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Supplementary information to:

Letter to the editor:

PRECISION REDOX MEDICINE IN ANDROLOGY: MOVING BEYOND EMPIRIC ANTIOXIDANT USE FOR EVIDENCE-BASED MALE INFERTILITY CARE

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Supplementary Table 1: Minimal phenotyping and trial endpoints for 'redox set-point'-guided antioxidant studies in male infertility

Domain	Minimum reporting elements (baseline)	Intervention monitoring (timing)	Endpoints (mechanistic + clinical)	Response categories (predefined)	Safety/stop criteria (avoid RS overshoot)
Population & baseline redox phenotype	Male infertility context (primary/secondary; idiopathic vs identified factor); abstinence duration; fever/acute illness history; major confounders (smoking, BMI/obesity, varicocele, metabolic disease, medications, current antioxidant use). Baseline redox status anchored to at least one 'integrated' seminal redox metric (e.g., ORP) and a conventional semen profile (concentration, motility, morphology)	Confirm no new antioxidant initiation outside protocol; document adherence and concurrent supplements	Baseline stratification into OS-dominant vs. 'low-ROS/possible RS susceptibility' strata (see categories)	OS-dominant: elevated ORP with impaired semen parameters Indeterminate/mixed: modest ORP elevation with variable semen metrics Low-ROS/RS-susceptible: low ORP/strong reducing tone *plus* poor functional signs (e.g., low capacitation proxy)	Exclude/hold if participant is already on high-dose multi-antioxidants and unwilling to wash out; require standardized washout period when feasible
Oxidative stress (OS) metrics	At least one integrated OS metric (preferred: seminal ORP) because ORP has been consistently associated with infertility, reduced motility/morphology, and higher SDF in recent datasets/meta-analyses referenced in the manuscript	Repeat ORP (or equivalent OS metric) at ~4–6 weeks and ~10–12 weeks (to capture sperm maturation cycle), plus at end-of-treatment	Primary mechanistic endpoint: change in ORP and directionality toward the physiological range; correlate with SDF and motility change	Responder (OS-corrector): ORP decreases toward physiologic window with parallel improvement in SDF and/or motility Non-responder: ORP unchanged with no functional gain	Stop/step-down if ORP drops sharply below baseline with concurrent reduction in capacitation proxy or motility (suggesting over-quenching)
Reductive stress (RS) proxies	At least one reducing-tone proxy, ideally from semen or sperm fraction: GSH/GSSG, NADH/NAD^+, NADPH/$NADP^+$, and/or a redox-buffering signature consistent with "over-reduction" Document "high antioxidant exposure" history	Repeat RS proxy at same timepoints as ORP; monitor symptom/lab signals compatible with over-reduction or impaired sperm signaling	Evidence of redox overshoot: rising reducing ratios with stable/worsening functional readouts	RS-shifted: ORP decreases but reducing-tone proxy rises and capacitation proxy worsens/plateaus	Protocol-defined discontinuation if reducing-tone proxy crosses a pre-set threshold *and* functional endpoints worsen (e.g., motility or capacitation proxy declines)

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Domain	Minimum reporting elements (baseline)	Intervention monitoring (timing)	Endpoints (mechanistic + clinical)	Response categories (predefined)	Safety/stop criteria (avoid RS overshoot)
Sperm DNA fragmentation (SDF)	Baseline SDF (assay specified, threshold pre-declared); SDF is central in the manuscript as a downstream consequence of high ROS burden and as a clinically relevant readout	Repeat SDF at end-of-treatment; optional interim at 6 weeks in high-baseline SDF	Co-primary mechanistic endpoint: ΔSDF (absolute and relative); assess concordance with ORP shift	Genomic responder: SDF decreases with ORP movement toward physiologic window Discordant: ORP improves without SDF improvement (suggests alternate drivers)	If SDF worsens while ORP falls markedly, consider RS overshoot or other confounders; pause therapy and reassess
Capacitation proxy (redox-dependent signaling)	At least one capacitation-associated signaling proxy because the manuscript emphasizes that physiological ROS pulses support capacitation signaling and excessive quenching can suppress it Examples: global tyrosine phosphorylation pattern post-capacitation stimulus; membrane cholesterol efflux marker; hyperactivation metric	Repeat at baseline and ~6–12 weeks or end-of-treatment; standardize incubation conditions	Mechanistic validation that redox movement improves, not suppresses, capacitation biology	Physiologic-shift responder: improved capacitation proxy with ORP normalization Over-quenching phenotype: reduced capacitation proxy despite lower ORP	Immediate review if capacitation proxy deteriorates after therapy initiation, especially with concurrent fall in ORP/reducing-tone rise
Clinical reproductive endpoints	Predefine whether cohort is natural conception vs ART Record female partner age and key female factors (to avoid misattribution)	Track through at least one attempt window (e.g., 3–6 months for natural conception; one ART cycle if applicable)	For natural conception: ongoing pregnancy (and, if feasible, live birth) For ART: fertilization rate (ICSI), usable blastocyst rate, miscarriage The manuscript highlights the need to avoid 'semen-only' surrogates	Clinically concordant responder: mechanistic gains (ORP/SDF/capacitation) accompanied by improved clinical outcome probability	Stop/modify if no mechanistic improvement by a prespecified interim look (e.g., 6 weeks) and patient is at risk of delay (advanced maternal age)

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Quality control & reporting	Assay reproducibility, intra-/inter-assay coefficient of variation where available; standardized abstinence; sample handling (time/temperature); operator training	Ongoing adherence checks; adverse event reporting; supplement accountability	Transparent reporting to allow synthesis across trials (reduces meta-analytic heterogeneity noted in the manuscript)	N/A	N/A