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Uncertainty and Equipoise: At Interplay Between Epistemology, Decision-Making and Ethics

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Abstract

In recent years, various authors have proposed that the concept of equipoise be abandoned since it conflates the practice of clinical care with clinical research. At the same time, the equipoise opponents acknowledge the necessity of clinical research if there are unresolved uncertainties about the effects of proposed healthcare interventions. Since equipoise represents just one measure of uncertainty, proposals to abandon equipoise while maintaining a requirement for addressing uncertainties are contradictory and ultimately not valid. As acknowledgment and articulation of uncertainties represent key scientific and moral requirements for human experimentation, the concept of equipoise remains the most useful framework to link the theory of human experimentation with the theory of rational choice. In this paper, I show how uncertainty (equipoise) is at the intersection between epistemology, decision-making and ethics of clinical research. In particular, I show how our formulation of responses to uncertainties of hoped-for benefits and unknown harms of testing is a function of the way humans cognitively process information. This approach is based on the view that considerations of ethics and rationality cannot be separated. I analyze the response to uncertainties as it relates to the dual-processing theory, which postulates that rational approach to (clinical research) decision-making depends both on analytical, deliberative processes embodied in scientific method (system II) and "good" human intuition (system I). Ultimately, our choices can only become wiser if we understand a close and intertwined relationship between irreducible uncertainty, inevitable errors, and unavoidable injustice.

Keywords

Clinical Equipoise; Informed Consent; Clinical Research; Research Ethics

Introduction

Clinical research involves a complex interplay of ethics (aimed at meeting the interests of society and clinical study volunteers), epistemology(whereby researchers and patients weigh hoped-for benefits of treatment against unknown harms)and decision-making (whereby all parties, e.g., investigators, IRB members, or trial volunteers use complex cognitive mechanisms to define acceptable benefit-risk ratios to justify the design, approval of and

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participation in clinical research). Is there a common link among these three aspects of clinical research?

In this paper, I expand on the arguments I articulated previously that uncertainty and the formulation of our response to it can be considered both as scientific and moral basis for clinical research.[1]

I "What makes clinical research ethical?"[2]

The ethics of clinical research are usually investigated from the perspective of the major moral theories – utilitarian, duty-oriented and right-based[3]. Ethical clinical investigations, can only occur with autonomous, voluntary, informed consent, which represents the right-based bedrock ethical principle of clinical research.[4] The key ethical research documents such as the Belmont report and Declaration of Helsinki specify that the goal of clinical research is to benefit future and not study patients. Thus, knowledge gained from research is justified from the utilitarian perspective of benefitting future patients.[3] However, as health care professionals we must consider our patients' best interests before we consider utilitarian goals that consider the best interests of others.[3] From this perspective, enrollment into clinical studies is justified only if patients will benefit more than they would if treated outside of the trial.[3] Many physicians believe that enrolling patients in well-designed studies benefits patients more than treating them outside of trials. For example, the National Comprehensive Cancer Network (NCCN), a consortium of 21 leading U.S. cancer institutions, asserts that "NCCN believes that the best management of any cancer patient is in a clinical trial".[5] This assertion, known as the "trial effect", is based on the "similarity position", which considers the ethics of clinical practice and research to be inseparable[6].

Some commentators have expressed their concerns that existing ethical documents fail to clearly distinguish between the nature of research and the ethics of clinical care [6,7]. Based on moral underpinning of differences between intentions vs. consequences[8], these authors argue that the ethics of clinical care should be distinguished from the ethics of clinical research. For example, Miller & Brody propose " a difference position" to conceptualize differences between the ethics of research and clinical practice[6]. They argue that the aim of clinical medicine is to provide optimal care for individual patients governed by the principle of therapeutic beneficence and non-maleficence[6]. In contrast, the goal of clinical research is to produce "generalizable knowledge" as "investigators are primarily interested in developing scientific knowledge about the groups of patients"[6]. While individual patients may benefit by participating in a trial, the primary goal is not to help patients but to generate new scientific knowledge. Thus, the interests of participants and researchers are fundamentally different. Because of this fundamental tension, Miller & Brody contend that clinical research has "inherent potential for exploiting research participants"[6]. Indeed, the history of clinical research is rife with examples of researchers putting their interests ahead of their patients' interests, thereby undermining patients' trust in the clinical research system [9–12]. Not surprisingly, study participants are often confused about the goals of clinical research. This state, known as therapeutic misconception, "exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study"[4].

In a seminal paper, Emmanuel et al. proposed 7 requirements for clinical research to be considered ethical[2] endorsing the concept of clinical equipoise as the important prerequisite for enrolling patients into a clinical trial[2]. However, according to Miller and Brody[6], the concept of equipoise is based on a "similarity position" and Emmanuel and colleagues'[2] proposed requirements are valuable only to the extent that they consider the fundamental

difference between research and practice " as the core value of protecting research participants from exploitation"[6]. In Miller and colleagues' view, clinical equipoise is neither necessary nor sufficient for ethical conduct of clinical trials, and represents a fundamentally mistaken concept that promotes a therapeutic misconception, and, hence, should be abandoned[6,13]. Miller and Brody opine that the honest null hypothesis can be stated more clearly without invoking equipoise, and "if the answer is already known, or the question is trivial, then there is no honest null hypothesis, and a clinical trial should not be conducted"[6]. That is, clinical trials should only be done if there are uncertainties about the effects of competing treatments. It is interesting that Miller and colleagues accept this view, while they argue for abandonment of the equipoise principle.[6,13] This brings me to the key point of my article: acknowledgment of uncertainty is a necessary condition for enrollment of participants into clinical trials, and equipoise is just one way to express ("measure") that uncertainty[1,14].

II Decision-making: Responding to uncertainty of hoped-for benefits and unknown harms of experimental treatments

Enrollment into clinical trials involves making choices that relate to uncertainties about hoped-for benefits and unknown harms that have not yet been observed by researchers or experienced by patients[15,16]. How do we make decisions under uncertainty? Since information upon which we can act is processed by our brains, decision-making ultimately depends on how we cognitively process information. According to the dual-processing theory human decisions rely both on experiential, intuitive (system I) and analytical, deliberative processes (system II) in balancing risks and benefits [17–19]. Thus, our view of a particular research proposal is a function of our responses to uncertainty under system I vs. II. My basic hypothesis is that decision-making in medical research is similar to decision-making in other areas of human activity and relies on the use of both cognitive systems to arrive at a satisfactory solution[20–22].

While there are many theories of decision-making [23], all major theories argue that rational decision-making requires integration of benefits (gains) and harm (losses)[24]. The theories differ in how they propose that benefits and harms should be integrated in a given decision. Here, I describe how our responses to risks and benefits depend on whether they are processed by system I or II cognitive machinery.

System II relies on a formal, analytical approach, often employing statistical and mathematical techniques. However, since this approach takes time, we rely on system I's quick cognitive response under typical real-life situations. We are often forced to use the "satisficing principle", by which adequate solutions depend on heuristics (rule-of-thumb solutions) [21,22,25] since we cannot employ formal analytical mechanisms for each of the 2,000 decisions that we typically make every day[26]. This principle implies that our cognition and decision-making process is error-prone; indeed, humans often make "predictably irrational choices"[27]. Regardless of which types of choices we make, our cognitive processes are governed by bounded rationality theory, according to which human inferences and decision-making depend both on experiential and analytical cognitive processes [18,22].

The fundamental question is: what constitutes a rational approach to clinical experimentation when faced with uncertainty about treatment effects that are yet to be observed?

A number of mechanisms/procedures have evolved to respond to uncertainties about hoped-for benefits and unknown harms of treatments proposed for testing in clinical trials[15,16].

1. Response to uncertainties using a rational, analytical (system II) cognitive process

In this view, the research enterprise has evolved to address epistemic uncertainties of importance to all constituencies interested in human subject investigations (trial patients, future patients, physicians, policy-makers). [1,28] Scientific method, in the form of clinical research, therefore, has become the main means to address and resolve uncertainties of interest to decision-makers[1,14,29]. In doing so, however, clinical research methods must retain scientific soundness (only treatments that are reliably shown to be safe and effective can be recommended to future patients) and ethical fidelity toward trial volunteers (who should not be exploited for research purposes but rather offered the best known treatments at the time of enrollment). [2] The resolution of (treatment) research question is of interest both to society and individual trial patients. [1]

Rational response to clinical uncertainties using the clinical trial method: taxonomy of clinical uncertainties—Uncertainties (about the treatment effects i.e., its benefits and harms) typically present in "grades & shades"[28]. Assessment of uncertainties involves qualitative judgments and attempts to measure it quantitatively using the language of probability.[28] These uncertainties range from complete [maximal] uncertainty to simply not having the factual confirmation for what is an otherwise sufficiently clear understanding of [treatment] effects.[1,28] We previously proposed that these uncertainties can be organized in qualitatively distinct categories, the main purpose of which is to tailor each of the uncertainties shown in Table 1 to specific clinical research designs.

We focus here on the second type of uncertainty shown in Table 1, categorized as "Alternate Futures" and classified as (clinical) equipoise[1]. In this situation, there is no evidence that one intervention should be favored over another. Researchers in non-medical fields have defined similar situations differently. For example, Keynsian economics defines the "principle of indifference," which states that when there is no evidence favoring one possibility over another, they should be assigned equal probabilities[30,31]. Information scientists define it as entropy, which in turn can be related to the uncertainty about choice [32]. In our taxonomy, the scenario "Alternate Futures" refers to maximum uncertainty as the effects of competing treatment alternatives that are considered equiprobable[1,14,33,34]. In this view, equipoise represents and effectively captures only one form of uncertainty (i.e., maximum uncertainty). As stated earlier, when it comes to clinical research these uncertainties need not be expressed precisely in quantitative terms. If researchers' and patients' interests do not directly conflict, (i.e., when we are in equipoise) the most rational and ethical way to resolve uncertainty is through RCTs.[1,28] However, our response to uncertainty also depends on "whose uncertainty is more morally relevant?" – the uncertainty of individual physicians (known as "theoretical equipoise")[35], patients ("indifference")[36], the treating physician and his patient ("uncertainty principle")[37,38], the community of expert practitioners, i.e. trialists ("clinical equipoise")[39,40], or the community of patients, advocacy groups, and lay people ("community equipoise").[41] The uncertainty level expressed as "indifference"[36] or "uncertainty principle"[37] affects patients' willingness to enroll in trials[1], while "community equipoise" influences a research agenda.[1] From the perspective of trial development to address uncertainties classified as "alternate futures", it is actually clinical equipoise[1,39] that affects design of the trial.

The taxonomy presented in Table 1 posits that uncertainties addressed by phase I and phase II trials are not classified as "equipoise".[1] This clarification avoids confusion about a mistaken role of equipoise as a criterion for all clinical trials. Patients and physicians may be uncertain if enrollment into phase II or I trials will result in any benefit, but they do not believe that there is a clear alternative to a new promising, but unproven therapy.[1] They may be uncertain, but they are not in equipoise.

Rational response to clinical uncertainties using clinical trial method: Synthesis of the existing research evidence to inform taxonomy of uncertainties—The purpose of clinical research is to generate new, reliable evidence about the effects of various healthcare interventions. However, clinical studies are not designed in the evidentiary vacuum – each is informed by the existing evidence. Ethical and epistemological questions relate to the methods that should be used to take existing evidence into account before the clinical trial is designed and ultimately approved. It has been argued that investigators have moral obligations to use the best current methods to assess existing knowledge before clinical research can be sanctioned [42,43]. In particular, investigators should perform research synthesis of the existing evidence using a systematic review to inform the study research design[44]. Indeed, it has been demonstrated that if the systematic reviews had been used, unnecessary deaths could have been avoided in a number of research studies. This is because by synthesizing the existing knowledge, systematic review help eliminate uncertainty about the effects of experimental treatments, thus making the proposed studies superfluous[45, 43,46]. This requirement to perform research synthesis before enrolling research participants into new trials is in effect in several countries, but not in U.S.[47, 48].

Other methods that are advocated to evaluate the existing knowledge are the use of practice guidelines to assess the existing standard of care, formal surveys of expert clinical practitioners, and publication of the trial's protocol to solicit critical appraisal and additional input that may inform the existing uncertainties about the effects of the proposed interventions [49].

The purpose of using the best available research techniques to assess the existing evidence is to inform rational and ethical research design, since potential participants in clinical trials should be given all relevant details about the trial, including the track record of new experimental treatments studied in earlier trials [33,50]. In fact, the use of these techniques is the only way to systematically assess existing knowledge, which in turn can inform research design (Table 1). Furthermore, assessment of previous studies is crucial to formulating our response to uncertainties to determine if there are circumstances when the ethics of clinical research and the ethics of clinical practice overlap. For example, we have shown that, on average, experimental treatments are neither more nor less successful than standard therapies once they have reached the stage of being tested in a RCT, indicating that equipoise exists in most trials[51]. When clinical equipoise exists, and researchers and patients interests are not in direct conflict, randomization provides the best odds for the individual patient to receive superior therapy, and thus represents the most rational way to resolve such uncertainty.[1]

The use of systematic methods to answer the research questions, would significantly improve the science and ethics of clinical research. Unfortunately, systematic methods are not routinely used; most research protocols use non-systematic methods to provide rationale for the study design and conduct.

Rational risk analysis: If an ethical duty of investigators (and the IRB) is to protect research participants, then the accurate communication and analysis of risk is required for autonomous informed consent. Traditionally, risk analysis involves quantitative, numeric analysis of perceived risks, which is described as the probability or frequency of typically, harmful events[52]. However, this approach neglects the role of system I, which treats "risks as feelings" (see next section).

2. Response to uncertainties using an experiential, intuitive (system I) cognitive process

While system II adheres to analytical and logical processes that often rely on formal mathematical and statistical techniques, system I is experiential in nature and is intuitively driven toward answering the holistic question "is this (proposed study) good for me?"[53]

"Risk as feeling"[19]: violation of normative rules of probability calculus— People's attitudes toward potential harms and benefits inherently differ, which is likely due to emotional influences on the way information is presented. If people are told that an activity, such as use of a device, installation of a nuclear plant in their neighborhoods, or enrollment into an experimental trial, is associated with low risk, they automatically infer that the activity is beneficial[19]. Similarly, when we are told that an activity is associated with high risk, we infer that it has no or minimal benefits [19].

This processing of information via cognitive I system is the main "culprit" of our systematic violation of the rationality rules under system II[18]. One of the major reasons for deviation from the normative rules governed by system II is violation of laws of the probability calculus[18]. For example, humans are prone to over-emphasize small probabilities and under-emphasize moderate and large ones.[54–59] Consequently, a change from impossible to possible has more impact than an equal change from possible to more possible, a phenomenon known as the possibility effect [54–59]. Likewise, a change from possible to certain has more impact than an equal change from possible to more likely, a phenomenon known as the certainty effect [54–59].

Furthermore, people consistently make choices as though utilities or consequences of our actions are a nonlinear function of outcomes of interest [60,61]. This explains, for example, why a gain of $100 is valued more by a pauper than by a millionaire[29]. Descriptive theories of choice, such as the prospect theory, predict that risk behavior depends on whether outcomes are perceived as gains or losses, relative to some reference point [55,56,58,62]. As a result, a decision-maker is characteristically being risk-averse when relative gains are considered, while a relative loss is accompanied by risk-seeking behavior [55,56,58,62].

People are generally risk-averse when the baseline probability of winning is high, but risk-seeking when it is low [55,56,58,62]. This difference in behavior may explain why patients enroll in risky phase I cancer trials: they believe that the success of the standard treatment is so low that it is worth undergoing the risk of experimental therapy for potential, albeit uncertain, benefits [63,64]. People are also risk-averse when the baseline probability of losing is low, but are risk seeking when the probability of losing is high [58,59,62–65]. This can explain why people undergo invasive screening tests such as colonoscopy for the detection of colorectal cancer; the risk of complications is relatively low, but the prospect of detecting cancer at an early curative stage is appealing [58,59,62–65].

Similarly, regret theory, in which the emotion of regret is a link between system I (emotion) and system II (cognition), explains why some women undergo annual screening mammography (SM) while others do not[24,66]. Since SM is associated with benefits (it can help avoid death due to breast cancer if cancer is detected at an early stage) and harms (it can lead to increased risk of dying from radiation-induced breast cancer), some women may regret more the act of commission (undergoing SM) than the act of omission (failure to undergo SM)[66,67].

Understanding how emotions affect decisions is highly relevant to informed consent, which is a key ethical requirement for patient autonomy. We appear to react to the same information on benefits and risks in "predictably irrational" manner as a function of the presentation format[27]. The people react in significantly different way if the identical

information is "framed" in terms of negative (e.g., mortality) or beneficial outcomes (e.g, survival), or presented in terms of relative vs. absolute treatment effects[68]. These effects, known as violation of description invariance ("framing effect") or procedure invariance ("elicitation effects")[69], led some authors to conclude that it is not possible to obtain consent that is truly informed[70]. According to this view, the value of informed consent to serve as an instrument because it adheres to ethical normative principle of transparent communication of benefits and risks is not applicable because the patients do not have stable values and preferences before enrolling in an experimental study[70, 71]. Rather, the patients' values are constructed during the process of elicitation, and they can easily be distorted by the "framing and elicitation effects"[71]. Consequently, MacLean argues that the value of informed consent lies in the process itself, because it helps construct the patients' values and represent the fairest way to respect patients' views about enrollment into trials. Since efforts are made to design fair consents and consenting processes, informed consent implies that the right decisions are made, even if they may not accurately reflect patients' preferences [70,71].

Benefit vs. harms: different attitudes towards the consequences of false positives vs. false negatives—The considerations I just highlighted may explain why we have different tolerance toward false positives vs. false negatives when it comes to treatment harms vs. benefits. Humans react to false-positive vs. false-negative data differently, in that we are more ready to falsely accept that treatment is harmful then to try to find out if it is unsafe to use[72]. This phenomenon explains why IRB and Data-Safety Monitoring Committees are more apt to stop trials early due to reported harms than to allow trials to continue so that the "truth" might be discovered[72,73]. On the other hand, when it comes to benefits we weigh false negatives more than false positives and are more ready to falsely accept that treatment does not work, requiring further data collection to increase our certainty that treatment is truly effective[72]. These decisions can be valued differently at individual vs. group (societal) levels. For example, some have argued that if people are willing to take risks, they should be allowed to have access to unproven and potentially harmful treatments[74,75]. The FDA, however, considers that open access to unproven drugs could potentially harm thousands people, and that these harms outweigh the potential economic consequences of abandoning drug development. By setting false negatives (typically at 20%) higher than false positives (typically at 5%) in the case of benefits, FDA requires higher burden of proof of treatment efficacy before approving it for every eligible patient. This (collective) decision differs from the way individuals react to risks and benefits; individuals are typically willing to accept treatment or enroll in the trial even when there is very small chance of benefit [57,74,75].

These considerations highlight a key ethical dilemma: whose uncertainty and values about benefits and risks count? Is it the group (society), or the individual (patient or physician), each of whom processes the risk/benefit information differently. One can argue that reactions related to enrollment into trials are predictably different according to dual-processing theory.

This discussion raises a fundamental question: what exactly constitutes rational decision-making? How should participants rationally respond to the uncertainties about the effects of hoped-for benefits and unknown harms in the setting ultimately guided by trust, but which is potentially exploitive? Framed this way, enrollment into clinical trials can be approached using decision-theoretical a rational approach to decisions under uncertainty [73,76]. According to decision-theory, maximization of expected utility is a normative criterion of rationality, and rational decision-makers should act according to this criterion (i.e., select treatment with the higher expected utility)[29]. Qualitative analysis, such as the use of taxonomy of uncertainties, may further complement the rational quantitative analysis of decision-making under uncertainty.

However, as explained above, humans constantly violate normative criteria of rationality. In the past, this was considered as evidence that humans are irrational [27,29]. Recent thinking, however, considers rationality to be mental states or processes that help us achieve our goals[77]. Achieving goals using formal, logical rules is consistent with rational approach. Achieving goals by violating these rules would also be considered rational[77]. Hence, rationality should take into account both formal principles of rationality and human intuitions about good decisions[24,78]. Rational approaches to participation in clinical trials, or any other aspect of decision-making, should therefore take into account cognitive processes at system I and II levels.

Relying on both cognitive system I and system II to define rational approach to ethics of clinical trials—As discussed, the ethics of clinical trials fundamentally encompass our response to uncertainties about future treatment effects. Our response to uncertainties is, however, a reflection of system I and II cognitive processes. Hence, strategies for responding to uncertainties about the ethics of clinical research must rely on both qualitative and quantitative methods. For example, a researcher's initial decision to undertake a clinical trial is typically based on personal conjecture about the effects of treatments to be tested. This unarticulated experience, governed by system I, forms the basis for further actions [1,18,19,23,79]. However, as discussed, decisions based on system I are efficient but are often incorrect. Hence, system II should subsequently be used to formulate a more quantitative, rational approach to resolution of uncertainties about treatment effects. According to this view, researchers use qualitative processes of system I to examine their background knowledge and experience in order to quickly decide which treatments options are viable for further testing[1]. As no all hypotheses can be formally tested, system I is used to economize to narrow down among the potentially a large number of hypotheses (treatment options) before investigators develop a research strategy that relies on the system II cognitive processes to explicitly articulate uncertainties about treatment effects and decide how best to address these uncertainties[18,79]. Similar cognitive processes are used when enrolling subjects into ongoing trials. Physicians may not mention trials for which patients may be eligible[80], presumably because they are relying on system I cognitive processes. Participants' reactions may also adhere to the same cognitive processes, i.e., patients want to know if a trial may benefit them, but they may not analytically assess the trial value. This reaction likely explains why many patients are uncomfortable with randomization, even if under some circumstances enrollment into a RCT[81,82], may be most rational answer to what patient should do when face the prospect for benefits but unknown risks [33,51,83].

Can the interests of trials and future patients be aligned? Is there common ground between ethicists and clinical researchers?—The section above describes the cognitive processes that may explain many observations and disagreements between ethicists and researchers related to clinical trial ethics. Can we offer a comprehensive approach to assessing clinical trial ethics that incorporates epistemological difficulties related to unknown treatment effects within the framework of cognitive theories of decision-making? While the task is certainly challenging, I believe it is a doable.

To start, we can recognize the importance of cognitive processes that play a role in our response to uncertainties about treatment effects. We need to articulate these uncertainties better[1,14,28], and ask "What is the best method to resolve underlying uncertainty [about treatment effects]?" To better articulate uncertainties, we should mandate that existing evidence be thoroughly assessed to inform "knowns and unknowns" about proposed interventions. As outlined above, this assessment should include the use of systematic reviews, survey of the best experts, assessment of testing successes in each field, etc.[43,49,84]. Since reliance on system I or II alone is not sufficient, we should develop techniques to enhance communication between two systems to minimize cognitive and decision

errors[24,67]. For example, we can ask researchers and participants to anticipate the consequences of decisions based on how they would feel if their decisions (i.e. participation in the trial when they should not have, and vice verse) would turn wrong[67,72]. This approach uses cognitive emotion regret as a link between systems I and II[67]; other approaches should also be explored. That is, we should both reflect and feel good about decisions, "blink as well as think".

Can we apply these principles so that the requirements of the 3 major moral theories are met: utilitarian, duty-oriented and right-based approaches to medical research on humans and find common ground between the views of ethicists and clinical researchers? I believe this situation exists only when we are able to articulate uncertainties as equipoise/ "uncertainty principle". When equipoise exists, we can apply a formal scientific method as the best way to resolve such uncertainties as through the use of RCTs. Hence, as argued before [1], enrollment into RCTs under equipoise is in the patient's best interest since it provides him/her with the best odds for receiving the best possible treatment. By enrolling patients in RCTs, society obtains the most credible information about the best treatments for future patients while preserving participants' autonomy, since the patients have opportunity to judge for themselves what is the best way to resolve uncertainties about their own situation, i.e., they can "exercise what makes people essentially humans"[3].

As repeatedly argued, assessment of uncertainties relies on both qualitative and quantitative judgments. The same principle applies to the operationalization of equipoise. It is sometimes naively assumed that equipoise means that people can only be enrolled in a RCT if uncertainty can be precisely quantified as a 50:50 chance of benefit. However, surveys of lay people and IRB members indicate that people are willing to enroll in RCTs (with equal chance to be randomized to experimental vs. standard treatments) even if the uncertainties about benefits are expressed as 70:30% [85,86]. Equipoise can be achieved even if the trial includes additional procedures that are not part of routine practice as long as randomization is considered the optimal way to resolve these uncertainties. The process demands application of careful judgment. In philosophical literature, this approach is closest to the Rawlsian principle of reflective equilibrium/considered judgment [87]. Rawls recognized that the quantitative approach to justice and ethics is not feasible and advocated the use of reflective equilibrium to arrive at difficult moral decisions. It is reflective since it still takes into account the key precepts of moral philosophy ultimately linking the theory of human experimentation with the theory of rational choice[87]. Judgments are said to be deliberative and considered because they are derived systematically with the least likelihood of distortion[87, 88].

In summary, although ethical theories often create a sharp distinction between clinical research and clinical practice, there are circumstances in which these are not mutually exclusive activities. In fact, when a given clinical uncertainty is matched with an appropriate clinical trial design, enrollment into a clinical trial represents the most rational and ethical way to address the interests of trial participants and society (future patients). Matching study design with a taxonomy of clinical uncertainties represents a viable mechanism to link the theory of human experimentation with the theory of rational choice, thereby assuring protection of human subjects while promoting advancement of medical science.[1] The process requires careful, reflective equilibrium/considered judgment, and relies on qualitative and quantitative assessments that consider intuition and formal principles of decision-making. This analysis adheres to what Hammond unforgettably calls irreducible uncertainty, inevitable errors, unavoidable injustice[89]. That is, we must clarify uncertainties related to our judgments and recommendations, handle false positives and false negatives in explicit and transparent way, specify what values we place on these errors, and understand

the potential for unavoidable injustice as the consequences of our decisions may affect different people in different ways.

Although it may not be possible to develop the "ultimate theory" of clinical trial research ethics that is satisfactory to all parties (society at large- future patients, investigators, research participants, each with different values and goals), the articulation of uncertainties and related concept of equipoise remains one of the most important ethical ideas proposed in history of clinical research.

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Table 1

Taxonomy of Clinical Uncertainties[*,$]

Level of Uncertainty	Study Design Matching a Given Uncertainty Level
Clear-enough future (e.g. preliminary data show dramatic treatment effects; so called “penicillin” effect)	Observational studies; single arm prospective studies with or without historical control can be used as reliable means to assess the effects of treatment(s) under consideration
Alternate Futures (a few discrete alternatives whose outcomes cannot be reliably predicted; clinical equipoise exists)	Randomized clinical trial as the best method to resolve this level of uncertainty.
A Range of Futures (a range of potential futures can be identified but no natural discrete scenarios has emerged) Many new drugs. Few data on safety and efficacy.	Single arm or randomized Phase II trials to address this level of uncertainty.
True Ambiguity (complete ignorance) A new chemical moiety, a few data on safety and efficacy	Further pre-clinical or phase I testing necessary to help shape our uncertainty in more solid direction

[*] Adopted from[1,90]

[$] [While each of these categories can be further sub-categorized by the quantitative expression in beliefs about the treatment effects within the category itself, such precise characterization of uncertainty in clinical research before the study began is probably not possible. Hence, qualitative or semi-quantitative categorization of uncertainties that can logically be matched with a given study design appears to be more useful. This point is important to emphasize, as some authors take literally minor statistical changes as evidence of resolution of uncertainty]. [A reader should I limit my discussion in this paper to therapeutic research; the taxonomy for diagnostic or prognostic research would likely be different].