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Review Article

Cutting-edge research in surgical oncology: A framework for decision-grade evidence

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ABSTRACT

Surgical innovation and oncologic practice are evolving rapidly. However, the evidence base supporting many interventions/decisions in surgical oncology remains vulnerable to bias, limited generalizability, and inconsistent reporting. To address this gap, this multidisciplinary review, developed through structured discussions among surgeons, methodologists, and data governance experts, proposes methodological principles to support the generation of credible, patient-relevant, and decision-oriented evidence in surgical oncology. The proposed framework emphasizes clinically actionable research questions, study designs proportionate to surgical realities, transparent comparator strategies, rigorous data governance, and communication aligned with guideline and policy decision-making. The paper also discusses the responsible integration of artificial intelligence (AI)-enabled methodologies and the opportunities created by the secondary use of health data within the European Health Data Space (EHDS). High-quality surgical oncology research requires methodological rigor, data integrity, and dissemination to be treated as integral components of clinical excellence.

1. Introduction, scope and intended use

This position paper is intended for surgeons, surgical departments, and multidisciplinary research teams involved in surgical oncology. It provides a practical methodological framework for generating evidence that can inform clinical guidelines, reimbursement decisions, and institutional strategies, with a view to technology transfer in the surgical domain. This is not a clinical guideline or a systematic review, but rather a methodological paper on decision-grade evidence in surgical oncology. It reflects discussions from an institutional meeting and the views of the participating experts. The working group was formed among participants of the Institutional Surgical Oncology Meeting held on 7-8 May 2026 and included clinicians and researchers from different surgical oncology subspecialties, together with complementary methodological expertise. The group was intended to provide multidisciplinary perspectives on recurrent challenges in surgical oncology research rather than formal representation of individual subspecialties or professional societies. Topics were identified during the meeting discussions and subsequently refined during manuscript development (Supplemental material 1 reports glossary of key terms). The initial framework was subsequently circulated among contributors for iterative review and modification until a final version acceptable to the contributing authors was reached. This was a consensus-informed process rather than a formal Delphi exercise or nominal group technique, and no predefined voting threshold was applied. The contribution of this framework does not lie in proposing individual methodological approaches as novel, but in integrating established and emerging methods into a decision-oriented pathway specifically tailored to surgical oncology. The framework links the clinical decision to the research question, study design, comparator strategy, data requirements, patient-relevant outcomes, and implementation. The manuscript was supported by a targeted narrative review of the relevant literature, including methodological publications and guidance identified through PubMed/MEDLINE searches, reference screening, and contributions from

members of the working group. As this was not a systematic review, no formal study-selection process or evidence grading was performed.

The paper focuses on adult surgical oncology, but its principles may apply more broadly with appropriate adaptation, particularly rare and reference networks where case volume, care organization, and research feasibility differ [1]. Decision-relevant evidence should also reflect outcomes and priorities that matter to patients and caregivers. Its aim is to support evidence that is credible and useable in practice (Box1).

2. Why surgical oncology research often fails to change practice

Surgical oncology produces a large body of clinical research, from feasibility studies to comparative effectiveness analyses [2]. However, their influence on guidelines, care pathways, and policy decisions remains variable. Many studies report safety, feasibility, or short-term outcomes without defining the decision they are intended to inform [2,3]. Evidence is less likely to change practice when research questions are not aligned with clinical, organizational, or policy needs, or when patient-relevant outcomes are insufficiently represented. Several factors contribute to this gap: a focus on technical rather than decision-relevant outcomes; the influence of surgeon expertise, center effects, and learning curves on study results; the difficulty of generating robust evidence in rare cancers or highly specialized settings; limited assessment of feasibility, implementation burden, and resource implications; and insufficient protocol, reporting, or analytical transparency. A recent analysis of surgical randomized trials also highlights persistent limitations in the reporting of characteristics relevant to external validity and generalizability [4]. The central issue is therefore not whether surgical oncology research produces results, but whether it generates evidence that is decision-aligned, methodologically robust, and sufficiently generalizable to inform healthcare recommendations.

3. Which research questions belong to surgical oncology?

Surgical oncology research covers several related domains: the natural history of surgically managed diseases; natural treatment outcomes, i.e. survival, quality of life, patients-reported outcomes and experiences (PROMs/PREMs), and surrogate outcomes such as relapse-free survival, etc.; surgical outcomes, including functional results; technical and procedural performance, such as detection rates, operative time, margin status, and perioperative complications; prognostic research and risk prediction; evaluation and implementation of innovations (including robotic surgery, image-guided procedures, digital technologies, and other technology-enabled interventions); postoperative recovery; de-escalation strategies; and integrated treatment approaches in localized or oligometastatic disease, including treatment sequencing and the role of preoperative therapies. Defining these domains is only the first step [3,5,6]. Across all of them, the goal should not be limited to documenting technical feasibility, but to generate evidence that informs clinical and organizational decisions, improves patient care, and remains relevant beyond the operating room.

4. From technical performance to decision-grade evidence

4.1. Clinical utility and decision-grade evidence

Much of surgical research focuses on technical performance, without clarifying whether the results translate into better patient outcomes or better clinical decisions [6,7]. Technical refinements do not automatically mean clinical value. To inform practice, surgical evidence should demonstrate not only feasibility and safety, but also a meaningful impact on patient-centered outcomes, treatment pathways, or resource use. Distinguishing technical or diagnostic performance from true clinical utility is therefore essential when evaluating new surgical strategies. Improvements in technical end-points may suggest progress; however, true clinical value is established when an intervention improves survival, quality of life, or other patient-important outcomes [7,8]. Evidence limited to technical performance is rarely sufficient to reshape guidelines or care pathways.

We use the term “decision-grade evidence” to describe evidence designed to inform a defined clinical, organizational, or policy decision, such as adoption or de-adoption of a technique, pathway redesign, technology investment, or credentialing. This concept is consistent with evidence-to-decision frameworks and estimand-based approaches, which emphasize alignment between research design and the decision to be informed [9,10]. This evidence requires proportionate methods, transparent and auditable data, standardized definitions, and timelines compatible with real decision-making (Box 2). It should also be aligned

Box 1
Key recommendations for decision-grade research in surgical oncology

1. **Start from the decision, not from the available data.** Define the clinical, organizational, or policy decision that the study is intended to inform and formulate the question using PICOTS and, where appropriate, an explicit estimand.
2. **Match the study design to the question and maturity of the intervention.** Randomization should be preferred when feasible, while pragmatic trials, registries, quasi-experimental designs, or target-trial emulation may be appropriate when conventional RCTs are impractical.
3. **Predefine the comparator strategy.** External or synthetic controls should be used only when contemporaneous randomization is not feasible and when comparability assumptions, data provenance, and sensitivity analyses can be transparently assessed.
4. **Account for the surgical context.** Surgeon and center expertise, learning curves, procedural standardization, technique modifications, and temporal changes should be incorporated into study design and analysis.
5. **Prioritize outcomes that matter to patients and decision-makers.** Technical end-points should not substitute for oncologic outcomes, functional recovery, quality of life, treatment burden, or other patient-relevant outcomes.
6. **Build research on auditable and reusable data.** Consecutive case capture, standardized definitions, prespecified analyses, transparent data provenance, and appropriate handling of missing data and confounding are essential.
7. **Evaluate innovation throughout its life cycle.** Novel procedures, robotics, devices, and digitally enabled technologies should progress from early development to comparative evaluation and long-term monitoring using structured frameworks
8. **Preserve scientific independence regardless of funding source.** Public and private funding can both enable innovation, but study design, data access, analysis, interpretation, and publication should remain scientifically independent and transparent.
9. **Use AI as an enabling methodology rather than a substitute for sound study design.** AI-based approaches require external validation, governance, monitoring for dataset shift and clinically meaningful assessment.
10. **Plan implementation and dissemination from the outset.** Evidence should be generated and communicated in formats that can support guidelines, health technology assessment, procurement, and clinical practice.

Box 2
Minimum elements of decision-grade surgical oncology research.

- "Surgical database" refers to a purpose-built data asset (i.e., a dedicated, harmonized, curated, governable, and auditable data resource) designed to support predefined clinical and organizational use cases in surgical oncology. Decisions to be informed may include adoption, de-adoption, credentialing, pathway redesign, and procurement.
- Clinical question explicitly framed according to PICOTS principles (population, intervention, comparator, outcome, time horizon, and setting), with clear specification of the target estimand and, where relevant, the strategy for handling intercurrent events.
- Time zero and eligibility rules specified upfront to minimize immortal-time and selection biases.
- Primary and key secondary end-points: should be built around at least one patient-relevant outcome, such as quality of life, functional recovery, return to baseline function, PROMs/PREMs or other measures reflecting patient benefit.
- Comparator strategy (if applicable): randomization plan, quasi-experimental approach, or target-trial emulation (with appropriate justification).
- Learning-curve plan (if applicable): run-in, proctoring/credentialing, clustering by surgeon/center).
- Data provenance and quality plan: data sources, data dictionary, audit trail, linkage/coding rules.
- Missing-data and confounding plan: prespecified approaches for handling missing data, measuring and adjusting for relevant cofounders, and conducting sensitivity analyses to assess the robustness of findings.
- Dissemination and implementation plan: who must act on the evidence and how it will be communicated.
- Patient and public involvement: who will be involved, at which stages, and how their input will influence design, conduct, interpretation, and dissemination.

with outcomes and thresholds of benefit considered meaningful by patients.

Large datasets and sophisticated analytical methods cannot compensate for biased data generation, while well-collected data may still be misinterpreted without methodological rigor [11]. Credible surgical oncology research therefore requires both reliable data infrastructure and sound analysis. This is especially relevant for registry-based research. Fig. 1 shows the pathway to decision-grade evidence in surgical oncology. Transparent case inclusion, standardized definitions, continuous quality control, adequate capture of confounders, stability of core variables over time, and adherence to FAIR principles are essential for decision-grade inference [12–14]. Table 1 provides an operational checklist for assessing data credibility and analytical robustness.

4.2. *Outcomes that decision-makers trust*

An outcome is a patient-level variable measured during follow-up (Supplemental Material 2). Outcomes should be meaningful, measurable, and clinically relevant [6–8]. Surgical studies should report absolute effect estimates and uncertainty, and should not equate statistical significance with clinical relevance. When appropriate, outcomes should combine short-term safety and process measures with longer-term oncologic end-points [6]. Surveillance windows should be prespecified, and competing events should be considered when they may affect interpretation.

Funding models should also be considered, particularly for capital-intensive innovations and emerging technologies. Public funding may be particularly important for independent comparative-effectiveness, de-adoption, and long-term outcome research, whereas industry collaboration may facilitate technological development and implementation. Regardless of the funding source, transparency and scientific independence in study design, analysis, interpretation, and reporting should be preserved [15].

Studies intended to inform institutional or policy decisions may also require implementation, health services, or economic evaluations [16].

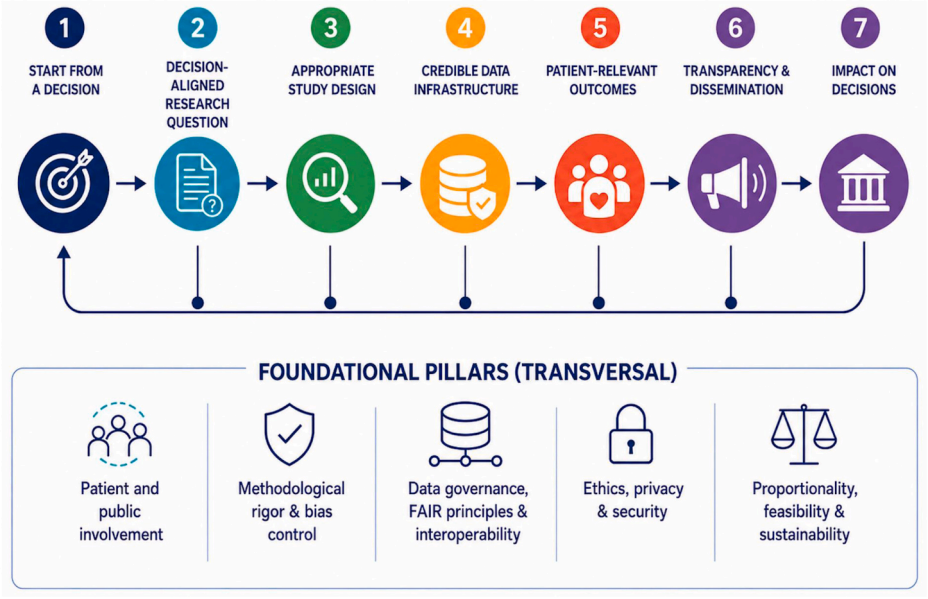


Fig. 1. The pathway to decision-grade evidence in surgical oncology.

Table 1
Data credibility in surgical oncology research (operational checklist).

Domain	Item	Operational question
Data generation	Target population	Is the target population clearly defined, with eligibility criteria specified and consistently applied?
Data generation	Case capture	Is case capture consecutive and complete for the defined population? If not, are gaps quantified and justified?
Data generation	Data traceability and audit trail	Are key variables traceable to who recorded them, when, and under which rules? Is an audit trail available?
Data generation	Variables and outcome definitions	Are outcomes and key variables standardized, with documented coding rules and versioning?
Data generation	Dataset construction and transformations	Are dataset assembly, variable derivation, transformations, and versioning documented and reproducible?
Data generation	Follow-up integrity	Is follow-up completeness assessed by center and, in comparative studies, by group? Are differential follow-up patterns addressed?
Data generation	Monitoring	Are quality checks and audit trails available and proportionate to the intended use of the dataset?
Data generation	Confounder capture	Are all relevant variables, including key prognostic factors, effect modifiers, known confounders, adequately defined and included among those planned for collection?
Analysis credibility	Protocol discipline	Is there a prespecified protocol and an archived analysis plan with dated versions?
Analysis credibility	Design and analysis coherence	Is the study design appropriate for the objective, and is the planned analysis consistent with that design? Is the planned information size adequate for the primary end-point or estimand, considering sample size, number of events, precision, clustering, learning curves, anticipated crossovers, missingness, and, where relevant, multiplicity control?
Analysis credibility	Estimand implementation	Is the estimand explicitly defined and consistently implemented across eligibility criteria, time zero, comparator or treatment strategies, follow-up window, outcome definitions, and handling of intercurrent events?
Analysis credibility	Bias threats addressed	Are key risks explicitly assessed and mitigated, including selection bias, immortal-time bias, confounding, time-varying confounding, and learning-curve effects?
Analysis credibility	Missingness assessment and handling	Is missingness quantified, are plausible mechanisms discussed, and is handling prespecified, with sensitivity analyses when needed?
Analysis credibility	Sensitivity analyses	Are sensitivity analyses prespecified for key assumptions, including unmeasured confounding, misclassification, and missingness?
Analysis credibility	Reporting	Are absolute effects and measures of uncertainty reported, not only relative measures, with clear interpretation?
Analysis credibility	Robustness checks	Are key assumptions examined and results stress-tested through alternative model specifications, influential centers or surgeons, different handling of intercurrent events, missingness, and, where relevant, non-proportional hazards?
Ongoing validity	Stability over time	Have changes in technology, surgical techniques, clinical pathways, case-mix, or data capture over time been assessed for their potential impact on the stability, interpretation, and applicability of findings?
Ongoing validity	Reproducibility	Can the primary analysis be rerun end-to-end from the documented dataset version and code?

Sustainability indicators may be included where feasible. Relevant domains include safety outcomes, such as 90-day major morbidity, unplanned reoperation, ICU admission, and mortality [17]; process outcomes; oncologic outcomes; patient-reported outcomes; and value metrics, including resource use and carbon footprint indicators when appropriate [18]. A suggested minimum core outcome set for decision-grade surgical oncology studies is provided in Supplemental material 3. Outcomes should be hierarchically classified as primary patient- or decision-relevant end-points, secondary validated surrogates, and exploratory technical or process indicators. This prevents surrogate or technical improvements from being overinterpreted as proof of clinical benefit.

4.3. Estimand-driven design in surgical oncology

Selecting an appropriate study design requires a clear definition of the treatment effect or research target that the study intends to estimate. The estimand framework, introduced in ICH E9(R1), provides a structured approach to align the clinical question, study design, end-point definition, analysis strategy, and interpretation of results [10].

An estimand is defined through five attributes: the target population, the treatment strategies being compared, the end-point of interest, the handling of relevant intercurrent events, and the summary measure used to quantify the treatment effect (Supplemental material 4). Explicit specification of these elements helps ensure that the study addresses the intended clinical or organizational decision.

This framework is particularly relevant in surgical oncology because intercurrent events are common and often clinically meaningful. Examples include failure to proceed to surgery after neoadjuvant treatment, conversion to another procedure, re-operation, treatment intensification, salvage therapy, or competing events such as non-cancer-related death. Different strategies for handling these events may answer different causal questions and therefore lead to different interpretations of treatment benefit. For example, when comparing neoadjuvant therapy followed by surgery with upfront surgery, progression before surgery may be considered part of the treatment strategy and included in the primary analysis (treatment-policy estimand), reflecting the real-world effectiveness of the strategy. Alternatively, a hypothetical estimand may seek to estimate the effect that would have been observed if all patients had proceeded to surgery. Both approaches may be valid, but they address different clinical questions. Similarly, in studies evaluating surgical de-escalation, the estimand should clarify whether conversions, re-interventions, or treatment escalation are considered treatment failures, components of the treatment strategy, or events to be handled separately. For pathway-level interventions such as enhanced recovery programmes, estimands should also specify how implementation delays, temporary interruptions, or center-level deviations are incorporated into the evaluation [10]. Explicit estimand definition can improve transparency, facilitate interpretation, and strengthen the link between evidence generation and decision-making in surgical oncology.

4.4. Patient and public involvement

Patient and public involvement (PPI) is an integral part of decision-grade evidence because research should reflect outcomes, preferences, and trade-offs that matter to patients. PPI refers to research conducted

with or in partnership with patients, survivors, caregivers, and members of the public who have direct or indirect experience of the disease [19,20]. It differs from research conducted to, about, or for patients. In surgical oncology, PPI should extend beyond outcome validation and should contribute to defining meaningful clinical benefit, acceptable trade-offs, and research priorities [6–8]. For this reason, PPI should be considered a core component of decision-grade research rather than a secondary domain.

PPI should contribute not only to outcome selection but also to defining meaningful thresholds of benefit, harm, and acceptable trade-offs from the patient's perspective [7,19]. Patients and patient representatives can help identify research priorities, refine clinically meaningful questions, assess the feasibility and acceptability of interventions, interpret study findings, and support dissemination and results implementation [21]. Potential benefits include improved relevance, transparency, implementation, and alignment with patient priorities. A documented PPI plan should specify who is involved, at which stages of the research process, how their input will inform the study, and how feedback will be provided to patient partners. Embedding PPI within research governance structures may further strengthen accountability and help align surgical innovation with patient-defined value.

5. Matching research questions to study designs

No single design fits all surgical questions [22]. Study design should reflect the research question, feasibility, ethical constraints, expected effect size, and maturity of the technique (Supplemental material 5). Several study designs may be appropriate in surgical oncology, but their value depends on the research question, the maturity of the intervention, and the decision to be informed (Fig. 2).

5.1. *Registry-based studies*

Registry-based retrospective studies are central to surgical oncology because they offer a pragmatic and sustainable way to generate clinically relevant evidence. A registry is a structured data infrastructure for a defined population and purpose, whereas a registry-based study uses that infrastructure to answer a prespecified question [12,13]. Its credibility depends on both the analysis and the quality and governance of the underlying registry [12,23]. A large sample size embedded in the real-world does not ensure reliability [24]. Registry-based studies require consecutive case inclusion, standardized variables and outcomes, continuous quality control, and prespecified analytical plans. Key data, including confounders and effect modifiers, should be sufficiently complete, stable over time, and consistently defined. When they are not, the limits of causal or prognostic interpretation should be stated clearly.

These studies are useful for describing disease trajectories after surgery, evaluating outcomes and comparative effectiveness when randomization is not feasible, and supporting prognostic research. Their strengths include feasibility, lower cost, large and heterogeneous populations, and representation of routine practice, especially in rare diseases, long-term outcomes, and rapidly evolving techniques [23,24]. However, they remain vulnerable to selection bias, residual confounding, center heterogeneity, and missing data. Questions requiring tightly controlled causal inference may still need randomized or at least prospective designs [23–25]. Registries intended to support robust clinical inference should be findable, auditable, and transparently governed, with increasing relevance with a view to the EHDS implementation [12–14,26]. Their sustainability also matters. Integration with electronic health records, structured extraction, interoperability, and partial automation can preserve efficiency and data quality over time. These same conditions enable responsible use of AI in research, whose value depends on traceability, standardization, auditability, and governance [27]. Registry-based studies are credible when their infrastructure is stable, transparent, and aligned with the research question.

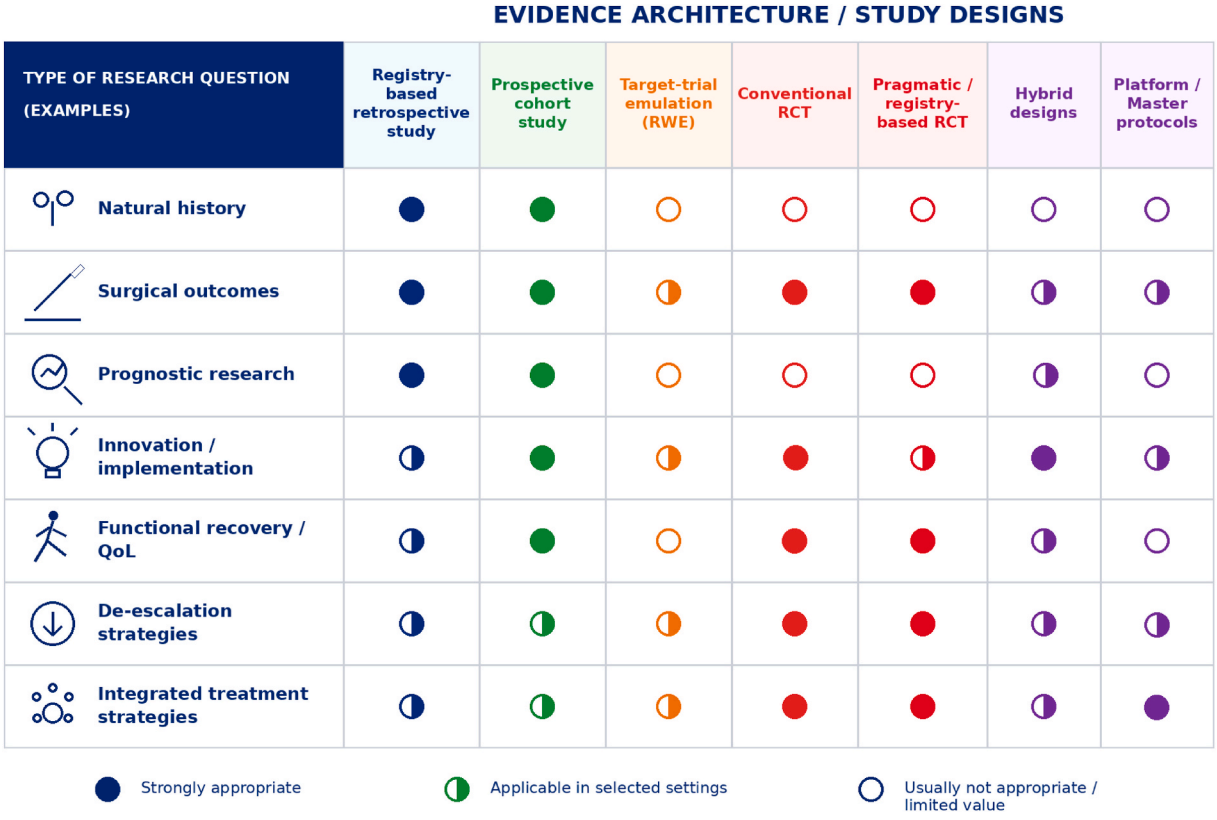


Fig. 2. Matching research questions to the most appropriate study designs.

5.2. RCTs and pragmatic trials

In the evidence-based medicine framework, experimental randomized controlled trials (RCTs) remain the gold standard for causal inference. In surgical oncology, they are especially important for strategy questions, including treatment sequencing, extent of resection, and integration of surgery with systemic or radiation therapies. Pragmatic trials may improve applicability to routine clinical practice [28]. Surgical trials nevertheless face specific methodological and recruitment challenges [29–32].

RCTs protect against selection bias and, particularly in sufficiently large trials, contribute to balancing known and unknown confounders, but surgical trials face specific challenges [30–32]. Procedures are difficult to standardize, blinding is rarely feasible, and outcomes may depend on surgeon expertise and institutional volume. Patient and surgeon preferences can limit accrual, while long recruitment periods may overlap with changes in technology or standard of care. While some RCTs on new technologies need to be "explanatory", being carried out at selected institutions, others should be pragmatic, focused, and supported by strong collaborative networks [28,29,33]. The evaluation of robotic and other technology-enabled surgical interventions requires additional consideration of learning curves, surgeon and center expertise, procedural standardization, and changes in the technology over time. Studies should therefore document relevant training and experience, the platform or technology evaluated, and implementation requirements. Beyond technical feasibility, comparative evaluation should address patient-relevant outcomes, oncologic effectiveness, resource use, and the organizational impact of introducing the technology into routine practice. The IDEAL framework provides a useful complementary approach for the staged evaluation of surgical innovation, from early development and exploration to comparative assessment and long-term monitoring. Its principles are particularly relevant to novel procedures and technologies, for which technique stabilization, learning curves, and iterative modifications may precede definitive comparative evaluation [33]. Matching the study design to the maturity of the innovation may help avoid premature conclusions based primarily on feasibility or early technical outcomes. Clinical equipoise should be clear at trial initiation and reassessed when evolving evidence or technology changes the perceived benefit–risk balance.

Pragmatic trials embed randomization within routine care, using broad eligibility criteria, flexible delivery, and outcomes relevant to patients and healthcare services [28]. Pragmatic designs may particularly benefit from patient involvement in selecting outcomes relevant to real-world recovery and treatment burden. In surgical studies, surgeon and center effects, as well as learning curves, should be addressed in the design and analysis rather than treated as post hoc limitations. Importantly, the randomization strategy should reflect the level at which the intervention acts: individual patients for patient-level treatment strategies, expertise-based designs when intervention delivery depends strongly on surgeon expertise, and cluster randomization for interventions delivered at the center or care-pathway level [34].

Registry-based randomized trials use existing clinical registries for screening, randomization, data capture, and follow-up. They may reduce costs, improve efficiency, and increase generalizability [35]. High-quality registries may also provide external or synthetic control cohorts when concurrent controls are not feasible. Key features include streamlined eligibility criteria, a minimal set of mandatory procedural standards, reliable routine outcome capture, and prespecified strategies to address crossovers, clustering, and learning-curve effects.

5.3. Hybrid and platform designs

When patient or surgeon preferences, fragile equipoise, or operational constraints limit conventional randomization, alternative randomized or hybrid approaches may improve feasibility. These may include registry-based randomized trials [35], randomized trials augmented with external real-world controls [36,37], or preference-informed complementary designs [38]. Expertise-based randomization may also be considered when operator expertise is integral to the intervention [39].

These designs require prespecified selection mechanisms and careful handling of learning curves, clustering, and treatment-by-setting interactions. Comparator strategies are discussed below.

In selected settings, randomization may be impractical or ethically challenging [40]. Examples include quasi-experimental before-after designs and single-arm studies. Their credibility depends on a clear time zero, consecutive inclusion, prespecified end-points, and an appropriate pre-specified comparative strategy. In general, external or synthetic controls may be considered under strict governance [36,37].

When innovation evolves rapidly and several interventions compete, master protocols and platform designs may improve efficiency and feasibility. Platform and multi-arm multi-stage designs evaluate multiple treatment arms within a single protocol, using prespecified interim rules to stop ineffective arms or add new ones [41]. Umbrella trials evaluate multiple therapeutic strategies within a common disease setting, typically according to predefined molecular subgroups [42]. Similar master-protocol principles may potentially be adapted to perioperative research in surgical oncology. For pathway-level interventions, such as ERAS variants or imaging-to-surgery workflows, cluster randomized or stepped-wedge designs may be appropriate when individual randomization is impractical [43]. These designs require prespecified adaptation rules and analyses that account for secular trends, implementation timing, clustering, and time effects.

5.4. Target-trial emulation

When randomization is not feasible and observational data are used to estimate causal treatment effects, target-trial emulation can help align eligibility criteria, time zero, treatment strategies, follow-up, and outcome definitions [44]. This approach helps reduce immortal-time and selection bias. Its validity depends on three conditions: adequate measurement of key confounders; sufficient overlap between treatment groups to avoid unstable extrapolation; and transparent handling of treatment changes, competing events, and missing data. Missing outcomes should be minimized and addressed through prespecified methods and sensitivity analyses. Complete-case analyses are appropriate only when missingness is rare and plausibly unrelated to prognosis. Target-trial emulation also provides a useful framework for constructing external or synthetic control cohorts.

The maturity of surgical evidence may also differ substantially across disease-specific settings. For example, in common cancers with an established evidence base, such as breast or colorectal cancer, research questions may increasingly concern de-escalation, comparative effectiveness, or optimization of established procedures and may therefore be suitable for randomized or pragmatic trials. Conversely, in rare tumors such as sarcomas, limited case numbers and referral patterns may make prospective multicenter registries, target-trial emulation, or carefully selected external comparators more realistic. In other settings, including rapidly evolving technology-enabled surgery, the main challenge may be the evaluation of learning curves, procedural standardization, and changes in the intervention over time before definitive comparative assessment. These examples illustrate that the appropriate study design depends not only on tumor type, but also on the maturity of the clinical question and the decision the evidence is intended to inform.

6. Comparator choice

Comparator choice is a major weakness in surgical research, particularly in observational, hybrid, and non-randomized interventional studies (Fig. 3) [45]. Comparator relevance should also consider whether compared outcomes reflect patient-prioritized dimensions of benefit and burden [7]. When contemporaneous randomization is not

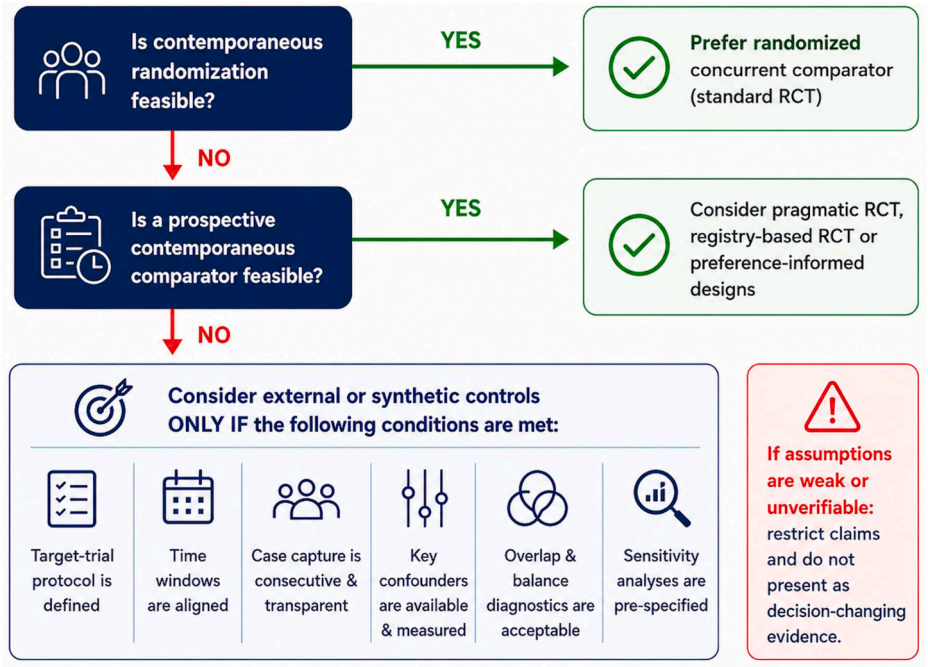


Fig. 3. Decision pathway for comparator selection in surgical oncology studies.

feasible, external or synthetic controls may be used under strict governance and transparent assumptions (Supplemental material 6). Both approaches rely on real patients, not simulated or artificial intelligence (AI)-generated individuals. Their main limitation is residual non-comparability between the external data and the index cohort. They should therefore be reserved for prespecified scenarios and supported by comparability diagnostics, sensitivity analyses, and data-quality assessment of the external source (Box 3). Transportability assumptions require explicit justification, especially when data come from different healthcare systems or time periods. Key principles are to prefer contemporaneous controls from the same care setting, prespecify external data sources, and justify their clinical comparability. Adjustment methods, overlap diagnostics, sensitivity analyses, data provenance, and audit trails should be defined in advance.

7. Bias threats and mitigation strategies

Surgical oncology studies are exposed to specific bias threats, including selection bias, immortal-time bias, confounding, learning-curve effects, center effects, missing data, and outcome misclassification. These threats should be anticipated at the design stage and addressed through prespecified eligibility criteria, clear time zero, appropriate comparator selection, standardized outcomes, adequate confounder capture, and sensitivity analyses. Key bias threats and mitigation strategies are summarized in Fig. 4.

8. AI-enabled evidence generation

AI and automation can support surgical oncology research through cohort identification, extraction of structured variables from free text, imaging-based end-points, risk prediction, benchmarking, and workflow analysis [27]. Their value depends on data quality, completeness, provenance, and comparability. AI can process complex real-world data, but models trained on routine clinical or pathological data inherit missingness, inconsistent coding, biased labels, and center-specific documentation patterns. AI also introduces specific risks, such as dataset shift, non-transparent preprocessing, irreproducible pipelines, and performance degradation over time. In surgical oncology, evolving techniques, pathways, and case-mix may further alter model behavior, making monitoring for drift essential. For decision-grade use, AI systems should be evaluated beyond discrimination alone. Relevant requirements include calibration, transportability, external validation,

Box 3
External or synthetic control cohorts: governance checklist

Use external controls only when contemporaneous randomization is unfeasible and assumptions are defensible.

- Pre-specify the external data source(s) and justify clinical comparability to the index cohort.
- Align time windows (standard of care, supportive therapy, imaging/staging practices).
- Define the target-trial protocol (eligibility, time zero, treatment strategies, follow-up).
- Make sure the external cohort includes consecutive patients
- Confirm overlap/positivity and report diagnostics (covariate balance, weights, effective sample size).
- Predefine sensitivity analyses (unmeasured confounding, outcome misclassification, missingness).
- Document provenance, coding, linkage steps, and audit trails for the external dataset, if any.
- State data access controls, privacy safeguards, and any constraints that limit reproducibility.
- Require independent methodological review when results are intended to change policy or procurement.



Fig. 4. Bias threats specific to surgical oncology research and key mitigation strategies.

clinically meaningful thresholds, and decision-analytic utility. Explainability should be task-specific and useful for the intended users, while human oversight should define how uncertain or conflicting outputs are reviewed [46]. AI may support prediction and pattern recognition. Minimum requirements for validation, explainability, governance, and appropriate reliance are summarized in Supplemental material 7. All this said, it is to be acknowledged that an ongoing major methodological debate concerns whether advances in artificial intelligence, including machine learning and digital twins, may contribute to the generation of causal evidence in medicine alongside RCTs.

9. EHDS and secondary use of health data

The European Health Data Space (EHDS) is an EU framework for the safe and ethical use and reuse of electronic health data across Member States. It distinguishes primary use for patient care from secondary use for research, innovation, and policy. The EHDS is expected to provide access to large-scale health data, structured information on data availability and quality, more standardized access procedures, and secure processing environments. Only non-personal outputs may be downloaded. The framework involves health data holders, health data access bodies, and health data users (Table 2) [26,47–49].

Health data users will need clear research questions, feasible analysis plans, appropriate sample size assessments, and a realistic understanding of available data. Early interaction with health data access bodies may help align study design with data availability and regulatory requirements. Because EHDS outputs from secondary use must be made public within 18 months, studies should be focused and operationally realistic from the outset [47,49]. The EHDS Regulation entered into force in 2025 and will be implemented progressively; the main provisions governing secondary use will apply from 26 March 2029, with specific provisions subject to earlier or later application [49]. For the field of surgical oncology, this framework may be especially relevant when rare procedures, referral pathways, and long-term outcomes require data linkage across institutions.

Table 2
Steps involved in the reuse of electronic health data under EHDS[a].

Step	Description
1. Data discovery via National Catalogues	Government bodies (HDABs) establish a national catalogue where Health Data Holders (HDHs) detail their datasets. Health Data Users (HDUs) identify relevant data through this catalogue.
2. Submitting a data access application	Health data applicants submit a data access application to the HDAB, specifying the intended purpose, legal basis, methodology, and data protection measures.
3. HDAB assessment	The HDAB assesses the application within three months. If approved, it issues a legally binding data permit outlining the scope of use, conditions, and obligations of the HDU.
4. Data provision by Health Data Holder	The HDAB notifies the relevant HDHs, which then have three months to provide the specific dataset to the HDAB.
5. Data preparation by the HDAB	After receiving the data, the HDAB has two months to make them available to the HDU, including application of relevant opt-out restrictions, pseudonymisation/anonymisation where required, standardisation, and data combination
6. Analysis in a Secure Processing Environment (SPE)	The HDABs provide a Secure Processing Environment (SPE) in which the HDU can analyse the data according to the agreed permit.
7. Publication of results	The health data user must make public the results or outputs within 18 months of completion of processing, subject to the extensions allowed by the Regulation

[a] Simplified overview of the secondary-use process established by Regulation (EU) 2025/327 (provisions apply from 26 March 2029).

10. How to make surgical evidence heard

Surgical evidence influences practice when it addresses relevant questions and is communicated to stakeholders able to translate evidence into action. Appropriate reporting standards should be followed according to study design [50–52]. Studies intended to influence guidelines, health technology assessment, or institutional adoption should additionally report outcomes and implementation requirements relevant to those decisions. Dissemination should extend beyond journals to scientific societies, pathway committees, multidisciplinary boards, and institutional dashboards. Patient involvement throughout the research process may further improve interpretability and implementation.

11. Conclusions

Surgical oncology research has generated several RCTs addressing major clinical questions. However, it has often focused primarily on technical success and feasibility. To influence clinical practice guidelines, care pathways, and technology transfer, studies must be designed around the clinical decision they aim to inform. This requires clear clinical questions, appropriate designs, reliable data systems, and transparent communication. This framework originated from a predominantly Italian multidisciplinary working group and was not developed as a formal European or international consensus. Broader international participation will therefore be important to further refine the framework and assess its applicability across different healthcare systems and surgical oncology settings. Departments committed to surgical innovation should also invest in methodological expertise and research literacy [53,54]. The value of surgical research will depend less on the number of studies produced than on their ability to answer questions that matter to patients and health systems.

CRediT authorship contribution statement

All named authors contributed to the intellectual development of the framework through participation in the multidisciplinary discussions and/or substantive critical revision of the manuscript, approved the final version, and agreed to be accountable for the work. **Conceptualization:** AG; **Methodology:** AG, IM, RP, PS, VM, NN, FR, AD, SF; **Writing – original draft:** AG, GB, NN; **Writing – review & editing:** All authors; **Visualization:** AG, IC, JC, FC; **Project administration:** AG, MTM; **Supervision:** AG.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used OpenAI ChatGPT solely for language refinement, editorial assistance, and graphical development and editing. All scientific content, concepts, methodological considerations, interpretations, recommendations, and the substantive content of the figures were provided and determined by the authors. All AI-assisted text and graphical materials were critically reviewed, revised where necessary, and approved by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflict of interest

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Appendix A. Supplementary data

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References

[1] Joint Action on Rare Cancers (JARC). Rare cancer agenda 2030: ten recommendations from the EU joint action on rare cancers. Milan: JARC; 2020. Available at: https://siope.eu/media/documents/rare-cancer-agenda-2030.pdf. [Accessed 28 March 2026].
[2] Neuman HB, Greenberg CC. Comparative effectiveness research: opportunities in surgical oncology. Semin Radiat Oncol 2014 Jan;24(1):43–8. https://doi.org/10.1016/j.semradonc.2013.09.003. PMID: 24314341.
[3] Fairhurst K, Potter S, Blazeby JM, Avery KNL. Recommendations for optimising pilot and feasibility work in surgery. Pilot Feasibility Stud 2024 Apr 18;10(1):64. https://doi.org/10.1186/s40814-024-01489-1. PMID: 38637818; PMCID: PMC11025276.
[4] Bahri S, Walshaw J, Bishop L, et al. Reporting of baseline characteristics in gastrointestinal cancer: a systematic review of surgical randomised controlled trials. Eur J Surg Oncol 2026 Jul;52(7):111854. https://doi.org/10.1016/j.ejso.2026.111854. Epub 2026 May 6. PMID: 42119194.
[5] Pollock RE, Morton DL. Principles of surgical oncology. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei cancer medicine. sixth ed. Hamilton (ON): BC Decker; 2003 [Chapter 38]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK13204/.
[6] Møller MH. Patient-important outcomes and core outcome sets: increased attention needed. Br J Anaesth 2019 Apr;122(4):408–10. https://doi.org/10.1016/j.bja.2019.02.007. Epub 2019 Feb 23. PMID: 30857595; PMCID: PMC6435936.
[7] Tregear M, Visco F. Outcomes that matter to patients with cancer: living longer and living better. EClinicalMedicine 2024 Sep 11;76:102833. https://doi.org/10.1016/j.eclinm.2024.102833. PMID: 39309725; PMCID: PMC11415949.
[8] Sherry AD, Miller AM, Parlapalli JP, et al. Overall survival and quality-of-life superiority in modern phase 3 oncology trials: a meta-epidemiological analysis. JAMA Oncol 2025 Jul 1;11(7):718–24. https://doi.org/10.1001/jamaoncol.2025.1002. PMID: 40451185; PMCID: PMC12127959.
[9] Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. Br Med J 2016 Jun 28;353:i2016. https://doi.org/10.1136/bmj.i2016. PMID: 27353417.
[10] EMA. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf. [Accessed 28 March 2026].
[11] Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014 Jan 11;383(9912):166–75. https://doi.org/10.1016/S0140-6736(13)62227-8. Epub 2014 Jan 8. PMID: 24411645; PMCID: PMC4697939.
[12] Prang KH, Karanatsios B, Verbunt E, et al. Clinical registries data quality attributes to support registry-based randomised controlled trials: a scoping review. Contemp Clin Trials 2022 Aug;119:106843. https://doi.org/10.1016/j.cct.2022.106843. Epub 2022 Jul 2. PMID: 35792338.
[13] Shiely F, O Shea N, Murphy E, Eustace J. Registry-based randomised controlled trials: conduct, advantages and challenges-a systematic review. Trials 2024 Jun 11;25(1):375. https://doi.org/10.1186/s13063-024-08209-3. PMID: 38863017; PMCID: PMC11165819.
[14] Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016 Mar 15;3:160018. https://doi.org/10.1038/sdata.2016.18. Erratum in: Sci Data. 2019 Mar 19;6(1):6. doi: 10.1038/s41597-019-0009-6. PMID: 26978244; PMCID: PMC4792175.
[15] Probst P, Knebel P, Grummich K, et al. Industry bias in randomized controlled trials in general and abdominal surgery: an empirical study. Ann Surg 2016;264:87–92. https://doi.org/10.1097/SLA.0000000000001372.
[16] Krahn M. Principles of economic evaluation in surgery. World J Surg 1999 Dec;23(12):1242–8. https://doi.org/10.1007/s002689900656. PMID: 10552115.
[17] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009 Aug;250(2):187–96. https://doi.org/10.1097/SLA.0b013e3181b13ca2. PMID: 19638912.
[18] MacNeill AJ, Lillywhite R, Brown CJ. The impact of surgery on global climate: a carbon footprinting study of operating theatres in three health systems. Lancet Planet Health 2017 Dec;1(9):e381–8. https://doi.org/10.1016/S2542-5196(17)30162-6. Epub 2017 Dec 8. PMID: 29851650.
[19] Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. Br Med J 2017 Aug 2;358:j3453. https://doi.org/10.1136/bmj.j3453. PMID: 28768629; PMCID: PMC5539518.
[20] Jones EL, Williams-Yesson BA, Hackett RC, Staniszewska SH, Evans D, Francis NK. Quality of reporting on patient and public involvement within surgical research: a systematic review. Ann Surg 2015 Feb;261(2):243–50. https://doi.org/10.1097/SLA.0000000000000768. PMID: 24950279.
[21] Stiles M, Dewan M, Manning G, et al. Patient and public involvement in the SPRUCE methodology study investigating electronic patient reported outcomes in oncology clinical trials. Res Involv Engagem 2025 Jul 1;11(1):70. https://doi.org/10.1186/s40900-025-00742-y. PMID: 40597429; PMCID: PMC12211921.
[22] Ceelen W, Soreide K. Randomized controlled trials and alternative study designs in surgical oncology. Eur J Surg Oncol 2023 Aug;49(8):1331–40. https://doi.org/10.1016/j.ejso.2023.03.001. Epub 2023 Mar 6. PMID: 36964056.
[23] Palis BE, Janczewski LM, Browner AE, et al. The national cancer database conforms to the standardized framework for registry and data quality. Ann Surg Oncol 2024

Sep;31(9):5546–59. https://doi.org/10.1245/s10434-024-15393-8. Epub 2024 May 8. PMID: 38717542; PMCID: PMC11300494.
[24] Naidoo P, Bouharati C, Rambiritch V, et al. Real-world evidence and product development: opportunities, challenges and risk mitigation. Wien Klin Wochenschr 2021 Aug;133(15–16):840–6. https://doi.org/10.1007/s00508-021-01851-w. Epub 2021 Apr 9. PMID: 33837463; PMCID: PMC8034870.
[25] Radulova O, Oehme F, Korn S, Praetorius C, Distler M, Weitz J. Registry or randomization - must it be evidence or could it be coincidence? Innov Surg Sci 2024 Jun 26;10(2):65–71. https://doi.org/10.1515/iss-2022-0028. PMID: 40778215; PMCID: PMC12327714.
[26] European Commission. European health data space regulation (EHDS). Available at: https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space-regulation-ehds_en#:~:text=The%20EHDS%20Regulation%2C%20first%20proposed,rules%20for%20the%20regulation%20operationalisation. [Accessed 28 March 2026].
[27] Shapiro MA, Stuhlmiller TJ, Wasserman A, et al. AI-Augmented clinical decision support in a patient-centric precision oncology registry. AI Precis Oncol 2024;1(1):58–68. https://doi.org/10.1089/aipo.2023.0001.
[28] Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016 Aug 4;375(5):454–63. https://doi.org/10.1056/NEJMra1510059. PMID: 27518663.
[29] McCulloch P, Taylor I, Sasako M, et al. Randomised trials in surgery: problems and possible solutions. Br Med J 2002;324:1448–51. https://doi.org/10.1136/bmj.324.7351.1448.
[30] Strobel O, Büchler MW. The problem of the poor control arm in surgical randomized controlled trials. Br J Surg 2013;100:172–3. https://doi.org/10.1002/bjs.8998.
[31] Solomon MJ, Pager CK, Young JM, et al. Patient entry into randomized controlled trials of colorectal cancer treatment: factors influencing participation. Surgery 2003;133:608–13. https://doi.org/10.1067/msy.2003.119.
[32] Blencowe NS, Mills N, Cook JA, et al. Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials. Br J Surg 2016;103:1377–84. https://doi.org/10.1002/bjs.10254.
[33] Barkun JS, Dimick JB, Clavien PA. Surgical research in patients: ideal time for an IDEAL checklist. Ann Surg 2019 Feb;269(2):208–10. https://doi.org/10.1097/SLA.0000000000003140. PMID: 30615599.
[34] Conroy EJ, Blazeby JM, Burnside G, Cook JA, Gamble C. Managing clustering effects and learning effects in the design and analysis of randomised surgical trials: a review of existing guidance. Trials 2022 Oct 11;23(1):869. https://doi.org/10.1186/s13063-022-06743-6. PMID: 36221107; PMCID: PMC9552436.
[35] Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research? J Clin Epidemiol 2016 Dec;80:16–24. https://doi.org/10.1016/j.jclinepi.2016.08.003. Epub 2016 Aug 20. PMID: 27555082.
[36] Xu J, van Eijk RPA, Ellis A, et al. On the two-step hybrid design for augmenting randomized trials using real-world data. Stat Biopharm Res 2025 Oct 8. https://doi.org/10.1080/19466315.2025.2547855. doi: 10.1080/19466315.2025.2547855. Epub ahead of print. PMID: 41127439; PMCID: PMC12539643.
[37] Sengupta S, Ntambwe I, Tan K, et al. Emulating randomized controlled trials with hybrid control arms in oncology: a case study. Clin Pharmacol Ther 2023 Apr;113(4):867–77. https://doi.org/10.1002/cpt.2841. Epub 2023 Jan 22. PMID: 36606735.
[38] Ali S, Hopkin G, Poonai N, et al. A novel preference-informed complementary trial (PICT) design for clinical trial research influenced by strong patient preferences. Trials 2021 Mar 12;22(1):206. https://doi.org/10.1186/s13063-021-05164-1. Erratum in: Trials. 2021 May 20;22(1):353. doi: 10.1186/s13063-021-05312-7. PMID: 33712062; PMCID: PMC7953803.
[39] Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. Br Med J 2005 Jan 8;330(7482):88. https://doi.org/10.1136/bmj.330.7482.88. PMID: 15637373; PMCID: PMC543877.
[40] Rebelo A, Klose J, Kleeff J, Ronellenfitsch U. Is it feasible and ethical to randomize patients between surgery and non-surgical treatments for gastrointestinal cancers? Front Oncol 2023 Mar 16;13:1119436. https://doi.org/10.3389/fonc.2023.1119436. PMID: 37007103; PMCID: PMC10061124.
[41] Choodari-Oskooei B, Blenkinsop A, Handley K, Pinkney T, Parmar MKB. Multi-arm multi-stage (MAMS) randomised selection designs: impact of treatment selection rules on the operating characteristics. BMC Med Res Methodol 2024 Jun 3;24(1):124. https://doi.org/10.1186/s12874-024-02247-w. Erratum in: BMC Med Res Methodol. 2024 Jul 2;24(1):143. doi: 10.1186/s12874-024-02267-6. PMID: 38831421; PMCID: PMC11145876.
[42] Strzebonska K, Waligora M. Umbrella and basket trials in oncology: ethical challenges. BMC Med Ethics 2019 Aug 23;20(1):58. https://doi.org/10.1186/s12910-019-0395-5. PMID: 31443704; PMCID: PMC6708208.
[43] Li F, Wang B, Heagerty PJ. What is a stepped-wedge cluster randomized trial? JAMA Intern Med 2025 May 1;185(5):593–4. https://doi.org/10.1001/jamainternmed.2024.8216. PMID: 40063042; PMCID: PMC12052484.
[44] Liang X, Zhang D, Wang H, Tahir MF, Chen L, Zhao X, et al. Importance of cohort and target trial emulation in clinical research. Cell Rep Med 2025 Apr 15;6(4):102081. https://doi.org/10.1016/j.xcrm.2025.102081. PMID: 40239630; PMCID: PMC12047467.
[45] Dettori JR, Norvell DC, Chapman JR. Grab control! Choosing the Right Comparison Group in an observational study. Glob Spine J 2019 Jun;9(4):456–8. https://doi.org/10.1177/2192568219847206. Epub 2019 May 9. PMID: 31218205; PMCID: PMC6562210.
[46] Vasey B, Nagendran M, Campbell B, et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. Nat Med 2022 May;28(5):924–33. https://doi.org/10.1038/s41591-022-01772-9. Epub 2022 May 18. Erratum in: Nat Med. 2022 Oct;28(10):2218. doi: 10.1038/s41591-022-01951-8. PMID: 35585198.
[47] European Commission. Health data access bodies – community of practice. Available at: https://health.ec.europa.eu/ehealth-digital-health-and-care/ehds-action/projects-supporting-ehds/health-data-access-bodies-community-practice_en. [Accessed 28 March 2026].
[48] Ho CH. Secondary use of health data for medical AI: a cross-regional examination of Taiwan and the EU. Asian Bioeth Rev 2024 Apr 6;16(3):407–22. https://doi.org/10.1007/s41649-024-00279-4. Erratum in: Asian Bioeth Rev. 2024 Aug 16;17(4):765-766. doi: 10.1007/s41649-024-00318-0. PMID: 39022371; PMCID: PMC11250748.
[49] Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (text with EEA relevance). Available at: https://eur-lex.europa.eu/eli/reg/2025/327/oj/eng. [Accessed 22 August 2026].
[50] Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. Br Med J 2025 Apr 14;389:e081123. https://doi.org/10.1136/bmj-2024-081123. PMID: 40228833; PMCID: PMC11995449.
[51] Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Int J Surg 2014 Dec;12(12):1500–24. https://doi.org/10.1016/j.ijsu.2014.07.014. Epub 2014 Jul 18. PMID: 25046751.
[52] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021 Mar 29;372:n71. https://doi.org/10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
[53] Are C, Yanala U, Malhotra G, et al. Global curriculum in research literacy for the surgical oncologist. Eur J Surg Oncol 2018 Jan;44(1):31–42. https://doi.org/10.1016/j.ejso.2017.07.017. Epub 2017 Dec 11. PMID: 29242017.
[54] van der Hage J, Sandrucci S, Audisio R, et al. The ESSO core curriculum committee update on surgical oncology. Eur J Surg Oncol 2021 Nov;47(11):e1–30. https://doi.org/10.1016/j.ejso.2021.10.003. Epub 2021 Oct 13. PMID: 34657781.