a The 5 foundational principles

Principles	Ethical foundations	Operational requirements
Beneficence	Social utilitarianism	Prioritize public health outcomes
Risk control	Biosecurity imperatives	Environmental/donor harm mitigation
Respect for autonomy	Informed consent tradition	Dynamic re-consent mechanisms
Scientific necessity	Resource efficiency norms	Minimal cell use justification
Fairness	Equity in healthcare access	Anti-stigmatization protocols

b The 8 general requirements

Requirements	Contents	Requirements	Contents
Scientific value	Research must advance knowledge with societal benefit	Personnel & facilities	Trained researchers and certified labs
Legal compliance	Strict adherence to national/ international laws and ethics codes	Resource management	Traceable handling of biomaterials and genetic resources
Ethics review	Mandatory institutional committees with domain expertise	Data governance	Secure data processing aligned with donor agreements
Informed consent	Dynamic donor consent with privacy protection	International cooperation	Cross-border projects must satisfy all jurisdictions' regulations

c The 3 special provisions

Research types	Key restrictions	Scientific rationale
Brain organoids	Electrophysiological activity monitoring; Complexity caps	Prevent perithreshold consciousness emergence
Human-animal chimeras	Strict control of human cell ratio	Limit CNS contribution to host cognition; Risks of cross-species biohybrids
ISEMs	Uterine implantation ban; shortest time rule; define termination conditions	Avoid synthetic embryogenesis completion

d The comparative analysis of ethical governance of human brain organoids, human-animal chimeras, and ISEMs

Subitems	Country/Region	Regulatory specificity	Key technical standards
Brain organoids - quantitative differences in consciousness risk regulation	China	Framework-based★★☆	Dynamic consciousness monitoring (no quantitative indicators)
	USA	Loose★☆☆	NIH bans funding for primate chimeras with human neural cells; No mandatory private-sector monitoring
	EU	Conservative★★☆	14-day rule default (ban on ≥14-day culture); Germany bans all neural behavioral tests
	Japan	Tiered★★☆	National approval required; Allows low-complexity models (no sensory input/output)
	South Korea	Specific★★★	Brain Organoid Guidelines (2024): Mandatory EEG monitoring; ≥60 Hz γ oscillation density triggers ethics
Subitems	**Country/Region**	**Human cell ratio limit**	**Key constraints**
Organoid-chimeras - hard limits on human cell ratios	China	Strict control(unquantified)	Bans germline transmission
	Japan	≤5% (embryonic stage)	Bans human cells in gonad/brain development
	Australia	≤1% (adult animals)	Dual licensing: Proof of scientific value+irreplaceability
	USA	No federal standard	States (e.g., California) ban human-primate chimeras; NIH projects require ≤0.1%
	EU	Banned	Oviedo Convention prohibits all human-animal chimeric embryos
Subitems	**Country/Region**	**Development termination point**	**Technical trigger conditions**
ISEMs - operational differences in termination mechanisms	China	Limit developmental stages	No defined morphological markers
	UK	Primitive streak appearance (approximately 14 d)	Mandatory destruction of primitive axis structures
	Australia	Early neural tube (approximately 21 d)	Morphological monitoring+auto-degrading culture media
	USA	No unified standard	ISSCR recommends ≤14 d; Private labs often extend to 28 d
	International consensus	Gastrulation	Bans body axis establishment and spatial cell fate differentiation

Fig. S1 The foundational principles, general requirements, special provisions, and comparative analysis of the Guidelines. CNS central nervous system, ISEMs integrated stem cell-based embryo

models, EEG electroencephalogram, NIH National Institutes of Health, ISSCR International Society for Stem Cell Research