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GRACE: A Five-Axis Classification of Evidence for Regenerative and Energy-Based Gynecology — Compartment, Phenotype, Intervention, Maturity and Anchor Outcome

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ABSTRACT

Background. Regenerative gynecology has expanded faster than its evidentiary architecture. Platelet-rich plasma (PRP), fractional CO2 and Er:YAG lasers, radiofrequency, adipose-derived products and exosome preparations are offered for conditions as different as genitourinary syndrome of menopause (GSM), vulvar lichen sclerosus, stress urinary incontinence, diminished ovarian reserve and recurrent implantation failure. Existing classification systems address isolated fragments of this problem: platelet-product nomenclatures describe the biologic, symptom and examination scores describe GSM severity, and regulatory rating schemes describe evidence for selected fertility add-ons. No framework links who the patient is, which tissue is treated, what exactly is applied, how mature the evidence is and which outcome must be measured.

Purpose. To propose GRACE (Gynecologic Regenerative Axis Classification of Evidence), a five-axis classification intended for clinical decision-making, trial design and reporting, evidence synthesis and responsible communication.

Development. GRACE was derived from two prior evidence syntheses by the authors — an umbrella review of regenerative and energy-based gynecology, which identified a sham gradient, a surrogate–outcome gap and instability of pooled estimates, and a comparative matrix of hormonal versus regenerative therapy for GSM, which produced a three-tier feasibility model — together with the VAGINA-R phenotype model (reported separately) and established platelet-product, GSM-terminology, vulvar-pain and core-outcome methodologies.

The framework. Each application is coded as Compartment–Phenotype / Intervention[descriptor] / Maturity / Outcome anchor. Axis C identifies six anatomical compartments; Axis P defines ten clinical-biological phenotypes plus a hormonal-risk modifier, mapped to the separately published VAGINA-R model; Axis I classifies standard, hormonal, biologic and energy-based interventions and makes product or dose descriptors mandatory; Axis M assigns one of four maturity levels (M1 endorsed, M2 signal-positive but not endorsed, M3 experimental, M4 preclinical) to each compartment–phenotype–intervention triplet; and Axis O specifies the anchor outcomes, with live birth as the obligatory anchor for reproductive phenotypes and at least 12-month durability for all.

Application. Applied to current evidence, local estrogen and vaginal prasterone for atrophic GSM are M1; vaginal laser for GSM is M2; radiofrequency occupies a lower M2 position; PRP for GSM, lichen sclerosus, stress urinary incontinence, ovarian reserve and implantation failure is M3; and exosome products are M4.

Conclusion. GRACE replaces marketing categories such as 'rejuvenation' with codable clinical entities and makes the evidential status of each regenerative claim explicit. A four-phase validation programme — modified Delphi consensus, inter-rater reliability testing, retrospective recoding of published studies and prospective validation within a phenotype-guided trial — is proposed before GRACE is recommended for routine use.

Keywords: Regenerative gynecology; classification; platelet-rich plasma; genitourinary syndrome of menopause; vaginal laser; radiofrequency; phenotype; evidence maturity; core outcome set; reporting standards.

Abbreviations: AE, adverse event; AMH, anti-Müllerian hormone; AUA, American Urological Association; AUGS, American Urogynecologic Society; CST, community state type; DHEA, dehydroepiandrosterone; FSFI, Female Sexual Function Index; GRACE, Gynecologic Regenerative Axis Classification of Evidence; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GSM, genitourinary syndrome of menopause; HFEA, Human Fertilisation and Embryology Authority; ICIQ-SF, International Consultation on Incontinence Questionnaire–Short Form; MCID, minimal clinically important difference; PGI-I, Patient Global Impression of Improvement; PRP, platelet-rich plasma; RCT, randomised controlled trial; RF, radiofrequency; RIF, recurrent implantation failure; SUI, stress urinary incontinence; UDI-6, Urogenital Distress Inventory-6; VHI, Vaginal Health Index; VMI, vaginal maturation index.

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INTRODUCTION

Few areas of women's health have expanded as quickly, or with as little shared vocabulary, as regenerative and energy-based gynecology. The clinical needs are real: genitourinary syndrome of menopause is chronic and progressive, vulvar lichen sclerosus is steroid-dependent, stress urinary incontinence carries a substantial quality-of-life burden, and diminished ovarian reserve remains one of reproductive medicine's least tractable problems. Into these gaps arrived procedures that are autologous or device-based, immediately billable and rhetorically attractive. In 2018 the US Food and Drug Administration warned that the safety and effectiveness of energy-based devices for vaginal 'rejuvenation' had not been established [1], and professional bodies have since cautioned against routine use outside research or formal clinical governance [2–4]. The 2025 AUA/SUFU/AUGS guideline classifies CO2 laser for GSM as experimental outside clinical trials [5].

In two preceding syntheses we examined this field from complementary angles. An umbrella review of regenerative and energy-based interventions across gynecology [6] identified three recurrent evidential pathologies. The first is a sham gradient: effect sizes shrink and often disappear as comparators move from before–after designs to active controls and then to double-blind sham. Sexual-function gains of roughly six FSFI points in before–after pooling vanish when analysis is restricted to randomised trials [7], and double-blind sham-controlled trials do not support fractional CO2 laser for GSM [8,9]. The second is a surrogate–outcome gap: intraovarian PRP improves AMH, FSH and antral follicle count in randomised trials without a demonstrated pregnancy benefit [10], and in recurrent implantation failure PRP improves clinical pregnancy in most meta-analyses but live birth in only one of five [11]. The third is estimate instability: 25 systematic reviews built on only 112 primary studies report live-birth estimates ranging from an odds ratio of 1.23 to 11.02 [12].

A second synthesis placed conventional hormonal therapy and regenerative interventions for GSM side by side in a single technical matrix [13]. It translated that matrix into a three-tier feasibility model: Tier 1, normatively endorsed (vaginal estrogen and vaginal prasterone); Tier 2, signal-positive but not endorsed (laser, with radiofrequency in a lower position); and Tier 3, experimental (PRP). Independently, a phenotype model for GSM — VAGINA-R, reported in a separate article together with its validation protocol [38] — was developed by the authors to test the hypothesis that women with GSM are not biologically homogeneous and that therapeutic response may depend more on the dominant vulvovaginal phenotype than on the choice of technology.

These three strands point to a common deficit. The field lacks not publications but a shared coding language. Platelet-product classifications exist — Dohan Ehrenfest's four families [14], PAW [15], PLRA [16], MARSPILL [17] and DEPA [18] — yet a 2025 scoping review found that such frameworks were rarely applied in gynecologic PRP studies [19]. GSM has an accepted definition [20] and examination scores [21], but no definitive diagnostic criteria [22]. Regulatory rating schemes such as the HFEA traffic-light system grade selected fertility add-ons [23] but do not describe the patient, the product or the required outcome. No existing system answers, in one code, the five questions a clinician, trialist, reviewer or regulator needs answered: where, in whom, with what, with what level of evidence, and measured how.

This position paper proposes GRACE — Gynecologic Regenerative Axis Classification of Evidence — to fill that gap. Its purpose is not to endorse any intervention but to make the evidential status of each regenerative claim explicit, comparable and auditable.

DEVELOPMENT OF THE FRAMEWORK

Sources

GRACE was constructed by the authors through structured integration of four sources: (i) the evidential pathologies and research agenda of the umbrella review [6]; (ii) the three-tier feasibility model, its tier-entry criteria and its consent requirements [13]; (iii) the VAGINA-R phenotype model [38]; and (iv) established external frameworks for GSM terminology [20], persistent vulvar pain [24], vaginal microbial community state types [25], platelet-product characterisation [14–18], core outcome set development [26] and Delphi methodology [27]. **Table 1** summarises the coverage of the main existing systems and the gap that GRACE is designed to close.

Design principles

Five principles, derived from the preceding syntheses, govern every axis.

- **Function before aesthetics.** The target is a measurable clinical entity — dyspareunia, dryness, tissue integrity, continence, sexual function, live birth — never an undefined notion of 'rejuvenation', 'revitalisation' or 'regeneration'.
- **Phenotype before technology.** Patient classification precedes the selection of PRP, laser, radiofrequency, photobiomodulation or any adjunct; two women with 'vaginal dryness' may carry different phenotypes and require different strategies.
- **Characterised intervention.** An intervention that cannot be described with its product or dose

descriptors cannot be classified and therefore cannot be pooled.

- **Evidence maturity attached to the triplet.** Maturity is a property of a specific compartment–phenotype–intervention combination, not of a technology: PRP is not 'experimental' in the abstract but experimental for a defined use.
- **Anchor outcome and durability.** Each phenotype has an obligatory outcome anchor that prevents surrogate endpoints from standing in for patient-important benefit, and every claim requires at least 12-month follow-up.

Table 1. Coverage of existing classification systems relevant to regenerative gynecology.

System	Domain classified	What it captures	What it does not capture
Dohan Ehrenfest families [14]	Platelet product	Leukocyte and fibrin content (P-PRP, L-PRP, P-PRF, L-PRF)	Dose, patient, indication, evidence, outcome
PAW [15]; PLRA [16]	Platelet product	Platelet concentration, activation, leukocytes, erythrocytes	Patient phenotype, anatomical target, evidence level
MARSPILL [17]; DEPA [18]	Platelet product and procedure	Method, spins, image guidance, light activation; dose, efficiency, purity	Clinical context and required outcomes
GSM terminology and examination scores [20,21]	Patient (GSM)	Genital, sexual and urinary domains; examination severity	Mechanistic phenotype; non-GSM indications; intervention
ISSVD/ISSWSH/IPPS vulvar pain [24]	Patient (vulvar pain)	Pain due to specific disorders versus vulvodynia; descriptors	Regenerative intervention and evidence
HFEA add-on ratings [23]	Evidence (fertility)	Traffic-light rating of add-ons, including PRP	Product characterisation; non-reproductive indications
Three-tier feasibility model [13]	Evidence (GSM)	Endorsed, signal-positive, experimental; consent rules	Phenotype; compartments beyond the vagina; preclinical products
VAGINA-R [38]	Patient (GSM)	Seven clinical-biological phenotypes	Product descriptors; evidence maturity; reproductive phenotypes

THE GRACE CLASSIFICATION

Code syntax

A GRACE code has five fields, written in a fixed order:

C-P[r] / I[descriptor] / M / O

C is the anatomical compartment; P is the primary phenotype, optionally followed by a secondary phenotype after '>' and by the hormonal-risk modifier 'r'; I is the intervention class with its mandatory descriptor in brackets, combinations being joined by '+'; M is the evidence-maturity level; and O lists the anchor outcome domains, followed by the minimum follow-up. For example, 'VG-ATR>NMS r / B1[P3-L(−)-A(−); 3 × 5 mL; 4-week interval] / M3 / T+S-12m' denotes a vaginal application in an atrophic phenotype with a secondary neuromuscular-sexual component in a woman with hormonal contraindication, treated with a leukocyte-poor, non-activated PRP within research (M3), with tissue and patient-centred anchors measured to 12 months.

Axis C — anatomical compartment

Six compartments are defined because the same product behaves differently, and is assessed differently, in each: VU, vulva and vestibule; VG, vagina; UB, urethra and bladder neck; PF, pelvic floor musculature and connective tissue; EN, endometrium and uterine cavity; and OV, ovary. Multi-compartment protocols list each compartment separately (for example, VG+VU), so that outcomes can be attributed.

Axis P — clinical-biological phenotype

Axis P maps the seven VAGINA-R phenotypes [38] and extends them to non-menopausal and reproductive indications (**Table 2**). In VAGINA-R, the final letter R denoted 'risk and hormonal reserve' (early menopause, hormone-dependent cancer, aromatase-inhibitor therapy). Because this characteristic modifies the choice of therapy rather than describing a tissue mechanism, GRACE converts it into a modifier, 'r', that can accompany any phenotype. Three phenotypes are added: DER, for histologically or clinically confirmed vulvar dermatoses such as lichen sclerosus; STR, for structural and support disorders, including vaginal laxity, stress urinary incontinence and prolapse; and REP, subdivided into REP-O (ovarian reserve) and REP-E (endometrial thickness, receptivity or adhesions). Pain phenotypes should be described with the 2015 ISSVD/ISSWSH/IPPS terminology [24], and microbial phenotypes, where sequencing is available, with community state types [25].

Phenotypes are not mutually exclusive. The primary phenotype is the one judged to drive the most bothersome

symptom; up to two secondary phenotypes may be recorded. This hierarchy allows trials to stratify randomisation and meta-analyses to restrict pooling to phenotypically comparable populations.

Table 2. Axis P phenotypes, their origin in VAGINA-R and minimum assessment.

Code	Phenotype	VAGINA-R origin	Defining features	Minimum assessment
ATR	Atrophic–hypoestrogenic	V	Dryness, fragility, pruritus, raised pH, low epithelial maturation	pH; VMI; VHI or examination score [21]
ALG	Algesic–inflammatory	A (first)	Burning, dyspareunia, vestibulodynia, hypersensitivity	Pain NRS; cotton-swab mapping; ISSVD descriptors [24]
URO	Genitourinary–urinary	G	Urgency, dysuria, recurrent UTI, mild incontinence	Urinary diary; UTI count; urine culture
INT	Compromised tissue integrity	I	Thin mucosa, fissures, low elasticity, petechiae	Examination score; photographic or histological documentation
NMS	Neuromuscular–sexual	N	Pelvic floor hypertonicity or weakness, myofascial pain, arousal or orgasmic dysfunction	Pelvic floor examination; FSFI; distress scale
MIC	Microbial alteration	A (second)	Dysbiosis, persistently raised pH, recurrent symptoms	pH; microscopy; CST where available [25]
DER	Dermatologic–inflammatory	New	Lichen sclerosus or other confirmed vulvar dermatosis	Clinical diagnosis; biopsy when indicated
STR	Structural–support	New	Vaginal laxity, SUI, prolapse	Validated questionnaire; objective leakage test; POP-Q where relevant
REP-O	Reproductive–ovarian	New	Diminished ovarian reserve, premature ovarian insufficiency	AMH; FSH; antral follicle count; prior IVF history
REP-E	Reproductive–endometrial	New	Thin endometrium, RIF, intrauterine adhesions	Endometrial thickness; hysteroscopy; implantation history
r (modifier)	Hormonal risk or reserve	R	Early or surgical menopause, hormone-dependent cancer, aromatase inhibitors	Oncological status; shared decision documented

Axis I — intervention class and mandatory descriptors

Axis I groups interventions into four families and requires a descriptor for each (**Table 3**). Standard non-hormonal care (S) and hormonal therapy (H) are included deliberately: they are the reference comparators against which regenerative claims must be judged, and local hormonal therapy remains the benchmark for objective change in atrophic GSM [28,29]. For platelet products, GRACE does not create a new nomenclature; it requires that an existing one be applied, preferably PAW or PLRA for composition and DEPA for dose and purity [15,16,18]. For energy-based devices, the descriptor must make doses comparable rather than merely similar; trials of CO2 laser for GSM have used different power settings, dwell times, dot spacing, stacking and session schedules [8].

Table 3. Axis I intervention classes and mandatory descriptors.

Code	Class	Examples	Mandatory descriptor
S1 / S2 / S3	Standard non-hormonal care	Moisturisers and lubricants; pelvic floor physiotherapy; psychosexual therapy	Product or programme, frequency, duration
H1 / H2	Hormonal therapy	Local estrogen or vaginal prasterone; systemic SERM (ospemifene)	Molecule, dose, route, regimen
B1	Platelet-derived	PRP, platelet-rich fibrin, platelet lysate	PAW or PLRA code; DEPA dose; volume per site; activation; sessions and interval
B2	Adipose-derived	Fat grafting, nanofat, stromal vascular fraction	Harvest site, processing, volume, cell count if processed
B3	Cell-based or cell-derived	Mesenchymal stromal cells, exosomes, conditioned media	Source, manufacturing, characterisation, regulatory status
B4	Biomaterials	Hyaluronic acid, polynucleotides, scaffolds	Product, concentration, volume, cross-linking
E1	Ablative fractional laser	Microablative CO2	Wavelength, power, dwell time, spacing, stacking, sessions
E2	Non-ablative laser	Er:YAG	Mode, fluence (J/cm²), pulse, passes, sessions
E3	Radiofrequency	Monopolar, quadripolar, microablative RF	Frequency, power, target temperature, exposure time, sessions
E4	Photobiomodulation	Low-level laser, LED	Wavelength, irradiance, fluence, time, sessions
E5	Other energy	Electromagnetic stimulation, focused ultrasound	Device parameters and schedule

Combinations are written explicitly (for example, B1+B4 or E1+B1). A study that does not report the descriptor is coded with '[NR]' (not reported), which in GRACE automatically caps evidence maturity at M3, because an uncharacterised intervention cannot be reproduced.

Axis M — evidence maturity

Axis M inherits the three tiers of the feasibility model [13] and adds a fourth level for products with no controlled human efficacy data (**Table 4**). Entry criteria for M1 to M3 are retained from that model: M1 requires a positive recommendation from at least one major society or regulator, regulatory approval for the indication and reproducible effects on objective and patient-reported outcomes; M2 requires a meta-analytic signal on at least one clinically relevant outcome with acceptable short-term safety, but with absent or negative guideline endorsement, low or very low certainty, or instability under sham control; M3 denotes insufficient controlled evidence to estimate effect with confidence. GRACE adds four rules that convert the evidential pathologies into explicit ceilings.

- **Sham rule.** A triplet whose benefit is not confirmed in double-blind sham-controlled trials cannot exceed M2, regardless of the magnitude of uncontrolled effects.
- **Surrogate rule.** A reproductive triplet (REP-O or REP-E) supported only by biomarker or clinical-pregnancy gains, without live-birth benefit, cannot exceed M3.
- **Characterisation rule.** A triplet whose supporting studies predominantly lack the Axis I descriptor cannot exceed M3.

Redundancy rule. Agreement among overlapping reviews does not count as independent confirmation; maturity is judged on the underlying primary trials, with overlap quantified.

Table 4. Axis M maturity levels, entry criteria and clinical and consent requirements.

Level	Entry criteria	Clinical role	Consent and documentation
M1 — Endorsed	Society or regulatory endorsement; approval for the indication; reproducible objective and patient-reported effects	First line	Standard informed consent; product-specific warnings documented
M2 — Signal-positive, not endorsed	Meta-analytic signal; acceptable short-term safety; low certainty or instability under sham	Conditional second line after documented M1 failure or contraindication; time-limited trial with predefined response criteria	Written disclosure that major societies do not support routine use, of expected durability and of reported harms
M3 — Experimental	Insufficient controlled evidence, or capped by the sham, surrogate or characterisation rule	Registered clinical research only	Research consent under ethics approval; no fee-for-service provision as established therapy; full product characterisation
M4 — Preclinical	No controlled human efficacy data	Not for clinical use; first-in-human studies only under regulatory authorisation	Regulatory and ethics approval; explicit statement that efficacy in humans is unknown

Within M2, a lower position (M2b) may be recorded when controlled evidence is almost absent, as the feasibility model did for radiofrequency relative to laser [13]. Upgrading requires positive evidence on the anchor outcome: from M3 to M2, at least one adequately powered, sham- or placebo-controlled randomised trial with a fully characterised intervention; from M2 to M1, guideline endorsement and reproducible benefit on anchor outcomes with durability of at least 12 months.

Axis O — anchor outcomes

Axis O defines five outcome domains: T, objective tissue measures (VMI, pH, VHI, histology); F, function (FSFI, ICIQ-SF, UDI-6, urodynamic or pad-test data, pelvic floor function); S, patient-centred outcomes (most bothersome symptom, PGI-I, responder rate defined by a prespecified MCID); R, reproductive outcomes, with live birth as the primary endpoint; and A, adverse events graded by severity. Each phenotype carries an obligatory anchor (**Table 5**). Adverse events and a minimum 12-month follow-up are required for all phenotypes, because absence of harm in short, small trials is not evidence of long-term safety. The set is offered as a starting point for a formal core outcome set developed according to the COMET Handbook [26]; the International Consultation on Sexual Medicine recommendations on GSM provide a complementary reference for sexual-health outcomes [30].

APPLICATION TO CURRENT EVIDENCE

Table 6 applies GRACE to representative uses, drawing on the evidence assembled in our two syntheses. The assignments illustrate the framework; they are provisional and should be revisited by the consensus process described in section 6.

Table 5. Obligatory anchor outcomes by phenotype.

Phenotype	Obligatory anchor	Recommended secondary outcomes
ATR	T (pH, VMI) + S (most bothersome symptom)	VHI; dyspareunia; FSFI
ALG	S (pain NRS during penetration) + F (FSFI pain domain)	Cotton-swab mapping; distress
URO	F (urinary diary, UDI-6) + S	Recurrent UTI count; urgency episodes
INT	T (examination score, histology where justified)	VHI; elasticity
NMS	F (pelvic floor function, FSFI) + S	Sexual distress; myofascial pain
MIC	T (pH, microscopy or CST) + S	Recurrence; need for rescue therapy
DER	T (histology or validated clinical score) + S (itch, pain)	Steroid-sparing effect; scarring progression
STR	F (objective leakage, ICIQ-SF) + S	Vaginal laxity questionnaire; sexual function
REP-O / REP-E	R (live birth)	Clinical pregnancy; AMH, follicle count or endometrial thickness as secondary only
All phenotypes	A (graded adverse events) + durability of at least 12 months	Retreatment rate; satisfaction

Table 6. Provisional GRACE assignments for representative uses.

GRACE code (abbreviated)	Key evidence	Maturity	Main reason
VG-ATR / H1[local estrogen] / T+S	Large objective effects on cytology and pH [28]; guideline recommendation [5]	M1	Endorsed; reproducible objective effect
VG-ATR / H1[prasterone 6.5 mg] / T+S	Dyspareunia benefit across five trials [31]; guideline recommendation [5]	M1	Approved and endorsed
VG-ATR / E1[CO2] / T+S	Positive pooled signals at low certainty [32]; null in double-blind sham trials [8,9]; experimental outside trials [5]	M2	Sham rule
VG-ATR / E3[RF] / T+S	Almost no controlled evidence; small underpowered trials [13]	M2b	Lower position within M2
VG-ATR / B1 / T+S	Single 60-participant double-blind trial [33]; 87 atrophy patients across 18 studies [34]	M3	Insufficient controlled evidence
VU-DER / B1 / T+S	Encouraging but minimally randomised [34]	M3	Insufficient controlled evidence
VG-STR / E1 or E3 / F+S	Before–after FSFI gains disappear in randomised trials [7]	M3	Sham rule; null under randomisation
UB-STR / B1 / F+S	Short-term urodynamic and symptom gains; 1–3-month follow-up [35]	M3	Durability unknown
OV-REP-O / B1 / R	Markers improve, pregnancy does not [10]; HFEA red rating [23]	M3	Surrogate rule
EN-REP-E / B1 / R	Unstable live-birth estimates across redundant reviews [11,12]; HFEA red rating [23]	M3	Surrogate and redundancy rules
Any / B3[exosomes]	Predominantly preclinical evidence; no pooled clinical estimates [36]	M4	No controlled human efficacy data

Two observations follow. First, no regenerative biologic currently reaches M2 for any gynecologic phenotype; the only interventions above M3 are hormonal therapy and, conditionally, laser. Second, the comparison of CO2 laser with vaginal estrogen in small randomised trials, which found similar improvement [37], does not by itself raise laser's maturity, because convergence of two unblinded active arms cannot distinguish shared efficacy from shared placebo response and regression to the mean.

INTENDED USES

Clinical decision-making

In practice, GRACE replaces menu-based selection with a sequence. The clinician first codes compartment and phenotype, including the modifier r, and then selects the highest-maturity intervention appropriate to that phenotype. Four rules from the feasibility model are retained [13]: offer M1 therapy to every symptomatic patient without

contraindication; define failure before escalating, meaning at least 12 weeks of documented adherence with objective reassessment; use M2 interventions as time-limited trials with predefined response criteria and discontinue them in the absence of MCID-level improvement; and confine M3 interventions to registered research. The phenotype axis adds a fifth rule: treat the mechanism that drives the most bothersome symptom. A woman with an NMS-dominant dyspareunia, for example, is first referred for pelvic floor assessment rather than for an energy-based procedure.

Trial design and reporting

For investigators, GRACE functions as a registration and reporting checklist (**Table 7**). Table 7 lists the minimum items only; an item-by-item coding manual, an extended checklist and pooling rules for reviewers are provided in a companion methodological article [39]. Declaring the full code at registration forces three decisions that the current literature often leaves implicit: which phenotype is eligible, how the product or dose is characterised, and which anchor outcome is primary.

Table 7. GRACE minimum registration and reporting items.

Item	Requirement
1. Compartment	All treated compartments listed separately
2. Phenotype	Primary and secondary phenotypes; modifier r; assessment instruments used
3. Intervention	Axis I class and full descriptor; combinations explicit; co-interventions reported
4. Comparator	Sham, placebo, active standard (S or H) or no treatment; blinding of participants, operators and assessors
5. Anchor outcome	Obligatory anchor of the phenotype as primary or co-primary; MCID prespecified
6. Follow-up	Minimum 12 months; retreatment and maintenance sessions reported
7. Safety	Adverse events graded by severity, including procedural pain, bleeding, scarring and chronic pain
8. Maturity statement	Current maturity of the studied triplet declared in the introduction and discussion

Evidence synthesis

For reviewers, GRACE defines the unit of pooling. Studies may be pooled only when compartment, primary phenotype and intervention class coincide and when descriptors fall within a prespecified range. Studies coded [NR] are analysed separately; decision rules for ambiguous cases are detailed in the companion coding manual [39]. Applied retrospectively, the coding also quantifies the reporting deficit itself — the proportion of studies that cannot be fully coded — which is a more useful measure of a field's maturity than the number of reviews it has produced.

Communication and ethics

Because every GRACE code names a clinical entity and a maturity level, it offers a disciplined vocabulary for patient information, professional education and public communication. A statement such as 'PRP for atrophic GSM is M3: experimental and offered only within research' is both accurate and understandable, whereas 'vaginal rejuvenation with growth factors' is neither. GRACE therefore supports the position, shared by regulators and societies, that terminology itself can be an evidential hazard [1,2].

VALIDATION PROGRAMME

GRACE is proposed as a version 1.0 framework. Before it is recommended for routine use, we propose four validation phases.

- **Phase 1 — Consensus.** A modified Delphi process reported according to CREDES [27], with a multidisciplinary panel of gynecologists, urogynecologists, reproductive specialists, pelvic floor physiotherapists, sexual-medicine specialists, pathologists, microbiome researchers, methodologists and patient representatives. Each axis, category and rule would be rated over two to three rounds, with consensus predefined as at least 75% agreement.
- **Phase 2 — Reliability.** Two or more independent raters would code a sample of published studies and clinical cases; agreement would be estimated per axis with kappa statistics, with a target of at least 0.70 before release.
- **Phase 3 — Retrospective recoding.** The primary studies included in our two syntheses [6,13] would be recoded to measure codability, axis-specific missingness and the effect of restricting pooling to code-concordant studies on effect estimates and heterogeneity.
- **Phase 4 — Prospective validation.** Within the planned REGEN-VAG study, whose design is reported with VAGINA-R [38], women with moderate or severe GSM would be allocated to standardised management or to phenotype-guided

management. The primary outcome would be an MCID-defined response at 6 months, with follow-up to 12 months and a biomarker sub-study (microbiome, local cytokines and matrix-remodelling markers) to test whether baseline phenotype predicts response.

Governance should include versioning, public documentation of changes and periodic re-assignment of maturity levels as new controlled evidence appears, so that GRACE functions as a living classification rather than a static opinion.

LIMITATIONS

GRACE is an author-derived proposal and has not yet undergone consensus or reliability testing. The maturity assignments in Table 6 involve judgement, particularly at the boundary between M2 and M3 and in the placement of radiofrequency. Phenotypes overlap, and the hierarchy of primary and secondary phenotypes may be difficult to apply in mixed presentations. Some descriptors, such as platelet counts in the final product or microbial community typing, require laboratory resources that are not universally available; GRACE accommodates this through the [NR] code, at the cost of capping maturity. The framework draws heavily on evidence in GSM and may require adaptation for postpartum, oncological and adolescent populations. Finally, patients were not involved in the initial design; their participation in Phase 1 is essential, particularly for the patient-centred anchor outcomes.

CONCLUSION

Regenerative gynecology rests on defensible biological reasoning but lacks the shared language of a therapeutic specialty. GRACE proposes that language in five axes: where the intervention is applied, in which phenotype, with what characterised product or dose, at what level of evidential maturity and measured by which anchor outcome. By incorporating the VAGINA-R phenotypes and the three-tier feasibility model, and by converting the sham gradient, the surrogate–outcome gap and estimate instability into explicit maturity rules, GRACE makes the status of every regenerative claim visible and auditable. Its central proposition is simple: in regenerative gynecology, the phenotype should be defined before the technology, the product should be characterised before it is pooled, and the outcome that matters to the woman should be measured before regeneration is claimed.

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This article proposes a classification framework based on previously published aggregate data and does not involve human participants, human material or human data collected by the authors.

Consent for publication

Not applicable.

Availability of data and materials

No new data were generated. All evidence discussed is contained in the publications and regulatory documents listed in the references.

Competing interests

This research has no relationship with manufacturers of vaginal energy-based devices, platelet-rich plasma systems, cell-based or exosome products, or menopausal hormone therapy products.

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Authors' contributions

MAP: conceptualisation, framework design and drafting. MAP and MHK: critical revision of the framework and the manuscript. All authors approved the final version.

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Use of artificial intelligence

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