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Comprehensive Guide to Randomized Controlled Trials in Radiology: Everything You Need to Know

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Abstract

Evidence-based medicine integrates clinical research, personal expertise, and patient values. The most robust forms of clinical evidence, such as randomized controlled trials (RCTs) and prospective studies, provide the strongest support for medical decision-making. RCTs are vital in radiology for evaluating new imaging technologies, contrast agents, and therapeutic procedures, despite challenges in translating preclinical findings to clinical practice. This guide discusses the history, principles, methodologies, and applications of RCTs in radiology, highlighting their role in advancing the field and supporting evidence-based practice.

Keywords
- EBM
- evidence-based medicine
- precision medicine
- radiology
- randomized controlled trials
- RCT

Introduction

The primary goal of every physician is to improve patient outcomes through precision decision-making. Over the past three decades, evidence-based medicine (EBM) has been crucial in this process, combining clinical research findings, referred to as the best "external evidence," with personal clinical expertise and patient values. As Greenhalgh and Donald stated in 2000, "evidence-based medicine involves using mathematical estimates of the risk of benefit and harm, derived from high-quality research on population samples, to guide clinical decisions in diagnosing, investigating, or managing individual patients."[1] Consensus panels have established that randomized controlled trials (RCTs) and prospective studies represent the most robust forms of medical evidence, while retrospective studies occupy an intermediate position. Case reports and expert opinions are considered to provide lower levels of evidence according to these panels.[2,3] ►**Fig. 1** depicts the hierarchical levels of evidence in descending order, a key component of EBM, which prioritizes seeking the highest level of evidence to address clinical questions.

RCTs are among the most reliable methods in clinical research for assessing the effectiveness and safety of medical interventions.[4] They offer a systematic approach to test hypotheses, reduce bias, and establish causation. In radiology, RCTs are critical for generating high-quality evidence on the efficacy of new imaging technologies, contrast agents, or

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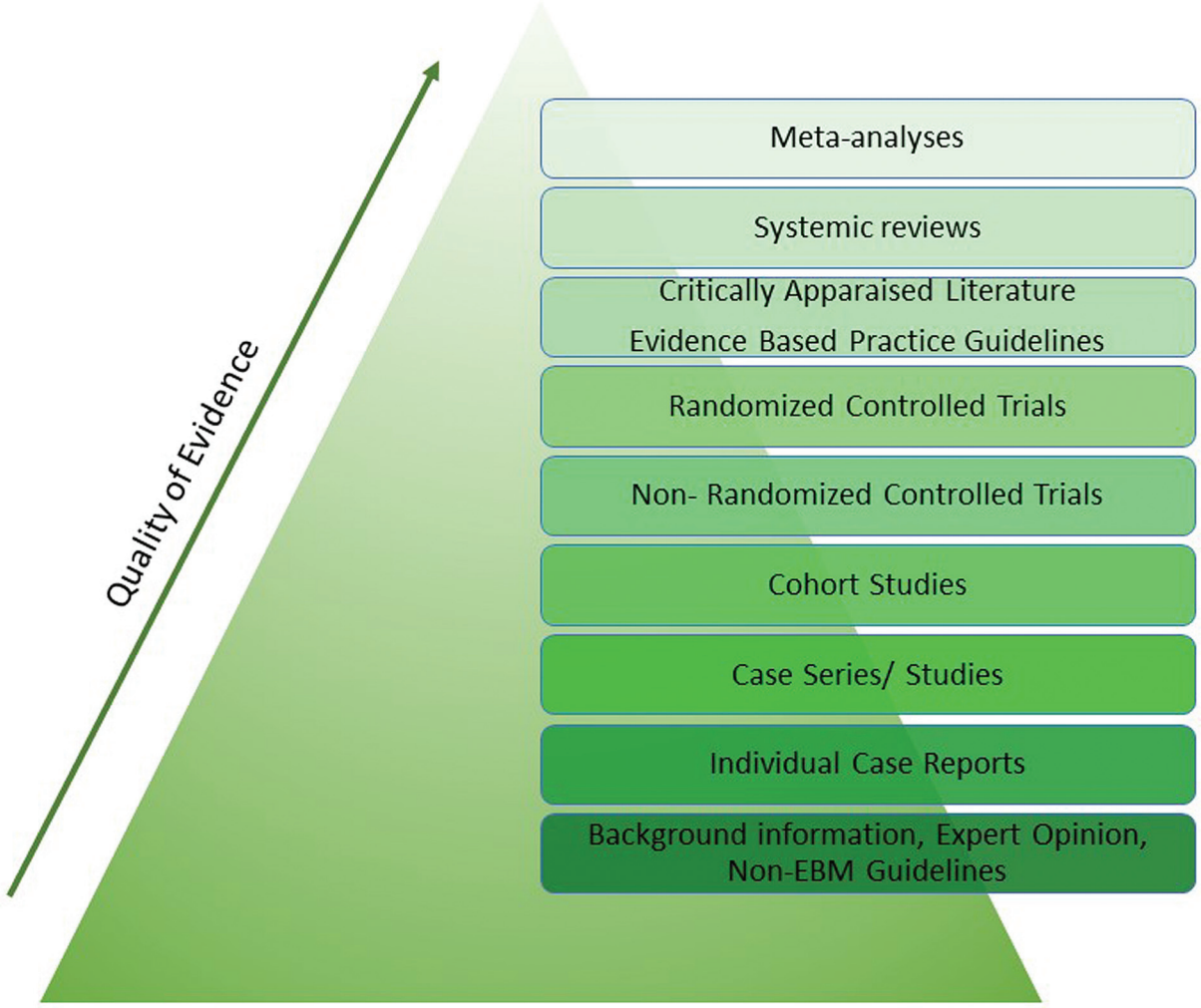

Fig. 1 The hierarchical levels of evidence in descending order, a key component of evidence-based medicine (EBM), which prioritizes seeking the highest level of evidence to address clinical questions.

therapeutic radiologic procedures. These trials assess the clinical benefits, potential risks, and cost-effectiveness of new technologies compared with current standards. A substantial body of literature provides numerous examples of instances where preclinical imaging trials have not progressed to clinical bedside applications. The transition from preclinical to clinical settings is fraught with challenges, as conducting RCTs in preclinical environments often encounters significant hurdles. These difficulties include the complexity of translating findings from animal models to human conditions, variations in imaging technologies, and the need for rigorous validation processes. As a result, while preclinical imaging trials may offer promising insights, overcoming these obstacles is crucial for their successful application in clinical practice.[5–7] By following stringent protocols and using blinding where feasible, RCTs support evidence-based practice, enhance patient outcomes, and advance the radiology field. This comprehensive guide explores the history, general principles, methodologies, and common applications of RCTs in radiology underlining its strengths and limitations, highlighting the essential role of RCT in EBM.

Types of Clinical Research Study Designs

In clinical research, our goal is to create a study that can yield valid and significant scientific conclusions using appropriate statistical methods applicable to real-world scenarios.[8] From an epidemiological viewpoint, clinical study designs are primarily categorized into two types: observational and experimental.[9] Observational studies serve as hypothesis generators and can be divided into two subtypes: descriptive and analytic. Descriptive observational studies aim to characterize the exposure and/or outcome, whereas analytic observational studies evaluate the relationship between the exposure and the outcome. Conversely, experimental studies focus on hypothesis testing and involve interventions to explore the connection between the exposure and the outcome.

Observational studies aim to answer questions regarding what, who, where, and when. Various study designs fall under the category of descriptive studies, including case reports, case series, ecological studies, cross-sectional studies, cohort studies, and case–control studies.

An experimental study design examines the effects of an intervention. In this approach, the investigator controls the risk factor, exposure, or treatment of interest. As hypothesis-testing studies, experimental designs offer robust evidence for establishing causality. These designs can be classified into three main categories: clinical trials, community trials, and field trials. Clinical trials, also referred to as therapeutic trials, involve participants with specific diseases who are assigned to different treatment groups. This design is regarded as the gold standard in epidemiological research. Clinical trials can be further categorized into randomized clinical trials, nonrandomized clinical trials, crossover clinical trials, and factorial clinical trials. Randomized clinical trials, also known as parallel-group randomized trials or RCTs, involve assigning participants with similar characteristics to either an intervention group receiving the experimental therapy or a control group receiving a placebo or standard care.[10] ►**Fig. 2** categorizes all of these study designs in a tabular format providing a comprehensive overview.

Historical Context

The origins of clinical trials can be traced back to around 600 B.C. when Daniel of Judah performed what is likely the earliest documented clinical trial. He evaluated the health outcomes of a vegetarian diet versus a royal Babylonian diet over 10 days. Although the trial had significant flaws by today's medical standards, its impact has persisted for over 2,000 years. Credit for the modern randomized trial is commonly attributed to Sir Austin Bradford Hill.[11] The Medical Research Council trials on streptomycin for pulmonary tuberculosis are widely acknowledged as a pivotal moment that marked a significant advancement in medicine. Since Hill's ground-breaking work, the methodology of RCT has gained widespread acceptance, leading to an exponential increase in the number of reported trials.

General Principles of Randomized Controlled Trials

RCTs rely on *random allocation* to ensure each participant has an equal chance of being assigned to either the intervention or control group, thereby minimizing selection bias and ensuring comparability between the groups at the outset. The *control group* in RCTs serves as a reference, receiving either a placebo, standard treatment, or an alternative intervention, facilitating comparative efficacy assessments of the intervention being studied. *Blinding*, also

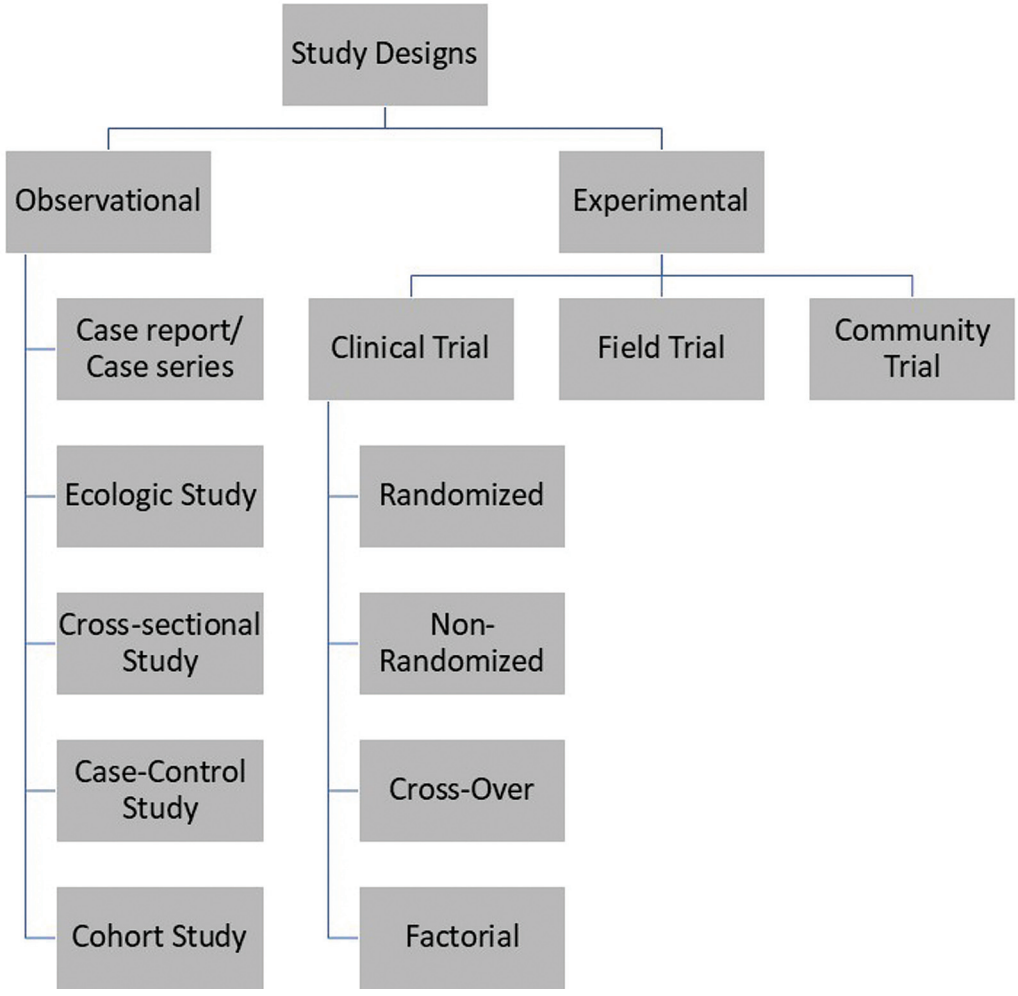

Fig. 2 Types of clinical research study designs.

known as masking, conceals group allocation from participants, investigators, or outcome assessors to prevent bias from influencing study outcomes, thus bolstering internal validity. RCTs have a *prospective approach* which means they are rigorously planned and adhere to a predefined protocol to prevent post hoc modifications that could introduce bias, ensuring the integrity of the study's objectives, methods, and statistical analyses. These trials use *predefined outcome measures*, such as clinical end points (e.g., mortality, disease recurrence), surrogate markers (e.g., biomarkers, imaging findings), or patient-reported outcomes (e.g., quality of life, symptom severity), to evaluate intervention effects.[12] ►**Fig. 3** outlines the factors contributing to a high-quality RCT. ►**Fig. 4** provides a flow diagram of RCTs illustrating the essential design elements and general principles.

Types of Randomized Controlled Trials

RCTs are classified into subtypes according to various considerations,[13] as outlined below:

- According to the different aspects of interventions evaluated: explanatory or pragmatic trials; efficacy or equivalence trials; and phases 1, 2, 3, and 4 trials.
- According to participants' exposure and response to the intervention: parallel, crossover, and factorial designs.[14]
- According to the number of participants: N-of-1 trials, sequential trials, and fixed trials.[15–17]
- According to the levels of blinding: single-blinded, double-blinded, triple-blinded, quadruple-blinded, depending on which groups—patients, treating physicians, study investigators, and statisticians—are blinded during the study.
- According to nonrandomized participant preferences: preference trials can have a Zelen design, comprehensive cohort design, or Wennberg's design.

Steps in Conducting Randomized Controlled Trials

The first step in conducting an RCT involves defining the *research question* and designing the study protocol. Researchers must specify the intervention(s), control group, outcome measures, eligibility criteria, and statistical analysis plan. The *study protocol* serves as a comprehensive blueprint for the trial, detailing all aspects of its design, conduct, and analysis. The protocol should adhere to ethical principles, regulatory requirements, and reporting guidelines (e.g., Consolidated Standards of Reporting Trials [CONSORT]) to ensure transparency and reproducibility.[18] Before commencing the trial, researchers must obtain *approval* from an Institutional Review Board or ethics committee. Ethical considerations include participant safety, informed consent, confidentiality, and equitable distribution of benefits and burdens. *Recruiting eligible participants* is critical to the success of an RCT. Researchers must adhere to inclusion and exclusion criteria specified in the protocol and employ appropriate recruitment strategies to ensure the representativeness and generalizability of the study population. *Random allocation of participants* to treatment groups minimizes selection bias and ensures comparability between the groups.[12,16] *Allocation concealment mechanisms*, such as centralized randomization or sequentially numbered, opaque, sealed envelopes, prevent foreknowledge of treatment

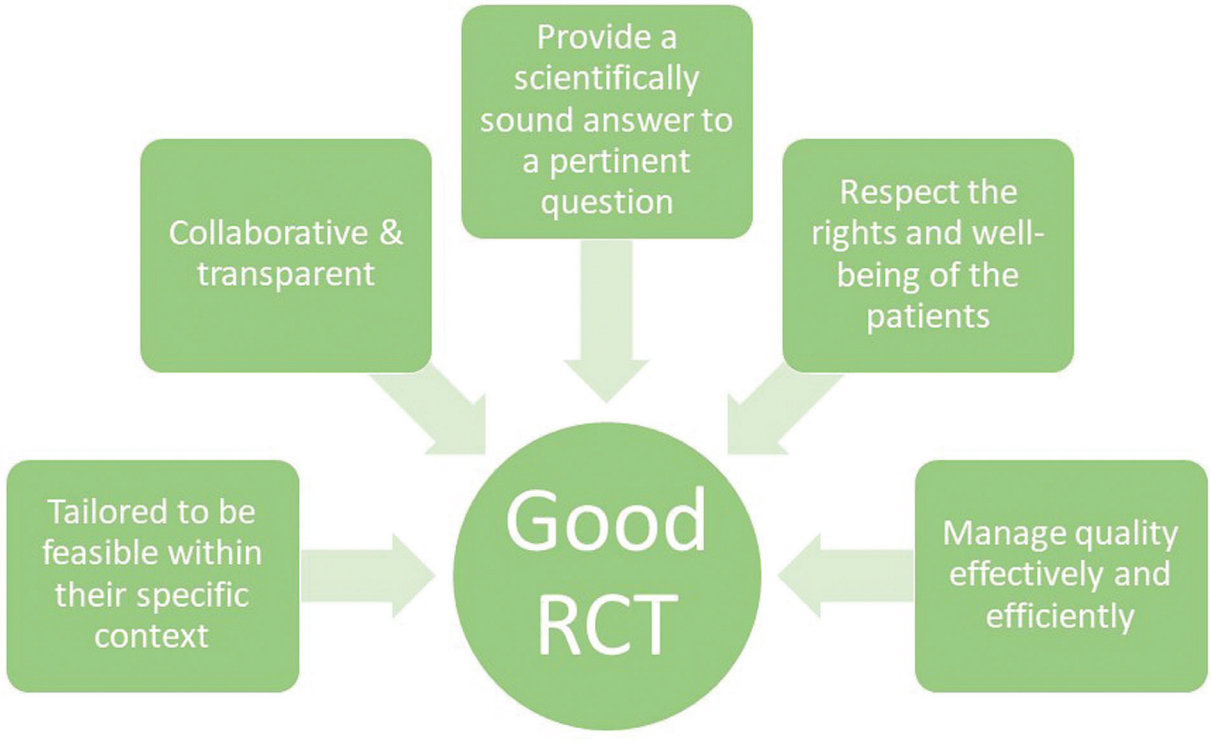

Fig. 3 Factors contributing to a high-quality randomized controlled trial (RCT).

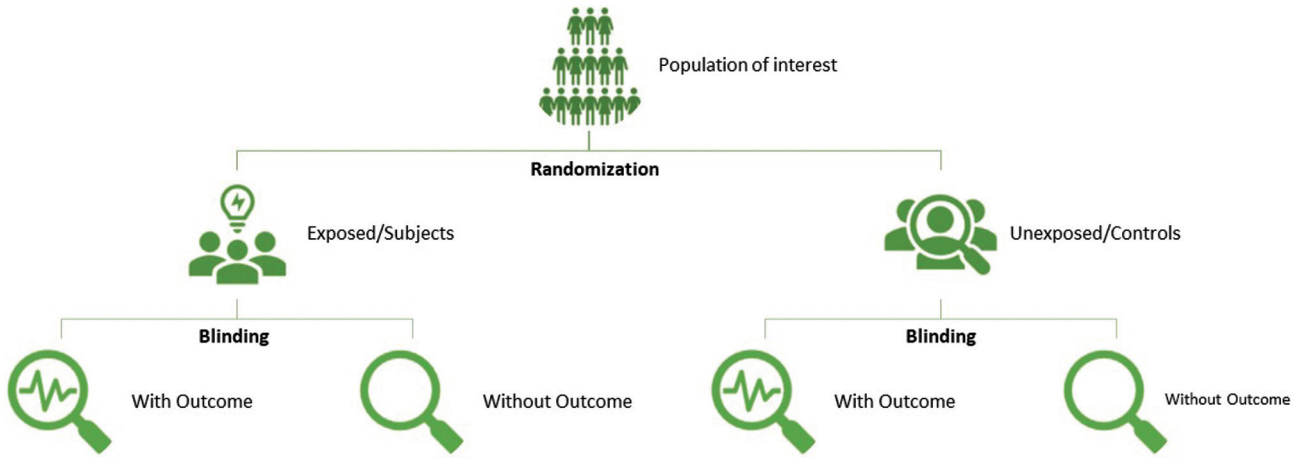

Fig. 4 Flow diagram of a randomized controlled trial (RCT) illustrating its essential design elements and general principles.

assignments, further enhancing the integrity of the randomization process. Participants assigned to the *intervention* group receive the experimental treatment, while those in the control group receive either a placebo, standard care, or an alternative intervention. Standardization of treatment protocols and adherence to study procedures are essential to minimize variability and ensure consistency across treatment arms.

Throughout the trial, researchers collect *data* on outcome measures at predefined time points. *Follow-up* visits, medical examinations, laboratory tests, imaging studies, and patient-reported assessments may be utilized to capture relevant end points and monitor participant progress. *Statistical analysis of trial data* involves comparing outcomes between the treatment groups using appropriate inferential methods. Statistical significance, effect size estimation, and confidence intervals are key components of the analysis. Upon completion of data analysis, researchers *interpret* the trial findings in light of the study objectives, methodology, and clinical relevance.[19] Transparent *reporting* of results in scientific publications, adhering to reporting guidelines such as CONSORT, facilitates critical appraisal, replication, and synthesis of evidence. *Sharing the trial results* with the scientific community, health care professionals, policymakers, and the public is essential for translating research findings into clinical practice. Peer-reviewed publications, conference presentations, clinical practice guidelines, and public health campaigns are common avenues for disseminating RCT findings.[12]

Trends and Challenges of RCT in Radiology

Alvin et al published an analysis in 2020 of research studies published in *Radiology* journal over the past decade, focusing on changes in the number and type of publications, particularly prospective clinical trials. Between 2009 and 2019, the number of prospective studies in *Radiology* declined from ~150 to 120, representing a 20% decrease. In terms of all original research published in *Radiology*, the proportion of prospective studies decreased from 45% in 2009 to 33% in 2019.[20] The decrease in prospective studies, including RCTs, within the radiology department can be attributed to several factors.

Radiologists face numerous barriers when initiating prospective clinical trials, especially if they lack prior experience or training. Fortunately, organizations such as the Radiological Society of North America provide training courses and fellowships designed to familiarize early-career radiologists and trainees with conducting rigorous research. For instance, the National Institutes of Health (NIH) Grantsmanship Workshop focuses on crafting competitive grant proposals, while introductory research courses cater to trainees and foreign medical graduates entering the field. Additional challenges faced by clinical radiologists include constraints related to time and financial resources. Increased allocation toward "research time" imposes greater strain on departmental budgets and effective clinical hours, posing practical limitations that many institutes struggle to address. According to Dewey et al, only a small fraction, 255 out of 17,531 NIH-funded clinical trials conducted between 2017 and 2018 were led by principal investigators from radiology or radiation oncology departments.[21] Also, the research focus in our field is evolving.

In recent years, artificial intelligence (AI) has become the focus of research in radiology. In 2019, AI and radiomics topics comprised 25% of all original research in *Radiology*, a significant increase from 1 to 2% seen in 2016.[20] The majority of AI studies to date have been retrospective analyses of existing databases. This surge of interest in AI has led to more studies with lower-quality evidence being published, as retrospective AI studies are inherently less likely to establish standards of care in radiology. Park et al discussed the necessity of RCTs in evaluating clinical AI, outlining why RCTs are essential and when they should be preferred over other evaluation methods.[22] Looking ahead, there is potential for next-generation AI systems to undergo rigorous testing as prospective studies. By using a randomized approach, these studies will minimize biases and provide robust evidence on how AI can enhance radiological practices and ultimately improve patient care.[23,24] Park and Han

have discussed such research ideas, while Lehman et al specifically evaluated an AI system for breast density within a mammography clinic.[25,26]

Common Research Areas for RCTs in Radiology

Imaging Modalities

RCTs in radiology often involve comparing different imaging modalities (e.g., magnetic resonance imaging [MRI], computed tomography [CT], ultrasound) or imaging protocols to assess their diagnostic accuracy, clinical utility, and cost-effectiveness in various clinical scenarios. RCTs have been instrumental in evaluating the efficacy of various *cancer screening modalities*, such as mammography for breast cancer, CT colonography for colorectal cancer, and low-dose CT for lung cancer, in terms of early detection, mortality reduction, and overdiagnosis rates.[27–30]

Diagnostic Accuracy

RCTs focus on evaluating the diagnostic accuracy of imaging tests, including sensitivity, specificity, positive and negative predictive values, and likelihood ratios, compared with reference standards such as histopathology or clinical follow-up. RCTs assess the diagnostic performance and prognostic value of imaging biomarkers (e.g., tumor size, enhancement patterns, metabolic parameters) in predicting treatment response, recurrence risk, and patient outcomes across different cancer types and stages. RCTs in emergency radiology assess the diagnostic accuracy and clinical impact of rapid imaging protocols, point-of-care ultrasound, and advanced imaging techniques (e.g., CT angiography, MRI) in triaging patients with acute conditions, such as trauma, stroke, and myocardial infarction, to expedite diagnosis and treatment.[31]

Therapeutic Interventions

RCTs may also investigate the efficacy and safety of interventional radiology procedures, such as image-guided biopsies, ablations, embolizations, and minimally invasive surgeries, compared with conventional treatments or alternative approaches. RCTs in interventional radiology evaluate the effectiveness and safety of image-guided procedures, such as radiofrequency ablation, transarterial chemoembolization, and percutaneous drainage, in treating various conditions, including liver tumors, renal masses, and vascular malformations.[32–37]

Clinical Outcomes

In addition to diagnostic performance, RCTs in radiology assess clinically relevant outcomes, such as patient survival, disease progression, treatment response, quality of life, and health care resource utilization, to inform clinical decision-making. RCTs investigate the role of imaging-guided therapies, such as stereotactic radiosurgery, brachytherapy, and selective internal radiation therapy, in delivering targeted treatments to tumors while minimizing damage to surrounding healthy tissues, improving local control rates, and prolonging survival.[38]

Radiation Exposure

Given the potential risks associated with ionizing radiation, RCTs involving radiation-based imaging modalities (e.g., CT, nuclear medicine) must carefully consider radiation exposure levels, dose optimization techniques, and long-term radiation-related risks to participants.[39]

Examples in Radiology

Lung Cancer Screening Trials

National Lung Screening Trial (NLST) was a landmark RCT that demonstrated the efficacy of low-dose CT screening in reducing lung cancer mortality compared with chest radiography among high-risk individuals, leading to the adoption of lung cancer screening guidelines.[27,28]

Digital Breast Tomosynthesis Trials

RCTs comparing DBT with conventional digital mammography have shown improvements in breast cancer detection rates, reduction in false-positive recalls, and increased specificity, leading to the incorporation of DBT into breast cancer screening programs.[29]

Stroke Imaging RCTs

RCTs evaluating advanced imaging techniques, such as perfusion CT, diffusion-weighted MRI, and CT angiography, have informed treatment decisions in acute ischemic stroke by identifying eligible patients for reperfusion therapies and guiding therapeutic time windows.[40–42]

Prostate MRI and Biopsy Trials

RCTs investigating the role of multiparametric MRI in prostate cancer diagnosis have demonstrated its superiority in detecting clinically significant tumors, guiding biopsy target selection, and reducing unnecessary biopsies compared with systematic transrectal ultrasound-guided biopsies.[31,43,44]

Hepatocellular Carcinoma RCTs

RCTs assessing the efficacy of radiofrequency ablation, transarterial chemoembolization, and radioembolization in treating HCC have informed treatment algorithms, improved local tumor control rates, and prolonged survival in patients with unresectable liver tumors.[32–35,37]

Post Hoc/Subset Analyses of RCT

Post hoc or subset analyses of RCTs involve examining specific subgroups of patients who were part of the original trial. These analyses can provide valuable insights into particular objectives related to radiological imaging, such as evaluating how different imaging techniques perform across various patient demographics or conditions. By focusing on these subsets, researchers can identify trends or patterns that may not be evident in the overall trial population, offering more targeted and nuanced findings. Examples include studies examining the relationship between radiological extranodal extension and outcomes such as disease-free survival, locoregional recurrence-free survival, and overall survival (OS) in patients with locally advanced head

and neck squamous cell carcinoma undergoing concurrent chemoradiotherapy.[45] Other studies investigate the feasibility of developing a deep learning algorithm for classifying brain metastases from non-small cell lung cancer (NSCLC) into groups based on epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement.[46] Additionally, the research assesses the prognostic value of the modified Advanced Lung Cancer Inflammation Index (ALI) compared with the original ALI, focusing on its impact on OS and progression-free survival in advanced NSCLC.[47] Finally, some studies evaluate the accuracy of the Neck Imaging Reporting and Data System in predicting disease status at the first posttreatment follow-up using contrast-enhanced CT.[48]

Strengths and Limitations

RCTs possess numerous strengths, establishing them as the highest standard of medical evidence.[4] Randomization, blinding, and control group allocation minimize bias and confounding, ensuring that observed differences between the treatment groups are attributable to the intervention under investigation thus ensuring high internal validity.[12] RCTs provide robust evidence for establishing causal relationships between interventions and outcomes, allowing researchers to make confident inferences about treatment efficacy and safety. Well-conducted RCTs with representative study populations and rigorous methodology yield findings that apply to broader patient populations, clinical settings, and health care contexts thus ensuring generalizability. RCTs serve as the foundation of EBM, guiding clinical practice, health care policy, and resource allocation by providing high-quality evidence for informed decision-making.

However, there are a few limitations of RCTs. They are often time-consuming, labor-intensive, and costly endeavors, requiring substantial investment in personnel, infrastructure, and research funding. Ethical considerations, such as using placebo controls or randomizing vulnerable populations, may limit the feasibility or acceptability of certain RCT designs. Strict eligibility criteria, homogeneous study populations, and controlled study conditions may limit the generalizability of RCT findings to real-world clinical practice. Challenges such as participant recruitment, retention, adherence, and protocol deviations can impact the feasibility and execution of RCTs, potentially compromising their validity and reliability.[49,50]

Summary

►**Table 1** lists all the essential subheadings under the topic RCT and provides references for further reading on each of these subheadings.

Conclusion

RCTs play a pivotal role in advancing the field of radiology by providing rigorous evidence to guide diagnostic and therapeutic interventions, improve patient outcomes, and inform health care policy and practice. Despite challenges in study design, implementation, and interpretation, radiology RCTs contribute invaluable insights into the efficacy, safety, and cost-effectiveness of imaging-based strategies across various clinical scenarios, ultimately enhancing the quality of care and the delivery of precision medicine. Radiologists have a great deal to learn about RCTs. Academic radiologists who perform research and radiologists who translate research results into practice should be familiar with the different types of these trials, including those conducted for diagnostic tests and interventional procedures. Radiologists also must be aware of the limitations and problems associated with the methodologic quality and reporting of the trials. We hope that this article serves as a valuable source of information about RCTs.

Table 1 Essential topics related to RCTs for further reading with relevant references

Topics for further read	References
Types of clinical research study designs	8–10
History of RCTs	11
General principles of RCTs	12,51
Types of RCTs	17–23,52–54
Steps in conducting RCTs (methodology and data analysis)	9,10,13,15,16,55
Ethics issues in clinical trials	56,57
Trends and challenges of RCT in radiology	17–23,58–60
Common research areas for RCTs in radiology	24–36
Examples of RCTs in radiology	24–26,28–32,34,37–45

Abbreviation: RCTs, randomized controlled trials.

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Conflict of Interest
None declared.

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