WHERE SCIENCE MEETS CONVICTION

Designing Nutraceutical Clinical Trials for EFSA Success

From Statistical Significance to Regulatory-Grade Evidence

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Editorial note: “Nutraceutical” is used as a sectoral umbrella term. It is not a harmonised legal category under EU food law. A favourable EFSA scientific opinion does not itself constitute authorisation of a health claim.

ABSTRACT

The European nutraceutical sector has become increasingly sophisticated in product formulation, ingredient standardisation, delivery technology and mechanistic research. Yet clinical substantiation frequently remains its weakest link. A technically attractive ingredient, a biologically plausible mechanism or even a statistically significant randomised controlled trial does not necessarily constitute evidence capable of substantiating a health claim under the European Food Safety Authority (EFSA) framework. The central problem is often not lack of science, but misalignment between the scientific question asked by the trial and the regulatory question that the evidence must answer.

EFSA's assessment of health claims is fundamentally relationship-based. The relevant unit of evaluation is not simply an ingredient, a biomarker or a clinical trial, but a defined relationship between a sufficiently characterised food or constituent and a clearly defined beneficial physiological effect in a specified target population under proposed conditions of use. Establishing that relationship requires more than obtaining a p value below 0.05. It requires methodological coherence, credible causal inference, appropriate endpoints, suitable participants, adequate exposure, transparent statistical planning, consideration of the totality of evidence and biological plausibility.

This article proposes a claim-first framework for nutraceutical clinical development, integrating current EFSA health-claim requirements with contemporary principles of randomised-trial methodology, SPIRIT 2025, CONSORT 2025 and estimand-based statistical thinking. It introduces several author-proposed regulatory-development tools, including the Claim–Evidence Alignment Matrix (CEAM), the Regulatory Evidence Chain, the Evidence Failure Mode and Effects Analysis (eFMEA) and the EFSA Pre-Mortem Review. The central proposition is simple: a successful nutraceutical clinical programme should not be engineered to make a product look effective; it should be engineered so that, whatever the result, the experiment gives a scientifically credible answer to a precisely formulated regulatory question.

Keywords: EFSA; nutraceuticals; food supplements; health claims; clinical trials; randomised controlled trials; regulatory science; causal inference; biomarkers; evidence generation; Regulation (EC) No 1924/2006.

CORE PRINCIPLE | EFSA success must mean evidentiary resilience, not outcome engineering.

The correct objective is not to design a trial that becomes "positive". It is to design a trial whose result—positive, null or negative—can be trusted because the regulatory question, methods and analysis were specified coherently in advance.

Terminological and regulatory scope

Throughout this article, "nutraceutical" is used as a practical sectoral term covering food supplements, foods or food constituents developed with a health-related positioning. It should not be interpreted as a distinct harmonised legal class in EU law. Likewise, the phrase "EFSA success" refers to scientific substantiation robust enough to support a favourable scientific assessment; authorisation of health claims remains a separate EU regulatory decision under Regulation (EC) No 1924/2006.

1. The Wrong Question: "How Do We Get a Positive Trial?"

A surprisingly large proportion of nutraceutical clinical development begins with a commercially understandable but scientifically dangerous question: how can we demonstrate that our ingredient works? That question should be replaced by a falsifiable one: what precise food–health relationship are we claiming, and what experiment could validly test whether that relationship exists?

Under Regulation (EC) No 1924/2006, health claims made on foods must be scientifically substantiated and may not be false, ambiguous or misleading. EFSA performs the scientific substantiation assessment, while authorisation remains within the EU decision-making procedure. Current EFSA guidance structures assessment around three foundational questions: whether the food or constituent is sufficiently defined and characterised; whether the claimed effect is a defined beneficial physiological effect measurable in vivo in humans, except claims based on nutrient essentiality; and whether a cause-and-effect relationship is

established between consumption and the claimed effect under the proposed conditions of use (EFSA NDA Panel, 2021a, 2021b).

This immediately changes the role of the clinical trial. A well-executed RCT cannot rescue an inadequately characterised ingredient, a non-beneficial claimed effect, an endpoint that does not measure the intended function, a population disconnected from the target population, or an intervention that cannot be bridged to the product and conditions of use ultimately proposed. Clinical development therefore begins before protocol writing. It begins with claim engineering.

2. Claim-First Development

Drug development commonly works from a Target Product Profile. Nutraceutical regulatory development benefits from an analogous planning device: a Claim Target Profile (CTP). The CTP is an author-proposed tool, not an official EFSA document. Its role is to force every pivotal design decision to point back to the exact claim being pursued.

The distinction between "supports cognitive health", "supports memory", "improves episodic memory" and "reduces age-associated decline in episodic memory" is not semantic decoration. These propositions imply different populations, outcome instruments, time horizons, statistical models and regulatory meanings. The claim therefore determines the experiment; the experiment should not be mined after the fact to discover the claim.

CTP dimension	Regulatory design question
Food / constituent	Exactly what material is the intended claim about?
Characterisation	Which chemical, botanical, microbiological or technological attributes define it?
Claimed effect	Exactly what beneficial physiological effect is proposed?
Target population	In whom is the effect claimed?
Conditions of use	Dose, frequency, matrix, timing and duration?
Primary outcome	What human measurement directly represents the claimed effect?
Meaningful effect	What magnitude would be physiologically relevant?
Mechanistic support	Is the proposed causal pathway biologically plausible in humans?
Commercial translation	Can the tested conditions realistically become the proposed conditions of use?

3. The Regulatory Evidence Chain

For nutraceuticals, causal evidence can be visualised as a chain: Identity → Exposure → Biological availability → Target engagement → Physiological response → Reproducibility → Claim. Each link poses a different scientific question, and weakness in one critical link may collapse the persuasive value of the entire package.

Identity requires that the tested material correspond to the material for which the claim is intended. Depending on the intervention, this may require definition of species, strain, cultivar, plant part, extraction

process, solvent, molecular composition, marker compounds, microbial viability, molecular-weight distribution, degree of polymerisation, purity, contaminants, stability and batch variability.

Exposure asks what participants actually received. Nominal dose is not equivalent to exposure when adherence, matrix effects, storage, dosing schedule, interaction with meals, concomitant supplements or medication may materially alter what reaches the organism.

Biological availability and target engagement can strengthen plausibility, but mechanistic changes are not automatically the claimed benefit. A biomarker may explain how an intervention acts without proving the beneficial physiological effect that the claim asserts. Mechanistic biomarkers explain; appropriately selected human outcome variables substantiate.

Reproducibility and totality of evidence complete the chain. One favourable experiment is evidence, not automatically a body of evidence. EFSA expects the totality of available pertinent evidence to be considered, including studies that show benefit, no effect or opposing effects.

4. Methodological Honesty as a Regulatory Asset

Methodological honesty is often framed as an ethical constraint on commercially sponsored research. It is also a regulatory optimisation strategy. Credibility increases when the sponsor prospectively commits to a clear primary objective, justified primary outcome, predefined analysis, handling of missing data, analysis populations, subgroup logic, multiplicity procedures, amendment governance and complete reporting.

This architecture restricts researcher degrees of freedom. That restriction is precisely the point. The evaluator must be able to distinguish what was hypothesised before observing the data from what was discovered after observing them. Exploratory analysis is legitimate. Presenting exploration as confirmation is not.

5. The Statistical-Significance Fallacy

One of the most persistent errors in commercial nutrition research is to equate $p < 0.05$ with claim substantiation. A statistically significant result does not by itself establish that the endpoint was prospectively designated, physiologically relevant, protected against multiplicity, robust to missing data, free from material bias, reproducible, applicable to the target population or coherent with the totality of evidence.

Scientific interpretation should focus on estimated effect size, uncertainty, physiological relevance, robustness, sensitivity to assumptions, consistency and evidentiary context. Statistical significance is one component of inference, not a regulatory verdict.

6. Primary Endpoints: One of the Most Expensive Decisions in the Trial

Endpoint selection should occur before sample-size calculation, randomisation and recruitment—and ideally before commercial teams harden the claim wording. The correct sequence is: beneficial physiological effect → measurement construct → validated outcome variable → statistical estimand → sample size.

An endpoint suitable for an academic publication is not automatically suitable for health-claim substantiation. Outcome variables should be assessed for construct validity, analytical validity, biological relevance, temporal relevance and regulatory relevance. EFSA domain-specific guidance repeatedly illustrates that appropriate outcome variables, measurement methods, study groups, duration and controls are central to the assessment of claim-specific evidence.

7. Biomarkers: Powerful Evidence, Dangerous Shortcuts

Contemporary nutraceutical research can quantify thousands of metabolites, microbial genes, inflammatory proteins, transcriptomic changes, lipidomic signatures, digital sleep parameters and behavioural signals. This creates enormous explanatory power—and enormous multiple-testing risk.

Omics platforms are particularly valuable for mechanism discovery, responder phenotyping, pathway mapping and hypothesis generation. They become dangerous when the trial is effectively converted into a fishing expedition followed by selective storytelling. A pivotal confirmatory question should remain identifiable even if the study contains thousands of exploratory measurements.

8. Population Engineering Without Population Manipulation

Trial populations should be sufficiently enriched to permit detection of an effect but sufficiently representative to support the intended claim. Selecting participants who have room for improvement can be scientifically appropriate. Selecting an extreme responder phenotype and later generalising to healthy consumers may not be.

Population design should explicitly consider target-population correspondence, baseline physiological status, ceiling and floor effects, disease status, medication and supplement use, dietary background, regression to the mean and external validity. These issues are particularly important for memory, sleep, stress, glycaemia, gastrointestinal function, immunity, joint function, lipids, blood pressure, appetite and weight management.

9. Dose Selection: The Commercial Dose Must Meet the Scientific Dose

A frequent development failure occurs when an RCT uses a dose chosen to maximise the probability of detecting an effect while the final commercial product delivers substantially less. The evidentiary bridge then becomes vulnerable.

Dose selection should integrate biology, prior evidence, safety, formulation, realistic intake, intended conditions of use and commercial feasibility. Where uncertainty is substantial, dose-ranging work may be scientifically and economically superior to immediately committing to one large confirmatory RCT. The decisive question is not “At what dose does something happen?” but “At what realistically consumable dose does the claimed beneficial effect reproducibly occur?”

10. Duration: Fast Biology Does Not Always Support Long-Term Claims

Trial duration should be derived from physiology, endpoint kinetics, expected onset, adaptation, persistence, intended consumption and claim semantics. A seven-day effect cannot automatically substantiate a sustained functional benefit.

The 2026 EFSA assessment of Anxiofit-1 illustrates the problem. Two short-term human intervention studies showed a selective effect after seven days on state anxiety, whereas a six-week RCT showed no effect at either 40 or 80 mg/day using a different psychometric tool. EFSA also found no evidence that the short-term effect could be sustained with continuous consumption and concluded that the evidence was insufficient to establish the proposed cause-and-effect relationship (EFSA NDA Panel, 2026a). Duration is therefore part of the scientific meaning of the claim.

11. Controls Must Control the Question

"Placebo-controlled" is not an adequate methodological description. The comparator must permit valid isolation of the intervention effect. In nutraceutical studies this may require matching colour, taste, aroma, viscosity, caloric content, macronutrient composition, packaging, dosing schedule and participant expectations.

Blinding can fail when active products possess recognisable sensory or physiological signatures. This matters particularly for subjective outcomes such as stress, sleep, appetite, mood, pain and cognition. Where feasible, the credibility of blinding should be assessed rather than assumed.

12. Randomisation Is Not Merely Drawing Names From a Hat

Credible randomised trials separate generation of the allocation sequence, concealment of that sequence, enrolment and assignment. Weak allocation concealment can introduce selection bias before treatment starts. Stratification may be appropriate for strongly prognostic variables in small or heterogeneous studies, but overstratification can make implementation fragile. Complexity should be proportional to the causal question.

13. Multiplicity: Where False Discoveries Hide

Nutraceutical studies often contain several cognitive tests, questionnaire domains, biomarkers, time points, doses, subgroups and microbiome outcomes. As testing expands, the probability of apparently positive findings expands with it.

Protocols should therefore separate confirmatory outcomes, key secondary outcomes, supportive secondary outcomes and exploratory outcomes. The distinction protects interpretation. Exploratory findings can generate excellent science; they should simply be reported as exploratory.

14. Missing Data Are Part of the Biological Story

Withdrawal is rarely biologically neutral. Participants may discontinue because of no perceived benefit, adverse effects, dosing burden, unpleasant taste, worsening symptoms or incompatibility with daily life. Complete-case analysis can therefore induce bias.

Missing-data handling should be prospectively specified and connected to plausible reasons for missingness. Estimand-based thinking is useful because it forces investigators to define exactly which treatment effect is being estimated and how intercurrent events affect that question. ICH E9(R1) is not an EFSA-specific legal requirement, but its framework for estimands and sensitivity analysis is highly relevant methodological infrastructure for regulatory-grade causal reasoning.

15. The Totality-of-Evidence Principle

A weak dossier is often organised around the sponsor's best study. EFSA evaluates the relationship, not the marketing narrative. Applicants are expected to present the totality of available pertinent evidence, including published and unpublished data, and to address the hierarchy and relevance of different evidence types (EFSA NDA Panel, 2021b).

Negative or contradictory evidence should be interrogated rather than hidden. Divergence can arise from ingredient characterisation, dose, population, duration, outcome choice, power, adherence, matrix effects, baseline nutritional status or methodological bias. Contradiction is not automatically fatal; unexplained contradiction is far more damaging.

16. What Recent EFSA Opinions Teach Us

Citicoline and memory (2024): EFSA considered citicoline sufficiently characterised and accepted improvement, maintenance or reduced loss of memory as a beneficial physiological effect in the proposed population. However, only one pertinent RCT showed benefit on episodic memory at 500 mg/day for 12 weeks; another study at 1 g/day for three months did not show the effect, and convincing mechanistic evidence was not provided. EFSA concluded that a cause-and-effect relationship had not been established (EFSA NDA Panel, 2024). Lesson: one favourable RCT does not neutralise inconsistent human evidence.

Anxiofit-1 (2026): short-term positive results did not overcome a longer negative trial, lack of evidence for persistence and lack of a plausible in-vivo mechanism. Lesson: an acute signal and a sustained health benefit are different propositions (EFSA NDA Panel, 2026a).

Oat beta-glucans and postprandial glucose peak (2026): EFSA considered oat beta-glucans sufficiently characterised; most of 16 pertinent human intervention studies supported reduction of postprandial glucose peaks; undesirable glycaemic or insulinaemic effects were not observed; the mechanism was considered well established; and quantitative conditions of use could be defined. EFSA concluded that a cause-and-effect relationship had been established (EFSA NDA Panel, 2026b). Lesson: regulatory strength emerges from convergence among characterisation, pertinent human effects, consistency, mechanism and workable conditions of use.

17. From Evidence Pyramid to Evidence Architecture

The classical evidence pyramid is helpful but incomplete for regulatory nutrition. A programme can possess an RCT at the top of the hierarchy and still be structurally weak if identity, endpoint relevance, population selection, commercial exposure, consistency or mechanistic plausibility are deficient.

A more useful conceptual model is multidimensional: Evidence strength ≈ internal validity × relevance × consistency × characterisation × biological plausibility × applicability. This is not an EFSA formula. The multiplicative form is deliberate: if a critical dimension approaches zero, the practical value of the entire evidence package can collapse.

18. The Claim–Evidence Alignment Matrix (CEAM)

The CEAM is an author-proposed pre-protocol instrument. Every major design decision is mapped to the intended claim. The purpose is to reveal misalignment before recruitment begins, when correction is still inexpensive.

Trial element	Claim-alignment question
Ingredient	Is this precisely the claimed constituent?
Batch specifications	Can commercial material reproduce the investigated material?
Population	Is this the intended claim population?
Baseline status	Is there physiological capacity to improve?
Dose	Can this become the condition of use?

Trial element	Claim-alignment question
Duration	Does it match the meaning of the claim?
Comparator	Does it isolate the causal intervention?
Primary endpoint	Does it directly measure the claimed effect?
Statistical estimand	What exact treatment effect is being estimated?
Missing-data strategy	Could attrition materially alter interpretation?
Secondary outcomes	Supportive, key secondary or exploratory?
Mechanistic endpoints	Do they explain the proposed relationship without replacing the claimed outcome?
Commercial product	Is bridging from trial material to marketed product scientifically defensible?

19. Evidence Failure Mode and Effects Analysis (eFMEA)

Food manufacturing routinely uses structured risk analysis. Clinical evidence generation should do the same. The author-proposed eFMEA examines plausible failure modes before the pivotal trial—for example inadequate ingredient characterisation, weak assay sensitivity, inappropriate population, ceiling effects, underpowered sample size, unrealistic effect assumptions, poor placebo matching, failed blinding, inappropriate duration, excessive multiplicity, attrition, weak adherence, batch inconsistency and inability to bridge the tested intervention to the commercial product.

Each failure mode can be scored by probability, regulatory severity and detectability before the trial. The objective is practical: discover the expensive problem while it is still cheap to correct.

20. The EFSA Pre-Mortem

Immediately before protocol lock, the multidisciplinary team should assume that EFSA has issued a negative opinion and ask what the NDA Panel would most plausibly write as the reason. Examples include insufficient characterisation, inappropriate outcome variables, methodological limitations, unrepresentative study population, inconsistent evidence, mismatch with conditions of use, weak biological plausibility or insufficient evidence for causality.

The exercise is deliberately adversarial. It forces the programme to be redesigned while those criticisms are hypothetical rather than after the expenditure of a pivotal trial.

21. Protocol Transparency Is Infrastructure, Not Decoration

The EU transparency framework materially changed the application environment. EFSA guidance implementing Regulation (EU) 2019/1381 explains that new pre-submission and application provisions apply to applications submitted from 27 March 2021. Studies commissioned or carried out with a view to supporting a regulated-product application are subject to study-notification obligations under the

transparency framework. The practical consequence is a stronger prospective documentary trail around evidence generation (EFSA NDA Panel, 2021a, 2021b).

That environment favours protocol discipline, transparent amendment management, complete evidence accounting and prospective analytical decisions. Prospective trial registration also remains an important international scientific norm.

22. SPIRIT 2025 and CONSORT 2025: A New Baseline for Trial Transparency

SPIRIT 2025 provides an updated 34-item minimum framework for randomised-trial protocols, with stronger emphasis on harms, intervention and comparator description, open science and transparent protocol content (Chan et al., 2025). CONSORT 2025 supersedes CONSORT 2010 and provides a 30-item minimum framework for reporting randomised trials, including an open-science section (Hopewell et al., 2025).

Neither document should be misrepresented as an EFSA statutory requirement. Their relevance is methodological: a nutraceutical trial whose methods cannot withstand contemporary protocol and reporting standards does not become more persuasive merely because the intervention is a food rather than a medicinal product.

23. Publication Strategy Must Not Dictate Trial Design

Academic publication and EFSA substantiation overlap but are not identical objectives. Journals may reward novelty, mechanistic observations, exploratory omics and unexpected subgroup signals. Regulatory assessment asks a more austere question: does the totality of pertinent scientific evidence establish the proposed cause-and-effect relationship?

The rational sequence is therefore **regulatory question → causal question → protocol → statistical analysis plan → study → reporting → publication, not interesting study → significant result → publication → search for a claim.**

24. Why Negative Trials Can Be Valuable

A rigorous negative trial can prevent years of weak product positioning, repeated underpowered studies, an indefensible claim application and scientifically unjustified marketing. It can identify an ineffective dose, unsuitable phenotype, wrong duration, inadequate formulation, insensitive endpoint or incorrect mechanism.

A clinical programme succeeds when it resolves uncertainty—not only when it confirms expectations. That is the strongest commercial argument for methodological honesty.

25. A New Definition of “EFSA-Ready”

An EFSA-ready programme should demonstrate five forms of coherence: material coherence, physiological coherence, population coherence, statistical coherence and evidentiary coherence. Material coherence means the investigated material is the claimed constituent. Physiological coherence means the endpoint represents a beneficial physiological effect. Population coherence links participants to the intended claim population. Statistical coherence aligns estimand, endpoint hierarchy, sample size, analysis and uncertainty with the predefined question. Evidentiary coherence situates the trial within the totality of human and mechanistic evidence.

These dimensions provide a more useful operational definition of readiness than the statement "we have completed a clinical trial."

26. From One Trial to an Evidence Development Programme

For many novel interventions, the optimal route is not a single pivotal RCT. A rational sequence is: regulatory landscaping; ingredient characterisation; mechanistic mapping; human proof-of-concept; confirmatory RCT; replication or triangulation where necessary; evidence synthesis; and only then final claim dossier construction.

This staged strategy reduces the probability of using a large confirmatory trial to answer questions that should have been resolved in smaller earlier studies.

27. Regulatory Science as Organised Skepticism

The strongest sponsor mindset is neither "we believe this product works" nor "we must prove this product works." It is: we have a biologically credible hypothesis; we will design the strongest feasible experiment capable of disproving it; and if the hypothesis survives repeated, coherent testing, conviction becomes evidence.

Conviction may initiate research. It cannot conclude it.

28. Conclusion

Obtaining scientific substantiation for an EFSA health-claim assessment cannot be reduced to conducting an RCT, and it cannot be reduced to statistical significance. The relevant scientific object is a specific and testable relationship between a characterised food or constituent and a defined beneficial physiological effect in a relevant human population under specific conditions of use.

The nutraceutical sector therefore needs to move from clinical validation as a marketing exercise toward regulatory-grade evidence engineering as a scientific discipline. This requires claim-first thinking, rigorous ingredient characterisation, endpoint governance, adequate controls, prospective hypotheses, sufficient power, explicit estimands, robust missing-data strategies, multiplicity control, transparent reporting, biological plausibility, totality-of-evidence review and willingness to accept an inconvenient result.

EFSA success should never mean designing studies to obtain favourable outcomes. It should mean designing studies so rigorous that a favourable outcome, if obtained, is difficult to dismiss. The strongest commercial evidence is not evidence designed to persuade. It is evidence designed to survive skepticism.

Author's Methodological Note

The Claim Target Profile (CTP), Regulatory Evidence Chain, Claim–Evidence Alignment Matrix (CEAM), Evidence Failure Mode and Effects Analysis (eFMEA), EFSA Pre-Mortem Review and five-dimensional concept of EFSA readiness are author-proposed methodological frameworks. They are not official EFSA terminology, statutory requirements or formally endorsed EFSA methodologies. They are intended to operationalise—not replace—applicable EU legislation, EFSA guidance and established principles of rigorous clinical-trial methodology.

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