EXCLUSION CRITERIA ARE NOT THE OPPOSITE OF INCLUSION CRITERIA: A SYSTEMATIC NARRATIVE REVIEW AND PRACTICAL GUIDE FOR CLINICAL AND HEALTH RESEARCHERS

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ABSTRACT

Background: **Eligibility criteria determine who can be recruited or enrolled into a study, whose data can validly answer the research question, and how far findings may be applied beyond the sample. A persistent methodological error is to treat exclusion criteria as the simple negative form of inclusion criteria.**

Aim: **To provide an educational, evidence-informed and practice-oriented review explaining why exclusion criteria are not the opposite of inclusion criteria and how investigators should construct, justify and report eligibility criteria.**

Methods: **A systematic narrative review approach was used. Searches of PubMed, Google Scholar, guideline repositories, regulatory documents and reporting-guideline websites were conducted for publications on inclusion criteria, exclusion criteria, eligibility, external validity, ethics, trial protocols, observational studies and evidence synthesis. Sources were screened for conceptual or methodological relevance and synthesised narratively.**

Results: **Thirty-two methodological, reporting, ethical and regulatory sources were retained. The synthesis showed that inclusion criteria define the target population required to answer the research question, whereas exclusion criteria are additional justified filters applied to otherwise eligible participants, records or studies because participation may create avoidable risk, threaten validity, prevent reliable measurement, make follow-up infeasible, or violate ethical fairness.**

Conclusion: **Eligibility criteria should be question-led, scientifically justified, ethically fair, operationally measurable and transparently reported. Reviewers and ethics committees should expect each exclusion criterion to have a clear rationale, not merely to restate non-inclusion.**

Keywords: Eligibility criteria; Inclusion criteria; Exclusion criteria; Clinical research; Research methodology; External validity.

INTRODUCTION

Eligibility criteria are among the most consequential methodological decisions in clinical and health research. They determine who may participate, which records, specimens or studies may be analysed, and to whom the final conclusions may reasonably apply. Across trial protocols, clinical-trial reports, observational studies, diagnostic accuracy studies, prediction modelling and evidence synthesis, major reporting and methodological guidance expects authors to state eligibility criteria clearly because they shape validity, interpretability and applicability.[1-7]

The known methodological distinction is straightforward but often under-applied. Inclusion criteria describe the key features of the target population needed to answer the research question, whereas exclusion criteria are features among those who meet the inclusion criteria that may interfere with study success, increase risk, distort measurement or bias results.[1] This distinction is also ethical. The Belmont principle of justice requires fair participant selection rather than selection driven by convenience, vulnerability or privilege, and ethical guidance expec ts exclusions based on group characteristics to be justified scientifically, ethically or practically.[8-13]

The problem addressed in this review is therefore not merely grammatical. In many protocols, dissertations and manuscripts, investigators write inclusion and exclusion criteria as mirror images: "include adults aged

18–65 years" and "exclude persons younger than 18 or older than 65 years"; "include children with confirmed malaria" and "exclude children without malaria". Such wording makes the protocol appear complete but adds no new methodological information, obscures the real reasons why otherwise eligible people or records may need to be excluded, and may weaken scientific, ethical and editorial credibility.

This topic is especially important for postgraduate medical research, where eligibility criteria often determine whether a study is feasible, ethically acceptable and publishable. The aim of this systematic narrative review is to clarify the conceptual distinction between inclusion and exclusion criteria, identify the legitimate functions of exclusion criteria, and provide practical tools that clinical and health researchers, supervisors, ethics committees and reviewers can use when developing or appraising eligibility criteria.

METHODS

Review design

This article was prepared as a systematic narrative review: systematic in search logic and transparency, narrative in synthesis and educational interpretation. The approach was appropriate because the review question is conceptual and methodological rather than a question about the pooled effect of an intervention. The review was informed by review typology literature, the Search, Appraisal, Synthesis and Analysis (SALSA) framework, PRISMA 2020 principles on transparent source selection, SANRA domains for narrative-review quality, and practical guidance on writing narrative reviews.[14-17]

Information sources and search strategy

Searches were undertaken and updated across PubMed, Google Scholar, Google, EQUATOR Network resources, Cochrane Handbook chapters, ClinicalTrials.gov, regulatory guidance repositories and ethics-guidance repositories. Search concepts included "inclusion criteria", "exclusion criteria", "eligibility criteria", "participant selection", "external validity", "generalisability", "fair subject selection", "clinical trial eligibility", "systematic review eligibility", "STROBE", "SPIRIT", "CONSORT", "TRIPOD", "STARD", "CIOMS" and "Belmont Report". A concise summary of information sources, core search terms, priority sources, synthesis approach and quality safeguards is provided in Supplementary Table S1.

Source selection and synthesis

Sources were considered eligible for the evidence base if they addressed definitions, functions, reporting, ethics, fairness, generalisability or practical application of eligibility criteria in human health research. Peer-reviewed methodological papers, empirical studies of eligibility restrictions, reporting guidelines, regulatory guidance and authoritative ethics documents were prioritised. Non-human research, duplicate reports, inaccessible full texts after reasonable attempts, unreferenced commercial summaries and sources without methodological relevance after full-text assessment were excluded.

The synthesis was narrative and educational. Extracted concepts were grouped by design relevance: clinical trials, observational studies, diagnostic accuracy studies, prediction modelling, qualitative research and systematic reviews. No meta-analysis was attempted because the unit of analysis was methodological guidance and conceptual reasoning rather than comparable quantitative outcomes.

RESULTS

Literature search output and included source characteristics

The updated search and source-selection process retained 32 sources for narrative synthesis. These

Table 1: Summary characteristics of sources included in the systematic narrative review

Source category	Number included	Examples of sources	Contribution to synthesis
Peer-reviewed methodological, empirical, ethics or review articles	15	Patino and Ferreira; Emanuel and colleagues; Van Spall and colleagues; He and colleagues; Murad and colleagues	Provided definitions, empirical evidence on restrictive eligibility and concepts of ethics, validity and generalisability.
Reporting guidelines and handbooks	7	SPIRIT, CONSORT, STROBE, STARD, TRIPOD and Cochrane guidance	Established how eligibility criter should be prespecified and reported across study designs.
Ethics, regulatory and good-practice guidance documents	10	Belmont Report, CIOMS, FDA, ICH, WHO, Health Canada and Friends of Cancer Research documents	Supported the ethical and regulatory requirement that exclusions should be justified, proportionate and not unnecessarily restrictive.

Table 2: Inclusion criteria and exclusion criteria: conceptual distinctions

Dimension	Inclusion criteria	Exclusion criteria	Editorial implication
Core question	Who or what belongs to the target population needed to answer the question?	Among those who belong, who or what should not participate or be analysed for a justified reason?	Do not duplicate inclusion criteria in negative form.
Usual timing	First-stage definition of eligibility.	Second-stage filter after provisional eligibility.	Screening logs should separate non-eligibility from exclusion.
Main logic	Scientific relevance and representativeness.	Safety, validity, measurement integrity, feasibility or ethical fairness.	Each exclusion criterion needs a written rationale.
Examples	Age range; diagnosis; setting; exposure; study design; publication type.	Contraindication; competing diagnosis; co-intervention; inability to obtain valid measurement; excessive risk.	Specify thresholds, time windows and source documents.
Common error	Being too broad or too narrow for the question.	Stating the opposite of inclusion or excluding by habit.	Reviewers may query external validity and fairness.

comprised peer-reviewed methodological, empirical, ethics or review articles; reporting guidelines and handbooks; and ethics, regulatory or good-practice guidance documents. Figure 1 summarises the PRISMA-informed source-selection flow, while Table 1 summarises the characteristics and contribution of the included source types.

The included sources were not treated as statistically combinable studies. Instead, they were used to construct an evidence-informed educational synthesis around four recurrent findings: inclusion criteria define study membership; exclusion criteria are justified filters applied after provisional eligibility; unjustified exclusions may harm internal validity, external validity, fairness and recruitment; and transparent reporting requires clear prespecification and rationale for each criterion.

Discussion/data synthesis

Conceptual anatomy of eligibility criteria

Eligibility criteria are best understood as a nested decision process. The research question first identifies the population of interest. Inclusion criteria then translate that population into observable, screenable features: age band, diagnosis, setting, disease stage, exposure status, specimen type, publication type or study design. Only after provisional eligibility has been established should exclusion criteria be considered. Exclusion criteria ask a different question: "Among those who belong to the target population, who or what should not be enrolled or analysed for a defensible reason?" The conceptual distinction is summarised in Table 2, and Figure 2 presents the same distinction as a two-stage decision process from population definition to final study population.

This sequencing explains why exclusion criteria should not be used to repeat the opposite of inclusion criteria. A person outside the age range is already not eligible; "age below the lower limit" is not a meaningful exclusion criterion unless the protocol has a special reason to track paediatric screen failures. A patient without the index disease is already outside a disease-defined cohort. A study that is not a randomised trial is already ineligible if randomised trials are the only eligible design. Rewriting non-membership as exclusion inflates screening lists while leaving substantive exclusions underdeveloped.

The grammatical point is also useful for scholarly writing: "criterion" is singular and "criteria" is plural. Thus, one should write "an exclusion criterion is" but "exclusion criteria are". More importantly, each criterion should be measurable. Vague words such as "unreliable", "too ill", "recent treatment", "poor compliance" or "significant abnormality" invite inconsistent screening and reviewer criticism unless thresholds, time windows and adjudication procedures are stated.

Why mirror-image exclusion criteria are problematic

First, mirror-image criteria are redundant. If the inclusion criterion is "children aged 6–59 months", then "exclude children younger than 6 months or older than 59 months" adds no scientific information. Redundancy makes protocols appear longer without making them safer or more rigorous. More importantly, it may distract investigators from defining the exclusions that truly matter, such as conditions that increase risk, interfere with measurement, invalidate follow-up or affect interpretation.

Second, mirror-image framing can obscure external validity. Excluding participants is sometimes necessary, but each exclusion narrows the eventual inference. In a systematic sampling review of randomised trials in high-impact journals, common medical conditions were used as exclusions in 81.3% of trials, age in 72.1%, co-medication in 54.1%, and only 47.2% of exclusion criteria were rated as strongly justified.[18] Other reviews have similarly shown high exclusion rates in trials of physical conditions and historical under-representation of older adults and women in important clinical-trial evidence.[19,20]

Third, unjustified exclusions can create ethical unfairness. The problem is not that every population must be included in every study; rather, exclusion must be based on scientific, safety or ethical reasons, not convenience or habit. Fourth, post-hoc exclusions threaten validity. Eligibility criteria should be prespecified, and criteria for excluding participants or data from analysis sets should be defined before outcomes are known.[2,3,21]

The legitimate functions of exclusion criteria

Exclusion criteria are defensible when they serve one or more legitimate functions. The first is safety: participation may expose the individual to disproportionate risk. Examples include contraindication to an investigational product, an unstable condition requiring urgent treatment, severe organ dysfunction that alters drug handling, or pregnancy/lactation when there is plausible product-related risk and no adequate safeguards. However, even safety exclusions should not become automatic group exclusions. Guidance on pregnant, breastfeeding or sex-specific participants increasingly emphasises individualised risk-benefit assessment and the public-health cost of evidence gaps when such groups are routinely excluded.[22,23]

The second function is scientific validity. Some characteristics may distort estimation or interpretation: a co-intervention that changes the outcome, a comorbidity that mimics the endpoint, inability to measure the outcome reliably, or prior exposure that invalidates baseline status. The third function is feasibility and data integrity: planned follow-up may be impossible, consent may be invalid in the absence of an appropriate legal pathway, or the necessary biological specimen may not be obtainable without unacceptable burden. The fourth function is ethical

Table 3: Practical examples of poor and improved eligibility wording

Research situation	Poor formulation	Improved formulation	Why the improved version is better
Randomised antimalarial trial	Exclude children without malaria.	Include children with protocol-defined confirmed malaria; exclude prior study-drug use within 48 hours, known hypersensitivity, or urgent clinical need incompatible with study procedures.	Absence of malaria is already non-inclusion. Real exclusions address safety, pharmacological interpretation and feasibility.
School-based asymptomatic malaria study	Exclude children outside 5–9 years.	Include children 5–9 years resident in selected communities; exclude acute illness requiring referral, severe oedema invalidating anthropometry, or recent antimalarial use if untreated parasitaemia is required.	The age range belongs in inclusion criteria; exclusions protect validity and child welfare.
Diagnostic accuracy study	Exclude children with negative reference test.	Include consecutive children with the clinical syndrome for which the test would be used; exclude missing paired index/reference tests or reference test performed outside the prespecified window.	Excluding negative reference tests would distort specificity and spectrum.
Qualitative study	Exclude non-mothers.	Include mothers with the lived experience under study; exclude participants for whom the interviewer has a direct care relationship if coercion or confidentiality risk cannot be managed.	Exclusion is based on ethical risk, not the negative of the sampling frame.
Systematic review	Exclude studies not on the topic.	Include studies meeting the PICO/design criteria; exclude duplicate reports, animal-only studies, inaccessible full texts after reasonable attempts, and sources without methodological relevance.	Non-topic records are simply not included; defensible exclusions occur after full-text eligibility assessment.

Table 4: Eligibility-justification matrix for protocol developers and postgraduate supervisors

Criterion proposed	Purpose served	Operational definition	Less exclusionary alternative?	Generalisability effect
Age limit	Scientific population definition or safety	Completed months/years; date source	Stratify by age or add safety monitoring	May limit paediatric/geriatric applicability
Pregnancy/lactation	Risk-benefit and pharmacological uncertainty	Pregnancy test, self-report, gestational age, breastfeeding status	Include with defined safeguards, registry or post-market study where appropriate	Routine exclusion creates evidence gaps
Comorbidity	Avoid confounding, competing risk or excessive danger	Named diagnosis, severity threshold, recent event window	Measure and adjust; stratify; exclude only unstable/severe cases	May reduce applicability to real-world patients
Recent medication	Avoid altered baseline biology or drug interaction	Medication name/class, dose, route, last-use window	Record exposure and adjust if clinically safe	May exclude patients receiving standard care
Follow-up feasibility	Protect data integrity and participant safety	Specific expected visit schedule and contact requirements	Remote visits, transport reimbursement, community follow-up	May disadvantage rural or low-income participants
Consent capacity	Respect for persons and legal validity	Capacity assessment and legal representative pathway	Include with proxy consent/assent where ethical and lawful	May exclude vulnerable groups from needed evidence



Figure 1: PRISMA-informed flow diagram of source identification, screening and inclusion for the systematic narrative review.

fairness: a criterion may prevent coercion, undue burden, therapeutic misconception or inequitable distribution of research risks. In all cases, the test is not "is this the opposite of inclusion?" but "what risk, bias, measurement problem, feasibility problem or ethical problem does this criterion prevent?"

Eligibility criteria across common research designs

In randomised clinical trials, inclusion criteria define the condition and population in which an intervention effect will be estimated; exclusion criteria should be the minimum necessary to protect participants and preserve interpretability. ICH E8(R1) and ICH E9 encourage attention to representativeness and adequate planning of the population to be studied.[24,25] Modern oncology initiatives have moved toward broader eligibility because overly restrictive criteria reduce enrolment, limit generalisability and can reinforce disparities.[26-29]

In observational studies, eligibility criteria define the cohort, case-control base or cross-sectional sampling frame. STROBE requires eligibility criteria and sources or methods of participant selection to be reported.[4] In causal observational research, target-trial emulation begins by specifying eligibility criteria for the hypothetical trial that the observational analysis seeks to emulate.[30] This makes eligibility a design tool, not an afterthought.

In diagnostic accuracy studies, eligibility criteria determine the spectrum of disease and non-disease in which sensitivity, specificity and predictive values will be estimated. STARD 2015 asks authors to report how potentially eligible participants were identified and on what basis participants were included or excluded.[5] In prediction modelling, TRIPOD requires eligibility criteria for participants and, for validation, differences between development and validation eligibility.[6] In systematic reviews, eligibility criteria are defined at the



Figure 2: Conceptual model showing why inclusion criteria and exclusion criteria answer different methodological questions.

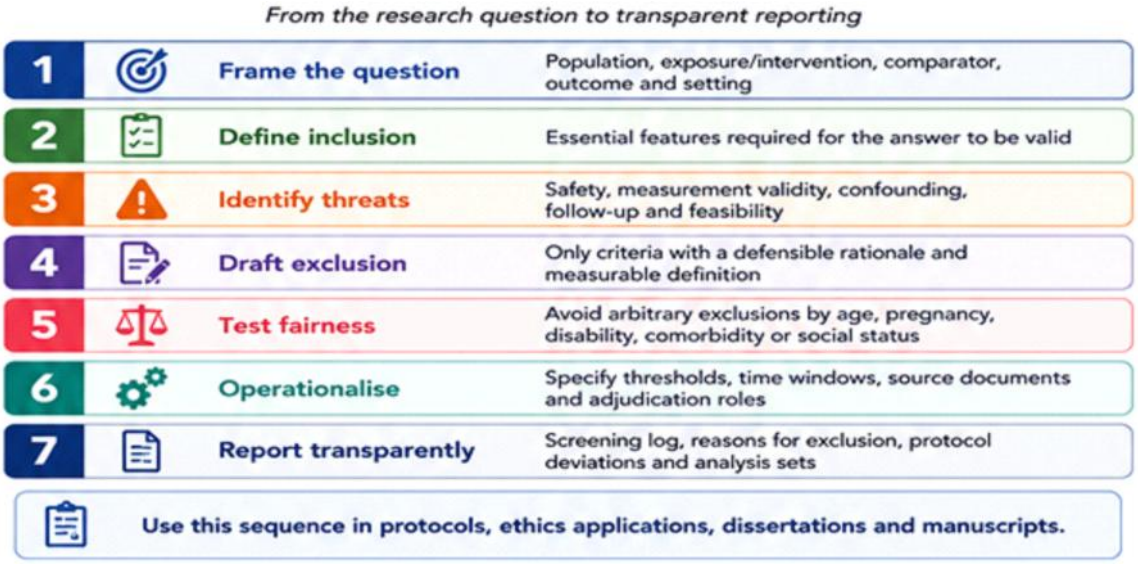


Figure 3: A practical algorithm for constructing defensible eligibility criteria from research questions to transparent reporting.

level of studies, participants, interventions, comparators, outcomes, settings, dates and language; they should be predefined, unambiguous and appropriate for meaningful synthesis.[7]

Practical examples: wrong and better formulations

Common poor formulations and improved alternatives across trials, observational studies, diagnostic accuracy studies, qualitative research and systematic reviews are compared in Table 3.

In a paediatric malaria intervention trial, for example, a weak formulation says: include children aged 6 months to 12 years with confirmed severe malaria; exclude children younger than 6 months, older than 12 years or without severe malaria. The exclusion list merely repeats non-membership. A stronger formulation states inclusion criteria as: children aged 6 months to 12 years; presentation to participating hospitals; malaria parasitaemia confirmed by microscopy or rapid diagnostic test according to protocol; clinical features meeting the study definition of severe malaria; and parent/guardian consent with child assent where applicable. Exclusion criteria should then address distinct issues: need for immediate intervention incompatible with study procedures; prior receipt of the study drug within a prespecified time window if it invalidates baseline pharmacology; known hypersensitivity to the study drug; concomitant enrolment in an interventional trial; or a condition that makes the planned measurement unsafe or uninterpretable.

Similarly, in a school-based study of asymptomatic malaria and nutritional status, inclusion criteria may be children 5–9 years resident in selected communities and apparently well at school-based screening. Exclusion criteria should not read "not aged 5–9 years" or "not resident". Better exclusions may include acute febrile illness requiring referral on the screening day, inability to obtain anthropometry despite repeat attempt, severe oedema invalidating weight-based indices, or recent antimalarial use within a period specified in the protocol if the objective is untreated asymptomatic parasitaemia.

For systematic reviews, inclusion may be peer-reviewed methodological articles, regulatory guidance and reporting guidelines addressing eligibility criteria in human health research. Exclusion should not be "not about eligibility criteria"; that is already non-inclusion. Defensible exclusions include non-human research, inaccessible full text after reasonable attempts, duplicate publications, unreferenced commercial summaries where a primary source is available, or sources without methodological relevance after full-text assessment.

A practical framework for writing defensible eligibility criteria

A reviewer-proof eligibility section should satisfy seven requirements. First, each inclusion criterion should map directly to the research question. Second, each exclusion criterion should have a written rationale. Third, thresholds should be operationalised: age in completed months or years; laboratory values with units; time windows for prior treatment; and diagnostic criteria with source documents. Fourth, investigators should avoid social, demographic or biological exclusions unless scientifically or ethically justified. Fifth, criteria should be feasible in the actual setting. Sixth, criteria should distinguish screening eligibility from analysis-set rules. Seventh, manuscripts should report numbers screened, excluded and enrolled with reasons, ideally using a flow diagram. Figure 3 presents this sequence as a practical algorithm, while Table 4 provides an eligibility-justification matrix that can be used during protocol development, ethics review and postgraduate supervision.

Table 5: Reviewer and ethics committee checklist: questions to ask before accepting eligibility criteria

Checklist question	What a strong manuscript/protocol should show
Does every inclusion criterion map to the research question?	A clear link to population, exposure/intervention, comparator, outcome, setting or study design.
Is any exclusion criterion merely the opposite of an inclusion criterion?	Redundant exclusions removed or moved into screening definitions.
Is each exclusion criterion justified?	A reason based on safety, validity, measurement, feasibility or fairness.
Are thresholds operational?	Exact laboratory values, dates, time windows, diagnostic definitions and adjudication roles.
Could a less exclusionary design achieve the same protection?	Monitoring, stratification, adjustment, subgroup analysis or adaptive safety review considered.
Could the criteria worsen inequity?	Age, sex, pregnancy, disability, comorbidity, geography or socioeconomic restrictions justified and proportionate.
Are screening failures and analysis exclusions separated?	Flow diagram and predefined analysis-set rules are provided.
Are implications for external validity discussed?	The discussion states who the results do and do not apply to.

For every proposed exclusion criterion, investigators should ask: What does it protect? What bias or risk would occur without it? Is there a less exclusionary alternative? How will it be measured? Who will decide? How will it affect generalisability? For manuscript appraisal, dissertation supervision and ethics review, Table 5 translates this framework into a concise checklist for deciding whether proposed eligibility criteria are scientifically justified, ethically fair and transparently reported.

Implications for African postgraduate medical research

For journals serving African postgraduate medicine, the topic has direct relevance. Many studies in the region are hospital-based, resource-constrained and conducted by postgraduate trainees who must balance scientific precision with feasibility. Poorly written eligibility criteria can lead to ethical queries, protocol amendments, recruitment delays, small samples, biased estimates and manuscripts that reviewers perceive as methodologically immature. Conversely, well-justified eligibility criteria demonstrate that the investigator understands the population, setting, risk profile and inference target.

The African context also makes external validity particularly important. Excluding children with comorbidity, pregnant women, older adults, rural participants, persons without perfect follow-up access, or patients with common co-medication may produce clean data but less useful evidence. The goal is not indiscriminate inclusion; it is justified inclusion. Where an exclusion is necessary, the rationale should be explicit. Where risk can be managed through monitoring, consent safeguards, referral pathways or stratified analysis, outright exclusion should be reconsidered. Authors should also discuss who the results do and do not apply to, because external validity, generalisability and applicability are central to clinical usefulness.[31,32]

CONCLUSION

Exclusion criteria are not the opposite of inclusion criteria. Inclusion criteria define who belongs to the target population needed to answer the research question. Exclusion criteria identify additional, justified reasons why an otherwise eligible person, record, specimen or study should not be included. The best eligibility criteria are question-led, prespecified, measurable, ethically fair, minimally restrictive and transparently reported. For authors, supervisors, ethics committees and reviewers, the practical rule is clear: never accept an exclusion criterion unless it can answer the question, "What specific risk, bias, measurement problem, feasibility problem or ethical concern does this prevent?"

Declarations

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Ethics approval: Not applicable; this was a review of published and publicly available methodological literature.

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Supplementary table S1: Search strategy summary for this systematic narrative review

Element	Description
Databases and sources	PubMed, Google Scholar, Google, EQUATOR Network, Cochrane Handbook, ClinicalTrials.gov, FDA, WHO, Health Canada, CIOMS and ICH guidance repositories.
Core search terms	inclusion criteria; exclusion criteria; eligibility criteria; participant selection; fair subject selection; external validity; clinical trial eligibility; systematic review eligibility; STROBE; SPIRIT; CONSORT; TRIPOD; STARD.
Priority sources	Peer-reviewed methodological papers, reporting guidelines, regulatory guidance, ethics guidance and authoritative review-methodology sources.
Synthesis approach	Narrative synthesis using SALSA logic; no quantitative pooling because the review question is conceptual and educational.
Quality safeguards	Prefer primary guideline sources; check claims against peer-reviewed or authoritative documents; avoid unreferenced commercial summaries where primary sources were available.