Chapter One

1.0 Statement of Thesis

For the past fifty years there has been an ongoing dialogue within the philosophical and medical literature which attempts to justify, ethically, the practice of conducting rigorous medical experimentation on human patients. The purpose of this thesis is to compare one particular principle whose genesis resulted from the ethical tensions within the dialogue. This principle is that of equipoise, and it will here be juxtaposed with similar terms within the tradition of philosophical skepticism. Once this similarity has been established, it will be possible to draw from the ancient tradition resources for analyzing the current literature on the modern principle.

Within the medical research context equipoise is generally considered to be a state of reasoned uncertainty concerning the relative merits of two or more competing treatment options for a specific disease and patient population. The legitimacy of equipoise as a guiding principle in clinical research ethics is currently a matter of considerable debate. In this thesis I claim that the use of the term "equipoise" in the medical research context is extremely similar to terms and concepts from the philosophical tradition of skepticism and as a result of this similarity I claim that it is possible to explain better the principle of equipoise's vulnerability to already published criticisms. A comparison of these criticisms might suggest a grim future for equipoise as a legitimate guiding principle for the ethical conduct of clinical research.

To accomplish this goal, this thesis is organized into three chapters. The first chapter will provide background into the nature of the particular problem equipoise was intended to resolve and provide an overview of how the principle of equipoise

arose, fell and formed the basis of subsequent modifications. The second chapter will compare the principle of equipoise with terms from the philosophical tradition of skepticism, as well as demonstrate the explanatory power of that comparison. The third chapter will prognosticate the future of equipoise, or equipoise-like concepts, based upon the analysis of chapter two.

At the last count, there were at least twenty different definitions or distinctions within the medical literature for the term "equipoise".[1] Rather than attempt to define and explain each of these nuanced points, chapter one will delve into three important voices which are most relevant to the analysis in chapter two: Charles Fried, Benjamin Freedman, and Fred Gifford. First, though, to understand the ongoing equipoise dialogue it is necessary to appreciate the nature of clinical research and the ethical tension between conducting controlled research and providing care.

1.1 Scope and Limitations of this Study

In this thesis the term "clinical research" will be used only to represent comparative clinical trials of two or more medical treatments, pharmaceutical or surgical. Additionally, this thesis focuses upon research in which a physician-researcher offers trial enrollment to her patient, as this is the intersection between providing medical care and performing medical experimentation on patients. There could be situations in which a patient seeks out a researcher in order to request trial enrollment, but as long as such a situation occurs outside of the patient-physician relationship it is not subject to the principles reviewed and analyzed in this thesis.

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[1]Fred Gifford, "Freedman's 'Clinical Equipoise' and 'Sliding-scale all-dimensions-considered equipoise'," *Journal of Medicine and Philosophy* 25 (2000): 423. Alex London, "Equipoise and international human-subjects research," *Bioethics* 15 (2001): 312-332. and Scot Halpern, "Evidence-based equipoise and research responsiveness," *American Journal of Bioethics* 6 (2006): 1-4.

Hence, the scope of this thesis is limited to only the ethical tensions of physicians who also act as researchers by enrolling patients into clinical trials.

In the United States, medical research involving humans is subject to the guidance and oversight of the Food and Drug Administration (FDA). The FDA has adopted a standardized model for clinical research which consists of three phases of clinical trials. Phase I trials usually require the enrollment of healthy volunteers to determine the safety of a treatment, often to determine a safe dosage range for a drug. Phase II clinical trials are typically non-randomized trials which seek to enroll ill patients whose disease has not been alleviated or eliminated by the existing treatments commonly used by physicians for the patient's ailment. Unlike Phase I clinical trials, enrollment into Phase II clinical trials often entails a physician offering trial enrollment to her patient as an alternative to standard medical treatment. This offer of trial enrollment is generally considered to be consistent with the ethical norms of medical practice since all other treatments have failed to alleviate the patient's disease.

This thesis, however, is focused on the ethical tensions that arise when physicians offer Phase III clinical trial enrollment to patients. Phase III clinical trials, unlike most Phase I or Phase II trials, are designed to provide a concurrent comparison treatment – often a placebo or the best available treatment for the specific disease. This comparison is necessary to determine if the new treatment under investigation is as safe or effective as existing treatments. The morally relevant aspect of Phase III clinical trials for this thesis is that they commonly involve a physician offering enrollment into a clinical trial in which the patient could receive either an experimental treatment or the comparator treatment (either standard treatment or placebo). Frequently in Phase III

clinical trials the patient's treatment allocation is determined by a randomizing procedure. The ethical principles analyzed in this thesis have been presented as guiding principles to determine when a physician may ethically offer Phase III randomized trial enrollment to her patient.

1.1.1 Guiding Ethical Principles in Clinical Research

So what does a useful guiding ethical principle do that a useless one would not? It seems that a useful guiding ethical principle would have all or at least most of these qualities: (1) it would be based upon sound rationale; (2) it would be possible for a moral agent to fulfill all of the requirements entailed in the principle; (3) the principle would be able to give specific guidance in all or most cases in which it would be implemented; and lastly, (4) the principle would not always give the same guidance – meaning that it would not always allow trial enrollment or, conversely, never allow trial enrollment. Thus a guiding principle of research ethics should be rationally defensible, achievable, give specific guidance, and be able to distinguish between morally distinct situations.

1.2 Introduction to the Randomized Controlled Trial

It is widely regarded within contemporary medicine that the most dependable source of clinical evidence for resolving questions of treatment superiority (or non-inferiority) is the randomized clinical trial (RCT). The RCT, first introduced into clinical research in 1946,[2] has grown in popularity to the extent that it has taken on the

[2] Medical Research Council Streptomycin in Tuberculosis Trials Committee, "Streptomycin treatment for pulmonary tuberculosis," *British Medical Journal* 2 (1948): 769-782. The first randomized clinical trials began in 1946 but were not published until 1948.

moniker, or cliché, of "The Gold Standard"[3] of proper clinical intervention research. In a RCT two or more treatment regimens are compared by randomly allocating the treatments under comparison to eligible patients as they are enrolled into the study. Once a predetermined number of patients have been enrolled into the study the results from the treatment groups are then analyzed statistically and compared against every other treatment group in the study for such outcomes as mortality, morbidity, clinical symptoms, or other (so called "surrogate") clinical outcome measures.

The randomized experimental design of the RCT was first modeled after R.A. Fisher's 1926 agricultural experiments in which he decided to "arrange the plots [of land] deliberately at random, so that no distinction can creep in between pairs of plots treated alike and pairs treated differently."[4] Fisher had intended that this procedure would approximate random error. One of the earliest supporters of randomization in clinical trials, Sir Austin Bradford Hill, advocated randomization not because it provided a good estimate of random error but because it prevented the physician-researcher from consciously or unconsciously prejudicing the results of the experiment through selection bias.[5]

While the RCT offered the physician-researcher greater experimental stringency in clinical research it also created difficult ethical problems. Ethical concerns regarding the physician's role in experimentation arose not long after the introduction of RCTs into clinical research.[6] Specifically, the ethical concern that has

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[3] Ted Kaptchuk, "The double-blind, randomized, placebo-controlled trial: gold standard or golden calf?" *Journal of Clinical Epidemiology* 54 (2001) 541.
[4] R.A. Fisher, "The arrangement of field experiments," *Journal of the Ministry of Agriculture* 33 (1926): 506-507.
[5] Richard Doll, "Controlled trials: The 1948 watershed," *British Medical Journal* 317 (1998): 1218.
[6] Otto Guttentag, "The Problem of Experimentation on Human Beings: The Physician's Point of View," *Science* 117 (1953): 210.

been most difficult to resolve is how to reconcile the fiduciary duty of the Hippocratic "patient centered" medical ethic, also termed the "therapeutic obligation", with the requirements of experimental design – strict randomization of treatment allocation.[7] Randomization of treatment allocation is antithetical to providing personal care to the patient based upon his individual particularities. Instead of a physician choosing a treatment that optimally fits her patient's specific needs, the patient's treatment is chosen by a randomizing device – such as whether a three digit number within a sealed envelope is odd or even. Personal care entails having the physician make individualized decisions based upon the specifics of the patient; however, this decision making process is one of the known biases that randomization is intended to remove. Thus personal care, in the context of experimentation, is equivalent to selection bias according to many proponents of the RCT. Starkly put, the physician-researcher must manage the significant tension between upholding the therapeutic obligation and following the experimental design requirements which have become the standard operating procedure of clinical research.

1.3 Introduction of Equipoise into the Dialogue

In an effort to skirt both the apparent ethical dilemma brought on by the randomization procedure and the emerging burden of regulatory requirements imposed upon researchers several proponents of the RCT, in the 1950's and 1960's, put forward related rationalizations for enrolling patients into RCTs – often without obtaining consent – based upon a state of uncertainty as to which of two or more possible treatments is the superior treatment. Sir Austin Bradford Hill was one such researcher

[7] Fred Gifford "The Conflict Between Randomized Clinical Trials and the Therapeutic Obligation," *Journal of Medicine and Philosophy* 11 (1986): 348.

who was not shy in declaring his opposition to always obtaining consent from patients.[8] Hill describes the situation where he deemed obtaining consent unnecessary as the situation where the physician is unsure which treatment is superior prior to the initiation of the clinical investigation. Hill paints this situation as follows:

> …the customary situation of the controlled trial is… an ignorance of the relative merits of two (or more) treatments. To dispel that ignorance you decide to give one treatment to one of your patients and the other treatment to another of your patients… Having made up your mind that you are not in any way subjecting either patient to a recognized and unjustifiable danger, pain, or discomfort, can anything be gained ethically by endeavouring to explain to them your own state of ignorance and to describe the attempts you are making to remove it? And what is true of two patients is equally true of 20 or 200. Once you have decided that either treatment *for all you know* may be equally well exhibited to the patient's benefit, and without detriment, is there any real basis for seeking consent or refusal?[9]

In an attempt to respond to researchers such as Hill, the constitutional lawyer and philosopher of ethics Charles Fried coined the term "equipoise" to give a name to this ideal situation of ignorance that physician-researchers had offered as a rationalization for enrolling patients into RCTs, often without obtaining consent.[10]

Any fair interpretation of Fried's essay should admit that the introduction of the term "equipoise" into the medical literature was, at most, an unanticipated side-effect of his broader thesis. Unlike most aspects of his thoroughly researched essay, Fried provides no references or footnotes to indicate why he chose the word "equipoise" as the name for the idealized state of balanced evidence (or lack of evidence) that

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[8] It should also be noted here that Sir Austin Bradford Hill was a statistician not a physician. The writings of Dr. Guttentag, cited in footnote 5, offer an alternative view of the patient-physician relationship that is roughly contemporary to Hill.

[9] Sir Austin Bradford Hill, "Medical Ethics and Controlled Trials," *British Medical Journal* 1 (1963): 1047-1048.

[10] Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, Clinical Studies 5. (Amsterdam: North-Holland; New York: American Elsevier, 1974), 51. For more examples see Jackson, DM as well as Martini, Paul in *Clinical investigation in medicine: Legal, ethical, and moral aspects; an anthology and bibliography*, ed. Irving Ladimer and Roger W. Newman 1963.

physician's were describing as a rationale for enrolling patients into RCTs. He never formally defines equipoise and instead characterizes the concept in vague terms.

Rather than a commentary on the equipoise concept, Fried's main thesis is a philosophical argument in support of the claim that patients have a specific right to "personal care" in the context of the patient-physician relationship, even in experimentation. The right of personal care, to Fried, is that the patient has a right to have his specific particularities taken into consideration when the physician providing care makes any medical decision. By defining and defending a set of rights for patients in the context of clinical research he directly responds to those who felt there was no ethical basis for the requirement of obtaining consent in clinical research.

Fried introduces the term "equipoise" within the section of the paper in which he ascertains that RCTs really do create ethical dilemmas for physicians. He suggests that the physicians who propose the epistemological situation of equipoise as a means of skirting the ethical dilemma are missing the real ethical problem. Primarily, "doing one's best" for the patient is not so much about prescribing the "best known" therapy as it is about focusing on investigating the individual patient in the examination room as a specific unique case and creating a healing plan for that person based on that individual's particular physical situation, diagnostic picture, values and life plans. The sentiment within the clinical research community that without randomization there can be no certainty is precisely what Fried feared would encourage physicians not to investigate too closely the specifics of the individual patient.

Fried's essay constructs a patient's right to personal care from a philosophical basis of underlying principles. The right to personal care is founded upon a person's

right to maintain his individual personal integrity. Section 4.3.4 of his essay spells out four fundamental principles which justify this right to maintain personal integrity: lucidity, autonomy, fidelity and humanity.[11]

When a physician withholds from the patient the fact that his treatment will be selected by a process of random assignment the physician is impinging upon the patient's interest in self preservation and maintaining his personal integrity. First, the physician has not been completely candid with the patient and has thus infringed upon his autonomy to make life choices for himself. Second, the patient has entered into a fiduciary relationship with the physician with the expectation that the physician would have his particular interests in mind when giving advice or making decisions. Fried explains further that even within the situation of equipoise:

> One might say that the individual patient has perhaps not been sacrificed in the crude sense that the best available treatment has been withheld from him, but he has been sacrificed in that for the sake of experimental design his interest in having his particular circumstances investigated has been sacrificed.[12]

In light of this conclusion, randomization within the RCT constitutes a violation of a patient's right to personal care and his interest in self preservation. The patient's fully informed consent is required for the patient to temporarily surrender this fundamental right for the sake of actively participating in the trial. That the physician and other experts are in an equivocal epistemological situation regarding the superiority of alternative treatments has no bearing on either the patient's right to know if his treatment will be assigned at random or the patient's right to choose whether he wants to participate in the experiment.

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[11] Ibid. 101-104.
[12] Ibid. 53.

With the requirement of informed consent now accepted in the medical research community as essential to ethical science, the equipoise concept has lost its unfortunate connection to the act of withholding information from patients. Equipoise, instead, became important because of its ability to justify the process of rigorous controlled experimentation without the "crude" sacrifice of giving a patient a known inferior treatment. Since consent is now required, the subsequent dialogue on equipoise has focused on ensuring that patients are not materially disadvantaged at any point within a RCT by receiving a treatment that is likely inferior.

1.3.1 Equipoise

The principle of equipoise has been defined in several ways by different authors. For the purposes of this thesis I will only present two ways of conceiving the principle of equipoise. Neither of these definitions can be expressly found in Fried's 1974 essay; instead these ways of conceiving the principle of equipoise were attributed to Fried by his first commentators, perhaps incorrectly.[13]

The first definition of the principle of equipoise can be stated as an honest belief, informed by all data prior to an RCT (from *in vitro* studies, animal models, Phase I and Phase II trials involving human subjects), that the trial will begin with a viable null hypothesis.[14] Consider a superiority trial of standard treatment A and experimental treatment B for disease D in a specific patient population P. For a superiority trial the alternative hypothesis is that experimental treatment B is superior to the standard treatment A (H_A: B > A for D in P). The null hypothesis for this trial would be that experimental treatment B is not superior to the standard treatment A (H_0:

[13] Paul Miller and Charles Weijer, "Rehabilitating equipoise," *Hastings Center Report* 13 (2003): 96.
[14] Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 141.

$B \leq A$ for D in P). For equipoise to exist in this situation a physician-researcher would have to judge honestly that, all available data considered, the null hypothesis is just as likely to be true as the alternative hypothesis (probability of H_0 = probability of H_A). For the sake of brevity let us call this definition "hypothesis equipoise" (HE). If the physician-researcher believed that it is more likely that H_A is true than H_0, then it would be a violation of her therapeutic obligation for her to offer RCT enrollment to her patient rather than provide B. By offering RCT enrollment in this case she is allowing the possibility that her patient could receive a treatment that she believes is inferior to B.

The second, more restrictive, definition of the principle of equipoise is that equipoise exists when the physician-researcher has no treatment preference between treatments A and B for her specific patient.[15] This simpler definition may actually have more clinical relevance because rather than being a judgment on the relative probabilities of competing hypotheses for a defined patient population, the physician must determine if she is cognitively and professionally indifferent between treatments A and B in light of the unique particularities of the patient sitting before her. This judgment requires much more than an estimation of the likely outcomes of A compared to B across the patient population. The individual patient's values, expectations, and life plans must be weighed by the physician in this determination of indifference.[16]

To uphold the therapeutic obligation the physician must be in equipoise in regards to the specific clinical situation and values of her patient and not just be

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[15] Arthur Schafer, "The ethics of the randomized clinical trial," *New England Journal of Medicine* 307 (1982): 723.

[16] Fried considered that this would make genuine equipoise virtually impossible to achieve. Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, Clinical Studies 5. (Amsterdam: North-Holland; New York: American Elsevier, 1974), 51-52.

indifferent to treatments A and B for the patient population in the abstract. This definition entails HE because it requires an estimation of likely outcomes for patients in a similar situation to the individual patient, but it also requires the inclusion of several variables specific to the individual patient that are absent in HE. This more complete definition of the principle of equipoise we will call individual physician equipoise (IPE). More formally:

> IPE exists when in the judgment of the physician-researcher she has no treatment preference between standard treatment A and experimental treatment B for her individual patient (who fits the criteria for inclusion into patient population P) after considering all of the data entailed in making an HE determination and simultaneously taking into account her individual patient's values, expectations, and life plans.

This definition of IPE has the important ethical implication that if a physician-researcher does have a decided treatment preference for her individual patient then it would be unethical for her to offer trial enrollment because there would be a chance (depending on the trial design, often a 50:50 chance) that her patient would receive the treatment she believes to be inferior. This situation risks a violation of the therapeutic obligation and it is therefore considered unethical for a physician-researcher to offer RCT enrollment when she has a treatment preference.

IPE sets a highly restrictive standard as a requirement for fulfilling the therapeutic obligation during clinical research. It was noted in Section 1.1.1 that guiding ethical principles should be achievable and the IPE principle seems to be an unachievable standard for the ethical conduct of research. This lofty standard would

prevent the implementation of many potential RCTs; and consequently would limit the advancement of medical science. This effect of IPE was considered unacceptable and as a result several alternative justifications for enrolling patients into RCTs – including modifications of IPE were proposed. One such modification of equipoise, presented by Benjamin Freedman, has become the "standard answer"[17] to resolving the tension between fulfilling the therapeutic obligation and testing important medical hypotheses via the RCT.

1.3.2 Criticisms of equipoise

Benjamin Freedman has authored the most practical modification to Fried's equipoise concept after showing the inadequacies of the principle of equipoise. Rather than addressing Fried's vague and brief descriptions of the equipoise concept, Freedman aims his criticisms at the early commentators of Fried's equipoise. These commentators were unable to resolve the ethical tension brought on by enrolling patients into RCTs; because, according to Freedman, these commentators had interpreted the equipoise concept in a narrow and restrictive manner. The interpretation of equipoise they described was analogous to the IPE definition; and which Freedman terms "theoretical equipoise". Freedman's arguments against IPE will be critical to the analysis in chapter two and will be discussed in more detail there; so, for that reason, in this section I will only briefly summarize his criticisms of IPE.

Freedman's first criticism of IPE is that it can potentially be disturbed by the smallest acquisition of information. Preliminary data from laboratory or early phase studies may disturb a physician-researcher's equipoise before a RCT even begins.

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[17] Robert Veatch, "Indifference of subjects: an alternative to equipoise in randomized clinical trials," *Social Philosophy and Policy* 19 (2002): 300.

Similarly, the patient could divulge some personal information about himself that may have a bearing on which treatment might be preferable for him. As soon as the physician-researcher begins to believe that one treatment is superior to the other for her particular patient, she is obligated to her patient to provide the treatment that she believes is superior. For this reason Freedman describes IPE as "balanced on a knife's edge".[18] Fried also saw this as a problem for equipoise as the justification for offering RCT enrollment. Fried voices this concern by stating:

> I would suppose that a group of patients could be so defined that the risks and benefits of the two available courses of action were quite evenly balanced. But, when a particular patient is involved, with a particular set of symptoms, a particular diagnostic picture and a particular set of values and preferences …, then one may doubt how often a physician carefully going into all of these particularities would conclude that the risks and benefits are truly equal.[19]

This important criticism of the principle of equipoise raises serious doubts about the possibility of such a cognitive state ever honestly occurring in the mind of the physician-researcher. Even if a physician-researcher were to be in a state of equipoise for a particular patient at the beginning of a trial; what are the chances that such a state would persist through the entire course of the trial as preliminary data accumulates? Clearly, this rationale cannot justify the continuation of a trial all the way until statistical significance has been reached.

The second criticism of IPE is that it requires simple "one-dimensional" hypothesis to fulfill the necessity of a perfect balance of evidence. This is problematic because clinical choice between A and B is often multi-dimensional in nature.

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[18] Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 143.
[19] Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, Clinical Studies 5. (Amsterdam: North-Holland; New York: American Elsevier, 1974), 51-52.

Standard treatment A may be more effective than experimental treatment B at combating disease D; but A may cause serious side effects or complications that prevent it from being the preferred treatment in the multi-dimensional sense. For example, the drug Amphotericin B is highly active against *Histoplasma capsulatum*, an invasive fungal infection; however, the original deoxycholate formulation of Amphotericin B has long been known to cause significant nephrotoxicity which could ultimately lead to kidney failure.[20] For this reason the less active drug, itraconazole, which has drawbacks of its own (hepatotoxicity and poor gastrointestinal absorption), eventually became the treatment of choice for mild to moderate manifestations of disseminated *Histoplasma* infections.[21] The multi-dimensionality of treatment choice, Freedman contends, is virtually impossible to formulate under the conditions of IPE; as he explains, it requires "the formulation of a rigorous calculus of apples and oranges".[22] As a result, IPE requires too simple a conceptual framework to ethically justify RCTs and a new concept is, therefore, sorely needed.

1.3.3 Clinical Equipoise

Freedman's alternative to the "theoretical equipoise" interpretation entails viewing equipoise as a relative balance of opinion across the community of competent physicians rather than within the mind of a single individual physician. By this view there is no requirement for a perfect balance of opinion or evidence; rather, as long as two or more "schools" of competent physicians exist who disagree about the preferable

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[20] Norman Bell et al, "On the nephrotoxicity of amphotericin B in man" *American Journal of Medicine* 33 (1962) 64.
[21] L. Joseph Wheat et al, "Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America" *Clinical Infectious Diseases* 45 (2007): 819.
[22] Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 143.

treatment for a specific patient population, then there is a need for methodologically rigorous clinical research to disturb the difference of opinion towards a strong consensus in one or the other direction. Freedman's modification of equipoise is termed the principle of "clinical equipoise"; and this modification involves a situation where there is a genuine controversy within the medical community as to which of two or more competing treatment options is best for a specific patient population.[23]

> More formally, clinical equipoise exists between standard treatment A and experimental treatment B for disease D in patient population P if, and only if, at least a reasonable minority of competent physicians prefer treatment A to treatment B (and vice versa) for D in P.

Clinical equipoise has several conceptual and practical advantages over the original equipoise concept. Primarily, clinical equipoise does not require that the individual physician-researcher be completely ambivalent to the treatments under investigation. Under clinical equipoise, the physician-researcher may have a decided preference for experimental treatment B; but so long as other competent physicians in the medical community still prefer standard treatment A, proponents of clinical equipoise contend that there is nothing unethical about her offering RCT enrollment to her patients in which A is compared to B. The rationale given for randomization in this case is that when the state of clinical equipoise exists it might be by pure chance that the patient has seen this particular physician who has a preference for B when the patient could just as likely have gone to see another physician who prefers A.[24]

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[23] Ibid. 144.
[24] Ibid. 144.

Additionally, the clinical equipoise modification seems to be a more coherent concept within the medical research endeavor. Clinical equipoise entails the view that medical knowledge is collective in nature; and that clinical questions are resolved only when a consensus within the medical community is reached. The original equipoise concept does not easily cohere with the communal nature of medical knowledge as the balance of evidence is to be judged only within the mind of the individual physician; this difference further explains the attractiveness of clinical equipoise over previous equipoise concepts.

These conceptual improvements of (1) allowing the individual physician-researcher to have a treatment preference; and (2) viewing medical knowledge as a consensus within the competent medical community, were intended to provide a rationale that would allow most RCTs to proceed all the way until statistical significance has been reached. The ethical requirement of equipoise within the mind of the individual physician was deemed far too unstable to base the continuance of enrolling patients. Fried thought that such an even balance was rare if not psychologically impossible for an individual to have, let alone maintain throughout an experiment. Freedman concurred and through his clinical equipoise concept made the judgment of the individual physician-researcher subordinate to the consensus of competent physicians. Under IPE if the physician believes that A is better than B; then to offer trial enrollment and take a chance that the patient would receive B would risk violating the therapeutic obligation. However, under clinical equipoise if a physician has a treatment preference but other physicians prefer a different treatment, then it is not considered “substandard care” for a physician to offer trial enrollment. It is truly a

community standard for "standard of care" rather than an individual one. The change in level from the mind of the individual to the disagreement within the medical community produces a far less restrictive and more stable ethical requirement for the conduct of RCTs. As a result, the principle of clinical equipoise has become the standard answer to resolve the physician-researcher's dilemma of offering RCT enrollment to patients while simultaneously upholding the therapeutic obligation of always doing what is best for the individual patient.

1.3.4 "RCT Dilemma" Criticism of Clinical Equipoise

Freedman's solution to the physician-researcher's tension fundamentally changed the focus of the equipoise debate. The dialogue changed from the possibility of equipoise existing within the mind of an individual physician-researcher to whether the medical community standard espoused by Freedman truly resolves this difficult tension. One of the more systematic criticisms of clinical equipoise was offered by the philosopher Fred Gifford. Gifford's primary criticism of clinical equipoise, which he calls the "RCT dilemma", poses a significant argument against clinical equipoise as an ethical justification for enrolling patients into an RCT.[25] The RCT dilemma critique emphasizes that medical knowledge does not come into existence instantaneously at the conclusion of a RCT which has reached statistical significance. Instead, RCTs are lengthy experiments that take months or years to conclude and during that period the incoming results are likely to change medical opinion across the community, thereby causing an ethical problem for physician-researchers as the trial draws closer to completion. The flaw in Freedman's clinical equipoise concept which Gifford

[25] Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," *Bioethics* 9 (1995): 129.

recognizes is that in Gifford's view, the accumulation of preliminary data may be enough for a majority of physician's to form a strong consensus on the preferred treatment before statistical significance within the trial has been reached.

It is important to note that Gifford is not the first person to recognize this ethical problem brought on by the epistemological realities of RCTs. Fried may have anticipated the RCT dilemma and seems to have thought that the problem was a serious one. Fried writes:

> …it would seem that there is a continuing duty on the part of the patient's physician to inform himself about the progress of the experiment and to inform his patient about any significant new information coming out of the experiment that might bear on patient's choice to remain in the study or seek other types of therapy. This is an important issue in RCT's involving long term courses of treatment. If patients abandon one alternative on the basis of early, inconclusive results, no definitive conclusion can be drawn from the trial.[26]

Fried anticipated this epistemological problem at the level of the individual physician-researcher within the context of the patient-physician relationship and subsequently saw the problem as possibly impinging upon the patient's right to make fully informed autonomous decisions concerning trial enrollment.

Similarly, the bioethicist Robert Veatch published another version of this epistemological problem in 1979, before the equipoise dialogue really developed after Freedman's original clinical equipoise paper in 1987. Veatch's argument was focused on the difficulties of reviewing longitudinal or sequential studies and the preliminary data these study designs produce prior to completion. Veatch acknowledged that Gifford's argument focuses on the same problem as his previously published "problem

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[26] Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, Clinical Studies 5. (Amsterdam: North-Holland; New York: American Elsevier, 1974), 35.

of preliminary data" when he stated "this is a problem of randomized clinical trials that has long concerned me".[27] Veatch emphasized the moral obligation of physicians, data and safety monitoring board (DSMB) members and institutional review board (IRB) members to disclose fully to patients what is known about treatments prior to enrollment in a study.[28] The "problem of preliminary data" rests upon the distinction between what a physician-researcher considers a significant difference and what a patient would consider a significant difference between treatments. The physician-researcher is trained, perhaps indoctrinated, to consider only those results with a 5% (P=0.05) or less likelihood of being falsely positive as "significant results" whereas the patient's threshold of significance may be considerably less stringent. The physician-researcher might not consider a preliminary result with a 7% (P=0.07) chance of being false positive significant enough to disclose the result to the patient. Perhaps as Veatch suggests, such a result would not be significant enough to end the trial and publish as conclusive results, yet, the patient may consider such a preliminary result as convincing enough to base the decision to enter the trial or not.[29] Thus, this epistemological issue for the ethical conduct of RCTs had been noted for some time; but Gifford's contribution, beyond a full explication of the problem, is that Freedman's clinical equipoise does not resolve the dilemma any more than the original equipoise concept.

Gifford is careful to distinguish between two different decisions to be made with data from RCTs – individual "present patient decisions" (whether to offer RCT

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[27] Robert Veatch, "Indifference of subjects: an alternative to equipoise in randomized clinical trials," *Social Philosophy and Policy* 19 (2002): 307.
[28] Robert Veatch, "Longitudinal Studies, Sequential Design, and Grant Renewals: What to Do with Preliminary Data," IRB: Ethics and Human Research 1 (1979): 1-3.
[29] Ibid. 1.

enrollment or another alternative to the patient being seen at the moment) and generalized "policy decisions" (whether to approve the drug, device or surgical procedure for widespread use within a defined population of patients).[30] Gifford contends that less evidence, that is, less certainty, is required to make a decision for the "present patient" than for the "policy" judgment because the moral consequences of a wrong "present patient" decision are significantly less than those of a wrong "policy" judgment.[31] If an error of judgment is made for the present patient, then that individual may suffer unnecessarily, or perhaps worse, die as a direct result of the error; however, if an error is made in making a policy decision, then hundreds or thousands of similar patients may suffer or die. This distinction is critical to Gifford's critique of clinical equipoise because it demonstrates how a physician-researcher could feel justified in recommending that her patient not enroll in a RCT (or recommending her already enrolled patient to withdraw) based upon interim data but still maintain that the broader clinical controversy has yet to be resolved.

Gifford's "present patient decision" versus "policy decision" distinction is more robust when the individual particularities of the present patient are taken into consideration. Interim data may show trends that are pertinent to the values and life plans of a particular patient and may affect his choice in participation, but are less important – perhaps completely irrelevant – when viewed across the entire patient population. The physician may acknowledge that for a given patient population as a whole there is insufficient evidence to declare which of two treatments is superior; but for an individual patient there is enough evidence to provide reasonable medical

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[30] Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," *Bioethics* 9 (1995): 130.
[31] Ibid. 130.

advice. When, in the middle of conducting a RCT, physician-researchers have enough evidence to make decisions for individual patients but not policy decisions the true dilemma has emerged – the RCT may falter due to insufficient enrollment and as a result the policy decision will not be decided; or for the sake of acquiring enough data for a policy decision, the interests of the present patient are sacrificed, and the therapeutic obligation ignored, for the good of future patients and the RCT continues.

1.3.5 Sliding-Scale All-Dimensions-Considered Equipoise

In response to his RCT dilemma critique of clinical equipoise, Gifford proposes a modification of Fried's original equipoise concept which he contends would more likely allow RCTs to continue on, ethically, until statistical significance has been reached. This new modification, "sliding-scale all-dimensions-considered equipoise" (SSADCE), arises out of an explication of the multi-dimensionality and complexity of the judgment that A is better than B for disease D afflicting the individual patient I.[32] Gifford's solution is multifaceted and, he concedes, likely impossible to implement. He envisions a situation where physician-researchers provide constantly updated information on the progress of the trial to both patients already in the study and patients that are to be offered enrollment into the study. It is up to the well informed patients to assess if, all-dimensions-considered, they are in individual patient equipoise for the treatments under investigation.[33] If the patient is in equipoise, all things considered,

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[32] This realization is similar to Freedman's assumption that the superiority of X to Y is a "portmanteau measure", not the result of a single outcome variable. See Benjamin Freedman, "Equipoise and the Ethics of Clinical Research." *New England Journal of Medicine* 317 (1987): 143.

[33] The importance of the physician's equipoise is not well formulated in Gifford's SSADCE solution. It seems that his purpose is less about who is in SSADCE and more about how an individual's values can affect that equipoise. He does state that "it is surely the subject's values that are most important". See Fred Gifford, "Freedman's 'Clinical Equipoise' and 'Sliding-Scale All-Dimensions-Considered Equipoise'," *Journal of Medicine and Philosophy* 25 (2000): 419.

then the patient will enroll in the study (or remain enrolled). If the patient is not in all-dimensions-considered equipoise then he may decline enrollment (or withdraw from the study). Gifford contends that there is likely enough variability in values within the patient population that even when the average patient is no longer in all-dimensions-considered equipoise, as a result of the accumulating evidence, there will be enough patients with different values and life plans to keep enrollment in the study at a viable level until statistical significance has been reached.[34]

As a form of individual patient equipoise the SSADCE proposal effectively removes the physician from the decision making process, and as a result circumvents the central ethical dilemma of the equipoise dialogue. As long as the patient is somehow provided with up to date interim data from the trial the physician has upheld her duty of care to her patient. Whether the patient enrolls (or remains enrolled) or declines enrollment (or withdraws from the study) is a personal choice based upon the patient's particular situation and values – it has nothing to do with the enrolling physician's equipoise or the community of physicians' equipoise.

The sliding-scale all-dimensions-considered modification of the equipoise concept reverts the level of importance from the medical community back to that of the individual – except now it is the individual patient and not the individual physician who must be in equipoise. This change along with the emphasis on the multi-dimensionality of patient treatment preference is intended to allow RCTs to progress further, perhaps all the way to statistical significance, despite the incoming data that might force the enrolling physician to decide upon a preference or the community of physicians to arrive at a treatment consensus.

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[34] Ibid. 418.

In a recent article Gifford laments the fact that no one has responded to his arguments against clinical equipoise and his proposed SSADCE.[35] Perhaps no one has responded to his SSADCE proposal because Gifford even admits from the start that it does not seem practical to implement SSADCE; or perhaps, because the dialogue has come full circle again and Gifford's proposal suffers from the same fragility as the original equipoise concept. What is more curious is that no one has attempted to respond to his arguments against clinical equipoise.

As there are no published criticisms of the sliding-scale all-dimensions-considered equipoise proposal or responses to his arguments against clinical equipoise I would like to offer briefly my own response. My intent here is not to pose formal criticisms of SSADCE or the RCT dilemma; but rather to suggest possible reasons for the lack of published responses to these important arguments. My primary concern with the SSADCE proposal is that it focuses on the patient's state of equipoise. As the patient's informed consent is already a requirement for enrollment in an RCT, what does patient equipoise (in any form) add to this other than an interesting examination of why a patient might consent to enrollment? Moreover, if the tension caused by offering RCT enrollment is a concern over whether the physician is upholding her therapeutic obligation to her patient, then would it not be most appropriate to focus on the physician's role and cognitive state in this process? One could respond that the patient's values and expectations are vital inputs for the physician to consider when upholding the therapeutic obligation; but those inputs are already present in the original IPE concept. It seems that the SSADCE proposal has some of the difficulties of the

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[35] Fred Gifford, "So-called 'Clinical Equipoise' and the Argument from Design," *Journal of Medicine and Philosophy* 32 (2007): 137.

original IPE concept (instability in light of new data) as well as the problem of not addressing the physician's professional opinions, thoughts or preferences in upholding her Hippocratic duties within the research context.

That Gifford's SSADCE proposal has not gained widespread support is not altogether surprising, given the complex nature of SSADCE and the likelihood of difficulties implementing such a proposal. However, the fact that no one has published a systematic response to Gifford's "RCT dilemma" argument against clinical equipoise is curious. The "RCT dilemma", as Gifford presents it, provides a significant argument against clinical equipoise that requires attention if clinical equipoise is to remain the guiding principle to ensure that the therapeutic obligation is upheld during RCTs.

While this is not intended to be a complete analysis of the RCT dilemma argument, there are two aspects which could be considered weaknesses. First, Gifford's distinction between the importance of a "present patient" decision and "policy" decision seems to be based upon utilitarian ethics in which the consequences of an error in judgment on a large patient population are compared to the consequences of an error in judgment on an individual patient. Less evidence is required for a present patient decision than a policy decision simply because an error in judgment with the present patient decision will likely only harm one individual whereas an error made on a policy decision will affect many patients. While this distinction and the reasoning behind it may be valid, the use of utilitarian logic within the equipoise dialogue is suspect. If utilitarian reasoning were legitimately applicable in the equipoise dialogue it could then be argued that there are no ethical problems associated

with RCTs at all- an individual patient's needs and rights would always acquiesce to the greater needs of patients as a class.

A distinction must be made between medical reasoning which is consequentialist in nature but still focused on producing the best consequences for an individual patient and utilitarian reasoning which focuses on producing the best total consequences for all those who could be affected by an action. Certainly patient-centered consequentialist reasoning is essential to the physician's medical decision making processes; however, only in extreme cases, such as triage or perhaps severe communicable diseases, are the consequences to future patients or the consequences to the larger patient population given greater moral weight and consideration than the consequences for the individual patient. Historically, the consequences for the individual patient are nearly always given priority, and it is this prioritization that forms the basis of the patient-physician relationship. It is this patient-physician relationship which requires equipoise-like concepts to ensure that, during experimentation, the individual patient's needs and rights are not sacrificed for the sake of others.

A second possible weakness in Gifford's "RCT dilemma" is that his criticism of clinical equipoise rests upon a fully rational clinical epistemology in which present patient decisions and policy decisions are reasonably made by medical experts based upon the quantity and quality of evidence inputs. This does not account for factors at the medical community level that are not fully rational, but are likely involved in the determination of both present patient and policy decisions. Specifically, the evidence based medicine (EBM) movement, which can be described as a both a methodological

and social movement within medicine, has influenced clinical judgment by blurring Gifford's distinction between the evidentiary requirements of present patient decisions and policy decisions. This blurring effect of EBM has raised the evidentiary requirements for making present patient decisions by setting statistically significant RCT results as the standard of evidence for basing seemingly all clinical decisions. If the EBM movement has indeed increased the evidentiary requirements for basing present patient decisions to that of policy decisions, then Gifford's distinction has been undermined. Without such a distinction the RCT dilemma cannot occur. These brief, and by no means comprehensive or convincing, thoughts on SSADCE and the RCT dilemma are intended only to point out some possible weaknesses in Gifford's arguments because no counter arguments have been published.

1.4 Conclusion to Background

This brief introduction to the equipoise dialogue has focused on the important voices of Charles Fried, Benjamin Freedman and Fred Gifford. Following Fried's initial commentary, Freedman and Gifford have introduced evolving versions of the equipoise concept in an attempt to determine when a physician-researcher may ethically offer RCT enrollment to her patient. The two influential versions of equipoise – IPE and clinical equipoise – have come under significant criticism. The effect of these criticisms, whether psychological or epistemological, is the conclusion that both IPE and clinical equipoise have significant difficulties of actualization in praxis.

Chapter Two

2.0 Equipoise and Skepticism

The RCT equipoise dialogue within the medical ethics literature has progressed with little reference to the history of philosophy. Counter-arguments to individual physician equipoise (IPE) and clinical equipoise arise out of the realities of conducting randomized clinical trials (RCTs) and the complex nature of clinical practice. Yet, without reference to the history of philosophy the ongoing dialogue over equipoise has little underlying coherence. Demonstrating that the terminology and content of the equipoise dialogue has striking analogs in the ancient tradition of philosophical skepticism establishes a framework with which to understand the now well-known fatal flaws in IPE and the emerging body of work on the inadequacies of clinical equipoise.[36] In order to demonstrate that the RCT equipoise debate relates to the larger tradition of philosophical skepticism, I will first link the term "equipoise" to a frequently occurring term in the literature of philosophical skepticism. Next, I will show both how the two terms are used similarly within each respective philosophical dialogue, and also how some counter-arguments against skepticism and against IPE and clinical equipoise seem congruent. First, though, a brief introduction to philosophical skepticism is required.

2.1 The Tradition of Philosophical Skepticism

Philosophical skepticism entails both an attitude towards knowledge propositions and a method of inquiry. Skepticism as an attitude of doubt towards knowledge propositions can be attributed to the first "skeptic," Pyrrho of Elis, in the

[36] All references to "skeptics" and "skepticism" are meant to refer to Pyrrhonism rather than Academic skepticism or more recent skeptics. The tradition of philosophical skepticism is too long and diverse to encompass all versions of skepticism in this thesis.

fourth century B.C.E.[37] Skepticism as a systematic method of inquiry can first be attributed to Aenesidemus and his "Ten Tropes."[38] While a doubting disposition is relevant to the equipoise dialogue presented in the first chapter, skepticism as a method of inquiry provides a more direct link to the equipoise dialogue.

The classic skeptical method, regardless of the actual arguments used, follows a distinct pattern: (1) the skeptic notes that opinions differ in a particular area of inquiry; (2) the skeptic accepts that no criterion of truth exists to distinguish between differing opinions; (3) arguments for *isostheneia* – the equal power of opposing opinions are given; (4) *epochē* – the suspension of judgment follows; and (5) at the conclusion of this inquiry the state of tranquility, *ataraxia,* is attained.[39] Much of the ancient skeptic literature is focused on providing examples of how opinions can differ and how these differing opinions are of equal power. The skeptic accepts the premise (often implicitly) that conflicting opinions cannot both be true. Skeptics require a criterion to determine which of two or more conflicting opinions is true; however, they argue, often at length, against the possibility that such a criterion exists. Without a criterion for determining which of two conflicting opinions is true (and accepting the implicit premise that both opinions cannot be true because they conflict), the skeptic is forced to decide the truth by other means.

Next the skeptic attempts to determine the truth by means of deciding which of the two opinions seem stronger or more likely. If one opinion was clearly more plausible or reasonable, then perhaps the inquiry could be concluded and the truth

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[37] Myles Burnyeat, Introduction to *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983), 2.
[38] Ibid. 6.
[39] Myles Burnyeat, "Can the Skeptic Live His Skepticism" in *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983), 121.

determined. For the skeptic this task is not so simple. Skeptics use the tropes or modes (eight to fifteen examples refined and recycled throughout history)[40] to force the enquirer to accept that opposing opinions on the matter at hand are of equal strength or equally likely to be true.[41] This state in which evidence or opinions are equally convincing to the enquirer is called *isostheneia*. Once convinced by skeptical arguments that *isostheneia* exists, the enquirer is forced to suspend judgment (*epochē*) on the inquiry until new evidence or arguments can settle the matter. As soon as the enquirer has reached the point where the last option is to suspend judgment, the search for true knowledge must be postponed. While this outcome might disappoint those seekers of the truth outside of the skeptic tradition, especially modern day researchers, an ancient skeptic preferred this situation. When the ancient method of skepticism does not lead to true knowledge (which is virtually always) it leads to something perhaps better – a euphoric peace of mind which the ancient skeptics called *ataraxia*.

It must be noted here that the skeptical attitude towards knowledge propositions is important to the outcome of the skeptical method sketched above. A modern

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[40] According to Sextus Empiricus there are ten traditional modes or arguments which bring about a suspension of judgment. These first ten are based upon: (1) trope of variety in animals; (2) trope of differences in human beings; (3) trope of different structures of the sense organs; (4) trope of circumstantial conditions; (5) trope of positions and intervals and locations; (6) trope of intermixtures; (7) trope of quantities and formations of the underlying objects; (8) trope of the fact of relativity; (9) trope of frequency or rarity of occurrence; and (10) trope of customs, laws, and dogmatic convictions (Outlines of Pyrrhonism I 36-38). For example to bring about a suspension of judgment as to the color of an object the skeptic could use the third trope of differences in structures of sense organs. To this end Sextus uses this example among many others: "sufferers from jaundice declare that objects which seem to us white are yellow, while those whose eyes are bloodshot call them blood-red" (Outlines of Pyrrhonism I 44). Since three people perceive the same object differently Sextus contends that it is best to suspend judgment on the question as to the actual color of the object. Later skeptics developed five more tropes intended to induce the suspension of judgment: (1) trope of discrepancy; (2) trope of infinite regress; (3) trope of relativity; (4) trope of hypothesis; and (5) trope of circular reasoning. The trope of infinite regress, for example, states "we assert that the thing adduced as a proof of the matter needs a further proof, and this again another, and so on *ad infinitum*, so that the consequence is suspension, as we possess no starting point for our argument" (Outlines of Pyrrhonism I 166-167) For more examples see Sextus Empiricus. *Outlines of Pyrrhonism*. trans. R.G. Bury. Buffalo: Prometheus Books: 1990.

[41] Gisela Striker, "The Ten Tropes of Aenesidemus" in *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983), 105.

enquirer might prevent the outcome of *ataraxia* by taking an educated guess or choosing that which seems the most probable. While this might seem reasonable to us, the ancient skeptics were not inclined to make this concession. The ancient skeptic wants to be absolutely certain that he has attained the truth. An ancient skeptic would rather claim ignorance than take a chance at being wrong.

2.2 Equipoise and Skepticism

The RCT equipoise dialogue has several elements in common with philosophical skepticism and can, therefore, be viewed as a modern parallel of the tradition of philosophical skepticism. The relevance of this view shall be discussed in chapter three.

2.2.1 Analogous Terminology

The point in the skeptic's method which provides the closest connection to the RCT equipoise dialogue is *isostheneia*. In translations of the skeptic literature from the Greek, the term *isostheneia* is often replaced by the term "equipollence." "Equipollence" comes from the Old French word *equipolence*,[42] which was ultimately derived from Latin *æquipollentia*; [43] these two words, "*æquus,*" meaning equal and "*polēns*" meaning power, expresses the idea that two or more opinions, theories, or sets of evidence are "equal in force, power, effectiveness or significance" to an unbiased judge.[44] Likewise, the term "equipoise" contains the French root "*poids,*" meaning weight; this root suggests that two objects under comparison, whether physical objects

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[42] Oxford English Dictionary, 2nd ed., http://bert.lib.indiana.edu:2055/cgi/entry/50077296?single=1&query_type=word&queryword=equipollence&first=1&max_to_show=10

[43] Ibid. http://bert.lib.indiana.edu:2055/cgi/entry/50077296?single=1&query_type=word&queryword=equipollence&first=1&max_to_show=10

[44] American Heritage Dictionary, 4th ed., http://dictionary.reference.com/browse/equipollence

or immaterial things – opinions, theories, or sets of evidence – are of equal weight (physical or epistemological) when compared side by side as if on scales.[45]

The etymology of "equipoise" reveals that some of the oldest known uses of the term were in connection to skepticism. In 1678 the philosopher John Norris used the term "equipoise" in a passage in which he praises Descartes' assimilation of profound skepticism to build his philosophy upon:

> So great reason had the excellent *Des-Cartes* to lay the foundation of his philosophy in an equipoise of mind; and to make the removal of these prejudices the very entrance and beginning of wisdom.[46]

It is unclear from this passage if Norris is using "equipoise" interchangeably with "equipollence"; but what is clear is that "equipoise" is Descartes' state of mind during the skeptical meditation that leads to his *cogito*, the skeptical starting point for his philosophy.

A second early example of the use of the term "equipoise" in connection to skepticism was published by the prolific author Samuel Johnson in a satirical article in 1759 in which he creates humorous caricatures of amateur philosophers including a skeptic. Johnson describes the skeptic, Sim Scruple, as a man who:

> lives in a continual equipoise of doubt, and is a constant enemy to confidence and dogmatism. Sim's favourite topick of conversation is the narrowness of the human mind, the fallaciousness of our senses, the prevalence of early prejudice, and the uncertainty of appearances.[47]

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[45] Oxford English Dictionary, 2nd ed, http://bert.lib.indiana.edu:2055/cgi/entry/50077292?query_type=word&queryword=equipoise&first=1&max_to_show=10&sort_type=alpha&result_place=1&search_id=5rag-m29Cb0-7562&hilite=50077292

[46] John Norris, *A collection of miscellanies: consisting of poems, essays, discourses and letters, occasionally written*, 9th ed. (London, 1740) Eighteenth Century Collections Online. Gale Group 127. http://bert.lib.indiana.edu:2259/servlet/ECCO?c=1&stp=Author&ste=11&af=BN&ae=T186443&tiPG=1&dd=0&dc=flc&docNum=CW116067067&vrsn=1.0&srchtp=a&d4=0.33&n=10&SU=0LRK&locID=iuclassb&finalAuth=true

[47] Samuel Johnson, "*The Idler*," November, 17, 1759, no. 83, http://www.gutenberg.org/files/12050/12050-8.txt

This passage not only links the term "equipoise" with doubt in opposition to dogmatism; but also the name of the character "Scruple" means doubt associated with a hesitation to act which alludes to a major criticism of skepticism – that it encourages lethargy.[48] As with the John Norris passage, Johnson's use of the term does not clearly allude to equipollence, just a state of mind that is connected with persistent doubt. In light of the similar meanings and roots of the words "equipoise" and "equipollence" and the substantial connection between these early examples of the term "equipoise" and philosophical skepticism, there seems to have been a common usage of "equipoise" pertaining to skepticism that has been lost in contemporary language.

2.2.2 Similar Uses of the Terms "Equipoise" and "Equipollence"

What is more revealing than the similar meanings of the terms "equipoise" and "equipollence" and the etymology of equipoise in connection to skepticism, is the manner in which the two terms are used in each respective dialogue. As a step in the skeptical method of inquiry, arguments for equipollence are the justification for *epochē* – the suspension of judgment on the matter until more evidence or clearer arguments are presented which can change the balance of force between opposing opinions or arguments. Parallel to this concept is the contemporary use of equipoise as a necessary epistemological condition for the ethical commencement and continuance of a RCT.

If the requirement of equipoise is to be met, then there must be a balance of evidence (in the case of IPE) or opinion (in the case of clinical equipoise) concerning the relative merits of two therapies. The state of equipoise between two competing therapies allows the physician (IPE) or medical community (clinical equipoise) to

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[48] Oxford English Dictionary, 2nd ed., http://dictionary.oed.com.proxy.ulib.iupui.edu/cgi/entry/50217085?query_type=word&queryword=scruple&first=1&max_to_show=10&sort_type=alpha&search_id=mMvx-F67piD-8557&result_place=1

suspend judgment on the question of which treatment is superior until more evidence is obtained. In the contemporary case of medical research, however, suspension of judgment is not indefinite – a determination is to be made at the completion of the RCT, presumably once statistically significant results are obtained. The balanced state of evidence or opinion on a clinical controversy expressed as "equipoise" is the ethical justification for suspending judgment throughout a clinical trial. Thus, both equipoise and equipollence elicit a suspension of judgment, in some form, on a matter of inquiry.

2.2.3 IPE and Skepticism

Skeptics claim ignorance as to the true realities of the external world; as a result, skeptics can only give personal reports of what they perceive without the assumption that what they perceive is real. Hence, when a skeptic states that equipollence exists between two competing arguments, what he is assenting to is merely that he perceives the two arguments to be equally convincing. A skeptic will never claim that two opposing arguments are actually equally plausible, only that he perceives them to be so. The state of equipollence is therefore an assessment of perception within the mind of an individual. Mirroring this concept, the IPE concept requires that the individual physician be cognitively indifferent, all things considered, between two competing treatment regimens based upon her assessment of the current evidence. In IPE what is of ethical consequence is that the physician's assessment of the competing treatment options indicates that neither treatment seems superior to the other. If real differences between the two therapies exist, then they will become known at the conclusion of the experiment. Thus both IPE and philosophical skepticism are focused on assessments of individual perception and judgment. Clearly the IPE

concept is similar to this account of philosophical skepticism, but what of Freedman's clinical equipoise concept?

2.2.4 CE and the Tropes

The relation between the debate over skepticism and the RCT equipoise dialogue is not limited merely to the usage of the original IPE concept. Freedman's clinical equipoise concept can also be described in skeptical terms. The state of equipollence within the mind of the skeptic comes about by an honest assessment of how the individual perceives the force of opposing arguments or sets of evidence. Typically, the Tropes lead the ancient skeptic to perceive that a state of equipollence exists because differing informed opinions have been raised on the matter of inquiry. The philosopher Gisela Striker describes the Tropes as collections of examples chosen to "show… that the same objects appear different to different observers."[49] The Tropes bring about suspension of judgment by giving examples that lead one to assent to the fact that the differing appearances or opinions are all well founded and of equal force. Analogously, clinical equipoise is intended to bring about a (temporary) suspension of judgment due to the fact that there are differing expert opinions or beliefs within the clinical community about which treatment is best for a specific patient population.

Freedman's clinical equipoise solution allows the individual physician-researcher to have a treatment preference; however, the fact that some clinicians prefer the other treatment compels the physician-researcher to offer RCT enrollment to her patients – a contemporary form of suspending judgment – until conclusive results will move the collective opinions of the medical community toward a consensus. The fact

[49] Gisela Striker, "The Ten Tropes of Aenesidemus" in *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983), 99.

that other competent physicians disagree with her points to the possibility that the physician-researcher's preferred treatment could actually be inferior. The community conflict criterion of clinical equipoise compels the individual physician-researcher to offer her patients RCT enrollment rather than her preferred treatment in much the same way as the Tropes induce a skeptic to suspend belief.

Both clinical equipoise and the Tropes intend to compel the individual to suspend judgment on a matter of inquiry because opinions or beliefs differ on the subject. In the skeptic Agrippa's "disagreement" trope, just as in clinical equipoise, it is the mere fact that a controversy exists that induces a suspension of judgment. The prominent skeptic Sextus Empiricus briefly explains Aggripa's disagreement trope as:

> That based on discrepancy leads us to find that with regard to the object presented there has arisen both amongst ordinary people and amongst philosophers an interminable conflict because of which we are unable either to choose a thing or reject it, and so fall back on suspension."[50]

This straightforward argument simply claims that it is reasonable to suspend judgment when a conflict between people arises. In another passage in which Sextus attempts to show that all matters of inquiry are subject to one or all of the tropes he adds: "For if … it is a matter of unsettled controversy, the necessity of our suspending judgment will be granted."[51] An analog to the disagreement trope can be found in what Gifford calls the "evidential warrant rationale" for assenting to clinical equipoise, which he states as "the fact that other experts have different opinions counts as a reason to alter one's view of what the evidence warrants, or to give up one's confidence."[52] In both

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[50] Sextus Empiricus *Outlines of Pyrrhonism*, trans. R.G. Bury (Buffalo: Prometheus Books, 1990), 63.
[51] Ibid. 66.
[52] Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," *Bioethics* 9 (1995): 139.

Aggripa's disagreement trope and clinical equipoise, the individual who has an opinion or preference is compelled to suspend judgment because an intractable conflict causes them to reconsider her assertions. On the basis of similarities in terminology, etymology, and usage it seems reasonable, therefore, to conclude that both IPE and clinical equipoise can be described using the concepts of philosophical skepticism.

2.2.5 A Brief Aside on the Usage of Equipoise and Equipollence

The analogous usage and meanings of the terms "equipoise" and "equipollence" point to the likelihood that it was not a mere coincidence that a philosopher of Fried's standing slipped "equipoise" into the a dialogue on the ethics of RCTs. There is at least one small textual clue which can be interpreted as evidence that Fried was likely aware of this allusion to philosophical skepticism. Fried argues that "a posture of doubt between two therapies" is not sufficient justification to proceed without fully informed consent from patients.[53] The phrase "posture of doubt" seems to express both Fried's criticism of equipoise – that IPE is probably impossible to attain – as well as a suspicion that physician-researchers were merely taking the "position" that uncertainty exists with regards to the preferred treatment for her patient rather being in a genuine state of epistemological uncertainty on the matter. Certainly, it requires much interpretation and extrapolation to tie this brief quote of Fried's to philosophical skepticism; however, it seems at least plausible that the connection between "equipoise" in the RCT dialogue and skepticism was an intentional association.

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[53] Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy*, Clinical Studies 5. (Amsterdam: North-Holland; New York: American Elsevier, 1974), 154.

2.2.6 Comparison of Counter-arguments to Equipoise and Skepticism

The connection between equipoise and philosophical skepticism is strengthened and made more relevant to the RCT equipoise dialogue when counter-arguments to equipoise and philosophical skepticism are compared. The philosophical tradition of skepticism has long been a target of philosophers from the Stoics to Descartes and Hume. A complete survey of counter-arguments to skepticism cannot be made in this space; however, as a starting point, Hume's reply to the skeptical challenge is especially relevant to the criticisms of IPE.

Some of the published criticisms of the IPE concept are remarkably similar to Hume's strategy to undermine skepticism, notably one influential criticism published by Benjamin Freedman. Hume contends that skeptical arguments may be impossible to refute by reason alone. However, Hume does not find this conclusion to be problematic because skeptical arguments, and the doubt that they produce, seemingly have no lasting consequences on human life. In effect, he concedes the skeptical arguments but at the same time points to the fact that they cannot prevent belief and activity. Hume's first point is to argue that skepticism (Pyrrhonism) is unique among philosophical sects in that it is contrary to human life and function:

> A Stoic or Epicurean displays principles, which may not only be durable, but which have an effect on conduct and behavior. But a Pyrrhonian cannot expect, that his philosophy will have any constant influence on the mind: or if it had, that its influence would be beneficial to society. On the contrary, he must acknowledge, if he will acknowledge anything, that all human life must perish, were his principles universally and steadily to prevail.[54]

[54] David Hume, *Enquires Concerning Human Understanding and Concerning The Principles of Morals*, ed. P.H. Nidditch (Oxford: Clarendon Press 1975), 160.

What is important for the comparison to the equipoise dialogue is the assertion that skepticism does not exert any lasting power over human thought processes; Hume proceeds to explain the frail nature of philosophical skepticism by noting that while skeptical arguments appear intractable to resolve, they do not have an influence on the realities of human life. He proceeds to argue that:

> And though a Pyrrhonian may throw himself or others into a momentary amazement and confusion by his profound reasonings; the first and most trivial event in life will put to flight all his doubts and scruples, and leave him the same, in every point of action and speculation, with the philosophers of every other sect, or with those who never concerned themselves in any philosophical researches. When he awakes from his dream, he will be the first to join in the laugh against himself, and to confess, that all his objections are mere amusement, and can have no other tendency than to show the whimsical condition of mankind, who must act and reason and believe; though they are not able, by their most diligent inquiry, to satisfy themselves concerning the foundation of these operations, or to remove the objections, which may be raised against them.[55]

Thus Hume's challenge to skepticism is that though skeptical arguments may be convincing in a philosophical sense, they do not prevent anyone from believing in the realities of life. Skeptical arguments, while perhaps intractable, comprise a philosophy that does not affect human conduct because they cannot overcome the human tendency to believe and act upon those beliefs.

To see how Hume's challenge to skepticism is applicable to the RCT equipoise dialogue, compare Hume's argument about the effect of the "first and most trivial event" to this passage written by Benjamin Freedman:

> Theoretical equipoise is overwhelmingly unstable; that is, it is disturbed by a slight accretion of evidence favoring one arm of the trial. … We may say that theoretical equipoise is balanced on a knife's edge.[56]

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[55] Ibid. 160.

Hume argues that the student of skepticism is quick to disregard the force of skeptical arguments as soon as a mundane life event awakens him from his skeptical musings; and while not entirely analogous Freedman explains how the physician-researcher in the epistemological state of theoretical equipoise (IPE) is poised to make a treatment preference for her patient at the first evidential indication that one treatment is superior to its comparator. Neither skepticism nor IPE is likely to produce and maintain an honest suspension of belief.

Hume's challenge to skepticism provides a strong analog to Freedman's "knife edge" criticism of IPE, but unfortunately criticisms of the tropes are not so clearly analogous to criticisms of clinical equipoise. The tropes have largely been ignored by philosophers rather than refuted. This appears to be so simply because they are not very convincing to modern readers.[57] As a result of this neglect there is not sufficient material for comparing the form in which criticisms to the tropes take and the form of the RCT dilemma or other criticisms of clinical equipoise. Yet even the vague criticism of not being able to convince one to suspend judgment has, to some degree, shown up in the equipoise dialogue in relation to clinical equipoise. Gifford eventually rejects the evidential warrant rationale for assenting to the clinical equipoise principle, in part, because it is an untenable proposition to claim that it would never be rational to act upon one's own opinion, even when others disagree.[58] Thus, for Gifford the underlying reason for assenting to clinical equipoise is unconvincing. Unfortunately,

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[56] Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 143.
[57] Gisela Striker, "The Ten Tropes of Aenesidemus" in *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983), 96.
[58] Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," *Bioethics* 9 (1995): 139.

due to the lack of specific arguments against the tropes further comparisons of counter-arguments between clinical equipoise and the tropes are not possible.

Despite the lack of specific criticisms of the tropes, comparisons can be made using the conclusions drawn from the RCT dilemma criticism of clinical equipoise and the conclusions drawn from the critiques if IPE and philosophical skepticism. The purpose of Freedman's "knife edge" criticism is that IPE (or "theoretical equipoise" as he calls it) is fleeting and would rarely, if ever, persist within the mind of an individual physician throughout a clinical trial because of accumulating evidence. However, as the discussion of Fred Gifford's work in Chapter One revealed, clinical equipoise may also be susceptible to similar epistemological criticisms. Gifford's "RCT dilemma" points to an epistemological weakness in clinical equipoise, namely that clinical equipoise does not account for the effect of accumulating evidence, and the corresponding increase in certainty of knowledge, during a trial. The community of clinical experts will likely come to a consensus on which treatment is preferable for the "present patient" prior to the point where statistical significance is met for a "policy decision". In this way clinical equipoise can be criticized as unstable, just perhaps to a lesser degree than IPE and philosophical skepticism are criticized for being ephemeral in nature. Regardless of whether the argument is a psychological one, such as Fried's argument against the possibility of IPE ever occurring within the mind of a physician; or an epistemological one, such as Freedman's knife edge argument against IPE and Gifford's RCT dilemma argument against clinical equipoise, the effect is the same – these ethical principles cannot be actualized in the real world.

2.3 Conclusion to Equipoise and Skepticism

While the analogs between philosophical skepticism and the RCT equipoise dialogue are imperfect and incomplete, there do appear to be some striking similarities in terminology, usage and significant counter-arguments, either epistemological or psychological, afflicting both dialogues and preventing the actualization of these philosophies. There may be other, possibly revealing, connections between skepticism, medicine, and medical epistemology that will not be pursued here.[59] If these connections between the RCT equipoise dialogue and philosophical skepticism are valid and convincing; then what, if any, relevance might they have on the course of the ongoing RCT equipoise dialogue? This topic is the focus of the final chapter.

[59] For a brief overview of the epistemological differences between ancient medical sects see Roy Porter, *The Greatest Benefit to Mankind: A Medical History of Humanity*, (New York: W.W. Norton 1998), 70-71, 89. An excellent account of the interplay between skepticism and medicine can be found in John Christian Laursen, "Medicine and Skepticism: Martin Martinez (1684-1734)," in *The Return of Scepticism from Hobbes and Descartes to Bayle*, ed. Gianni Paganini (Dordrecht: Kluwer Academic Press, 2003), 305-325. An interesting description of Methodism (the skeptic sect of ancient medicine) can be found in I.E. Drabkin, "The Fielding H. Garrison Lecture': Soranus and His System of Medicine," Bulletin of the History of Medicine 25 (1951): 503-518. Finally, for a historical argument on how physicians influenced the philosophy of skepticism as it pertains to causation see Jonathan Barnes, "Ancient Skepticism and Causation", in *The Skeptical Tradition*, ed. Myles Burnyeat (Berkeley and Los Angeles: University of California Press, 1983) 150-153.

Chapter Three

3.0 Discussion of Equipoise and Skepticism

In the previous chapter elements of the RCT equipoise dialogue have been linked to similar characteristics of the tradition of philosophical skepticism. The intent was to provide a history of philosophy framework with which to view the RCT equipoise dialogue and to reveal some underlying coherence within the contemporary RCT debate. My investigation and comparison with philosophical skepticism reveals that both IPE and clinical equipoise have significant obstacles to their actualization as guiding ethical principles – which are similar in effect to problems that plagued ancient skepticism.

First, it seems that the original IPE concept has been abandoned, much as skepticism has been abandoned, largely on epistemological grounds. No critic has claimed that it would be unethical for a physician-researcher to offer trial enrollment to her patient based upon her own IPE between standard treatment A and experimental treatment B. The rub against IPE has always been that it is epistemologically impossible for a physician-researcher to remain in IPE throughout a RCT, if it were ever psychologically possible for her to be in IPE at any time in the first place. If it were possible for such a state, then IPE would likely be the preferred ethical principle to justify RCT enrollment. This is so because traditional Hippocratic medical ethics is founded upon the fiduciary nature of the relationship between the individual physician to the individual patient. Providing medical care, in its traditional and simplest form, occurs within a personal relationship between one physician and one patient. As RCT enrollment is typically offered within the patient-physician relationship it is only

reasonable that the ethics of RCT enrollment should reflect the fiduciary nature of this relationship. The medical community in aggregate has far less clear duties to the individual patient, if any, and thus community standards require further justification.

It seems likely that IPE was replaced by clinical equipoise primarily as a result of the epistemologically fleeting nature of IPE, not due to some ethical superiority of clinical equipoise over IPE. Contrary to Freedman's contention that IPE was ethically irrelevant,[60] Gifford has contested this claim by insisting that the individual physician has a clear obligation to choose that treatment which she thinks is best for her patient because her individual professional judgment carries moral weight.[61] Still others have suggested that both IPE and clinical equipoise are necessary criteria for the ethical justification of RCTs, but each is important for different reasons. It has been argued that clinical equipoise is required to justify the formation and design of a trial as well as its continuance or early termination; whereas IPE is required for an individual physician to enroll her patient into the trial.[62] Thus, it seems that IPE is not ethically inferior to clinical equipoise.

There is less debate concerning the question of whether IPE is epistemologically or psychologically possible to attain and maintain. Miller and Weijer have attempted to reformulate IPE with a more robust clinical community evidentiary standard in which the individual physician's equipoise can only be disturbed by evidence that would be convincing to her colleagues.[63] Yet this attempt to

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[60] Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 143.
[61] Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," *Bioethics* 9 (1995): 137.
[62] Miller and Weijer, "Rehabilitating Equipoise," *Hastings Center Report* 13 (2003): 114.
[63] Ibid. 113-114.

reformulate IPE upon a more stable epistemological ground ignores Gifford's substantial criticisms published prior to this reformulation which illustrate the limitations of the clinical community standard to allow RCTs to continue all the way to statistical significance. Thus, there still has not been a systematic argument in favor of the possibility and sustainability of IPE throughout an RCT. The current state of the equipoise dialogue reveals that no one is challenging the ethics of IPE, just its feasibility as a guiding principle. It is, more or less, an abandoned principle presumably as a result of epistemological flaws.

3.1 Extending Criticisms against IPE and Skepticism to Clinical Equipoise

The reasons outlined above for the abandonment of IPE, mirrored by similar criticisms against skepticism, point to the idea that it is the epistemological foundation of clinical equipoise that will determine its long term viability as a guiding ethical principle for conducting RCTs. There is an emerging body of published epistemological criticisms of clinical equipoise which have yet to be addressed by proponents of clinical equipoise. In Section 1.4 Gifford's "RCT dilemma" and Veatch's "problem of preliminary data" were presented as significant epistemological criticisms to clinical equipoise which have yet to be overcome. There are other published epistemological criticisms of clinical equipoise that for the sake of brevity will not be described here.[64] Yet taken here as a whole, the cumulative effect of these criticisms are enough to question if clinical equipoise will continue to be an appealing principle for justifying RCTs.

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[64] See Richard Ashcroft, "Equipoise, Knowledge, and Ethics in Clinical Research and Practice," Bioethics 13 (1999). for an examination of how CE cannot easily be justified on Bayesian grounds. Also see Fred Gifford, "Community-Equipoise and the Ethics of Randomized Clinical Trials," Bioethics 9 (1995): 140. for the "preponderance of experts" critique which reveals an ambiguity in CE as to what counts as evidence.

3.2 The Future of Clinical Equipoise

The common element between criticisms of IPE, philosophical skepticism, and clinical equipoise is the inability of the necessary epistemic or psychological states to be actualized in praxis. The precedent to abandon clinical equipoise has already been set by the abandonment of IPE in the wake of the criticisms of its transient nature. If these epistemological criticisms against clinical equipoise are not systematically addressed in the published literature, it is difficult to see how they will not adversely affect its status as the "standard answer" to justify RCTs ethically. That it has some analogs with philosophical skepticism; an abandoned epistemology, does not bode well for clinical equipoise.

Perhaps, picking up the analogy from Chapter Two again, these unanswered criticisms of clinical equipoise will cause it to become less convincing as a justification for RCT enrollment just as the Tropes no longer seem able to convince a modern scholar to suspend judgment. Yet this will likely only happen when there is a viable alternative justification that will not be susceptible to these epistemological criticisms. There are currently published alternatives to clinical equipoise, such as the non-exploitation principle[65], which deserve critical attention and could perhaps, with significant improvement, prove to be viable alternatives to clinical equipoise. Particularly, if an alternative to clinical equipoise is to be viable it must be coherent with respect to several epistemological aspects such as: what constitutes evidence for knowledge claims, when does the accumulating evidence change belief to knowledge, whose knowledge or belief is ethically relevant, and at what point has enough evidence

[65] Franklin Miller and Howard Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *The Hastings Center Report* 33 (2003): 26.

been accumulated to end the RCT. As this essay has brought to light by way of a history of philosophy comparison; if clinical equipoise is eventually abandoned, then the difficulties in developing an alternative to clinical equipoise will likely be epistemological rather than ethical in nature.

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