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Rational Prescribing Under Diagnostic Uncertainty Requires Explicit Therapeutic Trials, Reassessment Thresholds, and Stopping Rules

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ABSTRACT

Prescribing before diagnosis is settled is common in clinical medicine, but empirical treatment becomes difficult to interpret when the therapeutic objective, expected time course and exit conditions remain implicit. Diagnostic uncertainty is not itself an indication for treatment. A therapeutic trial is defensible only when exposure is clinically justified despite unresolved diagnosis, the treatment has a plausible relation to a defined target problem, and the clinician can specify what observations would alter the decision to continue, modify or stop. This commentary argues that empirical prescribing should be designed prospectively as a bounded clinical test. The central requirement is not formal N-of-1 experimentation in every patient, but enough prospective structure to distinguish treatment utility from diagnostic confirmation and to reduce therapeutic drift. Apparent improvement may reflect pharmacological benefit, spontaneous fluctuation, regression toward a usual state, expectancy effects or concurrent care; nonresponse can be equally ambiguous. Reassessment timing must follow mechanism, risk and the information likely to emerge during treatment. Explicit stopping rules complete the logic by making continuation an active decision. This approach narrows the legitimate role of empirical treatment while improving the interpretability and reversibility of prescribing under uncertainty.

Keywords: Diagnostic uncertainty, Empirical therapeutic trial, N-of-1 reasoning, Treatment response, Reassessment, Deprescribing

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Introduction

Diagnostic uncertainty is a normal feature of clinical care, not an exceptional failure of diagnosis. A systematic review of definitions and measures found that the construct is variably framed, often as the clinician's subjective inability to provide a sufficiently accurate explanation of the patient's problem, and that uncertainty can change as information accumulates[1]. That dynamic quality matters for prescribing. A diagnosis may be provisional while treatment is still clinically justified because symptoms are burdensome, untreated risk is material, or a reversible intervention is available. Yet the same uncertainty can also make treatment hard to interpret. Once a medicine is started, improvement may be attributed to the suspected diagnosis, nonresponse may trigger premature escalation, and an initially provisional prescription may persist after its original rationale has weakened.

The communication literature has made substantial progress in describing how clinicians should acknowledge uncertainty without abandoning patients to it. Diagnostic excellence requires explicit recognition that confidence is incomplete and that future information may change the working explanation[2]. Reviews of uncertainty communication emphasize discussion of ambiguity, emotional support, shared decision making and contingency planning[3]. In primary care, however, uncertainty is communicated inconsistently: some clinicians state it

explicitly, others imply it through language or plans, and some omit it altogether; patient experience also varies with the form and context of communication[4]. These findings establish the importance of transparency, but communication alone does not specify how a treatment started under uncertainty should be governed over time. The prescription itself can create an unintended signal of diagnostic closure unless its provisional status is made operational.

Structured approaches to clinical uncertainty already encourage clinicians to recognize uncertainty, acknowledge it, partner with patients and seek support when needed[5]. The remaining problem addressed here is narrower and pharmacologically specific: when is an empirical therapeutic trial rational, and what makes its result interpretable? The proposed answer is that empirical treatment should be prospectively bounded. Before initiation, the clinician should identify the target problem, articulate why the treatment is justified despite unresolved diagnosis, connect the intervention to a plausible mechanism, define what benefit or harm can be observed, choose an observation window suited to the treatment and condition, and specify what will trigger continuation, modification, diagnostic reassessment or discontinuation. This is not an argument for treating every uncertain diagnosis. It is a discipline for the subset of cases in which treatment is already clinically defensible and where the consequences of therapeutic drift can be reduced by explicit precommitment.

When uncertainty can justify a therapeutic trial

A useful starting point comes from the literature on time-limited trials in critical illness. An American Thoracic Society workshop defined a time-limited trial as a collaborative plan to use life-sustaining therapy for a defined period while monitoring the patient's response and reassessing whether treatment should continue in light of prespecified goals[6]. The context is substantially different from routine prescribing under diagnostic uncertainty, and the critical-care construct cannot simply be transplanted into ambulatory pharmacotherapy. Its relevant contribution is the prospective logic: treatment begins because a decision must be made under uncertainty, but continuation is not assumed. Goals, duration or milestones, and a reassessment event are established in advance.

The broader critical-care literature also shows why this logic should be transferred cautiously. Time-limited trials are described inconsistently, applied to heterogeneous clinical situations and supported by an evidence base that remains incomplete[7]. The concept is strongest as a method of structuring decisions under uncertainty, not as proof that every bounded treatment strategy improves outcomes. For empirical prescribing, the key entry condition is more demanding than uncertainty alone. The treatment must be independently defensible on expected benefit, foreseeable harm, reversibility, urgency and available alternatives. If objective testing can be obtained promptly without unacceptable delay, if treatment would materially obscure later diagnosis, or if exposure carries substantial irreversible risk, the case for an empirical trial weakens even when the diagnosis remains uncertain.

Prospective boundaries can nonetheless change clinical behaviour. In critically ill patients with advanced medical illness, implementation of structured communication around time-limited trials was associated with reductions in nonbeneficial intensive-care treatment[8]. That finding should not be generalized as causal evidence for routine outpatient prescribing, but it illustrates an important behavioural mechanism: once a treatment is initiated, continuation acquires inertia. A prespecified reassessment point interrupts that inertia by requiring a new decision. The corresponding question in pharmacotherapy is not simply whether the patient is “better,” but whether the observation made during treatment is sufficiently informative to justify the next exposure.

A rational empirical therapeutic trial thus has an admissibility test before it has an efficacy test. First, there must be a clinically important target problem. Second, the proposed treatment must have a plausible relationship to that target that does not depend on the uncertain diagnosis being correct in every detail. Third, the expected consequences of delaying treatment must be weighed against the diagnostic and safety costs of starting it. Fourth, the target must be observable with enough reliability that subsequent change can alter management. Finally, the clinician should be able to define an exit condition. If no plausible observation would lead to stopping, modifying or reconsidering the working diagnosis, the prescription is not functioning as a therapeutic trial; it is functioning as open-ended treatment initiated during uncertainty.

Turning treatment into a prospective within-patient test

N-of-1 methodology provides the clearest formal model for asking whether an intervention produces a reproducible effect in a particular patient. Randomized, repeated crossover designs can compare treatment and control periods within the same person and reduce some forms of between-person heterogeneity that complicate population-level inference[9]. Their relevance to routine prescribing lies in the design principles they make

explicit: define the outcome before treatment, establish a meaningful comparator, account for timing and carryover, repeat observations when feasible, and separate the decision rule from knowledge of the eventual result. Most empirical prescriptions will not meet the standards of a formal N-of-1 randomized trial, nor should they be presented as if they do. The useful question is which elements of prospective within-patient reasoning are necessary to make an ordinary therapeutic trial interpretable.

The limits of N-of-1 evidence are equally instructive. A scoping review of randomized trials evaluating the impact of N-of-1 approaches on clinical outcomes identified only 12 eligible trials, many of which were small or underpowered; only one showed a significant primary-outcome benefit[10]. A systematic review in neurology found applications across several disorders but substantial variation in design and reporting[11]. These findings argue against turning "N-of-1" into a label for any individualized trial of treatment. The approach is most informative when outcomes can change on a time scale compatible with treatment periods, treatment effects are sufficiently reversible, carryover can be managed, and repeated measurement is practical.

Methodological quality can be decisive. A systematic review of 115 medical N-of-1 publications found that only a small fraction met all evaluated single-case evidence standards, with recurring problems in design, effect estimation and treatment of serial correlation[12]. Routine clinical trials of therapy will often be less formal than published N-of-1 studies, but they should not abandon the basic logic that protects causal interpretation. A before-and-after observation is weak when symptoms fluctuate naturally, when co-interventions change simultaneously, when the outcome is vaguely defined, or when the assessment occurs only after the patient or clinician has already formed a preferred explanation.

For prescribing practice, a prospective within-patient test can be specified without excessive procedural burden. The target should be concrete enough to observe: frequency of a symptom, functional capacity, a validated symptom score where appropriate, a measurable physiological variable, or another clinically meaningful endpoint. Baseline status should be documented before exposure when feasible. The expected direction of benefit and the time during which it could plausibly appear should be stated. Important adverse effects should have their own monitoring plan because harm may emerge on a different time scale from benefit. Adherence, dose changes and major co-interventions should be noted when they could alter interpretation. Where washout, rechallenge or alternating treatment periods are safe and clinically justified, they can strengthen causal inference; where they are unsafe, the limits of inference should be accepted rather than concealed.

The resulting structure does not convert routine care into research. It makes explicit what the clinician is already relying on when interpreting treatment response. The difference is prospective discipline. If the outcome is defined only after improvement is observed, or if the duration is extended whenever the expected effect fails to appear, the trial becomes vulnerable to post hoc reasoning. If the observation window, target and decision rule are specified in advance, a negative or equivocal result can meaningfully redirect care.

Why apparent response cannot validate diagnosis

The most consequential interpretive error in empirical prescribing is to treat improvement during treatment as confirmation of the suspected diagnosis. Controlled statin rechallenge studies illustrate why that inference can fail even when the patient's symptoms are genuine. In a series of randomized, placebo-controlled N-of-1 trials among patients who had previously stopped or considered stopping statins because of muscle symptoms, overall symptom scores did not differ significantly between atorvastatin and placebo periods[13]. The result does not imply that statins cannot cause muscle toxicity. It shows that temporal association between exposure and symptoms, even when repeatedly experienced, may not identify the pharmacological cause.

The SAMSON crossover trial extended this distinction by including statin, placebo and no-tablet months. Symptom burden was similar during statin and placebo periods, and the timing of symptom onset and offset did not discriminate active treatment from placebo[14]. In selected patients with previous statin intolerance, the act and expectation of tablet taking accounted for much of the symptom pattern attributed to statins. These studies are especially relevant to diagnostic uncertainty because they separate three questions that are often conflated: Did the patient's state change? Did the treatment cause that change? Does the observed change support the underlying diagnosis?

Placebo and nocebo mechanisms provide one explanation for why those questions diverge. Expectations, prior experiences, conditioning, information from clinicians and the wider therapeutic context can alter symptom perception and clinical experience[15]. Spontaneous fluctuation and regression toward a patient's more usual state can produce the same temporal pattern. Concurrent behavioural changes, rescue treatment, natural recovery and

measurement variability add further ambiguity. A clinically meaningful improvement can still justify continuing a treatment when benefits exceed burdens, but therapeutic utility and diagnostic validation are separate judgments. This distinction also changes the interpretation of nonresponse. Failure to improve may weaken one therapeutic hypothesis, yet it may also reflect inadequate exposure, poor adherence, an insensitive endpoint, wrong timing, irreversible pathology, competing disease mechanisms or an intervention that affects only part of the target problem. Escalation is not automatically the correct response. When a trial is inconclusive, the appropriate next step may be to change the measurement strategy, obtain objective diagnostic evidence, stop treatment and observe, or reformulate the clinical question.

The most informative reassessment asks two linked questions. The first is pragmatic: has the patient experienced enough benefit, harm or lack of benefit to justify a change in treatment? The second is inferential: how much should the observation change confidence in the proposed mechanism or diagnosis? Those answers may differ. A medicine can be worth continuing even when the diagnosis remains uncertain, and a diagnosis can remain plausible despite an unsuccessful therapeutic trial. The purpose of the trial is to improve a decision under uncertainty, not to manufacture certainty from temporal association.

The recurrent patterns that create false confidence can be made explicit before a therapeutic trial is interpreted. **Table 1** separates the observed clinical pattern from its competing explanations and from the diagnostic inference that the pattern can legitimately support.

Table 1. Interpreting observed change during an empirical therapeutic trial

Observed pattern during the trial	Pharmacological interpretation that remains plausible	Competing explanations that must remain open	Diagnostic inference that is justified	Corrective reassessment action
Target improves after treatment starts	Treatment may be producing clinically useful benefit	Natural fluctuation, regression toward usual state, placebo or expectancy effects, concurrent care, behavioural change	Increases confidence only when response is sufficiently specific and alternative explanations are weak; usually does not confirm diagnosis by itself	Compare with baseline and expected time course; review co-interventions; continue only if benefit is meaningful and the trial remains safe
Target worsens after treatment starts	Treatment may be ineffective or causing harm	Disease progression, nocebo effects, unrelated symptoms, withdrawal from prior therapy, measurement variability	Does not by itself prove adverse drug causation or disprove the working diagnosis	Assess severity and timing of harm; stop promptly when safety requires; consider dechallenge or alternative evidence
No meaningful change is observed	Treatment may lack efficacy for the target	Insufficient dose or exposure, poor adherence, wrong observation window, insensitive endpoint, irreversible pathology	Weakens the therapeutic hypothesis only to the extent that the trial had adequate exposure and measurement	Verify exposure and endpoint validity; avoid automatic escalation; stop or redesign the trial when interpretability is poor
Improvement occurs after treatment is stopped	Withdrawal may have removed an adverse effect or unnecessary burden	Natural recovery, co-intervention, expectancy effects, delayed disease change	Can support a treatment-related contribution when timing and mechanism are coherent, but remains non-diagnostic alone	Document dechallenge trajectory; reassess indication; consider rechallenge only when clinically justified and safe
The same pattern recurs on rechallenge	A treatment-related effect becomes more plausible	Reproducible expectancy or contextual effects, carryover, correlated symptom fluctuation	Strengthens causal inference when challenge conditions are controlled; diagnostic inference still depends on specificity	Examine washout, blinding or comparator feasibility and consistency of timing; integrate objective evidence
Response is mixed, unstable or endpoint-dependent	Partial effect or competing mechanisms may exist	Measurement noise, multiple symptom generators, adherence variability, time-varying disease	Usually remains inconclusive	Narrow the target, improve measurement, seek independent diagnostic evidence, or terminate the trial if it cannot answer the intended question

Note: The table distinguishes therapeutic usefulness, pharmacological causation and diagnostic inference. Rechallenge or withdrawal should only be considered when clinically appropriate and safe. No observed pattern is intended as a universal diagnostic test.

Observation windows and reassessment thresholds must follow mechanism and risk

An empirical therapeutic trial becomes interpretable only when its timing reflects the biology of the target problem, the pharmacology of the intervention, the expected speed of benefit, and the consequences of waiting. A fixed reassessment interval applied across medicines would create false precision. Some therapeutic effects

should become apparent rapidly; others require sustained exposure. Toxicity can emerge before benefit, after benefit, or only after cumulative exposure. Diagnostic information may also arrive during the trial and render the original observation window obsolete. The relevant question is therefore not simply how long a medicine should be "tried," but what clinical event or elapsed period will provide enough information to reconsider the initial decision.

Guidelines for gastro-oesophageal reflux disease illustrate a setting in which empiric pharmacological treatment can be appropriate when the clinical presentation is sufficiently compatible and alarm features do not dictate another pathway[16]. The logic is not that improvement after acid suppression proves gastro-oesophageal reflux disease. Instead, an empiric course may be clinically reasonable because the treatment has a plausible mechanism, common symptoms can be followed, and subsequent response or nonresponse can inform management. The same reasoning cannot be transferred indiscriminately to conditions in which treatment materially alters later diagnostic testing. Adult asthma guidance places substantial emphasis on objective demonstration of variable airflow limitation and related diagnostic evidence, with recognition that confirmation becomes more difficult once controller treatment has already been established[17]. In such settings, the diagnostic cost of beginning treatment can itself become part of the entry decision.

Antimicrobial therapy provides another form of temporal reasoning. Empiric broad-spectrum treatment may initially be justified by the consequences of undertreating serious infection, yet new microbiological and clinical information can rapidly change that justification. Among hospitalized patients with pneumonia who had negative cultures, de-escalation of broad empiric antibiotics by the fourth hospital day occurred in only a minority of patients despite the emergence of information that could support narrowing[18]. The specific day used in that study is not a universal stopping threshold. Its wider relevance is that diagnostic evidence acquired after treatment initiation should actively reopen the prescribing decision rather than merely accumulate in the record.

Prospective stewardship interventions demonstrate how such reopening can be operationalized. A multicentre randomized trial of an opt-out protocol for antibiotic de-escalation in patients with suspected sepsis used structured safety assessment and an explicit opportunity to discontinue unnecessary empiric therapy[19]. A reassessment threshold of this kind is fundamentally different from an automatic stop date. It identifies a point at which continued exposure must again be justified in light of updated evidence.

A therapeutic trial may therefore contain several clocks. One concerns the earliest plausible onset of benefit. Another concerns the latest point by which meaningful benefit should have appeared if the therapeutic hypothesis is correct. A third concerns toxicity or other unacceptable burden. A fourth may be informational: a laboratory result, imaging study, specialist assessment or change in clinical trajectory that reduces the value of continued empiricism. These clocks need not coincide. A medicine may require continued observation for efficacy while nevertheless demanding immediate cessation for harm, or a trial may end before its planned duration because new diagnostic evidence makes further empirical exposure unnecessary.

The practical specification is consequently conditional rather than numerical. Before treatment begins, the prescriber should know what is being watched, when it could reasonably change, what new evidence would shorten or extend observation, and which developments require action before the planned checkpoint. **Table 2** organizes these variables without turning disease-specific examples into universal thresholds.

Table 2. Prospective specification of a therapeutic trial under diagnostic uncertainty

Clinical trial context	Target problem being tested	Mechanistic expectation	Observation window logic	Evidence of meaningful benefit	Unacceptable harm or burden	Meaning of nonresponse	Stopping or next-decision logic
Empiric acid suppression for a compatible reflux presentation	Troublesome reflux-type symptoms sufficiently characteristic to justify a treatment trial	Reduction of acid-related symptom generation	Long enough for an adequate therapeutic exposure, but shortened if alarm features or alternative diagnostic evidence emerge	Reproducible improvement in the predefined symptom target and associated function	Clinically important adverse effects, treatment burden, or emergence of features requiring diagnostic investigation	May weaken the therapeutic hypothesis but does not by itself exclude reflux disease or establish an alternative diagnosis	Stop, modify or investigate further if meaningful improvement is absent, treatment is poorly tolerated, or the diagnostic context changes

Empiric broad-spectrum antimicrobial therapy while serious infection is being evaluated	Immediate infection-related risk for which delayed active treatment could be harmful	Early antimicrobial coverage while causal evidence is incomplete	Reassessed as microbiological results, clinical stability and alternative diagnoses become available	Improvement compatible with infection control together with evidence that continued antimicrobial coverage remains justified	Toxicity, superfluous spectrum, new evidence against bacterial infection, or unnecessary exposure	May reflect wrong pathogen, wrong diagnosis, inadequate source control, insufficient treatment, or noninfectious disease	Narrow or stop when new evidence removes the rationale for broad empiric coverage; escalate only when updated evidence supports doing so
Within-patient symptomatic treatment with a measurable reversible outcome	A specific symptom or functional deficit that can be repeatedly observed	Treatment should produce a temporally coherent change in the target	Matched to treatment onset, washout, carryover and natural variability	Change that is clinically meaningful and, where feasible, reproducible across observations	Adverse effects, functional deterioration, or inability to continue safely	May represent ineffective treatment, inadequate exposure, insensitive measurement or an unsuitable target	Stop or redesign the trial if the treatment cannot produce interpretable information within a clinically acceptable period
Medication review in high-burden polypharmacy	Ongoing need for each medicine relative to current goals and treatment burden	Withdrawal of an unnecessary or harmful medicine should reduce burden without unacceptable loss of disease control	Follow-up extends beyond the act of discontinuation to detect recurrence, withdrawal effects and changing priorities	Reduced medication burden with preserved or improved relevant clinical state	Recurrence of important symptoms, destabilization of controlled disease, or withdrawal-related harm	Absence of deterioration may support continued discontinuation; deterioration requires causal reassessment rather than automatic reinstatement	Continue withdrawal when the previous indication no longer justifies exposure; reinstate or modify when clinically important deterioration is plausibly related
Selected antihypertensive deintensification in an older patient with controlled pressure	Whether treatment intensity exceeds what is required for acceptable control in that individual	Removal of one medicine may reduce treatment burden while maintaining adequate blood-pressure control	Requires predefined follow-up because loss of control may emerge after withdrawal	Maintenance of clinically acceptable blood-pressure control without new treatment-related burden	Clinically important pressure rise, symptoms or other evidence that reduced intensity is unsafe	Suggests that the withdrawn medicine may still be necessary, but interpretation depends on adherence and concurrent changes	Reinstate or modify therapy if predefined control is lost; continue reduction when control remains acceptable and goals support it

Deprescribing near the end of life or in severe frailty	Whether a medicine's expected future benefit remains relevant to current prognosis and goals	Treatments with long time-to-benefit or disproportionate burden may no longer provide net value	Determined by prognosis, current goals, withdrawal risk and symptom consequences rather than chronic-disease convention alone	Reduced burden without loss of symptom control or other valued outcome	Withdrawal effects, symptom recurrence, distress or loss of a treatment still aligned with goals	May indicate that anticipated burden-benefit assumptions were incorrect	Stop medicines whose indication has expired in the current context; retain or reinstate treatment when it remains aligned with patient goals and near-term benefit

Note: These prescribing considerations require clinical adaptation. Observation windows and stopping actions must remain compatible with the medicine, target condition, patient context, and available diagnostic evidence.

Stopping rules prevent therapeutic drift

Starting treatment is usually documented more clearly than deciding why it should continue. Once a medicine enters the medication list, repetition can substitute for reassessment. Refill systems, fragmented care, uncertainty about the original indication and reluctance to disturb apparent stability can all convert an empirical trial into chronic treatment. A stopping rule counters that drift by making continuation contingent on renewed evidence that the medicine still serves a defined purpose.

Evidence from medication-review interventions shows that such reconsideration can materially alter prescribing. In older adults with multimorbidity and substantial polypharmacy, structured general-practitioner medication review reduced inappropriate prescribing and incorporated patient priorities into treatment decisions[20]. The relevance to empirical therapy is not the number of medicines removed. It is the act of reopening assumptions that otherwise remain embedded in a medication list.

Post hoc analyses of geriatric medication review provide a more specific example. Lack of an ongoing indication was a frequent reason for discontinuation, and many medicines stopped during the intervention remained discontinued months later[21]. An empirical prescription under diagnostic uncertainty should reach this question much earlier: if its original indication was provisional, what evidence transformed that provisional indication into a continuing one? Absence of an answer is itself a reason for reassessment.

Stopping should also be observed longitudinally. In the Shed-MEDS randomized trial, a patient-centred deprescribing intervention reduced medication burden as older adults moved from hospital to postacute care, with follow-up extending beyond the initial discontinuation decision[22]. Contemporary reviews similarly emphasize that deprescribing is heterogeneous and should incorporate clinical indication, treatment burden, patient priorities and monitoring after withdrawal[23]. Discontinuation therefore should not be treated as the end of observation. Recurrence, withdrawal phenomena, preservation of disease control and changes in patient function all contribute information about whether the stopped therapy was necessary.

The outcome evidence also prevents stopping rules from becoming an ideological preference for fewer medicines. An updated systematic review and meta-analysis found no significant overall reduction in mortality among randomized studies of polypharmacy deprescribing, although effects differed across interventions and populations[24]. A pragmatic randomized trial targeting anticholinergic and sedative burden in frail community-dwelling older adults likewise illustrates how implementation, drug class and population characteristics shape what deprescribing can achieve[25]. These results support a limited inference: reduced treatment exposure does not by itself establish a favourable health outcome. Explicit stopping rules structure reassessment, but their clinical benefit cannot be inferred from medication reduction alone.

Nor can a stopping rule be copied uncritically from a list of potentially inappropriate medicines. The 2023 American Geriatrics Society Beers Criteria identify medication-context combinations in which risks commonly outweigh benefits, while explicitly preserving the role of clinical judgment and shared decision making[26]. Randomized evidence from the OPTIMISE trial showed that, in selected adults aged 80 years or older with controlled systolic blood pressure, removal of one antihypertensive could preserve short-term pressure control within the trial's noninferiority design[27]. That finding supplies a model of monitored deintensification, not a mandate for routine antihypertensive withdrawal.

The dependence of stopping logic on clinical context becomes still clearer near the end of life. STOPPFrail version 2 provides criteria intended for severely frail older people approaching end of life, where prognosis, treatment burden and time-to-benefit alter the relevance of conventional long-term prevention[28]. Those criteria would be inappropriate as a generic stopping rule for younger or less frail populations. The principle that transfers is that continuation should be tested against the patient's present therapeutic horizon, not against the historical fact that a medicine was once indicated.

A complete empirical therapeutic trial therefore has terminal states as well as an initiation state. Continue means that the observed benefit is sufficiently meaningful and the remaining burden sufficiently acceptable to justify another period of exposure. Modify means that the trial has generated information but the original dose, target, measurement strategy or working explanation requires revision. Stop means that benefit is absent, harm is unacceptable, the indication has disappeared, or the trial cannot answer the question it was intended to address. A fourth outcome—seek independent diagnostic evidence—may accompany any of these states when treatment response has failed to resolve the underlying uncertainty.

These decisions are linked over time rather than arranged as a one-way algorithm. Apparent benefit can prompt continuation while leaving diagnostic confidence unchanged. New harm can terminate treatment before efficacy is fully assessed. New laboratory or imaging evidence can end a trial even when symptoms are improving. Withdrawal can itself become an observation period when recurrence is clinically informative and rechallenge is safe. **Figure 1** places these relationships on a therapeutic timeboard so that prescribing, observation and reassessment remain visibly separate from diagnostic confirmation.

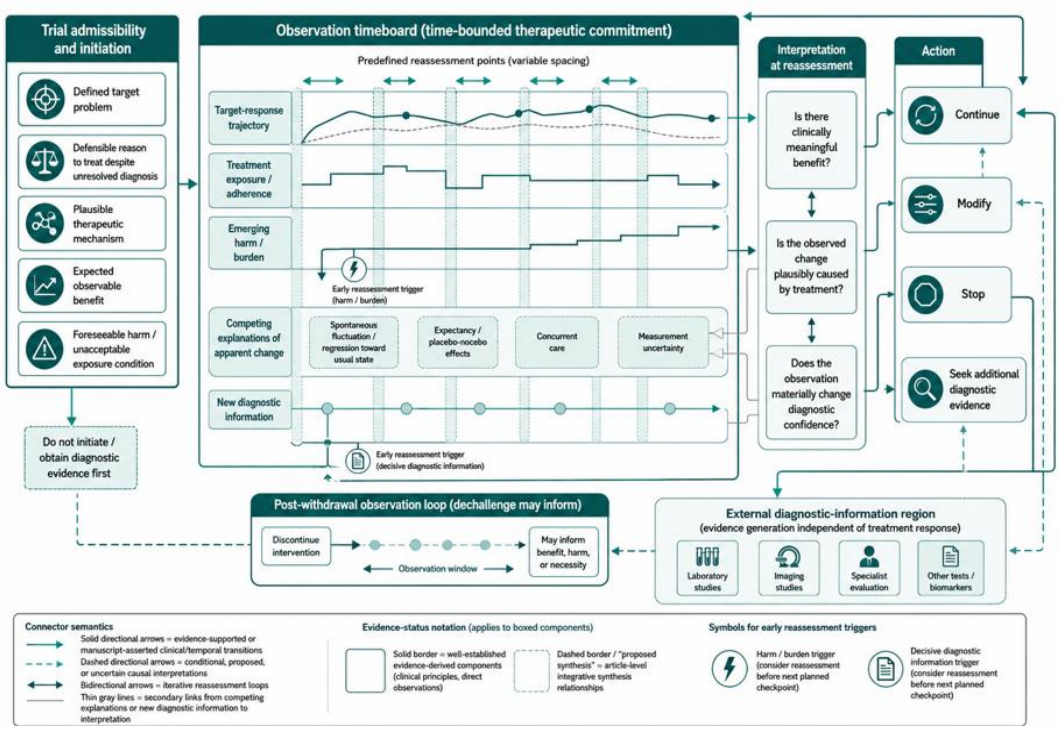

Figure 1. Therapeutic trials as time-bounded prescribing commitments under diagnostic uncertainty

When a therapeutic trial should not be started—or cannot resolve uncertainty

The discipline of a bounded trial is most valuable when it also identifies cases in which empirical treatment is a poor experiment. The first exclusion is clinical: treatment should not be started merely because diagnostic certainty is unavailable. If the expected benefit is small, the intervention carries material irreversible risk, urgent objective testing is available, or treatment will compromise the ability to obtain that evidence, observation without treatment may be more rational.

Asthma diagnosis illustrates the problem of diagnostic interference particularly clearly. Objective evidence can become harder to obtain once anti-inflammatory treatment changes the underlying physiological signal[17]. The broader principle is that treatment has an informational cost whenever it alters the very phenomenon that later

testing is intended to measure. That cost belongs in the initiation decision alongside conventional benefit and harm.

A second exclusion is methodological. Some targets fluctuate too unpredictably, progress too slowly, or cannot be measured with enough reliability for an individual therapeutic trial to separate treatment effect from background variation. Reviews of N-of-1 research show both the restricted conditions under which repeated within-person comparison is informative and the frequency with which published studies fail important methodological standards[10]. Weak measurement, carryover, inadequate observation periods and post hoc outcome selection can make an apparently structured trial no more interpretable than an ordinary before-and-after observation[12].

A third failure state occurs when competing explanations cannot realistically be separated. Expectancy effects are not measurement errors that can simply be removed from every clinical encounter; they are part of the response to treatment and may themselves influence patient benefit or burden[15]. If an intervention is clinically useful, that usefulness can matter even when the pharmacological component of benefit is uncertain. What must be avoided is converting that pragmatic benefit into unjustified diagnostic certainty.

The same caution applies to stopping. The overall randomized evidence does not show that deprescribing polypharmacy produces a universal mortality benefit[24]. Criteria designed for older adults, selected patients with controlled hypertension, or severely frail people approaching the end of life each operate within their own clinical boundaries[26-28]. A rule that is rational in one population can become unsafe or irrelevant when detached from that population's prognosis, treatment goals and baseline risk.

The most defensible role for empirical therapy under uncertainty is consequently limited. It is appropriate where treatment is already clinically justified, the target and expected time course are sufficiently clear, the exposure can be monitored safely, and the resulting observations have a realistic chance of changing the next decision. It becomes irrational when exposure substitutes for diagnostic work, when no observation could trigger stopping, or when the clinician interprets any change as confirmation of the original diagnosis.

Conclusion

Empirical prescribing under diagnostic uncertainty can be rational, but only under conditions stricter than the simple availability of a plausible treatment. A therapeutic trial should begin with an explicit target problem and a treatment whose expected benefit justifies exposure despite unresolved diagnosis. Its observation period should be matched to mechanism, risk and the timing of new information. Reassessment should be triggered prospectively rather than left to routine follow-up, and continuation should require renewed justification.

The central interpretive safeguard is to separate three questions that clinical practice often compresses into one: whether the patient improved, whether the treatment caused that improvement, and whether the observation materially supports the suspected diagnosis. Those questions may produce different answers. Improvement can justify therapeutic continuation without confirming diagnosis; nonresponse can justify stopping without disproving it.

Stopping rules complete the therapeutic trial by preventing a provisional prescription from becoming indefinite through inertia. Their purpose is not to maximize medication withdrawal but to preserve the reversibility and interpretability of treatment decisions. When treatment cannot generate information that would alter management, when diagnostic testing should take precedence, or when risk exceeds the value of empiricism, the rational therapeutic trial is the one that is never started.

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