Summary of safety and clinical performance

SpermGrad™/SpermGrad RTU™

This summary of safety and clinical performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions for Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1 Device identification and general information

1.1	Device trade name	SpermGrad/SpermGrad RTU
1.2	Manufacturer's name and address	Vitrolife Sweden AB, Gustaf Werners gata 2, SE-421 32 Västra Frölunda, Sweden
1.3	Manufacturer's single registration number (SRN)	SE-MF-000002389
1.4	Basic UDI-DI	735002591ABDDK
1.5	Global Medical Device Nomenclature (GMDN) code	44046
1.6	Class of device	Class III
1.7	Year when the first certificate (CE) was issued covering the device	CE-marked in 2002 (SpermGrad) and 2012 (SpermGrad RTU)
1.8	Authorized representative if applicable; name and SRN	Not applicable
1.9	NB's name (the NB that will validate the SSCP) and the NB's single identification number	DNV Product Assurance AS Veritasveien 1, 1363 Høvik, Norway 2460

2 Intended use of the device

2.1 Intended purpose

SpermGrad/SpermGrad RTU are medical devices intended for use in Assisted Reproductive Technology (ART) as media for gradient sperm separation.

2.2 Indication and target population

The Indication for use of SpermGrad/SpermGrad RTU is "medium for gradient sperm separation". The intended target group is an adult or reproductive-age population that undergoes IVF treatment or fertility preservation, respectively.

2.3 Contraindications and/or limitations

None.

3 Device description

3.1 Description of the device

SpermGrad/SpermGrad RTU are bicarbonate and HEPES buffered medium containing silane-coated, colloid silica particles. Based on their Indication for Use, SpermGrad/SpermGrad RTU will have sperm contact. The devices are sterile antibiotic-free media that are delivered in a 30 mL and a 125 mL bottle (Figure 1). They are available both as stock (SpermGrad) that require dilution and supplementation with other media, and as ready-to-use (RTU) solutions, SpermGrad RTU.

Figure 1. SpermGrad/SpermGrad RTU

Upper: Stock solution (use after dilution), Lower: Ready-to-use (RTU) solution

3.2 A reference to previous generation(s) or variants if such exists, and a description of the differences

There have been no previous versions of SpermGrad/SpermGrad RTU on the market.

3.3 Description of any accessories which are intended to be used in combination with the device

Not applicable.

3.4 Description of any other devices and products which are intended to be used in combination with the device

General equipment and sterile non-toxic disposables for the IVF lab including centrifuge, G-IVF PLUS and SpermRinse.

4 Risks and warnings

4.1 Residual risks and undesirable effects

All known and foreseeable risks and undesirable side-effects associated with the use of SpermGrad/SpermGrad RTU were identified, evaluated, and reduced as far as possible during risk management. SpermGrad/SpermGrad RTU are not intended to have patient contact and do not contain any medicinal substance. Hence, there were no risks with the potential to affect the patient or end users' health. All the identified risks concern the gametes and /or embryos and are acceptable after risk control measures.

4.2 Warnings and precautions

The precautions related to the use of SpermGrad/SpermGrad RTU are:

- Discard product if bottle integrity is compromised. Do not use SpermGrad if it appears cloudy.
- Re-use may result in microbiological contamination and/or property changes in the product.
- To avoid contamination Vitrolife strongly recommends that media should be opened and used only with aseptic technique.
- The risks of reproductive toxicity and developmental toxicity for IVF media, including Vitrolife's IVF media, have not been determined and are uncertain.
- Not for injection.
- Any serious incident that has occurred in relation to the device should be reported to the manufacturer.
- Discard the product according to standard clinical practice for medical hazardous waste when the procedure is finished.

4.3 Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

No FSCAs have been taken for SpermGrad/SpermGrad RTU during their lifecycle.

5 Summary of clinical evaluation and post-market clinical follow-up

5.1 Summary of clinical data related to equivalent device, if applicable

Not applicable.

5.2 Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

There is no clinical investigation conducted for SpermGrad/SpermGrad RTU before their CE-marking.

5.3 Summary of clinical data from other sources, if applicable

A systematic literature search was conducted during the clinical evaluation of SpemGrad/SpermGrad RTU to identify clinical data supporting the safety and performance of the devices. Several studies provided data on post-gradient sperm recovery including viability, morphology, motility, and progressive motility following the use of SpermGrad/SpermGrad RTU [1-14]. Successful clinical pregnancy and live birth were also reported [1, 5-8, 10, 15-18] with a total of at least 6055 children born from treatment cycles that included SpermGrad/SpermGrad RTU. Some studies [5, 8, 11, 19, 20] have reported results from comparing sperm preparation method. SpermGrad was used in the DGC and the data showed no significant differences on sperm parameters among the sperm preparation techniques. There were no deviations, or any adverse events relating the safety or performance of SpermGrad/SpermGrad RTU identified from the literature search.

No undesirable side-effect, trends or vigilance reports have been identified for EmbryoGlue during its post-market surveillance (PMS).

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, SpermGrad/SpermGrad RTU are intended to support gradient sperm separation. Based on that, the first measurable endpoint after the use of SpermGrad/SpermGrad RTU is sperm recovery rate (e.g., motility, progressive motility, viability). Data obtained on this endpoint from treatment cycles including their use is relevant to confirm the safety and performance. For SpermGrad/SpermGrad RTU, scientific literature data on total motility, total motile sperm count, and progressive motility following density gradient centrifugation using SpermGrad/SpermGrad RTU confirm their safety and performance. The clinical outcomes (CPRs, LBRs) reported in the scientific literature were in line with the yearly European results published by ESHRE [21]. Data from PMS and risk management also add support to the safety and performance of SpermGrad/SpermGrad RTU. No undesirable side-effects have been identified during their lifecycle and the benefit-risk profile is acceptable.

Together, these data confirm safety and performance of SpermGrad/SpermGrad RTU for their Indication for Use and clinical claim.

5.5 Ongoing or planned post-market clinical follow-up

There are no ongoing or planned PMCF studies for SpermGrad/SpermGrad RTU. However, post-market surveillance will continuously monitor the device during its time on the market and general PMCF procedures will be conducted to identify any emerging risks, complications or performance issues.

6 Possible diagnostic or therapeutic alternatives

ART is a treatment option for patients failing to conceive naturally as well as patients who have tried other treatments such as medications and surgical procedures without success. There are no other therapeutic alternatives at this stage.

Sperm preparation is an important step in ART cycles to ensure good sperm quality and eliminate seminal plasma and contaminating debris that are detrimental to fertilization. Similar devices allow separation of sperm based on density gradient centrifugation are available in the European Union or other international markets. The alternative option is the swim-up method.

The conventional swim up (SU) method and density gradient centrifugation (DGC) are the most frequently used and widely accepted sperm preparation techniques [22, 23]. Several studies have attempted to unravel which sperm selection technique is superior in terms of safety and effectiveness, however the results are inconsistent, and the conclusions are indecisive. Advanced sperm selection based on magnetic activated cell sorting (MACS), hyaluronan binding and microfluidic technique require more studies exploring the impact of these methods on ART outcomes.

As of now, there is no consensus recommending the use of a specific sperm separation medium over the other. It should be determined within individual laboratories as to which medium best suits the procedure.

7 Suggested profile and training for users

The end-user, being the IVF professional, is expected to be trained and qualified within the ART field, to understand the Indication for Use, and follow the Instructions for Use of SpermGrad/SpermGrad RTU. As no special design features or safety concerns were identified for SpermGrad/SpermGrad RTU, no specific training is required for end-users.

8 Reference to any harmonized standards and common specifications applied

- Medical Devices Regulation (EU) 2017/745 (MDR)
- EN ISO 14971:2019/A11:2021. Medical Devices. Application of risk management to medical devices. 31 December 2021.
- ISO/TR 20416:2020. Medical devices — Post-market surveillance for manufacturers. July 2020
- EN ISO 20417:2021. Medical devices — Information to be supplied by the manufacturer. December 2021
- MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies. April 2020
- MDCG 2019-9 Rev.1. Summary of safety and clinical performance. A guide for manufacturers and notified bodies. March 2022

The conformity assessment procedure is performed according to Annex IX in the MDR.

9 Revision history

Version	Date issued	Change Description	Revision validated by the Notified Body
v.1.0	2021-10-07	Initial version of SSCP for SpermGrad/SpermGrad RTU (REP-4270)	
v.2.0	2022-09-16	Update to address NCs: update concerns sections; 1, 6 &8 (REP-4270)	☑ Yes Validation language: English
v.3.0	2022-12-15	Annual update in 2022	
v.4.0	2023-10-12	Annual update in 2023	
v.5.0	2025-01-02	Annual update in 2024	
v.6.0	See publish date	Edit Section 6 and adjust the citation format	☑ Yes Validation language: English

10 References

1. Jeong, M., S.K. Kim, and K. Hoon, *Predictive value of sperm motility before and after preparation for the pregnancy outcomes of intrauterine insemination.* 2021. 48.
2. Talarczyk-Desole, J., et al., *A Potential Relationship Between Estrogen Receptors Polymorphisms, Sperm Function and in vitro Fertilization Success: A Preliminary Study.* POSTEPY HIGIENY I MEDYCYNY DOSWIADCZALNEJ, 2021. 75: p. 304-317.
3. Wang, X., et al., *Factors Affecting Artificial Insemination Pregnancy Outcome.* Int J Gen Med, 2021. 14: p. 3961-3969.
4. Zhang, Y., et al., *Diagnostic performance of discontinuous density gradient centrifugation for estimating human semen quality.* Andrology, 2021. 9(1): p. 196-203.
5. Cil, N., et al., *Retrospective comparison of the semen preparation techniques for intrauterine insemination: Swim-up versus density gradient method.* J Gynecol Obstet Hum Reprod, 2022. 51(3): p. 102321.
6. Jiang, L., et al., *Effect of early rescue ICSI and split IVF-ICSI in preventing low fertilization rate during the first ART cycle: A real-world retrospective cohort study.* Reprod Med Biol, 2022. 21(1): p. e12420.
7. Mei, J., et al., *Magnetic-activated cell sorting of nonapoptotic spermatozoa with a high DNA fragmentation index improves the live birth rate and decreases transfer cycles of IVF/ICSI.* Asian Journal of Andrology, 2022. 24(4): p. 367.
8. Rao, M., et al., *Cumulative live birth rates after IVF/ICSI cycles with sperm prepared by density gradient centrifugation vs. swim-up: a retrospective study using a propensity score-matching analysis.* Reprod Biol Endocrinol, 2022. 20(1): p. 60.

9. van Marion, E.S., et al., *Longitudinal surface measurements of human blastocysts show that the dynamics of blastocoel expansion are associated with fertilization method and ongoing pregnancy.* Reprod Biol Endocrinol, 2022. 20(1): p. 53.
10. Wang, Q.X., et al., *Random sperm DNA fragmentation index is not associated with clinical outcomes in day-3 frozen embryo transfer.* Asian J Androl, 2022. 24(1): p. 109-115.
11. Bibi, R., et al., *Analyzing the Differential Impact of Semen Preparation Methods on the Outcomes of Assisted Reproductive Techniques.* Biomedicines, 2023. 11(2).
12. Fancsovits, P., A. Lehner, and Z. Kaszas, *Intracytoplasmic sperm injection does not improve the outcome of IVF treatments in patients with advanced maternal age or low oocyte number: A randomized controlled trial.* JournalofGynecologyObstetrics andHumanReproduction, 2023. 52.
13. Zhang, J., et al., *Effect of calcium ionophore (A23187) on embryo development and its safety in PGT cycles.* 2023.
14. Kaleli, S., et al., *Evaluating the efficacy of ovulation stimulation with intrauterine insemination in women with diminished ovarian reserve compared to women with normal ovarian reserve.* Int J Gynaecol Obstet, 2023. 160(2): p. 620-627.
15. Chen, X., et al., *Rescue intracytoplasmic sperm injection improved cumulative live birth rate for cycles with second polar body extrusion rate <50% in young women: generalized addictive model.* Fertil Steril, 2024.
16. Zander-Fox, D., et al., *Improved fertilization, degeneration, and embryo quality rates with PIEZO-intracytoplasmic sperm injection compared with conventional intracytoplasmic sperm injection: a sibling oocyte split multicenter trial.* Fertil Steril, 2024. 121(6): p. 971-981.
17. Zhang, K., et al., *Decreased AKAP4/PKA signaling pathway in high DFI sperm affects sperm capacitation.* Asian J Androl, 2024. 26(1): p. 25-33.
18. Cakir, C., et al., *Reliability of hypo-osmotic swelling test on fresh and frozen-thawed ejaculated or testicular immotile sperm: A sibling oocyte study.* Eur J Obstet Gynecol Reprod Biol, 2024. 293: p. 132-141.
19. Do, M.T. and L.T. Dinh, *Improving IVF clinical results with centrifugation-free sperm preparation method.* Fertility and Sterility, 2021. 116(3): p. e280.
20. Lara-Cerrillo, S., et al., *Microfluidic sperm sorting improves ICSI outcomes in patients with increased values of Double-Strand Breaks in sperm DNA.* Rev Int Androl, 2023. 21(1): p. 100338.
21. Smeenk, J., et al., *ART in Europe, 2019: results generated from European registries by ESHRE.* Hum Reprod, 2023. 38(12): p. 2321-2338.
22. ESHRE Guideline Group on Good Practice in IVF Labs, et al., *Revised guidelines for good practice in IVF laboratories (2015).* Hum Reprod, 2016. 31(4): p. 685-6.
23. WHO, *WHO Laboratory Manual for the examination and processing of human semen. Sixth edition.* online available PDF, 2021.

(End of document)