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EVIDENCE-BASED MEDICINE AND THE LIMITS OF RANDOMIZED CONTROLLED TRIALS IN LIGHT OF THE NEW HEALTHCARE STANDARDIZATION SYSTEM IN UKRAINE

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Background. Evidence-Based Medicine (EBM) integrates the best available research evidence with clinical expertise and patient values. In practice, it may be reduced to a hierarchy in which Randomized Controlled Trials (RCTs) are treated as a universal criterion of validity. Order of the Ministry of Health of Ukraine No.845 of June 19, 2026, updated procedures for sectoral standards and adaptation of clinical guidelines, emphasizing evidence applicability to clinical context.

Aim. To clarify the place of randomized controlled trials in the classical and contemporary understanding of evidence-based medicine, systematize situations in which other study designs are required, and determine the relevance of the resulting methodological conclusions to the new healthcare standardization system in Ukraine.

Materials and Methods. The study employed bibliosemantic and comparative methods and systems analysis. Scientific publications available in the PubMed and Google Scholar databases for 2016–2026, selected fundamental publications from earlier years, as well as Order of the Ministry of Health of Ukraine No.845 of June 19, 2026. and the regulatory and methodological documents on the development of sectoral standards approved by this Order were analyzed. The study was conducted as a private initiative of the authors, without grant support or state registration of the research topic. The article outlines ethical considerations for authors of scientific papers regarding the use of EBM tools.

Research Ethics. The study was conducted without the involvement of patients or animals and therefore did not require approval by an ethics committee.

Results. RCTs are the most reliable design for estimating causal effects of many controlled interventions, but their superiority is not universal. Randomization may be ethically unacceptable, difficult in surgery, infeasible in rare diseases, insufficient for detecting rare or delayed harms, and unsuitable for some population-level and policy interventions. In such situations, observational studies, natural experiments, pragmatic trials, and real-world evidence may be informative. Order No.845 provides for selection, appraisal, and adaptation of clinical guidelines with consideration of evidence quality and applicability.

Conclusions. RCTs should be regarded as a powerful but research-question-dependent tool. Evidence appraisal should consider design appropriateness, quality of conduct, and applicability of findings, integrated with clinical expertise and patient values.

Keywords: *epidemiology, public health, research design, causality, clinical decision-making.*

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Introduction

The development of Evidence-Based Medicine (EBM) in the late twentieth century was a response to a fundamental problem in clinical practice: the rapid accumulation of medical information did not guarantee that physicians' decisions were based on the most reliable research findings. In its seminal article, the Evidence-Based Medicine Working Group (1992) [1] proposed a new approach to medical education and practice in which systematic appraisal of clinical research was intended to replace uncritical reliance on authority, tradition, and pathophysiological assumptions. Smith R. & Rennie D. (2014) [2] associate the emergence of the term evidence-based medicine with the research group at McMaster University and Guyatt G.H.

The classical definition formulated by Sackett D.L. et al. (1996) [3] had a fundamentally broader meaning than simply prioritizing a particular type of clinical study. Evidence-based medicine involved integrating the best available external research evidence with the individual clinical expertise of the physician when making decisions about a particular patient. The subsequent development of the concept strengthened the third component of this model – consideration of the patient's values, preferences, expectations, and specific circumstances. Thus, from the outset, evidence-based medicine was a decision-making approach rather than a synonym for a Randomized Controlled Trial (RCT).

For Ukraine, this issue is particularly relevant in the context of the continuing transformation of the healthcare system and the updating of regulatory approaches to the standardization of medical care. A new stage in this process began when Order of the

Ministry of Health of Ukraine No.845 of 19 Jun 2026 "Certain issues concerning the development of sectoral standards in healthcare" entered into force on 14 Aug 2026. The Order approved the Procedure for the development of sectoral standards in healthcare based on evidence-based medicine and the Methodology for the development and implementation of standards of medical and rehabilitation care, clinical protocols, and rehabilitation care protocols. Importantly, the Procedure provides not for the mechanical transfer of provisions from foreign documents but for a process of adapting clinical guidelines [4].

This regulatory update is taking place against the background of the prolonged reform of the Ukrainian healthcare system, which is accompanied by organizational, managerial, workforce, and resource-related challenges [5]. Therefore, the use of international clinical guidelines in domestic practice requires assessment not only of the methodological quality of the evidence base but also of whether the recommendations can be transferred to a particular population, clinical setting, and the resource conditions of Ukraine. This corresponds to one of the fundamental principles of evidence-based medicine: evidence should not be assessed in isolation but with regard to its applicability to a particular clinical decision.

Another issue is the preparation of future physicians for the critical use of evidence. Velychko V.I. et al. (2021) [6] found that 64.5% of the surveyed students were familiar with the principles of evidence-based medicine; however, the authors themselves emphasized that this did not indicate sufficient awareness or readiness to apply these principles in practice. Only 37% of employed students reported

that the institutions where they worked used the principles of evidence-based medicine. These findings support the need for more systematic development of competencies in searching for, critically appraising, and clinically applying evidence [6].

At the same time, the problem is not limited to knowledge of the technical algorithms of evidence-based medicine. Tonelli M.R. & Bluhm R. (2021) [7] drew attention to the insufficient emphasis placed in medical education on medical epistemology, that is, understanding the nature, value, and limitations of different types of medical knowledge. The authors emphasized that the concepts of a "hierarchy of evidence" and "best evidence" are themselves based on particular epistemological assumptions and should also be subject to critical analysis. Therefore, teaching evidence-based medicine solely as memorization of a formal hierarchy of study designs risks fostering an oversimplified view of RCTs as a universal criterion of scientific validity.

A similar problem in clinical practice was described by Greenhalgh T. et al. (2014) [8], who emphasized the need to restore the integration of research evidence with clinical context, professional expertise, and the characteristics of the individual patient in evidence-based medicine. One reason for this concern is the limited external validity of some RCTs. Rothwell P.M. (2005) [9] showed that the extent to which the results of a randomized trial can be transferred to patients in routine clinical practice depends on the characteristics of the included population, treatment setting, endpoints, and clinical environment. Therefore, adapting evidence to the Ukrainian healthcare system cannot be reduced to formally selecting the study design occupying the highest position in the traditional hierarchy.

Modern epidemiology and biostatistics are important methodological tools of evidence-based medicine. RCTs are characterized as the "gold standard" for evaluating intervention effects [10, p. 197–211], because randomization promotes comparability between study groups and reduces systematic bias. At the same time, a fundamentally important principle

is formulated within the same methodological context: there is no universally superior study design; different research questions require different designs, each of which has strengths and weaknesses, and the quality of study conduct cannot be replaced by its formally high position in the evidence hierarchy [10, p. 180–211].

The problem is directly related to research integrity. Shevchenko A.S. & Brown G.W. (2020) [11] considered evidence-based medicine to be one of the mechanisms for counteracting falsification in science, emphasizing the need for critical analysis of scientific information and verification of the reliability of evidence. However, the formal placement of a study at a high level of the hierarchy cannot in itself protect against methodological error, selective reporting of results, insufficient reproducibility, or inappropriate extrapolation of conclusions. Thus, counteracting unreliable scientific claims requires evaluation not only of the name of the study design but of the entire chain through which evidence is generated.

Wallace S.S. et al. (2022) [12] described the traditional hierarchy of study designs, in which preclinical studies, expert opinion, case reports, and analytical observational studies are followed by RCTs, with systematic reviews and meta-analyses placed at the top. At the same time, the authors explicitly emphasized that a design's position in the hierarchy should be considered together with the limitations of the individual study through careful critical appraisal.

Balshem H. et al. (2011) [13], in the GRADE guidelines, defined four levels of quality of a body of evidence – high, moderate, low, and very low. RCT evidence initially starts at a high level, but certainty may be downgraded because of risk of bias, imprecision, inconsistency, indirectness, and publication bias. Kostis J.B. & Dobrzynski J.M. (2020) [14] systematized 11 groups of RCT limitations, including low external validity, lack of representativeness of participants for the general population, the relatively short duration of many trials – 3–5 years – and difficulties in applying average RCT results to an individual patient.

Thus, there is a methodological tension between the justified recognition of randomized controlled trials as the most reliable way to estimate the causal effects of many controlled interventions and their simplified interpretation as a universal criterion of scientific evidence. Resolving this tension requires defining the limits of randomized designs and the roles of other sources of evidence.

The aim of the study was to clarify the place of randomized controlled trials in the classical and contemporary understanding of evidence-based medicine and to systematize clinical, ethical, and methodological situations in which other study designs are required to obtain reliable scientific evidence.

Materials and Methods

The study employed bibliosemantic and comparative methods and systems analysis. Scientific publications available in the PubMed and Google Scholar databases for 2016–2026 were analyzed, together with selected fundamental publications from earlier years required to examine the development of the concept of evidence-based medicine.

The search was conducted using the following keywords: evidence-based medicine, randomized controlled trial, hierarchy of evidence, research design, observational studies, limitations of randomized trials, natural experiments, real-world evidence, target trial emulation, sectoral standards in healthcare, clinical guidelines.

The bibliosemantic method was used to identify and synthesize statements concerning the evidentiary value of different medical research designs; the comparative method was used to compare their capabilities and limitations; systems analysis was used to determine the relationships among the nature of the research question, ethical acceptability, methodological appropriateness of the design, and applicability of the resulting evidence.

Order of the Ministry of Health of Ukraine No.845 of June 19, 2026 "Certain issues concerning the development of sectoral standards in healthcare", the Procedure for the development of sectoral standards in healthcare based on evidence-based medicine approved by this Order, and the Methodology

for the development and implementation of standards of medical and rehabilitation care, clinical protocols, and rehabilitation care protocols were analyzed separately [4]. The analysis addressed provisions concerning the adaptation of clinical guidelines, criteria for their selection and quality appraisal, and requirements for the development of standards and clinical protocols. These regulatory approaches were compared with international methodological models for evidence appraisal discussed in the analyzed literature, including GRADE, natural and pragmatic experiments, real-world evidence, and target trial emulation.

The study was conducted as a private initiative of the authors, without grant support or state registration of the research topic.

Research Ethics

The study was conducted without the involvement of patients or animals and therefore did not require approval by an ethics committee.

Results

The place of randomized trials in evidence-based medicine

Wallace S.S. et al. (2022) [12] placed RCTs at the highest level of primary studies in the traditional evidence hierarchy but cautioned that the formal level of a design does not replace critical appraisal of the limitations of the individual study. Balshem H. et al. (2011) [13] showed within the GRADE system that even a body of randomized studies may lose its initially high level of certainty because of risk of bias, imprecision, inconsistency, indirectness, and publication bias. Kostis J.B. & Dobrzynski J.M. (2020) [14] further demonstrated that the limitations of RCTs extend beyond statistical errors to external validity, duration of follow-up, sample representativeness, and applicability of results to an individual patient.

Concato J. et al. (2000) [15] compared 99 publications across five clinical topics and found that average effect estimates from well-designed cohort and case-control studies were similar to those from RCTs and did not show systematic overestimation of treatment effects. Benson K. & Hartz A.J. (2000) [16]

analyzed 136 publications concerning 19 different therapeutic interventions; in only 2 of the 19 comparisons did the pooled effect estimate from observational studies fall outside the 95% confidence interval of the pooled RCT estimate.

Borgerson K. (2009) [17] analyzed two common justifications for the traditional evidence hierarchy – the purported special ability of higher-ranked designs to establish causality and their lower susceptibility to bias – and concluded that these arguments alone are insufficient to provide an epistemological justification for a rigid hierarchy. This supports the need to evaluate not only the name of the design but also how it is implemented and the nature of the research question.

The new regulatory framework for standardizing medical care in Ukraine likewise provides no grounds for equating evidence quality solely with the formal type of primary study. Order of the Ministry of Health of Ukraine No.845 provides for the development of standards based on clinical guidelines, establishes a procedure for their adaptation, and sets requirements for selecting guidelines that comply with the principles of evidence-based medicine and have received a high rating using the AGREE instrument [4]. Thus, the regulatory model provides for prior appraisal of the quality and applicability of the synthesized evidence base rather than direct ranking of individual publications solely according to the label of their study design.

This approach is consistent with the GRADE system, in which a body of RCT evidence may initially have high certainty, but that certainty can be downgraded because of risk of bias, inconsistency, indirectness, imprecision, or publication bias [13]. The limitations of RCTs systematized by Kostis J.B. & Dobrzynski J.M. (2020) [14] further demonstrate that the high formal status of a design does not guarantee sample representativeness, adequate duration of follow-up, or applicability of an average result to an individual patient. Therefore, when adapting evidence to the Ukrainian context, not only the type of study but also the quality of its conduct, the

directness of the evidence, and the transferability of the results to the target clinical population are essential.

Ethical limits of randomization

The most obvious limit of a randomized experiment arises when assignment to the exposure under investigation would itself create foreseeable substantial harm. It is not ethically possible to randomize people to begin smoking, prolonged exposure to a carcinogen, a toxic occupational exposure, a dangerous dose of ionizing radiation, or another deliberately harmful exposure solely to demonstrate a causal relationship. Establishing such relationships necessarily relies on cohort studies, case-control studies, natural experiments, registry data, assessment of dose-response relationships, and convergence of epidemiological and biological evidence.

The World Medical Association (2025) [18], in the current version of the Declaration of Helsinki, states that a new intervention should, as a general rule, be compared with the best proven intervention. Placebo or no intervention is acceptable when no proven intervention exists or when compelling and scientifically sound methodological reasons justify its use, provided that participants are not exposed to additional risks of serious or irreversible harm. Thus, the absence of a placebo-controlled RCT when effective treatment already exists may result from ethical constraints rather than from an insufficient evidence base.

This has an important consequence for the interpretation of evidence. The absence of a randomized study may sometimes reflect not a lack of scientific work but the inadmissibility of the experiment itself. Therefore, requiring an RCT in such circumstances would replace the principle of evidence-based practice with a formal requirement that conflicts with the ethics of medical research.

The "parachute" paradox and the limits of the formal hierarchy

A classic illustration of this problem is the systematic review by Smith G.C.S. & Pell J.P. (2003) [19] on parachute use for preventing death and major trauma associated with gravitational challenge. The authors found no randomized trials of parachutes

and satirically demonstrated the absurdity of requiring an RCT as a necessary condition for accepting any obvious causal effect.

Yeh R.W. et al. (2018) [20] effectively continued this methodological experiment by conducting a randomized controlled trial of parachutes. The study included 23 participants who jumped from stationary aircraft on the ground; the mean height was approximately 0.6 m. There were no deaths or major injuries in either group. Randomization was formally performed, but the resulting answer did not apply to the conditions in which a parachute is actually intended to be used.

This example demonstrates the fundamental distinction between internal validity and applicability of results. Even a procedurally correct randomized study does not answer a clinical question if the study population, exposure, or conditions differ substantially from those to which the conclusion is intended to apply. Therefore, a design's place in the hierarchy cannot compensate for a mismatch between the research question and the experiment actually conducted.

Surgical interventions

Gaudino M. et al. (2022) [21], in a methodological analysis of randomized trials in cardiac and thoracic surgery, identified specific difficulties associated with this design: the impossibility of fully blinding the operator, dependence of outcomes on the surgeon's experience and learning curve, and difficulty in determining the point at which a new surgical technology can be sufficiently standardized for a valid comparison.

Robinson N.B. et al. (2021) [22] analyzed 388 surgical RCTs published between 2008 and 2020 in a systematic review. Surgeon experience was not controlled in 303 (78.1%) studies, and the quality of intervention delivery was assessed in only 17 (4.4%); 211 (54.4%) studies had some concerns regarding risk of bias, and 91 (23.5%) had a high risk of bias. These findings demonstrate that randomization alone does not eliminate sources of variability and bias that are specific to surgery.

The issue of placebo control is particularly complex in surgical research. Hetzler P.T. 3rd et al. (2023) [23], in a systematic review

of 172 randomized sham-controlled trials, found that simultaneous blinding of participants, personnel, and outcome assessors was achieved in only 15 (8.7%) studies; 36 (20.9%) involved open surgical access, and 49 (28.5%) involved general anesthesia. The authors separately identified challenges related to informed consent and risks inherent in the sham intervention itself.

Rare diseases and small populations

Kempf L. et al. (2018) [24] identified the small size of the available population, limited knowledge of the natural history of disease, difficulty determining the frequency and variability of clinically meaningful events, geographic dispersion of patients, and the high proportion of children among them as major challenges in clinical trials of rare diseases. The authors emphasized that standard designs are not optimized to obtain sufficient information on efficacy and safety in small populations and proposed considering enriched populations, crossover, adaptive, and N-of-1 designs.

Li Y. & Izem R. (2022) [25] additionally highlighted difficulties in achieving adequate statistical power and recruiting participants in small and heterogeneous populations, the lack of natural-history data for selecting endpoints and follow-up duration, and ethical and recruitment problems associated with randomization to placebo. The authors discussed the use of natural-history data, tailored endpoint selection, and novel design and analytical strategies to make more efficient use of limited data.

The problem is not that randomization loses its methodological value. Rather, requiring a traditional large parallel-group RCT may make the generation of evidence practically impossible. Evidence-based medicine must therefore balance the control of bias against the actual characteristics of the population being studied.

Páez A. et al. (2022) [26] developed a sequential algorithm for evaluating new therapeutic devices. The authors considered RCTs necessary primarily for genuinely novel devices for which a measurable therapeutic advantage over existing treatment

is claimed; where no such basis exists, an IDEAL stage 2b study was proposed as the basic stage of clinical evaluation, followed by observational and registry-based approaches for detecting signals of harm.

Rare, delayed, and unexpected harms

Randomized studies are designed primarily to evaluate prespecified effects in samples of limited size over a defined follow-up period. These very characteristics limit their ability to detect very rare, delayed, or unexpected adverse effects.

Sawchik J. et al. (2018) [27] explicitly stated that RCTs are not the design of choice for detecting rare, delayed, or unexpected effects related to drug safety. The authors also noted that strict inclusion criteria produce homogeneous samples that do not allow the safety profile of a drug to be fully characterized; observational studies therefore have important complementary value for assessing the benefit-risk balance.

Phillips R. et al. (2019) [28] analyzed 184 reports of RCTs of drug interventions published in four leading medical journals. Spontaneous collection of adverse events was described in 62% of the reports, but specific prompts for their detection were provided in only 29%; recurrent events were ignored in 84% of the studies, and 47% performed formal testing of binary adverse events despite insufficient statistical power. Hong H. et al. (2021) [29] showed that an individual RCT often includes too few participants to detect a rare but serious adverse event and compared Bayesian and frequentist methods for meta-analysis of such events, including situations with sparse events and zero cells.

Population-level, social, and policy interventions

One of the most fundamental limitations of the traditional RCT model concerns public health. Many determinants of health operate not at the level of an individual patient but at the level of the family, community, city, health-care system, or state. These include legislative changes, tax policy, transport infrastructure, urban planning, environmental policy, social protection, reorganization of healthcare delivery, and other system-level interventions.

Ogilvie D. et al. (2020) [30] showed that population-level and system-level interventions are often implemented as natural experiments and are therefore more complex and less predictable to evaluate than a typical RCT. The authors proposed not merely "tolerating" non-randomized designs but using them as a legitimate source of practice-oriented evidence when the aim is to reduce critical uncertainty about real-world policy rather than merely to obtain an unbiased average effect estimate.

Crane M. et al. (2020) [31] analyzed 46 natural-experiment studies in obesity prevention conducted between 1997 and 2017: 19 evaluated policy interventions, including food labeling, advertising, and taxation, and 17 evaluated changes to the built environment. The authors noted that only a small number of studies used stronger quasi-experimental approaches, such as repeated measurements before and after an intervention, time-series analyses, or comparisons of changes with an unexposed group. Craig P. et al. (2025) [32, p. 17–18, 22–24], in the new MRC/NIHR framework, justified the use of a systems perspective, mixed methods, and stakeholder involvement and emphasized that there is no single best method or simple hierarchy of stronger and weaker designs for natural experiments.

Thus, requiring an RCT as the only form of convincing evidence in public health may have a paradoxical consequence: the largest-scale determinants of health may receive a lower formal level of evidence precisely because they cannot be converted into individually randomized, laboratory-controlled interventions.

External validity and representativeness

Kostis J.B. & Dobrzynski J.M. (2020) [14] identified as limitations of RCTs the participation of relatively healthier individuals with a particular disease who may not represent the full clinical population, as well as the typical duration of many trials of 3–5 years, which may be insufficient to evaluate lifelong or delayed effects. Sawchik J. et al. (2018) [27] separately linked the limited representativeness of safety data to strict inclusion criteria that produce overly homogeneous study populations.

Zuidgeest M.G.P. et al. (2017) [33] defined pragmatic trials as a means of filling the evidence gap concerning the comparative effectiveness of treatment strategies in routine clinical practice while retaining the strength of randomization. The authors emphasized that the choice of real-world clinical setting, population, mode of intervention delivery, comparator, and endpoints is crucial for this design.

Bilinski A. et al. (2025) [34] used analytical modeling to evaluate the consequences of excluding pregnant participants from RCTs using thalidomide, COVID-19 vaccines, and dolutegravir as examples. According to their model, an RCT of thalidomide involving 200 pregnant participants receiving the drug might have caused approximately 33 severe adverse outcomes in children, but the knowledge obtained could potentially have prevented approximately 8,000 congenital anomalies, or 99.6% of thalidomide-associated birth defects in 1956–1962. For COVID-19 vaccination, the model suggested that including pregnant participants in trials might have prevented approximately 20% of COVID-19-related maternal deaths and stillbirths in the United States between March and November 2021.

When randomization may be unnecessary

A distinct situation arises not when conducting an RCT is impossible, but when the additional informational value of randomization may be disproportionate to its ethical or practical costs. This primarily concerns very large and immediate effects in circumstances where the natural course of the condition is well known, an alternative explanation is unlikely, and delaying access to an intervention for the sake of a formal experiment may be unacceptable.

Djulbegovic B. et al. (2021) [35] analyzed 134 regulatory approvals of drugs and medical devices based on non-randomized comparisons and applied signal detection theory to FDA and EMA decisions. The authors found that a difference of approximately one order of magnitude between a new treatment and a historical control may serve as a guide for deciding whether a subsequent RCT is necessary, while explicitly noting the need

for further refinement of the effect-size threshold above which randomized verification may be unnecessary.

Target trial emulation

Terman S.W. et al. (2025) [36] described target trial emulation as an approach in which, before analyzing observational data, investigators specify the protocol of an ideal RCT – eligibility criteria, interventions, treatment assignment, start and duration of follow-up, endpoints, and analysis plan – and attempt to reproduce these elements using the available data. The authors emphasized that this approach helps formulate the causal question more precisely and avoid some time-related and selection biases but does not eliminate measurement error or residual confounding.

This approach does not transform an observational study into a randomized one and does not eliminate residual confounding, measurement error, or problems with the quality of real-world data. Its advantage lies elsewhere: specifying the target trial forces the researcher to define the causal question explicitly and may prevent a number of common design errors in observational research.

Cashin A.G. et al. (2025) [37] developed the TARGET Statement – consensus recommendations for reporting observational studies that estimate causal effects by explicitly emulating a target trial. The recommendations were developed using the EQUATOR approach to standardize reporting of the hypothetical trial protocol, the way it was emulated, and the analytical decisions required to assess the risk of bias.

Discussion of Results

The present analysis shows that the apparent contradiction between recognizing RCTs as the "gold standard" and stating that there is no universally superior design is only superficial. The first statement applies to a particular class of questions – the comparative causal effect of controlled medical interventions. The second applies to the entire range of questions addressed by medicine, epidemiology, and public health. If these levels are not distinguished, the

methodological advantage of randomization is transformed into an inappropriate universal rule.

Sawchik J. et al. (2018) [27] explicitly classified rare, delayed, and unexpected adverse drug effects among the safety questions for which RCTs are not the design of choice. Phillips R. et al. (2019) [28], after analyzing 184 RCT reports, found substantial heterogeneity in the collection and analysis of adverse events: recurrent events were ignored in 84% of studies, and 47% used formal testing of binary adverse events despite insufficient statistical power. Hong H. et al. (2021) [29] separately demonstrated that an individual RCT is often too small to detect rare serious harm, meaning that its quantitative assessment requires specialized methods for meta-analysis of rare events. Ogilvie D. et al. (2020) [30] justified natural experiments as an independent source of evidence for population-level and system-level interventions. Crane M. et al. (2020) [31] supported this using 46 obesity-prevention studies, most of which evaluated policies and changes to the built environment. Craig P. et al. (2025) [32, p. 17–18, 22–24], in the new MRC/NIHR framework, systematized study design, the systems perspective, mixed methods, and approaches to causal analysis in such natural experiments.

Therefore, a universal linear hierarchy of evidence should be replaced by at least two sequential questions. First, it is necessary to determine which type of design is capable of answering the particular research question. Second, the quality with which that design has been implemented must be assessed. A high formal rank cannot compensate for an inappropriate population, unsuitable comparator, non-representative endpoint, inadequate follow-up, or high risk of bias.

The methodological limitations of surgical RCTs identified in this study are consistent with the analysis by Gaudino M. et al. (2022) [21], who highlighted the impossibility of fully blinding the operator, the learning curve, and the dependence of outcomes on the surgeon's experience. Robinson N.B. et al. (2021) [22] quantified the scale of these

problems: surgeon experience was not controlled in 303 of 388 (78.1%) surgical RCTs, while intervention quality was not assessed in 371 (95.6%). Hetzler P.T. 3rd et al. (2023) [23] demonstrated another aspect: among 172 sham-controlled surgical RCTs, complete simultaneous blinding of participants, personnel, and outcome assessors was achieved in only 15 (8.7%), while the sham procedures themselves could involve invasive access and anesthesia.

Kempf L. et al. (2018) [24] linked the difficulties of RCTs in rare diseases to small and geographically dispersed patient populations, insufficient knowledge of the natural history of disease, and challenges in achieving adequate statistical properties; as alternatives to a standard parallel-group design, they considered enriched, crossover, adaptive, and N-of-1 designs. Li Y. & Izem R. (2022) [25] supplemented this list with a lack of natural-history data for selecting endpoints and follow-up duration, heterogeneity of small populations, and ethical and recruitment difficulties associated with placebo control, supporting specialized design and analytical strategies for more efficient use of limited information.

Of particular importance is the distinction between absence of evidence and evidence of absence. If a particular question has not been studied in an RCT because randomization was ethically or practically impossible, this does not automatically mean that no causal relationship exists. However, the opposite extreme is equally problematic: the inability to conduct an RCT does not automatically confer validity on any observational result. Such data require control of confounding, assessment of alternative explanations, sensitivity analyses, replication in independent data sources, and, where possible, triangulation across different methods.

In this context, evidence-based medicine can counter scientific falsification not through mechanical ranking of publications but through methodological transparency, reproducibility, critical appraisal, and comparison of independent sources of evidence [11]. The randomized status of a study should not

function as a quality label that relieves the reader of the need to examine its methods.

Stavytskyi V.V. (2026) [38] critically described the transformation of EBM from a methodological tool into a dogmatic system and associated this transformation with the absolutization of RCTs and a rigid evidence hierarchy. In another publication, Stavytskyi V.V. (2026) [39] reconstructed the development of EBM at McMaster University and contrasted the approach of Sackett D.L., centered on combining evidence with clinical judgment, with a more standardized interpretation that the author associates with Guyatt G.H. Both publications are discursive in nature; their relevance to the present study lies in documenting the contemporary Ukrainian debate on the limits of a formalized evidence hierarchy.

The contemporary Ukrainian discussion concerning the limits of a formalized evidence hierarchy has acquired additional practical relevance since Order of the Ministry of Health of Ukraine No.845 entered into force. At the same time, the content of this regulatory act should not be interpreted as a formal rejection of the evidence hierarchy or as direct regulatory recognition of all non-randomized designs as equivalent to RCTs. The Order establishes something different: sectoral standards are to be developed according to the principles of evidence-based medicine and on the basis of high-quality clinical guidelines subjected to procedures for selection, appraisal, and adaptation to the Ukrainian healthcare system [4].

It is precisely the need for adaptation that makes the external validity of evidence fundamentally important. Rothwell P.M. (2005) [9] showed that the results of even a methodologically sound RCT may have limited applicability to patients who differ substantially from the study population. Greenhalgh T. et al. (2014) [8] likewise emphasized that evidence-based medicine should integrate scientific evidence with clinical context, professional judgment, and the individual needs of the patient. For the Ukrainian standardization system, this means that adaptation of an international guideline

should include critical appraisal not only of the level of evidence but also of its directness and applicability to the specific conditions in which medical care is provided.

In contrast, the classical concept of Sackett D.L. et al. (1996) [3] remains relevant precisely because it requires integration of different components of a decision. External evidence should be the best available for the particular question, clinical expertise is required to assess its applicability, and patient values and preferences determine whether the decision is acceptable for the individual. None of these components can be completely replaced by another.

At the same time, the contemporary methodological toolkit of evidence-based medicine extends beyond the classical explanatory RCT. Ogilvie D. et al. (2020) [30] proposed a practice-based evidence pathway for public health in which natural experiments are used to evaluate real-world policies and reduce critical uncertainty. Zuidgeest M.G.P. et al. (2017) [33] showed that pragmatic trials can assess comparative effectiveness in routine clinical practice while retaining the advantages of randomization. Terman S.W. et al. (2025) [36] substantiated target trial emulation as a way of bringing causal analysis of observational data closer to the logic of a hypothetical RCT, while Cashin A.G. et al. (2025) [37] standardized the reporting of such studies in the TARGET Statement. These approaches do not negate the advantages of randomization; rather, they broaden the methodological toolkit for questions for which a classical RCT is inappropriate, insufficient, or practically infeasible.

Therefore, the model proposed in this study – "question – appropriate design – quality of conduct – body of evidence – applicability" – should be regarded as the authors' methodological synthesis of the results of the analysis rather than as a provision of Order of the Ministry of Health of Ukraine No.845. The new regulatory framework creates a practical need for high-quality selection and adaptation of evidence, whereas the choice of an appropriate design for a particular research

question is supported by the broader contemporary methodological literature.

Thus, the model "question – appropriate design – quality of conduct – body of evidence – applicability" is more appropriate than a universal evidence pyramid. Within this model, randomized research retains a leading role where randomization matches the research question and is ethically and practically feasible. In other situations, evidence should be provided by the strongest available appropriate design, and the uncertainty associated with such evidence should be explicitly reflected in its interpretation.

Conclusions

Randomized controlled trials retain a leading role in establishing the causal effects of many controlled therapeutic and preventive interventions but are not a universal criterion of scientific evidence. Their advantage lies in the ability of randomization to reduce confounding and selection bias, but randomization does not eliminate errors in design, conduct, analysis, reporting, or transfer of results to other populations.

There are research situations in which a classical randomized controlled trial is ethically unacceptable, practically infeasible, or methodologically insufficient. These include studies of knowingly harmful exposures, some comparisons when proven effective treatment already exists, certain surgical and procedural interventions, rare diseases, detection of very rare or delayed harms, and a substantial proportion of population-level, social, environmental, and policy exposures or interventions.

Evidence appraisal should begin not with the formal position of a publication in a universal hierarchy but with the appropriateness of the study design for the research question. Risk of bias, precision, directness, consistency, external validity, ethical acceptability, and reproducibility of the findings should then be assessed.

The methodological tension between the high evidentiary value of randomized controlled trials and the impossibility of their universal application can be resolved by the principle of matching the design to the

nature of the research question. The classical meaning of evidence-based medicine is consistent not with the absolutization of a single design but with the use of the best available, methodologically rigorous, and ethically acceptable evidence, followed by its integration with clinical expertise and patient values.

For the Ukrainian healthcare system, the practical significance of these findings lies in the need to combine the requirements of the new standardization system introduced by Order of the Ministry of Health of Ukraine No.845 with critical appraisal of the quality, directness, and applicability of the evidence base. The principle proposed in this study of matching study design to the nature of the research question may serve as a methodological guide when interpreting evidence, although it is not a separate regulatory requirement of Order No.845. For medical science and practice in Ukraine, it is appropriate to move away from the absolutization of a single design toward the use of the best available, methodologically rigorous, and ethically acceptable evidence, followed by assessment of its applicability and integration with the physician's clinical expertise and patient values.

Prospects for Further Research

Further work should focus on developing practical criteria for selecting a study design according to the type of clinical or medico-social research question and on adapting such criteria for editorial and peer-review assessment of medical publications. The role of real-world evidence, natural experiments, and target trial emulation in contemporary evidence appraisal systems requires separate analysis.

Declarations

The authors declare no conflicts of interest.

All authors consented to publication of the article under the terms of the Creative Commons BY-NC-SA 4.0 license and the public agreement with Kharkiv National Medical University as the founder and publisher of the journal, and to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing,

and editing this manuscript, no generative AI tools or services were used to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of

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Contribution	A	B	C	D	E	F
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Notes:

A – concept;

B – design;

C – data collection;

D – statistical processing and interpretation of data;

E – writing or critical revision of the article;

F – approval of the final version for publication and agreement to be accountable for all aspects of the work.

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ДОКАЗОВА МЕДИЦИНА ТА МЕЖІ РАНДОМІЗОВАНИХ КОНТРОЛЬОВАНИХ ДОСЛІДЖЕНЬ У СВІТЛІ НОВОЇ СИСТЕМИ СТАНДАРТИЗАЦІЇ ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ

Актуальність. Доказова медицина (ДМ) інтегрує найкращі доступні наукові докази з клінічним досвідом лікаря та цінностями пацієнта. Проте на практиці її іноді спрощують до жорсткої ієрархії, у якій рандомізовані контрольовані дослідження (РКД) розглядають як універсальний критерій наукової достовірності. Наказ Міністерства охорони здоров'я (МОЗ) України № 845 від 19.06.2026 оновив порядок розробки галузевих стандартів на засадах ДМ та адаптації клінічних настанов, що актуалізує оцінку застосовності доказів до конкретного клінічного контексту.

Мета. Уточнити місце рандомізованих контрольованих досліджень у класичному та сучасному розумінні доказової медицини, систематизувати ситуації, у яких необхідні інші дизайни, та визначити значення отриманих методологічних висновків для нової системи стандартизації охорони здоров'я України.

Матеріали та методи. Дослідження виконано з використанням бібліосемантичного та порівняльного методів, системного аналізу. Проаналізовано наукові публікації, представлені в базах даних PubMed та Google Scholar за 2016–2026 рр., окремі фундаментальні праці попередніх років, а також Наказ МОЗ України від 19.06.2026 № 845 і затверджені ним нормативно-методичні документи щодо розробки галузевих стандартів. Дослідження проведено як приватна ініціатива авторів, без грантової підтримки та державної реєстрації теми. Стаття містить етичні застереження для авторів наукових статей щодо використання інструментів ДМ.

Етика дослідження. Дослідження проведено без залучення пацієнтів та тварин, тому не потребувало згоди етичної комісії.

Результати. РКД є найнадійнішим дизайном для оцінювання причинного ефекту багатьох контрольованих втручань, але їхня перевага не є універсальною. Рандомізація може бути етично неприйнятною, складною в хірургії, нездійсненною при рідкісних хворобах, недостатньою для виявлення рідкісної або відстроченої шкоди та непридатною для частини популяційних і політичних втручань. У таких ситуаціях доказову цінність можуть мати спостережні дослідження, природні експерименти, прагматичні випробування та дані реальної клінічної практики. Наказ МОЗ № 845 передбачає відбір, оцінювання та адаптацію клінічних настанов з урахуванням якості й застосовності доказів.

Висновки. РКД слід розглядати як потужний, але залежний від дослідницького питання інструмент. Оцінювання доказів має враховувати відповідність дизайну питанню, якість виконання та застосовність результатів із подальшою інтеграцією з клінічним досвідом і цінностями пацієнта.

Ключові слова: епідеміологія, громадське здоров'я, дизайн дослідження, причинність, прийняття клінічних рішень.

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