IVF fertilization rates are preferable when assessing clinical performance of a fertilization medium. Data published or available after use of Universal IVF Medium show fertilization rates of 61-77% for IVF, 41.7-89.6% for ICSI, and 59.3 -100% for IVF/ICSI. Cleavage rates were 76.6-98.2%, blastocyst rates were 50-66.6%, implantation rates were 10-100%, clinical pregnancy rates were 0-68.6%, live birth rates were 16.6-100%, and miscarriage rates were 0-53%. There were no data published after standard IVF/ICSI treatment using benchmark or similar devices.

Based on this, there are no trends of any negative effects of Universal IVF Medium on clinical outcome, and the device is performing according to state of the art, as well as benchmark and similar devices.

7.2.2 Overall Conclusion of Clinical Performance

In summary, clinical results after ART are dependent on patient population, as well as external confounding factors like clinical/laboratory procedures/equipment/skills. Based on the data presented and reviewed against current knowledge/state of the art, as well as data on benchmark or similar devices, it can be concluded that Universal IVF Medium is performing well, when used as intended by professionals within ART and as intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer. However, after request from the British Standards Institution (BSI) to perform proactive PMCF for all Class III devices, proactive PMCF is performed on a continuous basis. The data to be collected are clinical experience data from at least one (1) clinic where they have been using Universal IVF Medium for a minimum of 50 patients. According to the current PMCF plan (PMCF033P, version B), final signed data summaries must be available and included in an updated version of the CERs by Q2 2025. However, as this device is part of a product family where not all data have been collected at the time of this report, the CER will include proactive PMCF according to PMCF033P, version B, with inclusion of all collected data available at the time of the CER which will also be included in the final PMCF report (PMCF033R, version B) according to the schedule (PMCF033P, version B).

7.3 State of the Art

A total of 11 publications are available for evaluation of state-of-the-art relating to the type of device and procedure. These publications were identified in the latest search covering the period 2023.Jan.01 – 2024.Dec.31. The current state-of-the-art is discussed in section 5.8, while the four (4) new publications are discussed here.

In summary, there are no changes in state-of-the-art prohibiting the use of subject device, benchmark, or similar devices.

Universal IVF Medium forms part of a group of devices (*in vitro* fertilization culture medium) characterized by common and stable designs with little evolution, and well-known clinical safety and performance characteristics. The device is intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer. Various systematic review and meta-analyses have been performed on issues related to these procedures, but evidence for one procedure or medium being superior to another is yet to be established:

- A recent systematic review and meta-analysis by Siristatidis et al. (2023), investigating the risks of congenital anomalies and perinatal outcomes following embryo transfers at different developmental stages (blastocyst vs. cleavage-stage) and whether embryos were cryopreserved or not (fresh vs. frozen), included two (2) randomized controlled trials (RCTs) and 31 observational studies. The authors found no statistically significant differences in the risk of congenital anomalies between blastocyst and cleavage-stage transfers. However, blastocyst transfers were associated with increased odds of delivering male neonates. The review also revealed that frozen blastocyst transfers were linked to a significantly decreased risk of low birth weight compared to both fresh blastocyst and cleavage-stage transfers, but an increased risk of perinatal death compared to fresh cleavage-stage transfers. Fresh-cleavage transfers also showed a statistically significantly lower risk of preterm delivery (PTD) in multiple pregnancies compared to all other transfer modalities. Despite these findings, it is important to note that the results have very low certainty of evidence, as most data come from observational studies. The authors emphasize the need for further research to clarify these risks, particularly regarding cryopreservation and its long-term effects on offspring (Siristatidis et al. 2023).

- Good practice recommendations from the ESHRE Add-ons Working Group involve not supplementing embryo culture medium with growth factors, since recent reviews showed that the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) did not reduce live birth rate or miscarriage rate compared to conventional media without this addition. It is also recommended to add hyaluronic acid (HA) to transfer media, which is a promotor of cell-to-cell adhesion and produces a viscous solution that has been proposed to inhibit the expulsion of the embryo. Recent reviews show an increase in live birth rate with a transfer media with a high concentration of HA compared to a media with no or low HA. It is also recommended to monitor for multiple pregnancies as it is theorized that the use of an adherence compound could allow implantation of lower-quality embryos, and thereby cause an increased rate of miscarriages (ESHRE Add-ons working group et al. 2023).

- The review by Sciorio and Rinaudo (2023) reported on how different current culture conditions may affect oocyte and embryo viability. They report that culture media mainly contain pyruvate, lactate, and glucose as carbohydrate sources, as well as salts, sodium bicarbonate buffer, amino acids, EDTA, an antibiotic such as gentamicin, and a pH indicator such as Phenol Red. However, many comparative studies are underpowered or flawed in study design to determine whether one culture media is superior to another. The composition of amino acids requires special attention. They support several processes during embryo development; however their addition may increase the production of ammonium during incubation, which may be resolved by performing a media change during a sequential system. A more recent approach involves using a stable dipeptide form, such as alanyl-glutamine or glycyl-l-glutamine, to effectively minimize ammonium buildup in modern embryo culture media and prevent the creation of a toxic environment for embryos. They also report that supplementation of macromolecules in culture media, such as human serum albumin (HSA), support embryo development and improve live birth rates. Hyaluronic acid is commonly added to culture media, and has been reported to enhance implantation and clinical pregnancy rates, especially in women over 35 and those with poor-quality embryos (Sciorio and Rinaudo 2023).

- A systematic review and meta-analysis by Sonigo et al. (2024) reported on neonatal outcomes in response to various IVF culture conditions. They found pregnancy related complications, as well as the risk of miscarriage and stillbirth were similar across the different media. The network meta-analysis did not show any significant impact of different culture media on birthweight or preterm birth (Sonigo et al. 2024).

Table 7-4: Summary of publications on State of the Art for Subject Device identified in latest search

Reference	Indication/ Procedure	Type of Article	Key Message	Alternative Treatment Explanations	Contribution to State of the Art
(ESHRE Add-ons working group et al. 2023)	ICSI, Sperm testing, IVF	Good practice recommendations from the ESHRE	From the recommendations collected in this publication, the following ones are applicable to fertilization: - Artificial oocyte activation (AOA) is currently not recommended for routine clinical use. AOA is recommended for complete activation failure (0% 2PN), very low fertilization (<30% fertilization), or globozoospermia - Sperm DNA damage testing is currently not recommended for routine clinical use - Sperm hyaluronic acid binding assay (HBA) is currently not recommended for routine clinical use - Intravaginal or intrauterine culture devices are currently not recommended for routine clinical use. - ICSI is not recommended for non-male factor infertility	Recommended alternatives for fertilization: - AOA in certain situations such as complete activation failure (0% 2PN), very low fertilization (<30% fertilization), or globozoospermia. - Use of standard IVF for non-male factor infertility. - Although not recommended, other alternatives for fertilization: - HBA to predict sperm fertilizing potential - Use of intravaginal or intrauterine culture devices to enable women feel fertilization was more natural as a result of feeling closer to their embryos while carrying the device	Current data indicate that AOA can be beneficial in certain circumstances and that ICSI is not recommended for non-male factor infertility

Reference	Indication/ Procedure	Type of Article	Key Message	Alternative Treatment Explanations	Contribution to State of the Art
(Sciorio and Rinaudo 2023)	Embryo culture	Review	As it is already well-known, each factor (type of media, oxygen concentration, plastic dish, oil, temperature, etc.) involved in a gamete or embryo manipulation has an impact on fertilization and embryo development and therefore, they must be well-controlled. A stable temperature of 37ºC during oocyte manipulation has been associated with improved fertilization rate. IVF laboratories must have excellent quality control systems to prevent possible impact on fertilization of specific molecules or chemical compounds Processes that would benefit from microengineering include oocyte collection, micromanipulation, identification of follicular aspirates and isolation of individual oocyte cumulus masses and removal of the cumules mass fertilization (conventional or by ICSI)	Alternative to static embryo culture: technology of microfluidic devices, which could provide a dynamic environment resembling the moving environment that embryos have in vivo as they travel from the oviduct to the uterus.	Sciorio and Rinaudo reinforces the fact that a stable temperature of 37ºC during oocyte manipulation has been associated with improved fertilization rate. Although not yet considered state of the art, the use of microfluidic devices and AI are gaining importance in the field of assisted reproduction and therefore worth mentioning

Reference	Indication/ Procedure	Type of Article	Key Message	Alternative Treatment Explanations	Contribution to State of the Art
(Siristatidis et al. 2023)	Embryo transfer	Systematic review and network meta-analysis	Current very-low certainty of evidence shows that there may be little-to-no difference in the risk for congenital anomaly or adverse perinatal outcome of pregnancy following blastocyst- vs cleavage-stage embryo transfer, although there was a slightly increased probability of a male neonate following blastocyst transfer. When considering cryopreservation, frozen-blastocyst transfer was associated with a reduction in the risk for low birth weight (LBW) compared with both fresh-transfer modalities, and fresh-cleavage transfer may be associated with a reduction in the risk for perinatal death compared with frozen-blastocyst transfer.	Given the increasing prevalence of cryopreservation and extended culture of embryos, there are several types of embryo transfer, including the fresh-blastocyst, fresh-cleavage, frozen-blastocyst and frozen-cleavage interventions.	Through the literature search, 550 studies were retrieved and 33 were included in the systematic review to analyze congenital anomalies and perinatal outcomes following all four treatment modalities (i.e. fresh-blastocyst, fresh-cleavage, frozen-blastocyst, frozen-cleavage). Any congenital anomaly constituted the primary outcome, whereas preterm delivery (delivery < 37 weeks), low birth weight (LBW; < 2500 g), gender of the neonate (male), perinatal death and healthy neonate (defined as liveborn neonate, delivered at term, weighing ≥ 2500 g, surviving for at least 28 days post-birth and without any congenital anomaly) were considered as secondary outcomes. There was no significant difference found in the risk for any congenital anomaly between blastocyst- and cleavage-stage transfer (RR, 0.80 (95% CI, 0.63–1.03); 10 studies; n = 192,442; I2 = 85.5%). An increased probability of a male neonate was observed following

Reference	Indication/ Procedure	Type of Article	Key Message	Alternative Treatment Explanations	Contribution to State of the Art
					blastocyst- vs cleavage-stage transfer (RR, 1.07 (95% CI, 1.06–1.09); 18 studies; n = 227,530; I2 = 32.7%). No significant differences in other secondary outcomes or significant subgroup differences between liveborn singletons and multiple pregnancies were observed. The network meta-analysis showed a significantly lower risk for LBW following frozen-blastocyst vs fresh-blastocyst (RR, 0.76 (95% CI, 0.60–0.95)) or fresh-cleavage (RR, 0.74 (95% CI, 0.59–0.93)) transfer. Frozen-blastocyst transfer was associated with an increased risk for perinatal death compared with the fresh-cleavage method (RR, 2.06 (95% CI, 1.10–3.88)). The higher probability of a male neonate following blastocyst transfer remained evident in the network comparisons. All outcomes were assessed to be of very-low certainty of evidence. High-quality randomized controlled trials (RCTs) with separate data on fresh and frozen cycles and consistent reporting of culture

Reference	Indication/ Procedure	Type of Article	Key Message	Alternative Treatment Explanations	Contribution to State of the Art
					conditions and freezing methods are mandatory. Individual participant data meta-analyses are required to address the substantial inconsistency resulting from current aggregate data approaches.
(Sonigo et al. 2024)	Embryo culture	Systematic review and meta/analysis	No difference was observed for neonatal outcomes according to the embryo culture conditions (different culture media, time-lapse vs standard incubator and hypoxia vs normoxia) evaluated in this review. Further research is needed about the safety of IVF culture conditions as far as future children's health is concerned.	The alternatives regarding embryo culture mentioned in this article are: - Hypoxia - normoxia: no statistical difference for birthweight and gestational age at birth - Time-lapse incubator vs standard incubator: the authors could not perform a meta-analysis due to different study groups between the studies.	This publication reinforces the safety or various culture media used in IVF; however, it also identifies the need for ongoing research to ensure long-term safety suggesting that while culture conditions might not impact immediate neonatal outcomes, other factors or long-term effects need further investigation.

7.4 Consideration of Side Effects

Based upon evaluation of clinical safety, clinical performance, materials used and techniques of the Universal IVF Medium, benchmark and similar devices through available literature data and PMS data, there have been no new risks or side effects identified for the type of device when used as intended. There have been no new risks, hazards, or side effects identified from the PMS data analyzed for a recent period of two (2) years (2023.Jan.01 – 2024.Dec.31) as part of this clinical evaluation report.

7.5 Clinical Benefit-Risk Analysis

The clinical benefit of Universal IVF Medium is that it provides optimal clinical and physiological conditions to support the biological function of gametes and embryos during *in vitro* fertilization, *in vitro* culture and embryo transfer. The product contains well-known components present in other ART media with similar intended purposes and is based on known technology.

Universal IVF Medium contains Ph. Eur. (European Pharmacopoeia)/USP (United States Pharmacopeia) grade HAS. Although the content of HAS is presenting a risk, the overall residual risk for Universal IVF Medium is judged to be acceptable. Pharmaceutical grade HAS is a standard component of ART media, which is also included in other CE marked media used for ART treatments. Besides HAS the medium contains other well-known components already present in other ART media with the same intended purpose, and which do not cause any concern regarding genotoxicity, carcinogenicity, or reproductive and developmental toxicity.

The Risk Management (RM) procedure (BSR-ENG-007) has been applied to the Universal IVF Medium. All RM activities have been conducted according to the procedure, and associated work instructions and forms, and the product Risk Management Report (RMF0108-RMR) has no outstanding items to be resolved. All potential risks associated with the intended purpose are minimized and acceptable as the combination of the severity and probability of the occurrence were mitigated as far as possible (AFAP). Post-production data was utilized to conduct RM for Universal IVF Medium, as described within the product PMS Plan (PMS033P) and Periodic Safety Update Report (PSUR) (PSUR033). Future PMS activities will be conducted according to BSR-QAR-042 (PMS procedure) and BSR-ENG-007 (Risk Management).

This clinical evaluation did not identify any publications showing changes in state of the art prohibiting use of the actual device, benchmark, or similar devices. Nor did the clinical evaluation identify any negative trends regarding performance or safety outcome after use of the actual device, benchmark, or similar devices. Finally, there were no records of Universal IVF Medium or benchmark devices in the adverse event and recall databases (USA, UK and Australia) and the product-related complaint ratio for Universal IVF Medium is 0.01 – 1.79%.

Based on the above, Universal IVF Medium has a positive benefit-risk profile and still provides a state-of-the-art environment intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer.

7.6 Product Literature and Instructions for Use

Universal IVF Medium product literature, marketing brochures, and Instructions for Use are consistent with the clinical data and cover all the hazards identified with risks for use of Universal IVF Medium. Apart from precautions and warnings of when to avoid using the product based on visual inspections, the IFU includes two cautions: 1) concerning the content of HAS (which is of biological origin from human blood) that notifies the user about the fact that all blood products should be treated as potentially infectious, and 2) concerning the content of gentamicin (antibiotic) that notifies the user not to use the product on patients that have a known allergy to gentamicin or similar antibiotics.

CooperSurgical is regularly gathering other clinically relevant information that may impact use of the device as part of PMS. Risk management processes, plans, and reports for the subject device are evaluated periodically for updates from PMS and during life cycle of device through the clinical evaluation process.

CooperSurgical product information or marketing literature is consistent with the indications for use and no claims are being made that contradict or compromise clinical safety, clinical performance, or intended purpose of the device.

8 Conclusions

This clinical evaluation is based on documentation related to clinical performance and safety of Universal IVF Medium. All data are benchmarked against state of the art (as defined in section 1), and any available data on benchmark or similar devices. Moreover, the evaluation of safety includes customer complaints and product recalls related to the actual device, as well as any adverse event reports, serious incidents, and product recalls for the actual device, benchmark and similar devices published in public safety databases.

Universal IVF Medium has been marketed since 1998, 510(k) cleared (FDA) since 2000 and CE-marked since 2009. The product is based on existing technology and only contains well-known components present in other ART media intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer.

A risk analysis has been performed for the Universal IVF Medium product family and all risks associated with the products have been reduced to an acceptable level when weighed against the benefits for the patient, and constitute no recognized risks for the mother/patient or user, when used as intended and by professionals within ART.

No records of adverse events, product recalls or other product related problems were identified through public safety databases (UK, USA, and Australia). Over the period between (January 01, 2023, to December 31, 2024), two (2) product complaints were collected internally, and evaluated per the Adverse Event Reporting (AER) Procedure, BSR-QAR-043. No Adverse Event Report (AER) or Medical Device Report (MDR) was identified. No new risks were identified based on the clinical evaluation of Universal IVF Medium.

There are no reports (reviews or meta-analysis) of any safety or performance issues related to the subject device, benchmark, or similar devices. Based on available clinical data, the clinical performance and safety of Universal IVF Medium is compliant with state of the art including acknowledged KPIs, and general ART records from Europe and Australia/New Zealand, without trends of any clinical safety or performance issues.

In conclusion, this CER supports continued CE-marking of devices in the Universal IVF Medium product family. The clinical evaluation demonstrates compliance with GSPRs 1, 2, 6 and 8 of the Medical Device Regulation (EU) 2017/745 Annex I, with clinical evidence documenting state-of-the-art clinical safety and performance, as well as a positive benefit-risk profile for the Universal IVF Medium product family, when used as intended by professionals within ART. Long-term safety and performance has been demonstrated through clinical use for >37 years. However, after request from the British Standards Institution (BSI) to perform proactive PMCF for all Class III devices, proactive PMCF is performed on a continuous basis. As this device is part of a product family where not all data have been collected at the time of this report, this CER is including proactive PMCF according to PMCF033P, version B, with inclusion of all collected data at the time of the CER which will also be included in the final PMCF report (PMCF033R, version B) according to the schedule (PMCF033P, version B).

Please, refer to **Table 8-1**, for the assessment on the clinical evidence to support the Intended purpose.

Table 8-1 Clinical Evidence Checklist

Intended purpose		
Universal IVF Medium is intended for fertilization of oocytes and culture through to cleavage stage, and can also be used for embryo transfer.		
List the indications involved:	**Sufficient clinical evidence (YES/NO)**	**ACTIONS (proactive PMCF)**
Fertilization	YES	N/A
Culture to cleavage stage	YES	N/A
Embryo transfer	YES	N/A

9 Review and Update Requirements

PMS data as part of the quality system is continually compiled by the manufacturer as per the established quality management system. Device-related adverse events and complaints are recorded with the explicit purpose to identify and investigate any residual risks associated with the use of the device. Furthermore, this clinical evaluation report will be actively updated.

There are documented organized methods and procedures in place to collect post market clinical data based on use of the device (BSR-QAR-042). The need for proactive PMCF (incl. PMCF study) will be continuously evaluated as part of the PMS. The PMS plan is based on any residual risks identified for the subject device, data from any proactive PMS sources, as well as complaints, vigilance, adverse event reports, recalls, and field corrective actions for the subject device as well as benchmark and similar devices.

This clinical evaluation report will be reviewed and updated at least every two (2) years based on the last review and approval date. A time period of two (2) years is sufficient for review and update for the Universal IVF Medium as these devices have a well-recognized safety profile, have been marketed for more than 37 years, and complaint rates are very low (0.01- 1.79% based on worldwide sales). Revision control is maintained for the CER, so that even if no changes are required or necessary, a revision will be made reflecting that information contained in the report has been reviewed, appraised, evaluated, and analyzed. Complaint rate values are well known and low as compared to the number of units sold and the overall usage of the device. This supports a review every two (2) years of the CER and as soon as data from proactive PMCF becomes available (PMCF033P, version B), which would identify any trends, issues, or concerns during this period that CooperSurgical can take corrective action for as necessary.

If complaint trends, customer feedback, or other post market clinical evidence such as unsolicited clinical investigations of the device or issues arising from benchmark or similar devices is identified or current trends increase, then a review will be performed at that time of the clinical evaluation report. Any adverse event report shall also require a review of the data presented in the clinical evaluation report; a formal review of the report does not need to be performed, but an assessment needs to be performed within the confines of the adverse event report to determine if the incident is different from already recognized clinical risks. Adverse events whether they require regulatory reporting or not can have an impact on the clinical benefit-risk assessment of the device which must be reviewed, analyzed, and updated. Any recall, field safety corrective action, or market withdrawal requires a review of the clinical evaluation report for impact on the clinical safety and clinical performance of the device as these instances may also affect the clinical benefit-risk assessment.

10 Bibliography

10.1 Included Articles from Literature Search

Appraisal criteria for articles accepted for inclusion for the literature review are provided in **Appendix 3: Literature Search Appraisal, Section 14.1.** Data appraisal and identification of the most relevant publications were based on relevance/appropriateness of the device, device application, patient

group and quality of report/data collection. Weighting and critical analysis of the literature were conducted for demonstration of the overall safety and performance for the device(s) under evaluation. Inclusion criteria also evaluated literature relevant to state of the art technology or treatments, if applicable.

	Start of Articles Related to Subject Device
1	Hatirnaz, Safak, Hatirnaz, Ebru, Urkmez, Sebati Sinan, Calıskan, et al. 2024. "Oocyte In-Vitro Maturation Primed with Letrozole-HCG versus FSH-HCG in Women with Oocyte Maturation Abnormalities: A Retrospective Study." Reproductive BioMedicine Online, January. https://doi.org/10.1016/j.rbmo.2023.103620.
2	Hatirnaz, Şafak, Hatirnaz, Ebru, Urkmez, Sebati Sinan, Celik, et al. 2024. "Comparison of Luteal Phase and Follicular Phase In-Vitro Maturation in Women with Oocyte Maturation Abnormalities." Reproductive BioMedicine Online, January. https://doi.org/10.1016/j.rbmo.2023.103648.
3	Hatakeyama, Shota, Koizumi, Kaori, Kuramoto, Goro, Horiuchi, et al. 2024. "Assisted Sperm Fusion Insemination Improves Fertilization Rates and Increases Usable Embryos for Transfer: A Clinical Sibling-Oocyte Study." F&S Reports, January. https://doi.org/10.1016/j.xfre.2024.11.006.
	Start of Articles Related to Benchmark or Similar Device(s)
	No articles were identified
	Start of Articles Related to State of the Art
1	ESHRE Add-ons working group, K Lundin, J G Bentzen, G Bozdag, T Ebner, J Harper, N Le Clef, et al. 2023. 'Good Practice Recommendations on Add-Ons in Reproductive Medicine'. Human Reproduction, September, dead184. https://doi.org/10.1093/humrep/dead184.
2	Sciorio, Romualdo, and Paolo Rinaudo. 2023. 'Culture Conditions in the IVF Laboratory: State of the ART and Possible New Directions'. Journal of Assisted Reproduction and Genetics, September. https://doi.org/10.1007/s10815-023-02934-5.
3	Siristatidis, C., M. Papapanou, V. Karageorgiou, W. P. Martins, I. Bellos, D. M. Teixeira, and N. Vlahos. 'Congenital Anomaly and Perinatal Outcome Following Blastocyst- vs Cleavage-Stage Embryo Transfer: Systematic Review and Network Meta-Analysis'. Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology 61, no. 1 (January 2023): 12–25. https://doi.org/10.1002/uog.26019.
4	Sonigo, C., Ahdad-Yata, N., Pirtea, P., Solignac, C., Grynberg, M., & Sermondade, N. (2024). Do IVF culture conditions have an impact on neonatal outcomes? A systematic review and meta-analysis. Journal of Assisted Reproduction and Genetics, 41(3), 563–580. https://doi.org/10.1007/s10815-024-03020-0

10.2 Excluded Articles from Literature Search

Appraisal criteria for articles that were excluded for review, including specific reasons for exclusion of each article, are provided in **Appendix 3: Literature Search Appraisal, Section 14.1**. Articles were reviewed for the relevance/appropriateness of the device, device application, patient group and quality of report/data collection. Depending on the relevance of the criteria, articles were weighted and rejected for being far from the: device, intended purpose, or patient group; or for containing poor data quality.

	Start of Device Literature Excluded
	No articles were identified for exclusion after appraisal.

	Start of Benchmark or Similar Device(s) Literature Excluded
1	Hatakeyama, Shota, Koizumi, Kaori, Kuramoto, Goro, Horiuchi, et al. 2024. “Assisted Sperm Fusion Insemination Improves Fertilization Rates and Increases Usable Embryos for Transfer: A Clinical Sibling-Oocyte Study.” F&S Reports, January. https://doi.org/10.1016/j.xfre.2024.11.006.
	Start of State of the Art Literature Excluded
1	Choi, Jung-Won, Sung-Woo Kim, Hee-Sun Kim, Moon-Joo Kang, Sung-Ah Kim, Ji-Yeon Han, Hoon Kim, and Seung-Yup Ku. 2024. ‘Effects of Melatonin, GM-CSF, IGF-1, and LIF in Culture Media on Embryonic Development: Potential Benefits of Individualization’. International Journal of Molecular Sciences 25 (2): 751. https://doi.org/10.3390/ijms25020751.
2	Cutting, E, Horta, F, Dang, V, van Rumste, MME, and BWJ Mol. 2023. ‘Intracytoplasmic Sperm Injection versus Conventional in vitro Fertilisation in Couples with Males Presenting with Normal Total Sperm Count and Motility’. Cochrane Database of Systematic Reviews, no. 8. https://doi.org/10.1002/14651858.CD001301.pub2.
3	Kamath, MS, Vogiatzi, P, Sunkara, SK, Woodward, & B. (2024). Oocyte activation for women following intracytoplasmic sperm injection (ICSI). https://doi.org/10.1002/14651858.CD014040.pub2
4	Kathryn A Voss, Yu-Fu M Chen, Daniel A Castillo, Wendy S Vitek, & Snigdha Alur-Gupta. (2024). Ovulation-induced frozen embryo transfer regimens in women with polycystic ovary syndrome: A systematic review and meta-analysis. Journal of Assisted Reproduction and Genetics. https://doi.org/10.1007/s10815-024-03209-3
5	Kuroda, K. (2024). Management strategies following implantation failure of euploid embryos. Reproductive Medicine and Biology, 23(1), e12576. https://doi.org/10.1002/rmb2.12576
6	Leah Cooper, Emma Manuel, Min Xu, & Samantha B Schon. (2024). In vitro fertilization, intracytoplasmic sperm injection, in vitro maturation, and embryo culture. Systems Biology in Reproductive Medicine. https://doi.org/10.1080/19396368.2024.2439838
7	Narges Karami, Adeleh Taei, Poopak Eftekhari-Yazdi, & Fatemeh Hassani. (2024). Signaling pathway regulators in preimplantation embryos. Journal of Molecular Histology. https://doi.org/10.1007/s10735-024-10338-7
8	Sallam, Hassan, Florence Boitrelle, Simone Palini, Damayanthi Durairajanayagam, Lodovico Parmegiani, Sunil Jindal, Ramadan Saleh, Giovanni Colpi, and Ashok Agarwal. ‘ICSI for Non-Male Factor Infertility: Time to Reappraise IVF?’ Panminerva Medica 65, no. 2 (June 2023): 159–65. https://doi.org/10.23736/S0031-0808.23.04869-3.
9	Tire, Betul. 2023. ‘Potential Effects of Assisted Reproductive Technology on Telomere Length and Telomerase Activity in Human Oocytes and Early Embryos’. Journal of Ovarian Research.
10	Tong Wu, Jinfeng Yan, Kebing Nie, Ying Chen, Yangyang Wu, Shixuan Wang, & Jinjin Zhang. (2024). Microfluidic chips in female reproduction: A systematic review of status, advances, and challenges. Theranostics. https://doi.org/10.7150/thno.97301
11	Yang, Liu, Fuxiang Liang, Rongyan Zhu, Qi Wang, Liang Yao, and Xuehong Zhang. 2024. ‘Efficacy of Intracytoplasmic Sperm Injection in Women with Non-Male Factor Infertility: A Systematic Review and Meta-Analysis’. Acta Obstetricia Et Gynecologica Scandinavica 103 (1): 30–41. https://doi.org/10.1111/aogs.14698.

10.3 Included Articles from Previous Version(s) of the CER

This list of articles was cited in the previous version of the CER for the subject device, and also selected for inclusion in the current CER.

	Start of Articles Related to Subject Device

1	Bekzatova, K, and M Shishimorova. 2021. “P–694 Natural Cycle vs Accumulation of Oocytes. Which Strategy Is Better for Women with the Poor Ovarian Response (POR)?” Human Reproduction 36 (Supplement_1): deab130.693. https://doi.org/10.1093/humrep/deab130.693.
2	Ferraretto, Xavier, Karima Hammas, Marie-Astrid Llabador, Solenne Gricourt, Julie Labrosse, Johanna Lousqui, Sylvie Epelboin, Sarah Tubiana, and Catherine Patrat. 2021. “Early Embryo Development Anomalies Identified by Time-Lapse System: Prevalence and Impacting Factors.” Reproductive BioMedicine Online 43 (4): 627–36. https://doi.org/10.1016/j.rbmo.2021.06.010.
3	Kidera, Nobuyuki, Tomonori Ishikawa, Toshihiro Kawamura, and Naoyuki Miyasaka. 2022. “Impact of Paternal Age on IVF and Pregnancy Outcomes with Only Normal Sperm Parameters.” Taiwanese Journal of Obstetrics and Gynecology 61 (6): 1015–20. https://doi.org/10.1016/j.tjog.2022.02.050.
4	Uppangala, Shubhashree, Gail Fernandes, Sujith Raj Salian, Pratap Kumar, Riccardo Talevi, Guruprasad Kalthur, and Satish Kumar Adiga. 2020. “Reduced Ovarian Response to Controlled Ovarian Stimulation Is Associated with Increased Oxidative Stress in the Follicular Environment.” Reproductive Biology 20 (3): 402–7. https://doi.org/10.1016/j.repbio.2020.04.005.
5	Ajayi,RA, Parsons,JH, and Bolton,VN (2003). Live births after intracytoplasmic sperm injection in the management of oligospermia and azoospermia in Nigeria. Afr. J. Reprod. Health 7, 121-124
6	Barak,Y and others (1998). Does glucose affect fertilization, development and pregnancy rates of human in-vitro fertilized oocytes? Hum. Reprod 13 Suppl 4, 203-211
7	Coskun,S and others (2000). Day 5 versus day 3 embryo transfer: a controlled randomized trial. Human Reproduction 15, 1947-1952
8	De Geyter,C and others (2006). Comparative birth weights of singletons born after assisted reproduction and natural conception in previously infertile women. Human Reproduction 21, 705-712
9	Erb, K; ISM1 versus universal IVF medium trial report / ORIGIO A/S: Statistisk rapport: Universal IVF versus ISM1. 2004 (data on file)
10	Eskild,A, Monkerud,L, and Tanbo,T (2013). Birthweight and placental weight; do changes in culture media used for IVF matter? Comparisons with spontaneous pregnancies in the corresponding time periods. Hum. Reprod. 28, 3207-3214
11	Frydman,N and others (2004). Improvement of IVF results and optimisation of quality control by using intermittent activity. Reproductive BioMedicine Online 9, 521-528
12	Hambiliki,F, Sandell,P, Yaldir,F, and Stavreus-Evers,A (2011). 9518[PII];21120597[pmid]: A prospective randomized sibling-oocyte study of two media systems for culturing cleavage-stage embryosGÇöimpact on fertilization rate. J Assist Reprod Genet 28, 335-341
13	Holst,N and others (1990). Optimization and simplification of culture conditions in human in vitro fertilization (IVF) and preembryo replacement by serum-free media. J. In vitro Fert. Embryo. Transf. 7, 47-53
14	Jaroudi,K and others (2004). Zygote transfer on day 1 versus cleavage stage embryo transfer on day 3: a prospective randomized trial. Human Reproduction 19, 645-648
15	Karaki,RZ and others (2002). Blastocyst culture and transfer: a step toward improved in vitro fertilization outcome. Fertility and Sterility 77, 114-118
16	Karamalegos,C and Bolton,VN (1999). A prospective comparison of 'in house' and commercially prepared Earle's balanced salt solution in human in-vitro fertilization. Hum. Reprod. 14, 1842-1846
17	Kattera,S and Chen,C (2003). Short coincubation of gametes in in vitro fertilization improves implantation and pregnancy rates: a prospective, randomized, controlled study. Fertility and Sterility 80, 1017-1021
18	Kovacic,B, Vlaisavljevi,V, Reljic,M, and Lovrec,VG (2002). Clinical outcome of day 2 versus day 5 transfer in cycles with one or two developed embryos. Fertility and Sterility 77, 529-536

19	Laursen,SB, Andersen,CY, Hindkjær,J, and Erb,K (2003). A clinical study comparing PureSperm and SpermFilter for density gradient separation of human spermatozoa in assisted reproduction. Acta Obstetricia et Gynecologica Scandinavica 82, 929-935
20	Monks,NJ and others (1993). Development of embryos from natural cycle in-vitro fertilization: impact of medium type and female infertility factors. Hum. Reprod. 8, 266-271
21	ORIGIO A/S (2006). Clinical investigation report. EmbryoAssist versus Universal IVF Medium (data on file)
22	Sills,ES and others (2009). Clinical features and reproductive outcomes for embryos undergoing dual freeze-thaw sequences followed by blastocyst transfer: critique of 14 consecutive cases in IVF. Fertility and Sterility 91, 1568-1570
23	Staessen,C, Janssenswillen,C, De,CE, and Van,SA (1998). Controlled comparison of commercial media for human in-vitro fertilization: Menezo B2 medium versus Medi-Cult universal and BM1 medium. Hum. Reprod. 13, 2548-2554
24	Xella,S and others (2010). Embryo quality and implantation rate in two different culture media: ISM1 versus Universal IVF Medium. Fertility and Sterility 93, 1859-1863
	Start of Articles Related to Benchmark or Similar Device(s)
	No articles were identified
	Start of Articles Related to State of the Art
1	Chang, Yanan, Minghong Shen, Sha Wang, Xiao Li, and Hua Duan. 2022. “Association of Embryo Transfer Type with Infertility in Endometriosis: A Systematic Review and Meta-Analysis.” Journal of Assisted Reproduction and Genetics 39 (5): 1033–43. https://doi.org/10.1007/s10815-022-02460-w
2	Fancsovits, Peter, Csaba Pribenszky, Adam Lehner, Akos Murber, Zita Kaszas, Annamaria Nemes, and Janos Urbancsek. 2022. “Prospective-Randomized Study Comparing Clinical Outcomes of IVF Treatments Where Embryos Were Cultured Individually or in a Microwell Group Culture Dish.” Biologia Futura 73 (2): 229–36. https://doi.org/10.1007/s42977-022-00113-8.
3	Gaume, Rachel E., Ryan J. Heitmann, Jacqueline Luizzi, and Bruce D. Pier. 2021. “Large for Gestational Age after Frozen Embryo Transfer: An Evaluation of the Possible Causes for This Relationship.” F&S Reviews 2 (1): 21–31. https://doi.org/10.1016/j.xfnr.2020.10.002.
4	Glujovsky, Demián, Andrea Marta Quinteiro Retamar, Cristian Roberto Alvarez Sedo, Agustín Ciapponi, Simone Cornelisse, and Deborah Blake. 2022. “Cleavage-Stage versus Blastocyst-Stage Embryo Transfer in Assisted Reproductive Technology.” Edited by Cochrane Gynaecology and Fertility Group. Cochrane Database of Systematic Reviews 2022 (6). https://doi.org/10.1002/14651858.CD002118.pub6.
5	Heymann, Devorah, Liat Vidal, Yuval Or, and Zeev Shoham. 2020. “Hyaluronic Acid in Embryo Transfer Media for Assisted Reproductive Technologies.” Edited by Cochrane Gynaecology and Fertility Group. Cochrane Database of Systematic Reviews, September. https://doi.org/10.1002/14651858.CD007421.pub4.
6	Paffoni, Alessio, Marco Reschini, Valerio Pisaturo, Cristina Guarneri, Simone Palini, and Paola Viganò. 2021. “Should Rescue ICSI Be Re-Evaluated Considering the Deferred Transfer of Cryopreserved Embryos in in-Vitro Fertilization Cycles? A Systematic Review and Meta-Analysis.” Reproductive Biology and Endocrinology: RB&E 19 (1): 121. https://doi.org/10.1186/s12958-021-00784-3.
7	Zaat, Tjitske, Miriam Zagers, Femke Mol, Mariëtte Goddijn, Madelon van Wely, and Sebastiaan Mastenbroek. 2021. “Fresh versus Frozen Embryo Transfers in Assisted Reproduction.” Edited by Cochrane Gynaecology and Fertility Group. Cochrane Database of Systematic Reviews, February. https://doi.org/10.1002/14651858.CD011184.pub3

11 References

Ajayi, R. A., J. H. Parsons, and V. N. Bolton. 2003. “Live Births after Intracytoplasmic Sperm Injection in the Management of Oligospermia and Azoospermia in Nigeria.” *African Journal of Reproductive Health* 7 (1): 121. https://doi.org/10.2307/3583352.

Alper, Michael M. 2013. “Experience with ISO Quality Control in Assisted Reproductive Technology.” *Fertility and Sterility* 100 (6): 1503–8. https://doi.org/10.1016/j.fertnstert.2013.08.055.

ASRM Booklet for patients. 2018. “ASRM - Booklet for Patients.Pdf.”

Barak, Y., S. Goldman, Y. Gonen, Z. Nevo, B. Bartoov, and A. Kogosowski. 1998. “Does Glucose Affect Fertilization, Development and Pregnancy Rates of Human in-Vitro Fertilized Oocytes?” *Human Reproduction* 13 (suppl 4): 203–11. https://doi.org/10.1093/humrep/13.suppl_4.203.

Barberet, J, C Binquet, M Guilleman, A Doukani, C Choux, C Bruno, A Bourredjem, et al. 2021. “Do Assisted Reproductive Technologies and *in Vitro* Embryo Culture Influence the Epigenetic Control of Imprinted Genes and Transposable Elements in Children?” *Human Reproduction* 36 (2): 479–92. https://doi.org/10.1093/humrep/deaa310.

Bekzatova, K, and M Shishimorova. 2021. “P–694 Natural Cycle vs Accumulation of Oocytes. Which Strategy Is Better for Women with the Poor Ovarian Response (POR)?” *Human Reproduction* 36 (Supplement_1): deab130.693. https://doi.org/10.1093/humrep/deab130.693.

Berkhout, R P, C G Vergouw, M van Wely, A A de Melker, R Schats, S Repping, G Hamer, S Mastenbroek, and C B Lambalk. 2017. “The Addition of a Low-Quality Embryo as Part of a Fresh Day 3 Double Embryo Transfer Does Not Improve Ongoing Pregnancy Rates.” *Human Reproduction Open* 2017 (3). https://doi.org/10.1093/hropen/hox020.

Bertheussen, Kjell. 1993. “Growth of Cells in a New Defined Protein-Free Medium.” *Cytotechnology* 11 (3): 219–31. https://doi.org/10.1007/BF00749873.

Blake, Deborah, Peter Svalander, Meishan Jin, Christer Silversand, and Lars Hamberger. 2002. “Protein Supplementation of Human IVF Culture Media.” *Journal of Assisted Reproduction and Genetics* 19 (3): 137–43.

Bontekoe, Stephan, Neil Johnson, Deborah Blake, and Jane Marjoribanks. 2015. “Adherence Compounds in Embryo Transfer Media for Assisted Reproductive Technologies: Summary of a Cochrane Review.” *Fertility and Sterility* 103 (6): 1416–17. https://doi.org/10.1016/j.fertnstert.2015.03.010.

Calhaz-Jorge, C, C De Geyter, M S Kupka, J de Mouzon, K Erb, E Mocanu, T Motrenko, et al. 2017. “Assisted Reproductive Technology in Europe, 2013: Results Generated from European Registers by ESHRE†.” *Human Reproduction* 32 (10): 1957–73. https://doi.org/10.1093/humrep/dex264.

Chambers, Georgina M., Handan Wand, Alan Macaldowie, Michael G. Chapman, Cynthia M. Farquhar, Mark Bowman, David Molloy, and William Ledger. 2016. “Population Trends and Live Birth Rates Associated with Common ART Treatment Strategies.” *Human Reproduction* 31 (11): 2632–41. https://doi.org/10.1093/humrep/dew232.

Chang, Yanan, Minghong Shen, Sha Wang, Xiao Li, and Hua Duan. 2022. “Association of Embryo Transfer Type with Infertility in Endometriosis: A Systematic Review and Meta-Analysis.” *Journal of Assisted Reproduction and Genetics* 39 (5): 1033–43. https://doi.org/10.1007/s10815-022-02460-w.

Choi, Stephanie K Y, Christos Venetis, William Ledger, Alys Havard, Katie Harris, Robert J Norman, Louisa R Jorm, and Georgina M Chambers. 2022. “Population-Wide Contribution of Medically Assisted Reproductive Technologies to Overall Births in Australia: Temporal

Trends and Parental Characteristics." *Human Reproduction*, February, deac032. https://doi.org/10.1093/humrep/deac032.
Chronopoulou, Elpiniki, and Joyce C. Harper. 2015. "IVF Culture Media: Past, Present and Future." *Human Reproduction Update* 21 (1): 39–55. https://doi.org/10.1093/humupd/dmu040.
Cohen, Jean, Alan Trounson, Karen Dawson, Howard Jones, Johan Hazekamp, Karl-Gösta Nygren, and Lars Hamberger. 2005. "The Early Days of IVF Outside the UK." *Human Reproduction Update* 11 (5): 439–59. https://doi.org/10.1093/humupd/dmi016.
Coskun, Serdar, Johannes Hollanders, Saad Al-Hassan, Hamad Al-Sufyan, Hend Al-Mayman, and Kamal Jaroudi. 2000. "Day 5 versus Day 3 Embryo Transfer: A Controlled Randomized Trial." *Human Reproduction* 15 (9): 1947–52. https://doi.org/10.1093/humrep/15.9.1947.
Davies S., Karamolegos C., Karagianni A., Sisi P., Mendorou C., and Mastrominas M. 2018. "Male Factor Is the Most Important Factor Influencing the Frequency of Unequal Direct Cleavage Events as Visualized by Time-Lapse during Early Embryo Development." *Human Reproduction* 33 ((Davies S.) C/o Embryogenesis, Embryology, Maroussi, Athens, Greece): i210–11. https://doi.org/10.1093/humrep/33.Supplement_1.1.
De Geyter, C., M. De Geyter, S. Steimann, H. Zhang, and W. Holzgreve. 2006. "Comparative Birth Weights of Singletons Born after Assisted Reproduction and Natural Conception in Previously Infertile Women." *Human Reproduction* 21 (3): 705–12. https://doi.org/10.1093/humrep/dei378.
De Geyter, Ch, C Wyns, C Calhaz-Jorge, J de Mouzon, A P Ferraretti, M Kupka, A Nyboe Andersen, K G Nygren, and V Goossens. 2020. "20 Years of the European IVF-Monitoring Consortium Registry: What Have We Learned? A Comparison with Registries from Two Other Regions." *Human Reproduction* 35 (12): 2832–49. https://doi.org/10.1093/humrep/deaa250.
Eisenberg, Michael L., and David Meldrum. 2017. "Effects of Age on Fertility and Sexual Function." *Fertility and Sterility* 107 (2): 301–4. https://doi.org/10.1016/j.fertnstert.2016.12.018.
ESHRE. 2017. "The Vienna Consensus: Report of an Expert Meeting on the Development of ART Laboratory Performance Indicators." *Reproductive BioMedicine Online* 35 (5): 494–510. https://doi.org/10.1016/j.rbmo.2017.06.015.
———. 2018. "European Society of Hum Reprod and Embryology ART Fact Sheet. [Https://Www.Eshre.Eu/Press-Room/Resources.Aspx. Accessed May 2018]," February. https://www.eshre.eu/Press-Room/Resources.aspx. Accessed May 2018.
ESHRE Add-ons working group, K Lundin, J G Bentzen, G Bozdag, T Ebner, J Harper, N Le Clef, et al. 2023. "Good Practice Recommendations on Add-Ons in Reproductive Medicine." *Human Reproduction*, September, dead184. https://doi.org/10.1093/humrep/dead184.
Eskild, Anne, Lars Monkerud, and Tom Tanbo. 2013. "Birthweight and Placental Weight; Do Changes in Culture Media Used for IVF Matter? Comparisons with Spontaneous Pregnancies in the Corresponding Time Periods" 28 (12): 3207–14.
Fancsovits, Peter, Csaba Pribenszky, Adam Lehner, Akos Murber, Zita Kaszas, Annamaria Nemes, and Janos Urbancsek. 2022. "Prospective-Randomized Study Comparing Clinical Outcomes of IVF Treatments Where Embryos Were Cultured Individually or in a Microwell Group Culture Dish." *Biologia Futura* 73 (2): 229–36. https://doi.org/10.1007/s42977-022-00113-8.
Ferraretti, A.P., K. Nygren, A. Nyboe Andersen, J. de Mouzon, M. Kupka, C. Calhaz-Jorge, C. Wyns, L. Gianaroli, V. Goossens, and The European IVF-Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). 2017. "Trends over 15 Years in ART in Europe: An Analysis of 6 Million Cycles†." *Human Reproduction Open* 2017 (August):1–10. https://doi.org/10.1093/hropen/hox012.
Ferraretto, Xavier, Karima Hammas, Marie-Astrid Llabador, Solenne Gricourt, Julie Labrosse, Johanna Lousqui, Sylvie Epelboin, Sarah Tubiana, and Catherine Patrat. 2021. "Early

Embryo Development Anomalies Identified by Time-Lapse System: Prevalence and Impacting Factors." *Reproductive BioMedicine Online* 43 (4): 627–36. https://doi.org/10.1016/j.rbmo.2021.06.010.

Fertility Society of Australia and Reproductive Technology Accreditation Committee (RTAC). 2017. "Code of Practice for Assisted Reproductive Technology Units (Revised October 2017)," [https://www.fertilitysociety.com.au/wp-content/uploads/2017-RTAC-ANZ-COP-FINAL-1.pdf. Accessed May 2018].

Fitzgerald, Oisín, Katie Harris, Repon C Paul, and Georgina M Chambers. 2017. "Assisted Reproductive Technology in Australia and New Zealand 2015." *Sydney: National Perinatal Epidemiology and Statistics Unit (NPESU), the University of New South Wales Sydney*, October.

Frydman, Nelly, Rénato Fanchin, Anne Le Dû, Marie Catherine Bourrier, Gérard Tachdjian, and René Frydman. 2004. "Improvement of IVF Results and Optimisation of Quality Control by Using Intermittent Activity." *Reproductive BioMedicine Online* 9 (5): 521–28. https://doi.org/10.1016/S1472-6483(10)61636-7.

Gale, Jenna, Brigitte Corran, Vanessa Bacal, Jeffrey Haebe, Vincent Nguyen, and Doron Shmorgun. 2022. "Reduced Live Birth Rates after Embryo Transfer in Patients with Prior Cesarean Delivery: A Retrospective Cohort Study." *European Journal of Obstetrics & Gynecology and Reproductive Biology* 271 (April):250–54. https://doi.org/10.1016/j.ejogrb.2022.02.016.

Gaume, Rachel E., Ryan J. Heitmann, Jacqueline Luizzi, and Bruce D. Pier. 2021. "Large for Gestational Age after Frozen Embryo Transfer: An Evaluation of the Possible Causes for This Relationship." *F&S Reviews* 2 (1): 21–31. https://doi.org/10.1016/j.xfnr.2020.10.002.

Glujovsky, Demián, Andrea Marta Quinteiro Retamar, Cristian Roberto Alvarez Sedo, Agustín Ciapponi, Simone Cornelisse, and Deborah Blake. 2022. "Cleavage-Stage versus Blastocyst-Stage Embryo Transfer in Assisted Reproductive Technology." Edited by Cochrane Gynaecology and Fertility Group. *Cochrane Database of Systematic Reviews* 2022 (6). https://doi.org/10.1002/14651858.CD002118.pub6.

Hambiliki, Fredwell, Petra Sandell, Fatma Yaldir, and Anneli Stavreus-Evers. 2011. "A Prospective Randomized Sibling-Oocyte Study of Two Media Systems for Culturing Cleavage-Stage Embryos—Impact on Fertilization Rate." *Journal of Assisted Reproduction and Genetics* 28 (4): 335–41. https://doi.org/10.1007/s10815-010-9518-0.

Hansen, Michèle, and Carol Bower. 2014. "The Impact of Assisted Reproductive Technologies on Intra-Uterine Growth and Birth Defects in Singletons." *Seminars in Fetal and Neonatal Medicine* 19 (4): 228–33. https://doi.org/10.1016/j.siny.2014.03.002.

Hatakeyama, Shota, Koizumi, Kaori, Kuramoto, Goro, Horiuchi, et al. 2024. "Assisted Sperm Fusion Insemination Improves Fertilization Rates and Increases Usable Embryos for Transfer: A Clinical Sibling-Oocyte Study." *F&S Reports*, January. https://doi.org/10.1016/j.xfre.2024.11.006.

Hatirnaz, Safak, Ebru Hatirnaz, Sebati Sinan Urkmez, Canan Soyer Calıskan, Samettin Celik, Kaan Hatirnaz, Mingju Cao, Seang Lin Tan, and Michael H. Dahan. 2024. "Oocyte In-Vitro Maturation Primed with Letrozole-HCG versus FSH-HCG in Women with Oocyte Maturation Abnormalities: A Retrospective Study." *Reproductive BioMedicine Online* 48 (3): 103620. https://doi.org/10.1016/j.rbmo.2023.103620.

Hatirnaz, Şafak, Ebru Hatirnaz, Sebati Sinan Urkmez, Samettin Celik, Yeşim Civil Urkmez', Mingju Cao, Seang Lin Tan, and Michael H. Dahan. 2024. "Comparison of Luteal Phase and Follicular Phase In-Vitro Maturation in Women with Oocyte Maturation Abnormalities." *Reproductive BioMedicine Online* 48 (4): 103648. https://doi.org/10.1016/j.rbmo.2023.103648.

Heymann, Devorah, Liat Vidal, Yuval Or, and Zeev Shoham. 2020. “Hyaluronic Acid in Embryo Transfer Media for Assisted Reproductive Technologies.” Edited by Cochrane Gynaecology and Fertility Group. *Cochrane Database of Systematic Reviews*, September. https://doi.org/10.1002/14651858.CD007421.pub4.

Holst, Nicolai, Kjell Bertheussen, Finn Forsdahl, Mona Berger H�konsen, Lars Jul Hansen, and Hans Ingolf Nielsen. 1990. “Optimization and Simplification of Culture Conditions in Human in Vitro Fertilization (IVF) and Preembryo Replacement by Serum-Free Media.” *Journal of In Vitro Fertilization and Embryo Transfer* 7 (1): 47–53. https://doi.org/10.1007/BF01133884.

Jaroudi, K. 2004. “Zygote Transfer on Day 1 versus Cleavage Stage Embryo Transfer on Day 3: A Prospective Randomized Trial.” *Human Reproduction* 19 (3): 645–48. https://doi.org/10.1093/humrep/deh125.

Kamel, Remah. 2013. “Assisted Reproductive Technology after the Birth of Louise Brown.” *J Reprod Infertil* 14 (03): 96–109. https://doi.org/10.4172/2161-0932.1000156.

Karaki, Raja Z, Tarek M Lahloub, and Mohammed H Ibrahim. 2002. “Blastocyst Culture and Transfer: A Step toward Improved in Vitro Fertilization Outcome” 77 (1): 5.

Karamalegos, C., and V.N. Bolton. 1999. “A Prospective Comparison of `in House’ and Commercially Prepared Earle’s Balanced Salt Solution in Human in-Vitro Fertilization.” *Human Reproduction* 14 (7): 1842–46. https://doi.org/10.1093/humrep/14.7.1842.

Kattera, Suresh, and Christopher Chen. 2003. “Short Coincubation of Gametes in in Vitro Fertilization Improves Implantation and Pregnancy Rates: A Prospective, Randomized, Controlled Study.” *Fertility and Sterility* 80 (4): 1017–21. https://doi.org/10.1016/S0015-0282(03)01154-3.

Kidera, Nobuyuki, Tomonori Ishikawa, Toshihiro Kawamura, and Naoyuki Miyasaka. 2022. “Impact of Paternal Age on IVF and Pregnancy Outcomes with Only Normal Sperm Parameters.” *Taiwanese Journal of Obstetrics and Gynecology* 61 (6): 1015–20. https://doi.org/10.1016/j.tjog.2022.02.050.

Kovačič, Borut, Veljko Vlaisavljević, Milan Reljič, and Vida Gavrić Lovrec. 2002. “Clinical Outcome of Day 2 versus Day 5 Transfer in Cycles with One or Two Developed Embryos.” *Fertility and Sterility* 77 (3): 529–36. https://doi.org/10.1016/S0015-0282(01)03212-5.

Kushnir, Vitaly A., David H. Barad, David F. Albertini, Sarah K. Darmon, and Norbert Gleicher. 2017. “Systematic Review of Worldwide Trends in Assisted Reproductive Technology 2004–2013.” *Reproductive Biology and Endocrinology* 15 (1): 6. https://doi.org/10.1186/s12958-016-0225-2.

Labs, ESHRE Guideline Group on Good Practice in IVF, Maria José De los Santos, Susanna Apter, Giovanni Coticchio, Sophie Debrock, Kersti Lundin, Carlos E Plancha, et al. 2016. “Revised Guidelines for Good Practice in IVF Laboratories (2015)†.” *Human Reproduction* 31 (4): 685–86. https://doi.org/10.1093/humrep/dew016.

Laursen, Steen B, Claus Yding Andersen, and Johnny Hindkj. 2003. “A Clinical Study Comparing PureSperm and SpermFilter for Density Gradient Separation of Human Spermatozoa in Assisted Reproduction.” *Acta Obstet Gynecol Scand*, 7.

Leese, H. J. 1988. “The Formation and Function of Oviduct Fluid.” *Reproduction* 82 (2): 843–56. https://doi.org/10.1530/jrf.0.0820843.

Li, Z., Y. A. Wang, W. Ledger, and E. A. Sullivan. 2014. “Birthweight Percentiles by Gestational Age for Births Following Assisted Reproductive Technology in Australia and New Zealand, 2002-2010.” *Human Reproduction* 29 (8): 1787–1800. https://doi.org/10.1093/humrep/deu120.

Liu, Jing, Mingpeng Zhao, Haoyang Zhang, Junliang Zhao, Hongjiao Kong, Mengge Zhou, Yichun Guan, Tin Chiu Li, Xingling Wang, and David Yiu Leung Chan. 2022. “Associations between Ambient Air Pollution and IVF Outcomes in a Heavily Polluted City in China.”

Reproductive BioMedicine Online 44 (1): 49–62. https://doi.org/10.1016/j.rbmo.2021.09.026.

Logsdon, Deirdre M., Courtney K. Grimm, Rachel C. West, Heidi J. Engelhorn, Rebecca Kile, Laura C. Reed, Jason E. Swain, et al. 2022. "Maternal Physiology and Blastocyst Morphology Are Correlated with an Inherent Difference in Peri-Implantation Human Embryo Development." *Fertility and Sterility* 117 (6): 1311–21. https://doi.org/10.1016/j.fertnstert.2022.02.018.

Luke, Barbara, Daksha Gopal, Howard Cabral, Judy E. Stern, and Hafsatou Diop. 2017. "Pregnancy, Birth, and Infant Outcomes by Maternal Fertility Status: The Massachusetts Outcomes Study of Assisted Reproductive Technology." *American Journal of Obstetrics and Gynecology* 217 (3): 327.e1-327.e14. https://doi.org/10.1016/j.ajog.2017.04.006.

Meintjes, M., S. J. Chantilis, D. C. Ward, J. D. Douglas, A. J. Rodriguez, A. R. Guerami, D. M. Bookout, B. D. Barnett, and J. D. Madden. 2009. "A Randomized Controlled Study of Human Serum Albumin and Serum Substitute Supplement as Protein Supplements for IVF Culture and the Effect on Live Birth Rates." *Human Reproduction* 24 (4): 782–89. https://doi.org/10.1093/humrep/den396.

Monks, N. J., K. Turner, M. A. Hooper, A. Kumar, S. Verma, and E. A. Lenton. 1993. "Development of Embryos from Natural Cycle In-Vitro Fertilization: Impact of Medium Type and Female Infertility Factors." *Human Reproduction (Oxford, England)* 8 (2): 266–71. https://doi.org/10.1093/oxfordjournals.humrep.a138035.

Nagy, Zsolt Peter, Alex C. Varghese, and Ashok Agarwal. 2012. *Practical Manual of in Vitro Fertilization: Advanced Methods and Novel Devices. 1st Edition*. 1st edition. New York: Springer.

Nardelli, Alexa A, Tania Stafinski, Tarek Motan, Kristin Klein, and Devidas Menon. 2014. "Assisted Reproductive Technologies (ARTs): Evaluation of Evidence to Support Public Policy Development." *Reproductive Health* 11:76 (November):1–14. https://doi.org/10.1186/1742-4755-11-76.

NCC-WCH. 2013. "National Collaborating Centre for Women's and Children's Health. Fertility: Assessment and Treatment for People with Fertility Problems (NICE Clinical Guideline 156). 2nd Edition. London: Royal College of Obstetricians and Gynaecologists. Commissioned by the National Institute for Health and Clinical Excellence (NICE). [Https://Www.Nice.Org.Uk/Guidance/Cg156/Evidence/Full-Guideline-Pdf-188539453; Accessed May 2018]." https://www.nice.org.uk/guidance/cg156/evidence/full-guideline-pdf-188539453.

Newman, Jade E, Repon C Paul, and Georgina M Chambers. 2023. "Assisted Reproductive Technology in Australia and New Zealand 2021." National Perinatal Epidemiology and Statistics Unit (NPESU).

Paffoni, Alessio, Marco Reschini, Valerio Pisaturo, Cristina Guarneri, Simone Palini, and Paola Viganò. 2021. "Should Rescue ICSI Be Re-Evaluated Considering the Deferred Transfer of Cryopreserved Embryos in in-Vitro Fertilization Cycles? A Systematic Review and Meta-Analysis." *Reproductive Biology and Endocrinology: RB&E* 19 (1): 121. https://doi.org/10.1186/s12958-021-00784-3.

Rienzi, Laura, Clarisa Gracia, Roberta Maggiulli, Andrew R. LaBarbera, Daniel J. Kaser, Filippo M. Ubaldi, Sheryl Vanderpoel, and Catherine Racowsky. 2016. "Oocyte, Embryo and Blastocyst Cryopreservation in ART: Systematic Review and Meta-Analysis Comparing Slow-Freezing versus Vitrification to Produce Evidence for the Development of Global Guidance." *Human Reproduction Update*, November, humupd;dmw038v1. https://doi.org/10.1093/humupd/dmw038.

Sargisian, Nona, Birgitta Lannering, Max Petzold, Signe Opdahl, Mika Gissler, Anja Pinborg, Anna-Karina Aaris Henningsen, et al. 2022. "Cancer in Children Born after Frozen-Thawed

Embryo Transfer: A Cohort Study." Edited by Jenny E. Myers. *PLOS Medicine* 19 (9): e1004078. https://doi.org/10.1371/journal.pmed.1004078.

Schoolcraft, William B. 2016. "Importance of Embryo Transfer Technique in Maximizing Assisted Reproductive Outcomes." *Fertility and Sterility* 105 (4): 855–60. https://doi.org/10.1016/j.fertnstert.2016.02.022.

Sciorio, Romualdo, and Paolo Rinaudo. 2023. "Culture Conditions in the IVF Laboratory: State of the ART and Possible New Directions." *Journal of Assisted Reproduction and Genetics*, September. https://doi.org/10.1007/s10815-023-02934-5.

Setti, Amanda Souza, Daniela Paes de Almeida Ferreira Braga, Patricia Guilherme, Assumpto Iaconelli, and Edson Borges. 2022. "High Oocyte Immaturity Rates Impact Embryo Morphokinetics: Lessons of Time-Lapse Imaging System." *Reproductive BioMedicine Online*, June, S1472648322004151. https://doi.org/10.1016/j.rbmo.2022.06.005.

Sfontouris, Ioannis A., Wellington P. Martins, Carolina O Nastri, Iara G. R. Viana, Paula A. Navarro, Nick Raine-Fenning, Sheryl van der Poel, Laura Rienzi, and Catherine Racowsky. 2016. "Blastocyst Culture Using Single versus Sequential Media in Clinical IVF: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *Journal of Assisted Reproduction and Genetics* 33 (10): 1261–72. https://doi.org/10.1007/s10815-016-0774-5.

Shi, Yutoku, Hideto Yamada, Yuki Sasagawa, Kenji Tanimura, and Masashi Deguchi. 2022. "Uterine Endometrium Microbiota and Pregnancy Outcome in Women with Recurrent Pregnancy Loss." *Journal of Reproductive Immunology* 152 (August):103653. https://doi.org/10.1016/j.jri.2022.103653.

Sifer, Christophe, Jean-Christophe Pont, Raphael Porcher, Brigitte Martin-Pont, Brigitte Benzacken, and Jean-Philippe Wolf. 2009. "A Prospective Randomized Study to Compare Four Different Mineral Oils Used to Culture Human Embryos in IVF/ICSI Treatments." *European Journal of Obstetrics & Gynecology and Reproductive Biology* 147 (1): 52–56. https://doi.org/10.1016/j.ejogrb.2009.06.023.

Sills, Eric Scott, Gráinne U. Murray, Marc G. Genton, David J. Walsh, Graham D. Coull, and Anthony P.H. Walsh. 2009. "Clinical Features and Reproductive Outcomes for Embryos Undergoing Dual Freeze-Thaw Sequences Followed by Blastocyst Transfer: Critique of 14 Consecutive Cases in IVF." *Fertility and Sterility* 91 (4): 1568–70. https://doi.org/10.1016/j.fertnstert.2008.09.075.

Simopoulou, Mara, Polina Giannelou, Panagiotis Bakas, Laertis Gkoles, Theodoros Kalampokas, Konstantinos Pantos, and Michael Koutsilieris. 2016. "Making ICSI Safer and More Effective: A Review of the Human Oocyte and ICSI Practice." *In Vivo* 30:387–400.

Siristatidis, C, M Papapanou, V Karageorgiou, W P Martins, I Bellos, D M Teixeira, and N Vlahos. 2023. "Congenital Anomaly and Perinatal Outcome Following Blastocyst- vs Cleavage-Stage Embryo Transfer: Systematic Review and Network Meta-Analysis." *Ultrasound Obstet Gynecol*.

Smeenk, Jesper, Christine Wyns, Christian De Geyter, Markus Kupka, Christina Bergh, Irene Cuevas Saiz, Diane De Neubourg, et al. 2023. "ART in Europe, 2019: Results Generated from European Registries by ESHRE." *Human Reproduction*, October, dead197. https://doi.org/10.1093/humrep/dead197.

Sonigo, Charlotte, Naouel Ahdad-Yata, Paul Pirtea, Céline Solignac, Michael Grynberg, and Nathalie Sermondade. 2024. "Do IVF Culture Conditions Have an Impact on Neonatal Outcomes? A Systematic Review and Meta-Analysis." *Journal of Assisted Reproduction and Genetics* 41 (3): 563–80. https://doi.org/10.1007/s10815-024-03020-0.

Staessen, C., C. Janssenswillen, E. De Clerck, and A. Van Steirteghem. 1998. "Controlled Comparison of Commercial Media for Human In-Vitro Fertilization: Menezo B2 Medium

versus Medi-Cult Universal and BM1 Medium." *Human Reproduction* 13 (9): 2548–54. https://doi.org/10.1093/humrep/13.9.2548.

Swain, Jason E. 2010. "Optimizing the Culture Environment in the IVF Laboratory: Impact of pH and Buffer Capacity on Gamete and Embryo Quality." *Reproductive BioMedicine Online* 21 (1): 6–16. https://doi.org/10.1016/j.rbmo.2010.03.012.

Swain, Jason E. 2014. "Decisions for the IVF Laboratory: Comparative Analysis of Embryo Culture Incubators." *Reproductive BioMedicine Online* 28 (5): 535–47. https://doi.org/10.1016/j.rbmo.2014.01.004.

Swain, Jason E., Doug Carrell, Ana Cobo, Marcos Meseguer, Carmen Rubio, and Gary D. Smith. 2016. "Optimizing the Culture Environment and Embryo Manipulation to Help Maintain Embryo Developmental Potential." *Fertility and Sterility* 105 (3): 571–87. https://doi.org/10.1016/j.fertnstert.2016.01.035.

Swain, Jason E., and Martin Wilding. 2012. "Practical pH for the IVF Laboratory." *Journal of Reproductive and Stem Cell Biotechnology* 3 (2): 62–76. https://doi.org/10.1177/205891581200300205.

Tilia, Liza, Christos Venetis, Suha Kilani, Simon Cooke, and Michael Chapman. 2016. "Is Oocyte Meiotic Spindle Morphology Associated with Embryo Ploidy? A Prospective Cohort Study." *Fertility and Sterility* 105 (4): 1085-1092.e7. https://doi.org/10.1016/j.fertnstert.2015.12.018.

Uppangala, Shubhashree, Gail Fernandes, Sujith Raj Salian, Pratap Kumar, Riccardo Talevi, Guruprasad Kalthur, and Satish Kumar Adiga. 2020. "Reduced Ovarian Response to Controlled Ovarian Stimulation Is Associated with Increased Oxidative Stress in the Follicular Environment." *Reproductive Biology* 20 (3): 402–7. https://doi.org/10.1016/j.repbio.2020.04.005.

World Health Organization. 2010. "WHO Laboratory Manual for the Examination and Processing of Human Semen," no. 5th.

Wyns, C., C. Bergh, C. Calhaz--Jorge, Ch De Geyter, M S Kupka, T Montrenko, I. Rugescu, et al. 2020. "ART in Europe, 2016: Results Generated from European Registries by ESHRE." *Human Reproduction Open* 2020 (3): hoaa032. https://doi.org/10.1093/hropen/hoaa032.

Wyns, C, C De Geyter, C Calhaz-Jorge, M S Kupka, T Motrenko, J Smeenk, C. Bergh, A Tandler-Schneider, I.A. Rugescu, and V Groossens. 2022. "ART in Europe, 2018: Results Generated from European Registries by ESHRE." *Human Reproduction Open* 2022 (3): hoac022. https://doi.org/10.1093/hropen/hoac022.

Xella, Susanna, Tiziana Marsella, Daniela Tagliasacchi, Simone Giulini, Antonio La Marca, Alessandra Tirelli, and Annibale Volpe. 2010. "Embryo Quality and Implantation Rate in Two Different Culture Media: ISM1 versus Universal IVF Medium." *Fertility and Sterility* 93 (6): 1859–63. https://doi.org/10.1016/j.fertnstert.2008.12.030.

Youssef, Mohamed MA, Eleni Mantikou, Madelon van Wely, Fulco Van der Veen, Hesham G Al-Inany, Sjoerd Repping, and Sebastiaan Mastenbroek. 2015. "Culture Media for Human Pre-Implantation Embryos in Assisted Reproductive Technology Cycles." Edited by Cochrane Gynaecology and Fertility Group. *Cochrane Database of Systematic Reviews*, no. 11 (November), Art. No.: CD007876. https://doi.org/10.1002/14651858.CD007876.pub2.

Zaat, Tjitske, Miriam Zagers, Femke Mol, Mariëtte Goddijn, Madelon van Wely, and Sebastiaan Mastenbroek. 2021. "Fresh versus Frozen Embryo Transfers in Assisted Reproduction." Edited by Cochrane Gynaecology and Fertility Group. *Cochrane Database of Systematic Reviews*, February. https://doi.org/10.1002/14651858.CD011184.pub3.

Zegers-Hochschild, Fernando, G. David Adamson, Silke Dyer, Catherine Racowsky, Jacques de Mouzon, Rebecca Sokol, Laura Rienzi, et al. 2017. "The International Glossary on Infertility and Fertility Care, 2017." *Fertility and Sterility* 108 (3): 393–406. https://doi.org/10.1016/j.fertnstert.2017.06.005.

Zhang, Jun Qiang, Xiu Ling Li, Yuzhu Peng, Xirong Guo, Boon Chin Heng, and Guo Qing Tong. 2010. “Reduction in Exposure of Human Embryos Outside the Incubator Enhances Embryo Quality and Blastulation Rate.” *Reproductive BioMedicine Online* 20 (4): 510–15. https://doi.org/10.1016/j.rbmo.2009.12.027.

CE033R_Universal IVF Medium_2025.May.06_main

Final Audit Report 2025-05-07

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Status:	Signed
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12 Appendix 1: Data on file

13 Appendix 2: Literature Search Results

13.1 Background

The purpose of the systematic literature review is to provide a comprehensive analysis of the available published clinical scientific literature with the objective to assess and analyse the body of evidence relating to clinical safety and performance data for the subject device and comparable devices. The systematic literature protocol has been developed in accordance with the principles of MEDDEV 2.7/1 (Version 4) for Clinical Evaluations. The literature search timeframes typically align with the post market surveillance (PMS) reporting period(s) and results from the literature search are included in the clinical evaluation process, clinical evaluation report (CER) and PMS reports for the defined products for risk management consideration.

Manufacturers of comparable devices of interest include:

- FUJIFILM, Irvine Scientific

13.2 Objective

The search was conducted to identify published literature reporting clinical data for subject device and state of the art. Relevant characterization of the objective using the PICO scheme is shown in **Table 13-1**.

Table 13-1: PICO characterization of the search objective

PICO	Description
Patient(s)	Patients are all persons/couples who have been assessed suitable by a gynecologist to undergo IVF. This product is for ART treatment, whether the cause of infertility is male or female.
Intervention	Oocyte insemination and/or embryo culture and/or embryo transfer using the actual device, benchmark or similar device.
Comparator (if applicable)	Benchmark or similar device
Outcomes	Reported safety issues, fertilization rate, embryo cleavage/development rates, implantation/clinical pregnancy rates, live birth rate, and health of children born.

Literature Review Question: What clinical evidence regarding the safety and performance of the device and comparable products from other manufacturers and/or state of the art is described in the scientific, peer-reviewed literature?

Search date range: 2023.Jan.01 – 2024.Dec.31

13.3 Sources of Literature

This literature search is based on Yearly PMCF LRRs covering the above search date range.

The sources of literature are listed out in **Table 13-2** along with justification for each.

Table 13-2: Sources of Literature

Database Reference	Source of Literature	Justification
1	PubMed	PubMed comprises more than 35 million citations for biomedical literature from MEDLINE, life science journals, and online books. About 500,000 new records are added each year.
2	Cochrane Library	A collection of databases in medicine and other healthcare specialties provided by Cochrane and other organizations. At its core is the collection of Cochrane Reviews, a database of systematic reviews and meta-analyses which summarize and interpret the results of medical research.
3	ClinicalTrials.gov	ClinicalTrials.gov is a registry of clinical trials. It is run by the United States National Library of Medicine (NLM) at the National Institutes of Health, and is the largest clinical trials database, currently holding registrations from over 230,000 trials from 221 countries in the world.
4	ScienceDirect	ScienceDirect is a full-text scientific database offering journal articles and book chapters from more than 2,650 peer-reviewed journals and more than 42,000 books. There are currently more than 18 million publications. Fertility and Sterility and Reproductive Biomedicine Online are included in ScienceDirect (as well as several other journals within ART).
5	Human Reproduction	Human Reproduction is the official journal of ESHRE. It is made up of four individual publications: "Human Reproduction', 'Human Reproduction Update', 'Human Molecular Genetics' and 'HR Open'. It is a peer-reviewed scientific journal covering all aspects of human reproduction, including reproductive physiology and pathology, endocrinology, andrology, gonad function, gametogenesis, fertilization, embryo development, implantation, pregnancy, genetics, preimplantation genetic diagnosis, oncology, infectious disease, surgery, contraception, infertility treatment, psychology, ethics, and social issues.

13.4 Search Strategy

The search strings applied in the various Yearly PMCF LRR searches as well as results, are listed out in **Table 13-3**, while exclusions are documented in the Yearly PMCF LRRs.

Table 13-3: Search Strings

Search		Search Terms	Selected for further assessment for this CER
Scientific databases			
Yearly PMCF LRR 2023	Performance & Safety	“(Medi-Cult OR Medicult) OR Origio” AND (IVF OR "*In vitro* fertil*") SAGE AND (IVF OR “*in vitro* fertil*”) "LifeGlobal"	0

Search		Search Terms	Selected for further assessment for this CER
Scientific databases			
		CooperSurgical AND (IVF OR "*In vitro* fertil*")	
	State of the Art	"(oocyte AND insemination) AND (procedure OR method)" "((embryo AND culture) AND (media OR medium)) AND assisted reproduction" "((embryo AND transfer) AND (media OR medium)) AND assisted reproduction"	8
Yearly PMCF LRR 2024	Performance & Safety	"(Medi-Cult OR Medicult) OR Origio" AND (IVF OR "*In vitro* fertil*") SAGE AND (IVF OR "*in vitro* fertil*") "LifeGlobal" CooperSurgical AND (IVF OR "*In vitro* fertil*")	3
	State of the Art	"(oocyte AND insemination) AND (procedure OR method)" "((embryo AND culture) AND (media OR medium)) AND assisted reproduction" "((embryo AND transfer) AND (media OR medium)) AND assisted reproduction"	7

13.5 Selection Criteria

The Inclusion/Exclusion criteria that were applied to the new searches are listed out in **Table 13-4**.

Table 13-4: Inclusion/Exclusion Criteria

Search Category	Inclusion	Exclusion
Safety & Performance	• Relating to the intended purpose of actual device, benchmark or similar device • Relating to clinical performance or safety of actual device, benchmark or similar device • All types of study designs and publications • Published in English language and review of non-English literature for possible translation	• Relating to other species than human • Lack of info on elementary aspects • Duplicate publications • Citations only • Anecdotal evidence
State of the Art	• Applicable standards and guidance documents • Reviews and meta-analysis of publications and literature relating to current technology and practice in the medical field concerned; incl. evaluations of clinical performance and safety of the same type of devices • Published in English language	• Publications relating to state of the art published before first step towards regulation of ART media in May 2008 • Duplicate publications • Citations only • Publication only available as poster or abstract • Anecdotal evidence

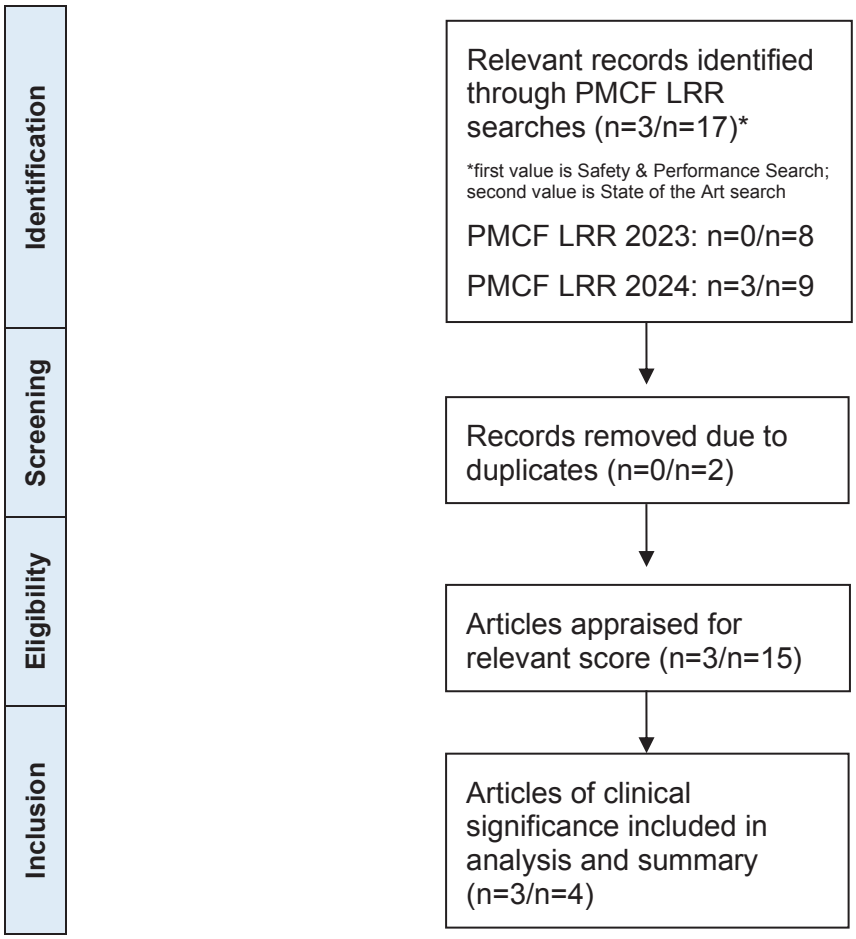
Publications meeting any of the listed exclusion criteria will be automatically rejected. For publications not automatically rejected, an appraisal will be conducted after screening and weighting based on relevancy scores to provide an overall accept / reject weighting according to **Appendix 3: Literature Search Appraisal**.

13.6 Literature Selection Process

All Yearly PMCF LRR searches had data assessed for suitability for inclusion using the same principles as described in the flowchart presented in the CEP (Appendix A, section 1.6), with 1st exclusion based on title and abstracts followed by 2nd exclusion based on full-text (all documented in the Yearly PMCF LRRs). To ensure data integrity during extraction, a second qualified individual reviewed the literature selection process.

Please refer to Figure 13-1 for a flowchart describing the total number of articles identified in the Yearly PMCF LRRs as relating to the device(s) covered in this CER, and any exclusions due to no relevant data.

Figure 133-1: Literature Selection Process



14 Appendix 3: Literature Search Appraisal

Following data appraisal and identification of the most relevant publications, the data and results found in the literature will be clinically analyzed for demonstration of the overall safety and performance for the device(s) under evaluation. The key findings regarding safety and performance from the in-depth appraisal will be summarized. New state-of-the-art technology or treatments, if applicable, will also be addressed. Whether or not any unexpected findings or new hazards supports the safety and performance of the device under evaluation when used as intended is / are to be made. The analysis / summary of the literature will be included in either the body of the CER or, if lengthy, provided as an attachment to the CER and summarized in the body of the CER.

Subject Device

Utilize Appraisal Criteria for Suitability table for conducting appraisal for articles related to the subject device, benchmark, or similar devices. This first table should not necessarily be used for state-of-the-art appraisal as often the information is not readily available so the article would not score as relevant. The result is a listing of articles used for analysis, evaluation, and summary for safety and performance.

Table 14-1: Appraisal Criteria for Suitability

Criteria for Suitability			
Suitability Criteria	**Description**	**Grading System**	
Appropriate device	Were the data generated from the device in question?	D1	Actual device
		D2	Benchmark device
		D3	Similar device
Appropriate device application	Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?	A1	Same use
		A2	Minor deviation
		A3	Major deviation
Appropriate patient group	Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1	Applicable
		P2	Limited
		P3	Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1	High quality
		R2	Minor deficiencies
		R3	Insufficient information

"Appropriate device" is graded **D1** when data were related to subject device, **D2** if data related to benchmark device; **D3** if data related to another device (e.g. non-relevant devices).

"Appropriate device application" is "same use" (**A1**), or "minor deficiencies" (**A2**) if the procedure slightly deviated from the Instructions for use (IFU) or if the products were tested under various conditions in experimental setups, or "major deficiencies" (**A3**) if the procedure differed significantly from the IFU.

"Patient population" is graded **P1** if all clinical data were generated from a patient group representative for the standard population; or **P2** if data were generated from a severely compromised patient population. **P3** is where the patient population is not the same.

"Acceptable report/data collection" is graded **R1** if the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment (= high quality); **R2** if minor deficiencies exist, e.g. if a few details were missing; and **R3** is referring to publications where important information concerning e.g. study population or treatment is missing which is of relevance to the conclusions, or if data are inconsistent.

Studies concerning head-to-head comparison of clinical performance and/or safety of the actual device against a benchmark or similar device are rated according to study design. Although there are exceptions, depending on the intended purpose of the device, a prospective randomized controlled study is generally preferable when the primary evaluation parameter is clinical outcome (e.g. implantation/ clinical pregnancy and live birth delivery rates) while a cohort study with prospective randomized sibling oocytes/zygotes is the most optimal study design for comparison of embryology parameters (e.g. fertilization, cleavage and blastocyst rates). Although clinical performance of Universal IVF Medium is primarily based on embryology parameters (fertilization and cleavage rates), it is very difficult/time-consuming to perform oocyte retrieval and impossible to perform follicle flushing, using more than one oocyte retrieval/flushing medium. Therefore, prospective randomized controlled studies are the most optimal study design for comparison studies and are rated highest.

Data related to the device under evaluation and any safety issues are weighted highest. After that, data are ranked according to outcome measures and data source type. Identification is taken into consideration for any alternative treatment method identified, or how the clinical application is relevant to the patient. When data are considered equally important, the data are listed according to sample size.

Results: When added together a score of 4 – 6 should be considered for inclusion into the clinical evaluation. Any score between 6 – 8 should be reviewed to determine if the publication has any clinical significance.

State of the Art

Utilize Appraisal Criteria for State of the Art table for conducting appraisal for articles related to state of the art including any identified benchmark devices. This second table should be used for state of the art appraisal as the questions are more qualitative and general in nature. This appraisal of state of the art is completed on full text of the articles to rank and score articles for use in state of the art discussion. The result is a listing of articles used for analysis, evaluation, and summary for state of the art.

Table 14-2: Appraisal Criteria for State of the Art

Criteria for Data Contribution		
Suitability Criteria	**Description**	**Quality Grading**
Data source type	Was the design of the study appropriate? e.g. clear endpoints? Is the clinical application appropriate for type of device?	T1: Yes
		T2: No
Outcome measures	Do the outcome measures reported reflect the intended performance of the device? Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	O1: Yes
		O2: No
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1: Yes
		S2: No

"Data source type" is graded **T1** if the design of the study was appropriate (e.g. proper inclusion of controls, all specimens/patients treated according to the same protocol, same type of data collected for all patients and data can be referred to the sperm selection technique used); otherwise, it is graded **T2**.

"Outcome measures" is graded **O1** if sufficient information exists for determining how the clinical application can be properly conducted or result in positive outcome to the patient (e.g. information provided showing the patient's clinical outcome is positive compared to alternative treatment or no treatment); otherwise, it is graded **O2**.

"Statistical significance" is grade **S1** if statistical significance is presented in the article either in a quantitative way, i.e. p-value, or in qualitative way, i.e. total number. If there is no analysis of the data or presenting of clinical outcomes, then it is graded **S2**.

Data related to any identified safety issues concerning the device type are weighted highest. After that, data are ranked according to outcome measures and data source type Identification is taken into consideration any alternative treatment method identified, or how the clinical application is relevant to the patient. When data were considered equally important, the data were listed according to sample size.

Results: If at least two of the scores are rate Yes (1), the publication should be considered for inclusion into the clinical evaluation.

14.1 Acceptance Appraisal Review

Citations for publications are listed in **Section 10: Bibliography**. This appraisal concerns the latest search results covering the period 2023.Jan.01 – 2024.Dec.31. Prior appraisals are presented in previous versions of the MDR CER as well as the MDD CER (CE033R Version B).

Moreover, the below appraisal does not include duplicates (publications identified in more than one Yearly PMCF LRR, or already included from the previous version of the CER), nor does it include reviews, meta-analysis or guidelines replaced by more recent versions.

Table 14-3: Accept/Reject Device Appraisal

#	Literature / Clinical Data Used in the Clinical Evaluation	Appropriate Device	Appropriate Device Appl.	Appropriate Patient Group	Acceptable Report / Data Col.	Additive Score	Accept / Reject
Subject Device							
Yearly PMCF LRR 2024							
1	Hatirnaz, Safak, Hatirnaz, Ebru, Urkmez, Sebati Sinan, Calıskan, et al. 2024. “Oocyte In-Vitro Maturation Primed with Letrozole-HCG versus FSH-HCG in Women with Oocyte Maturation Abnormalities: A Retrospective Study.” Reproductive BioMedicine Online, January. https://doi.org/10.1016/j.rbmo.2023.103620.	D1	A1	P1	R1	4	Accept
2	Hatirnaz, Şafak, Hatirnaz, Ebru, Urkmez, Sebati Sinan, Celik, et al. 2024. “Comparison of Luteal Phase and Follicular Phase In-Vitro Maturation in Women with Oocyte Maturation Abnormalities.” Reproductive BioMedicine Online, January. https://doi.org/10.1016/j.rbmo.2023.103648.	D1	A1	P1	R1	4	Accept

#	Literature / Clinical Data Used in the Clinical Evaluation	Appropriate Device	Appropriate Device Appl.	Appropriate Patient Group	Acceptable Report / Data Col.	Additive Score	Accept / Reject
3	Hatakeyama, Shota, Koizumi, Kaori, Kuramoto, Goro, Horiuchi, et al. 2024. “Assisted Sperm Fusion Insemination Improves Fertilization Rates and Increases Usable Embryos for Transfer: A Clinical Sibling-Oocyte Study.” F&S Reports, January. https://doi.org/10.1016/j.xfre.2024.11.006.	D1	A1	P1	R1	4	Accept
Benchmark Devices							
1	Hatakeyama, Shota, Koizumi, Kaori, Kuramoto, Goro, Horiuchi, et al. 2024. “Assisted Sperm Fusion Insemination Improves Fertilization Rates and Increases Usable Embryos for Transfer: A Clinical Sibling-Oocyte Study.” F&S Reports, January. https://doi.org/10.1016/j.xfre.2024.11.006.	D2	A1	P1	R1	5	Reject Not a comparative article

Table 14-4: Accept/Reject State of the Art Appraisal

#	Literature / Clinical Data Used in the Clinical Evaluation	Data source type	Outcome measures	Statistical significance	Additive Score	Accept / Reject
Yearly PMCF LRR 2023						
1	Siristatidis, C., M. Papapanou, V. Karageorgiou, W. P. Martins, I. Bellos, D. M. Teixeira, and N. Vlahos. 'Congenital Anomaly and Perinatal Outcome Following Blastocyst- vs Cleavage-Stage Embryo Transfer: Systematic Review and Network Meta-Analysis'. Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology 61, no. 1 (January 2023): 12–25. https://doi.org/10.1002/uog.26019.	T1	O1	S1	3	Accept
2	Sallam, Hassan, Florence Boitrelle, Simone Palini, Damayanthi Durairajanayagam, Lodovico Parmegiani, Sunil Jindal, Ramadan Saleh, Giovanni Colpi, and Ashok Agarwal. 'ICSI for Non-Male Factor Infertility: Time to Reappraise IVF?' Panminerva Medica 65, no. 2 (June 2023): 159–65. https://doi.org/10.23736/S0031-0808.23.04869-3.	T2	O2	S2	6	Reject Unsuitable study design
3	Choi, Jung-Won, Sung-Woo Kim, Hee-Sun Kim, Moon-Joo Kang, Sung-Ah Kim, Ji-Yeon Han, Hoon Kim, and Seung-Yup Ku. 2024. 'Effects of Melatonin, GM-CSF, IGF-1, and LIF in Culture Media on Embryonic Development: Potential Benefits of Individualization'. International Journal of Molecular Sciences 25 (2): 751. https://doi.org/10.3390/ijms25020751.	T2	O2	S2	6	Reject Unsuitable study design
4	Cutting, E, Horta, F, Dang, V, van Rumste, MME, and BWJ Mol. 2023. 'Intracytoplasmic Sperm Injection versus Conventional *in vitro* Fertilisation in Couples with Males Presenting with Normal Total Sperm Count and Motility'. Cochrane Database of Systematic Reviews, no. 8. https://doi.org/10.1002/14651858.CD001301.pub2.	T1	O1	S1	3	Reject No focus on culture media

#	Literature / Clinical Data Used in the Clinical Evaluation	Data source type	Outcome measures	Statistical significance	Additive Score	Accept / Reject
5	ESHRE Add-ons working group, K Lundin, J G Bentzen, G Bozdag, T Ebner, J Harper, N Le Clef, et al. 2023. 'Good Practice Recommendations on Add-Ons in Reproductive Medicine'. Human Reproduction, September, dead184. https://doi.org/10.1093/humrep/dead184.	T1	O1	S2	5	Accept
6	Sciorio, Romualdo, and Paolo Rinaudo. 2023. 'Culture Conditions in the IVF Laboratory: State of the ART and Possible New Directions'. Journal of Assisted Reproduction and Genetics, September. https://doi.org/10.1007/s10815-023-02934-5.	T1	O1	S2	4	Accept
7	Tire, Betul. 2023. 'Potential Effects of Assisted Reproductive Technology on Telomere Length and Telomerase Activity in Human Oocytes and Early Embryos'. Journal of Ovarian Research.	T2	O2	S2	6	Reject Unsuitable study design
8	Yang, Liu, Fuxiang Liang, Rongyan Zhu, Qi Wang, Liang Yao, and Xuehong Zhang. 2024. 'Efficacy of Intracytoplasmic Sperm Injection in Women with Non-Male Factor Infertility: A Systematic Review and Meta-Analysis'. Acta Obstetricia Et Gynecologica Scandinavica 103 (1): 30–41. https://doi.org/10.1111/aogs.14698.	T1	O1	S2	4	Reject No focus on culture media
Yearly PMCF LRR 2024						
9	Kamath, MS, Vogiatzi, P, Sunkara, SK, Woodward, & B. (2024). Oocyte activation for women following intracytoplasmic sperm injection (ICSI). https://doi.org/10.1002/14651858.CD014040.pub2	T1	O2	S1	4	Reject Focus on Artificial oocyte activation

#	Literature / Clinical Data Used in the Clinical Evaluation	Data source type	Outcome measures	Statistical significance	Additive Score	Accept / Reject
10	Kathryn A Voss, Yu-Fu M Chen, Daniel A Castillo, Wendy S Vitek, & Snigdha Alur-Gupta. (2024). Ovulation-induced frozen embryo transfer regimens in women with polycystic ovary syndrome: A systematic review and meta-analysis. Journal of Assisted Reproduction and Genetics. https://doi.org/10.1007/s10815-024-03209-3	T1	O1	S1	3	Reject No focus on culture media
11	Kuroda, K. (2024). Management strategies following implantation failure of euploid embryos. Reproductive Medicine and Biology, 23(1), e12576. https://doi.org/10.1002/rmb2.12576	T2	O2	S2	6	Reject Unsuitable study design
12	Leah Cooper, Emma Manuel, Min Xu, & Samantha B Schon. (2024). In vitro fertilization, intracytoplasmic sperm injection, in vitro maturation, and embryo culture. Systems Biology in Reproductive Medicine. https://doi.org/10.1080/19396368.2024.2439838	T1	O2	S2	5	Reject No focus on culture media
13	Narges Karami, Adeleh Taei, Poopak Eftekhari-Yazdi, & Fatemeh Hassani. (2024). Signaling pathway regulators in preimplantation embryos. Journal of Molecular Histology. https://doi.org/10.1007/s10735-024-10338-7	T1	O2	S2	5	Reject Focus on signaling pathways
14	Sonigo, C., Ahdad-Yata, N., Pirtea, P., Solignac, C., Grynberg, M., & Sermondade, N. (2024). Do IVF culture conditions have an impact on neonatal outcomes? A systematic review and meta-analysis. Journal of Assisted Reproduction and Genetics, 41(3), 563–580. https://doi.org/10.1007/s10815-024-03020-0	T1	O1	S1	3	Accept

#	Literature / Clinical Data Used in the Clinical Evaluation	Data source type	Outcome measures	Statistical significance	Additive Score	Accept / Reject
15	Tong Wu, Jinfeng Yan, Kebing Nie, Ying Chen, Yangyang Wu, Shixuan Wang, & Jinjin Zhang. (2024). Microfluidic chips in female reproduction: A systematic review of status, advances, and challenges. Theranostics. https://doi.org/10.7150/thno.97301	T1	O2	S2	5	Reject Focus on microfluidic chips

15 Appendix 4: CV/Resume and Declaration of Interest

Attached CV/Resume and Declaration of Interest or make a reference to where these are located.

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Declaration of Interest Form

First/ Last name of Author:	Emma Cartwright
First/Last name of Co-Author:	-
First/Last name of Reviewer(s):	Gemma Rutterford, Stephen Troup, Monica Puig, Hussein Sabtiy
First/Last name of other relevant participant(s):	-
PER/CER # and/or PER/CER Title:	CE033R - Clinical Evaluation Report for Universal IVF Medium

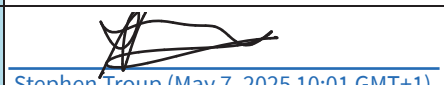
The undersigned individuals hereby certify that he/she did not at any time receive any payment or services (including from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.) except for the salary as an employee or a paid consultant of CooperSurgical, Inc.

The undersigned individuals hereby certify that he/she does not have any patents, whether planned, pending or issued, broadly relevant to the work completed in the above referenced PER/CER(s).

The undersigned individuals hereby certify that he/she does not have other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing (e.g. significant investment or ownership interest in the company), the assessment completed in the above referenced PER/CER(s).

The undersigned individuals hereby certify that he/she does not have any other relationships/conditions/circumstances that present a potential conflict of interest.

The undersigned individuals hereby confirm that the above statements are true and correct to the best of their knowledge and understand that a false statement may disqualify said individual as an author or reviewer for clinical evaluations for CooperSurgical, Inc.

Emma Cartwright, MDx External Consultant		Date:	May 6, 2025
Gemma Rutterford, Senior Medical Writer		Date:	May 6, 2025
Stephen Troup, Consultant Clinical Embryologist	 Stephen Troup (May 7, 2025 10:01 GMT+1)	Date:	May 7, 2025
Monica Puig, Regulatory Affairs Specialist		Date:	May 6, 2025
Hussein Sabtiy, Senior Director, Regulatory & Clinical Affairs & Product Maintenance IVF Media		Date:	May 7, 2025

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