

VALIDATING NEW MEDIA IN YOUR LAB

Interested in trying Gems media in your lab but not sure how to do it?

INTRODUCTION

This document outlines study design options for validating Genea Biomedx Gems embryo culture media in your lab.

The purpose of such study is to confirm the media's performance in your specific setting and build confidence in its use.

Note: Such studies are not intended to evaluate the media itself, which has over 30-year development history and over 10 years of global clinical use

KEY MESSAGES

- Choose the study type and level of stringency needed to build your confidence in the new media while ensuring feasibility and ease of the study execution.
- Ensure control and study groups have similar patient profiles and treatment variables; apply rigorous matching if needed.
- Ensure homogenous process and culture variables across test and control groups.
- If the goal is to test Gems media for embryo culture, use at minimum Gems Fertilisation media with it to ensure compatibility and ideally include as many Gems products as possible to benefit from the full suite.
- If using other manufacturers' products at any stage, match key media variables as close as possible and wash gametes and embryos thoroughly when switching between media.
- Confirm your incubator gas atmosphere meets Gems requirements; adjust CO₂ levels and measure pH if needed.
- Prevent media evaporation by minimising time for dish preparation, using a humid culture environment and/or an adequate oil overlay.

STUDY TYPE

Decide the type of study based on your specific circumstances, for example:

1 - PROSPECTIVE RANDOMISED SIBLING OOCYTE STUDY - Parallel culture of oocytes from the same patient using Gems vs. another medium

Advantages:

- Genetic consistency reduces confounding, allowing generalisability of outcomes.
- Enhanced statistical power with fewer subjects needed.
- Enables sensitive paired analyses (e.g. paired t-tests).

Limitations:

- Limited generalisability with small patient cohorts.
Smaller statistical power.
- Sample size restricted to patients with high oocyte yield, potentially skewing toward younger, high-reserve profiles.
- Delayed implantation/live birth data.
- Requires more incubator space and staff time per patient.

Summary:

An ideal design for testing discrete variables like culture media, using in vitro outcomes as surrogate markers for success and when the extra effort is acceptable.

2- PROSPECTIVE PATIENT COHORT STUDY - Culture of oocytes from defined patient groups using Gems vs. another medium

Advantages:

- Broader generalisability with diverse patient inclusion.
- Larger sample sizes enable subgroup analyses (e.g. age, cycle type).
- Reflects real-world clinical practice.
- Easier to integrate into routine lab operations.
- Faster access to implantation and live birth data.

Limitations:

- High biological variability introduces noise, complicating analysis.
- Larger sample sizes needed to offset inter-patient differences.
- Confounding factors (e.g. stimulation protocols, sperm quality) may require statistical adjustments.

Summary:

A practical design for clinical validation with minimal disruption to lab workflow, offering quick access to real-world outcome data.

3 - RETROSPECTIVE MATCHED CASE STUDY- Comparison of historical outcomes using previous media vs. current Gems media.

Advantages:

- Time- and cost-efficient using existing data.
- More scope for patient matching, controlling for confounders (e.g. age, protocol, cycle type).
- No changes needed to lab processes specifically for the study.
- Easier to include larger sample sizes.

Limitations:

- Dependent on quality and consistency of historical records.
- Poor matching can introduce bias.
- Lab changes over time may affect comparability.

Summary:

A low-effort option for retrospective validation, especially if lab conditions have remained stable during study periods.



PATIENT SELECTION CRITERIA

COMMON PATIENT INCLUSION CRITERIA INCLUDE:

- Female age ≥ 18 and ≤ 38 years
- Couples with ≤ 2 recorded IVF/ICSI embryo transfer cycles
- Non-severe male factor infertility
- Patients undergoing standard (i.e. not experimental) IVF protocol
- Patients with ≥ 2 good quality mature oocytes collected and suitable for fertilisation

These criteria can be defined further if desired for subgroup analysis, for example by expanding age ranges.

COMMON PATIENT EXCLUSION CRITERIA INCLUDE:

- PGT-M and PGT-SR cycles for monogenic/single gene disorders or chromosome structural rearrangements
- Cycles in which sperm is collected via TESE/TESA methods or in which cryopreserved sperm is used
- Severe male factor infertility
- Patients with poor responder history

Donor oocytes and PGT-A cycles offer ideal study groups, if feasible for the clinic. Patient consents may be required or be part of the standard clinical treatment enrolment consents, depending on individual clinics' practices.



OUTCOME MEASURES

- Standardised forms or digital tools should be used for data collection & reporting.
- Anonymisation, data privacy and ethical compliance must be ensured.
- Examples of outcome measures for embryo culture evaluation include:
 - Primary: Zygote development to blastocysts, their quality and utilisation.
 - Secondary: Implantation rates from fresh embryo transfers.
 - Tertiary: Implantation rates from fresh and cumulative (fresh & vitrified) embryo transfers.
- For a standard clinical validation, primary assessment of blastocyst development as surrogate marker for pregnancy outcomes and live birth success is usually sufficient.²
- Examples for other media evaluations include:
 - For sperm solutions: Sperm concentration, motility and progressive motility.
 - For vitrification/warming solutions: Embryo and blastomere survival and expansion rate.
- Ultimately, the clinic will decide its desired endpoints based on their preferences.

COMMON DATA VARIABLES AND OUTCOME MEASURES FOR EMBRYO CULTURE EVALUATION INCLUDE (POSSIBLE KEY VARIABLES IN BOLD):

PATIENT DATA	IN VITRO DATA	IN VIVO DATA
• Patient age • Stimulation protocol • Fertilisation method • Body Mass Index (BMI) • Infertility diagnosis • Duration of infertility • Previous IVF attempts • Ovarian reserve markers • Sperm parameters	• No. of eggs collected • Fertilisation rate • Embryo cleavage rate • % top-grade Day 3 embryos • Blastocyst formation rate • % top-quality blastocysts • % euploid embryos (if PGT-A) • Utilisation rate	• No. of embryos transferred • Biochemical pregnancy rate • Clinical pregnancy rate • Implantation rate • Miscarriage rate • Live birth rate

MEDIA SELECTION

As Gems media suite has been designed to work in concert within the whole suite^{3,4}, we strongly recommend not using only a single media product for a study. However, clinics ultimately decide what media to use for specific steps such as embryo transfer, ICSI, biopsy and others.

FOR THE BEST EMBRYO CULTURE RESULTS WE RECOMMEND USING AT MINIMUM:



**Fertilisation Medium
(FEM-20/50)**
For conventional IVF
and ICSI



**Cleavage Medium
(CLM-20/50)**
For sequential culture



**Blastocyst Medium
(BLM-20/50)**
For sequential culture



**Geri Medium
(ONE-20/50)**
For single-step culture

FOR THE BEST OVERALL OUTCOMES, WE RECOMMEND FURTHER USING:



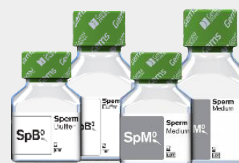
**VitBase
(VBS-20)**
For handling embryos in
non-gassed environment



**Vitrification/Warming
Sets (VIT-01 & WRM-01)**
For embryo vitrification &
warming



**Oocyte Retrieval
Buffer (ORB 20/50)**
For oocyte collection



**Sperm Buffer and Sperm
Medium (SPB-20/50 &
SPM-20/50)**
For sperm handling



**Sperm Wash
Gradient (SWG-01)**
For semen preparation

STUDY SET-UP

CULTURE VARIABLES BETWEEN THE TEST AND CONTROL GROUPS SHOULD BE AS HOMOGENOUS AS POSSIBLE TO AVOID INTRODUCING EXTRA CONFOUNDERS.

INCUBATOR:

- Although developed ideally for culture in Geri timelapse incubator, any other incubator can be used, provided that basic measures are taken to control media evaporation.
- Such measures include for example addition of humidity and/or adequate amount of oil on culture dishes.
- We recommend Geri or benchtop incubators for fast gas and temperature recovery.⁵

GAS:

- Gems suite has been developed for low oxygen environment.
- Ideal gas composition: 5% O₂, 6% CO₂, 89% N₂ at sea level.⁶
- At high altitudes CO₂ concentration may require adjustment based on the local atmospheric pressure.⁶
- Either pre-mixed gas or gas mixer set with target gas composition can be used.
- If CO₂ concentration has been adjusted to modify pH of another medium, it may need to be readjusted for the correct pH in Gems media.

pH:

- Gems suite media pH range at 37°C with 6% CO₂ are listed in the Instructions of Use as 7.30-7.50 for ORB, SPB, SPM, SWG, FEM, CLM, ONE and VBS, and 7.25-7.45 for BLM.^{3,4}
- pH drift may be observed initially during handling.
- As with any media, it is important to equilibrate media properly before use (min. 4 hours).
- pH of Gems media should be tested at the start of the study with appropriately validated and calibrated tools and processes.
- Such validated tools may include for example blood gas analysers*, calibrated pH meters with temperature compensation**, or systems specifically designed for incubators such as non-invasive continuous monitoring systems*** or stand-alone IVF-specific wireless pH meters****.

PATIENT NUMBERS & STUDY DURATION

- It is up to the clinic to decide the number of cases they require for validation.
- This varies based on the stringency of the study incl. the study type, whether aiming for non-inferiority or superiority study and any statistical methods employed.
- Often validation studies aim for non-inferiority with maximum acceptable difference to old method being 10%, Significance Level (risk of false positive) 5% and Power (probability of correctly finding that methods are not different if they truly are not different) 80%.
- In such cases patient numbers may vary from 50 to 100 to 150.
- Knowing the number of cycles per month allows assessing the length of the study, based on anticipated numbers of patients/cycles needed.

* Eg. Siemens EPOC; ** Eg. Mettler Toledo S470 pH meter; *** Eg. ESCO SAFE Sens; **** Eg. Raeyco GopHer

DURING STUDY

- Embryo wash steps are critical when transitioning from other media, especially from HEPES-buffered to bicarbonate-buffered, or between significantly different osmolalities.
 - We recommend 1 - 3 washes in new media drops or wells before moving gametes or embryos from one manufacturer's media to Gems media.
 - No washes or only 1 wash is usually enough when moving embryos within Gems suite.
- Ensure compatibility of other media suite products (for example Hyaluronidase, PVP, other gamete/embryo handling media) with Gems products, ideally choosing the media with the least difference to Gems.
 - Differences for example in osmolality, pH and recommended gas concentrations can be ascertained from their Instructions of Use.
- Appropriate oil overlay is critical to minimise media evaporation and resulting increase in osmolality, especially if using dry culture conditions.
 - For example, minimum of 4 mL oil for Geri Dishes, and min. 11 mL for 60 mm Falcon dishes.⁷

REFERENCES

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