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Countering medical nihilism by reconnecting facts and values

Ross Upshur [a,b,c,e,*], Maya Goldenberg [d,e]

[a] Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada
[b] Division of Clinical Public Health, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[c] Lunenfeld Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada
[d] Department of Philosophy, University of Guelph, Guelph, ON, Canada
[e] Institute for the History and Philosophy of Science and Technology, University of Toronto, Canada

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ABSTRACT

A pessimistic strain of thought is fomenting in the health studies literature regarding the status of medicine. Ioannidis's (2005) now famous finding that "most published research findings are false" and Stegenga's (2018) book-length argument for medical nihilism are examples of this. In this paper, we argue that these positions are incorrect insofar as they rest on an untenable account of the nature of facts. Proper attention to fallibilism and the social organization of knowledge, as well as Bayesian probabilities in medical reasoning, prompt us to ask why the cynics expect the results of quantitative studies to be incontrovertibly true in the first place. While we agree with Ioannidis and others' identified flaws in the medical research enterprise, and encourage rectification, we conclude that medical nihilism is not the natural outcome of the current state of research.

1. Introduction

While global markets for medical research and development continue apace, and patient groups clamour for more options and more access to treatment, the rumblings of a cynical view can be found in medical journals and the philosophical literature regarding the status of medical evidence and thereby the medical enterprise as a whole. A recent book coined the phrase "medical nihilism" (Stegenga, 2018), and the argument, while not properly nihilistic, fits with previous arguments that medicine is "broken" (Goldacre & Heneghan, 2015; Spence, 2014) insofar as its evidence base is of poor quality and untrustworthy. In short, the quality of medical evidence is deemed poor, and so our confidence in medical findings ought to be low. Despite the best efforts of evidence-based practice, studies undertaken by Ioannidis (Ioannidis, 2005) tells us that most research findings are probably false, and the philosophical doctrine of medical nihilism tells us that, on inductive grounds, we have little reason to expect otherwise (Stegenga, 2018). Abject cynicism and collective despair follow from there

In this paper we propose that such pessimism is unwarranted, not because medical evidence is good after all, but because these cynical conclusions rest on an untenable notion of the nature of facts. We work to counter the so-called medical nihilism by *reconnecting facts and values*, and thereby highlighting medical facts as emergent, defeasible, and socially situated.

Medical nihilism follows from a problematic implicit structuring of facts in evidence-based medicine (EBM) and in EBM renaissance and reform discourses as static or stable. Unable to achieve stable facts, the status of medicine is supposedly undermined. By challenging this account of facts, and its relation to values, that nihilistic conclusion is undercut. A turn to social epistemology scholarship on science and values, much of which is rooted in Peircean pragmatism, allows for a better framing of the nature of medical facts, and a better outlook on medicine that emphasizes epistemic humility and attention to the humane side of medicine (care). We conclude that the scientific account of the world *is* limited. It is at best suggestive, probably wrong, and difficult to find. Collective despair is only warranted, however, if things should have been otherwise.

2. Reconnecting facts and values

Ethics and epistemology, the pursuit of the good and the true, intersect considerably in thinking about medicine and health care. One way to commence the exploration of this entangled relationship is to examine the fact-value distinction and how it is interpreted in this context. The intersection between these concepts is articulated primarily with respect to discussions involving objectivity and subjectivity. The

* Corresponding author. Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada
E-mail address: ross.upshur@utoronto.ca (R. Upshur).

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streams of medicine that have a very strong, scientific self-identity usually claim a space for objectivity that will subordinate the subjective (Thompson & Upshur, 2017). The use of science is seen as a hedge against arbitrariness and believed to be a reliable buffer against pseudo-science (see, for example, the ongoing debate about alternative therapy).

Evidence-based medicine is a highly influential doctrine in clinical medicine that emphasizes the importance of understanding evidence as a measured quantity. Critics of EBM have argued for reconceiving medicine as values-based, narrative-based, or person-centred as a means to counterbalance the perceived neglect of the humanistic dimensions of clinical practice (Goldenberg, 2014). However, such focus seems to concede that EBM has in some sense an accurate description of the factual basis of medicine. Recent modifications to EBM such as EBM + seek to integrate the role of mechanism into the evidence base of evidence-based practice (www.ebmplus.org). More penetrating criticisms come from the challenges raised by meta-research and medical nihilism. The results of meta-research studies have indicated problems with replicability, study quality, and the dissemination of a seemingly large number of studies that are false (Ioannidis, 2005). Medical nihilism holds that as a consequence of this we have little reason on inductive grounds to have confidence in the vast output of medical research (Stegenga, 2018).

Examining the relationship of the fact–value distinction as understood by both EBM and its critics reveals a problematic characterization of medical facts. We will argue that medical facts are complex entities whose instability have been underplayed by EBM proponents. This point has been noticed and capitalized on by EBM critics oriented in meta-research and by proponents of medical nihilism. These critics, thus uncritically adopt that fact–value distinction by criticizing evidence based practice precisely for offering unstable facts. Yet, we will soon argue, the nihilistic conclusion only follows if things should have been otherwise, that is, the careful construction of medical facts *ought* to result in stable evidentiary claims. We will argue that social epistemology and the epistemological perspective of fallibilism provide a better account of medical factuality such that medical nihilism does not follow of necessity from a destabilized account of medical factuality.

3. Facts and values from the perspective of EBM

A recent paper by Kelly, Heath, Howick, and Greenhalgh (2015) provides an account of the role of facts and values in EBM. Like other EBM critics writing before them, Kelly et al. rightly note that failure to address values in a systematic way has hindered the development of EBM and furthermore given rise to the view that EBM has a structure akin to a rigid ideology. They seek to rectify this situation by arguing for an explicit and transparent account of the role values play in EBM (Kelly et al., 2015).

Their analysis starts with an acknowledgement of fallibility necessitating humility. They also acknowledge that values imbue the practice of medicine and the delivery of health care. These points strike us as correct. Yet, they seem to adhere to a strict fact–value dichotomy *despite* the concession that facts are somehow value-laden. They write:

Science aspires to be about the world as it is; values are about the world as it ought to be. Science seeks to get as close to the reality of the world as possible. Yet no matter how sophisticated our measurements become, we remain limited in our ability to access the truth because of our fallibility as observers and because of the intrinsic technical limitations of the instruments we use to do the observation. True essences if they may be said to exist at all are the province of philosophy, metaphysics and theology. What scientists are able to observe should not be confused with truth.

The world as we think it ought to be is the world of values. Different people will have different values, and it is very hard to resolve value-based disagreements on the basis of scientific evidence. But values are ever present. Our hopes, beliefs, politics and religions, about which we (appropriately) feel emotions, provide us with the frame or the lens with which we see the world, our ambitions for the future and our understanding of the past. Despite the caricature of the passionless objective (often male) scientist in a white coat, the questions scientists decide to ask, the methods they select, and the way they interpret results are chosen through a filter of often unacknowledged and subconscious values (Kelly et al., 2015).

This construction cements a sharp distinction between the task of science (the world as it is) and the world of values (the world as it ought to be), hence endorsing the "is/ought" or "fact/value" dichotomy. Values are also interpreted narrowly to be comprised of "social" or "contextual" values only, with little acknowledgement of the "epistemic" or "constitutive" values that influence all scientific practice.[1] Kelly et al. (Kelly et al., 2015) describe values entering into medicine in the following ways:

1. The role of values in deciding which questions to ask
2. The role of values in selecting methods for identifying and appraising research evidence
3. The importance of patient values in clinical decision-making
4. The importance of clinician values in prioritising (the so-called) evidence-based tasks
5. Values in the broader sense – is EBM delivering on its promise?

Conceiving of values as solely related to the "oughtness" of the world indicates that the value discourse they embrace is largely oriented to ethical values. Though touching on epistemic issues in their analysis of values, they fail to address the very ways in which epistemic, not just social, values enter science itself. The perspective seems to reinforce a sense in which the activity of evidence production in the health sciences is oriented to more objective knowledge, whereas values are more in the realm of the subjective or intersubjective. This division of objective and subjective knowledge is a vestige of evidence-based thought.

The account also underplays the extent to which the methods of EBM, as a means of describing the world "as it is", may be problematic. We will now analyze some of the problems associated with the "world as it is" account provided by EBM.

4. The problems of evidence and the nature of facts as facts

The concept of a "fact" is complicated in and of itself (see for example the entry on Facts in the Stanford Encyclopedia of Philosophy (Mulligan & Correia, 2013). Our purpose is not to elaborate or defend a particular conception of factuality in medicine and health care. Rather, we will restrict our claim to the uncontroversial proposition that whatever they may be, facts do not interpret themselves. Facts only make sense within a particular explanatory vocabulary. Regarding medicine and health care, there is a plethora of such explanatory vocabularies encompassing everything from the bench sciences (such as the vast range of biological disciplines including the growing number of "-omics") through to population level analyses (such as epidemiology, health services research and health economics).

[1] Use of the term "ought" in philosophical discourse has progressed from Hume's (1784/2007) classic distinction between "is" (empirical facts) and "ought" (social values). Henry Sidgwick (1874) presented the "oughtness" of non-natural facts in *Methods of Ethics*. Sidgwick reasoned that if there is a way the world *ought* to be, there must be a fact of the matter underpinning that ought, specifically non-natural properties. G. E. Moore (1903) later adopted Sidgwick's line of argument. Kelly et al. do not define their "ought" carefully, at times suggesting a Humean line with respect to values underpinning ethical judgments (p. 2), and at other times suggesting values to be distinct from either Humean or Sidgewick's sense of the term, specifically when Kelly et al. refer to the "world of values" as "the world as *we think* it ought to be" (p. 2; emphasis added). We thank Paul Thompson for bringing the ambiguity of "ought" to our attention.

It is also not controversial to state that for EBM, facts are largely the product of the analysis of quantitative data derived from well-designed empirical studies. Attendant to this commitment to quantitative data is a set of commitments to tenets from statistical science, including hypothesis testing, presenting effect sizes with confidence intervals, use of *p*-values and other analytic techniques. These metrics form the basis upon which EBM operates to make claims for therapeutic efficacy, diagnostic accuracy and other important practice-governing decisions. These conventions are followed by EBM critics and medical nihilists, and therefore shape the criticisms of and proposed reforms for EBM.

For instance, in an effort to address the prevalence of poor quality research in medicine, Benjamin et al. (Benjamin et al., 2018) published a provocative essay titled "Redefine statistical significance." Their proposal was "to change the default *p*-value threshold for statistical significance for claims of new discoveries from 0.05 to 0.005." The authors recognize that they are simply replacing one arbitrarily determined convention for another. The motivation for the proposal resides in concerns plaguing modern research: the reproducibility crisis, *p*-hacking, and abundant false positive results. They argue that the bar for deeming a result significant has been set far too low. They are clear that this recommendation is related only to new findings, and they remain neutral with respect to the standard of significance for "confirmatory or contradictory replications of existing claims." It is unclear why they impose this limit, as it would follow from their reasoning that the traditional threshold would be equally lax in these contexts. The authors also recommend moving away from hypothesis testing and embracing Bayes factors as a more robust form of summarizing evidence and adjudicating claims. However, they acknowledge that hypothesis testing is still widely taught and practiced so such a wholesale transformation in statistical thinking remains in the future.

Why should redefining statistical significance be important for medicine and health care? Statistical methodology, as noted above, remains the primary means by which propositions become evidential (read factual) in medicine and health care. Despite many criticisms of this stance (from both hermeneutic and mechanistic perspectives), it remains clear that in contemporary discourse, evidence is a quantitative measure, derived from identifiable and widely accepted methodologies that can be ranked in a hierarchical manner in order to be evaluated in terms of reliability and suitability for decision-making in both clinical and policy contexts. Benjamin et al.'s (Benjamin et al., 2018) formulation of the medical fact, thereby illuminates the aspirations of early 21st century biomedicine.

An immediate consequence of Benjamin et al.'s (Benjamin et al., 2018) shifting of the *p*-value is that evidence meeting this more stringent standard will be much harder to find in health care contexts. *P*-values are critically dependent on both the power of the proposed statistical test and the sample size of the study. They are deeply intertwined concepts.

However, most randomized control trials have relatively small sample sizes, so most currently designed and implemented studies would not be powered to detect effects at the proposed level of significance. Raising the *p*-value would therefore require either drastically increasing the sample size or detecting much larger treatment effects than are typically reported.

That these changes will occur is exceedingly unlikely and is borne out by several factors. One, with the reduction in baseline occurrence of certain events, composite endpoints are commonly used. Second, for rarer conditions, the patient population likely does not exist to meet such a standard. In competitive markets such as oncology trials this will produce undesirable consequences such as depletion of patient pools.

A corollary of this proposal is that much of what is currently considered evidential in medicine, that is, providing the grounds for belief and action would now be called suggestive. If one looks at meta-analysis, particularly *Cochrane Reviews*, 95% and confidence intervals and significance levels of $p > .05$ are the standards for determining whether an effect exists or not. Few Cochrane systematic reviews indicate effect sizes at the level being proposed.

Upshur has alternately argued that the consistent use of a single threshold value is both too lax and too restrictive (Upshur, 2001). The Benjamin proposal worries only about the former, and therefore pushes the threshold in a more stringent direction. Benjamin et al. (Benjamin et al., 2018) note that different fields have different thresholds (particle physics and genomic analysis, as examples) and that is acceptable in their minds. But moving in a more relaxed direction does not appear to be on the horizon of their thinking, which is peculiar given their Bayesean inclinations. For example, we may be persuaded on the basis of cost and safety that an agent may be worth trying even if evidence from a clinical trial or meta-analysis fails to meet the $p > .05$ standard of significance. The Benjamin proposal fails to address the issue of over restrictiveness and reinforces the ideal of a uniform standard of adjudication for quantitative evidence. There are many situations in clinical medicine where this threshold standard would likely rule out patient-centred choices. It is worth noting in this context that even R.A. Fisher argued against using the same standard of significance for each and every test of a hypothesis.

A second, and related concern with evidence is the recent research in the field of "meta-research", particularly the work of John Ioannidis (John P. A. Ioannidis, Fanelli, Dunne, & Goodman, 2015). In an influential paper he argued that most published research findings are wrong (Ioannidis, 2005; see also; Ioannidis, 2016). The abstract to his paper sets out the salient points:

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current [health-related] scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias (Ioannidis, 2005).

Notwithstanding the problematic nature of defining truth (to which we direct readers to more than 2000 years of philosophy and science), and treating studies themselves as possessing binary truth value, the question is why would we expect the results of quantitative studies using probabilistic methods to be incontrovertibly "true" in the first place? EBM's (and its critics') commitment to statistical methodology makes the stability of facts unlikely. Nonetheless, Ioannidis neatly itemizes problems with the vast body of observations in the published scientific literature, which, for better or worse, is the available evidence with which we have to work.

There are also issues facing systematic reviews and meta-analysis, designs often put at the pinnacle of evidence hierarchies according to their larger size and ability to control for bias. In a separate analysis he concludes: "The production of systematic reviews and meta-analyses has reached epidemic proportions. Possibly, the large majority of produced systematic reviews and meta-analyses are unnecessary, misleading, and/or conflicted" (Ioannidis, 2016). Using the PubMed database, Ioannidis calculates that the publication of systematic reviews and meta-analyses has increased rapidly: 2728% increase in systematic reviews and 2635% increase in meta-analysis from 1986 to 2015. He observes that there now may be more systematic reviews and meta-analysis published than randomized trials. He documents considerable overlap and duplication and concludes that there is a high degree of redundancy. He notes "Few systematic reviews and meta-analyses are both non-misleading and useful."

This already parlous situation is further complicated by what is called the scatter problem. The idea of systematic reviews and meta-analysis was to distill scientific evidence in order to promote more rational decision-making and improve clinical practice and inform policy and planning. This also should entail that these evidence sources should be easier to find in order to inform policy and practice. As Hoffman et al. (Hoffmann, Erueti, Thorning, & Glasziou, 2012) demonstrate, there is considerable and growing scatter, that is, studies are dispersed amongst the increasing number of scientific publications. As they conclude:

Publication rates of specialty relevant trials vary widely, from one to seven trials per day, and are scattered across hundreds of general and specialty journals. Although systematic reviews reduce the extent of scatter, they are still widely scattered and mostly in different journals to those of randomised trials. Personal subscriptions to journals, which are insufficient for keeping up to date with knowledge, need to be supplemented by other methods such as journal scanning services or systems that cover sufficient journals and filter articles for quality and relevance. Few current systems seem adequate (Hoffmann et al., 2012).

Ioannidis's famous argument that "most published research findings are false" is consistent with Stegenga's master argument for medical nihilism. They are both based on the same considerations, "namely the prevalence of biased methods employed by researchers with conflicts of interest, hypotheses with low prior probabilities, and small effect size" (Stegenga, 2018). The master argument for medical nihilism uses a Bayesian theory of scientific inference that represents one's confidence in the effectiveness of a medical intervention as a conditional probability P(H|E). H is a hypothesis regarding the effectiveness of the intervention, and E is the available evidence relevant to the hypothesis. Based on many of the same methodological and empirical considerations already raised in this section (following Benjamin et al. (2018) and Ioannidis (2005)), as well as some conceptual considerations regarding the nature of "magic bullet" interventions, Stegenga concludes that the likeliness of a the proposed effectiveness of the intervention being true is undermined. Therefore, we ought to assign low prior probability in H. When presented with E, we ought to have low estimation of the likelihood of that evidence being accurate. What follows, given Bayes' Theorem, is that even when presented with evidence for a hypotheses demonstrating the effectiveness of a medical intervention, we ought to be highly sceptical (low posterior probability in the hypothesis P(H|E)). In short, medical nihilism is compelling.

Where Ioannidis hopes to rectify the poor state of medical research by limiting investigations only to hypotheses with high prior probabilities (as this increases the posterior probabilities of the hypotheses and make the findings more likely to be true), medical nihilism's argument for the unlikeliness of the next big "magic bullet" intervention leads to very few assignments of high prior probability to hypotheses. Among those that do justify assignment of high prior probability, many of them not warrant testing. For example, it would be wasteful to test parachutes to see if they slow down skydiving falls (191). The nihilistic conclusion is that methodological tweaking is not enough to disarm the problems of medical research.

So, to summarize, the way we understand the "world as it is" according to EBM is in a rather dire condition. Much of what we have hitherto believed to be evidential may be considered at best suggestive, probably wrong and difficult to find! This conclusion may be considered dispiriting leading us to collective despair. It is scarcely surprising that medical nihilism has emerged as a philosophical stance towards medical evidence. As Stegenga argues, given extensive problems with bias, a less than robust theoretical basis for many interventions, issues with respect to the methodologies in medical research, that even "if we employ our best inductive framework, then our confidence in medical interventions ought to be low" (Stegenga, 2018). But collective despair is the wrong conclusions to draw. A reorientation towards fallibilism will help support this point.

5. Against collective despair: fallibilism and the fact-value relationship in medicine

Is medical nihilism the natural outcome of the current state of research? We argue in the negative and suggest that a way forward may be found in elements of pragmatic philosophy. In particular, fallibilism, anti-skepticism and acknowledging the entanglement of facts and values can helpfully address the challenges of medical evidence.

That most published studies are "false" in some way comes as no surprise to those whose epistemological perspective is cast in a fallibilist frame. C.S. Peirce wrote in 1902: "For fallibilism is the doctrine that our knowledge is never absolute but always swims as it were, in a continuum of uncertainty and of indeterminacy" (Peirce, 1955b). Evidence, from any study, or meta-study, expressed in probabilistic terms is not making any positive claim to truth, but rather supports the provisional acceptance of an effect, with appropriate acknowledgement of error. Indeed, most of the architecture of statistical thought is as much about determining error as it is about the veracity of the effect measured (Mayo, 2010).

Peirce recognized the significance of this in his writing about scientific inference. He notes that any experiment is intended to settle doubt and achieve some fixity of belief. But this fixity is inevitably transient and the emergence of new data, observations and theories will start another cycle of doubt and experiment. As he wrote:

But the scientific spirit requires a man to be at all times ready to dump his whole cartload of beliefs, the moment experience is against them. The desire to learn forbids him to be perfectly cocksure that he knows already (Peirce, 1955a).

It follows that we should not be appalled that most of the published research is probably false. Ioannidis's indictment of medical research is warranted on the grounds of poor methodology, but not because the literature might be false. Scientific findings are always provisional. The idea that fixity of belief can be an edifice built on provisional findings—evidence-*based* medicine—is the problem.

Further, Peirce argued that our reasoning is a collective property, and the advance of science is reliant on a community of inquirers. Given human finitude, there are only a small number of inferences and actions any individual can undertake in a lifetime and these are limited in number in comparison to the unlimited community. So at any given time, each of us undoubtedly holds a large number of beliefs that will subsequently be determined, over an expanded time horizon, to be unjustified or false. We likely do not have a clear sense of which beliefs these may be. Consequently there are potential effects to the credibility of a set of beliefs if certain beliefs change. Similarly, methods will be refined, and many approaches believed to be of use discarded. Hence, uncertainty is a hallmark of human life and the concerted, collective effort of the community of inquirers offers the best means for addressing this uncertainty with the most rigorous epistemic resources we have at our disposal. Humility and perseverance rather than nihilism may be better guides to improving our knowledge base.

But unlike the collective knowledge pursuit endorsed by Pierce and social epistemologists, that is, the idea that knowledge claims are validated by way of some type of critical interaction among persons, health care has, by broad convention, settled on evidence and evidence-based approaches as the best manner by which we can manage uncertainty.

Some have argued that EBM requires a renaissance (Greenhalgh, Howick, & Maskrey, 2014), some that it should be replaced, and some that it should bolster its claims to epistemic authority by additional engagement with other aspects of modern science represented by mechanisms (Russo & Williamson, 2007) or narratives (Greenhalgh, 1999). Common to all of these accounts is a commitment to evidence, largely regarded as facts with externalized properties that hold independent of our beliefs. The architecture of study design is intended to be a hedge against the intrusion of certain corrupting values, biases, or other distorting influences.

Yet, the meta-research and medical nihilism literature is suggesting

that certain distortions are increasingly creeping into the evidence base. Some of these relate to market forces and the influence of industry and still others likely attributable to external forces on scientists themselves (i.e. the need to publish, the proliferation of journals, the "sanctification" of systematic reviews, etc.) These distortions are seen as in some way contaminating the evidence base and undermining the objectivity of research. Stegenga, for example, puts great emphasis the problems of "malleability" of research methods and "discordance" of outcomes between similar studies and between meta-analyses that review the same primary literature. Both malleability and discordance are presented as reasons for nihilism (Stegenga, 2018, pp. 167–179). All the while, this framing of the problems of evidence is relevant to understanding how facts come to be facts in the first place.

What follows from this commitment to evidence is a vision of medical research that strives for firm truths. Acknowledging the limits of truth-seeking endeavours destabilizes the status of medicine as capable of establishing certainty. Yet full consideration of the fact–value interaction in medicine should not be understood as conceding that anything goes. We do not question the presence of corrupting influences on medical research, for example, but challenge the purity of fact as the desirable alternative to corrupt research.

6. Evidence and values

Hilary Putnam (2002) argues, from a perspective broadly informed by pragmatism, that the fact–value dichotomy has collapsed (Putnam, 2002). The arguments he elaborates are sophisticated and rely on a historical reconstruction of the way in which this distinction evolved in the first place. As with many fruitful ideas, the notion of the distinct nature of facts and values is often tracked back to the work of David Hume. Putnam clearly explicates the origin of the distinction as oriented to the sensationalist-empiricist epistemology and its associated theory of mind. Hume famously made a distinction between matters of fact, which derive from sensory experience, and relations of ideas, which describes the world of necessary connections such as mathematics and logic. Most of this apparatus is no longer accepted, and so one of the key pillars supporting this distinction is accordingly rendered questionable.

Putnam further goes on to document the evolution of the fact–value dichotomy in the work of Kant and in its clearest defense in the writings of logical positivists in the mid-20th century. He concludes "…the fact–value dichotomy is, at bottom, not a distinction but a thesis, namely the thesis that 'ethics' is not about 'matters of fact' (Putnam, 2002, p. 19). But just as facts were inadequately characterized, 'values' are undertheorized as well. The possibility of a division between fact and value, and its consequence, a truly value-free science, thereby becomes further out of reach. Putnam goes on to demonstrate how an adequate taxonomy of values extends beyond the domain of the ethical. That is, epistemic values are values as well.

Following from the work of classic pragmatists such as Peirce, James, and Dewey, it is recognized that experience is permeated by normativity:

In the philosophy of science, what this point of view implied is that normative judgments are essential to the practice of science itself. These pragmatist philosophers did not refer only to the kinds of normative judgments we call "moral" or "ethical", judgments of "coherence," "plausibility," "reasonableness," "simplicity," and of what Dirac famously called the beauty of a hypothesis, are all normative judgments in Charles Peirce's sense of "what ought to be" in the case of reasoning (Putnam, 2002).

On this interpretation, the concept of values is extended beyond the realm of the ethical and opens up the issue of what ought to be the norms of the practices of science itself. This is an area that EBM has not yet explored, as proponents seem to accept the value-neutral nature of the instruments of evidence creation. EBM critics Kelly et al. reproduced this account of values relevant to EBM as *social* (including ethical) values ("the world as it ought to be"). That EBM has tacit commitments to a set of epistemic values is no doubt the case. The task for a more robust concept is to elaborate these commitments and provide a more complete defense of such things as the evidence hierarchy. The advent of EBM + has made this engagement more explicit as there needs to be an account of the epistemic norms of certain knowledge production instruments over others in the practice of medicine. This is to say that even epistemic values are socially influenced.

There may still be some residual unease in those committed to a particular notion of objectivity that highlighting the normative or value-ladenness of science undermines objectivity.[2] Scientific objectivity, like the concept of factuality, is a complex topic. Much has been written about whether science should aspire to value freedom or minimally value neutrality. Putnam's arguments undercut these concerns in the sphere of economics, and his arguments can be extended to medicine and health care.

Stegenga, a philosopher of science, does not adopt a facile account of facts distinct from values, but his disdain for the malleability of research methods and discordant outcomes at least suggest that the role of values in epistemic activities is not fully thought through. That methods are malleable (Stegenga, 2018, p. 167), and that meta-analyses produce discordant outcomes (Stegenga, 2018, 175), should not be seen automatic signs of weak methodology or grounds for cynicism about the medical research enterprise. Instead they suggest that the context of justification is value-laden, and so are the assembling of and analyses of research papers for the purpose of meta-analysis. This finding, furthermore, does not warrant despair.

The relationship between the role of values and the practices of science have been carefully assessed by philosophers of science, especially those working with feminist and social epistemology frameworks. Feminist scholars historically challenged regressive science that reinforced female subordination. They did this not by denouncing scientific enterprise (i.e. a resort to nihilism), but by clarifying the ways in which values (including common sexist views) can enter even rigorous science and making cases for legitimate versus illegitimate value influences on science. Value-free science was shown to be mythical and also dangerous insofar as it evaded accountability and supported the political status quo (e.g. gender and racial hierarchies). Social epistemologists helpfully frame the terms for rigorous value-laden science (i.e. how values promote robust open inquiry rather than support wishful thinking) by attending to the social organization of knowledge production. Additionally, social epistemology and feminist philosophy of science strive to offer more accurate accounts of how, and under what conditions, scientific knowledge is established as (defeasible) facts, thereby forgoing the highly rationalist interpretations found in earlier Western philosophy of science.

Helen Longino's and Heather Douglas's scholarship stand out as particularly helpful for addressing the fact–value difficulties that we see as underlying current rousing of medical cynicism and nihilism. Longino's focus on the social process of scientific knowledge results in a recasting of what is meant by objectivity of science. Rather than defining scientific objectivity as concordance of theory to the facts, Longino proposes that social criticism is key to science's epistemic success (Longino, 1990, p. 62). Objectivity in science is thereby *interactive* — it emerges through open, critical dialogue among communities of scientists. Objectivity in science is achieved to the degree that the right conditions are met for the social process of inquiry. Specifically, scientific inquiry is "objective to the degree that it permits transformative criticism" (Longino, 1990, p. 280), p. 76).

[2] While proponents of value-free science generally accept the presence of epistemic values in science (Lacey, 1999), and limit their opposition to the intrusion of social values into scientific reasoning, they balk at the idea that epistemic value choice in science can be a matter of socially-influenced preference. Such a view breaks down the division between epistemic and non-epistemic or social values Longino (1990, 1996) supports this break down.

This account of science as social knowledge, and the attention to the sociological aspects of communities, leads Longino to collapse the distinction between constitutive (epistemic) and contextual (social) values:

I distinguish two kinds of values relevant to the sciences. Constitutive values, internal to the sciences, are the source of the rules determining what constitutes acceptable scientific practice or scientific method. The personal, social and cultural values, those group or individual preferences about what ought to be I call contextual values, to indicate that they belong to the social and cultural context in which science is done. The traditional interpretation of the value-freedom of modern natural science amounts to a claim that its constitutive and contextual features are clearly distinct from and independent of one another, that contextual values play no role in the inner workings of scientific inquiry, in reasoning and observation (Longino, 1987, p. 52).

Longino demonstrates that this straightforward account of keeping constitutive and contextual values apart is unsustainable. Gender bias in particular has a demonstrated capacity to creep in under the guise of constitutive value. However, this challenge does not invalidate claims to usable knowledge, or invite the sort on nihilistic despair now seen in philosophy of medicine and meta-science. Instead, it opens up the process of scientific knowledge production to closer critical scrutiny, particularly with respect to the social dimensions of the forces shaping scientific inquiry. Science is objective to the extent that it permits and supports transformative criticism, a social exercise that enables a consensus to qualify as knowledge (Longino, 2002).

Longino's conception of transformative criticism consists of the following elements.

- avenues for criticism: criticism is an essential part of scientific institutions (e.g., peer review);
- shared standards: the community must share a set of cognitive values for assessing theories;
- uptake of criticism: criticism must be able to transform scientific practice in the long run;
- e**quality of intellectual authority**: intellectual authority must be shared equally among qualified practitioners [3]

This socially embedded notion of objectivity as oriented in criticism is particularly well adapted to EBM, as one of its core commitments is to critical appraisal. However, the model of critical appraisal as espoused by EBM is one that solely relates to the cognitive work of individual clinicians, not to the process of the creation of evidence itself. Acknowledging the social process of science would better ground some of EBM's claims to legitimacy.

This acknowledgement is precisely the focus of meta-research and medical nihilism, at least insofar as the indictments of medical research target biases entering into methodology and impacting the resulting evidence. The message from Longino's philosophical intervention is that, contra Stegenga, "malleability" of methods (p. 167) and "discordance" of outcomes (p. 175–177), are not problems in themselves. The evidence is not distorted because different conclusions can be drawn, but because the wrong values enter into medical research consideration when, say, tiny effect sizes are hyped for the next blockbuster drug. The task, then, is not to throw out the medical enterprise, or to work towards non-malleability and harmony among meta-analyses. Instead, medical research must commit to epistemic practices that uphold and enforce the epistemic and social values that guide the best medical research. We believe that Stegenga would agree with this claim, but has not carried its full implications into his argument.

While Stegenga does not articulate the values that drive his investigation and nihilistic conclusion, they become apparent in his concluding chapter, where he suggests what ought to replace the "magic bullet" research enterprise that he resoundingly rejects. The primary social value that guides medical nihilism is a commitment to better health through more effective medicine and less harm. Stegenga wants to improve medical research and medical care through such measures as: stricter standards for detecting benefits and harms, closer scrutiny of corporate research, and a move away from pharmaceutical research into products with tiny effect size towards higher impact interventions like lifestyle interventions (diet and exercise) and neglected tropical diseases. Because the current system of research and regulation are not generating effective medical interventions with low harm profiles, Stegenga is open to radical reforms like socialized medicine, stricter FDA regulation, sequestration of medical research from drug companies (Schafer, 2004), incentive structures tied to addressing the global burden of disease (Pogge, 2005; Reiss & Kitcher, 2009), and the elimination of patents. He does not go so far as endorse particular reform routes, but only to point to the ways in which these various reforms correct some of the pervasive biases that plague medical research today. For example, corporate-sponsored research ought to be eliminated or seriously curtailed because the financial conflicts of interests built into the system result in more cases of scientific misconduct, the file drawer problem, and exaggerated findings in favour of the therapeutic.

The question remains whether nihilism is the necessary response to the obvious problems with medical research priorities and practices. We have argued that it is not, and attention to falliblism and the connection between facts and values informed this position. Where Longino's work structures revisionary work to modify a problematic system, medical nihilism concludes by throwing it out and (presumably) building something new. It is very likely that a social epistemology approach like Longino's would have the same effect of dismantling the problematic scaffolding and initiating radical reforms that are consistent with Stegenga's interest in better medicine and less harm. Longino's framework has the added benefit, however, of requiring clear articulation of those guiding values and subjecting them to democratic debate and revision in light of competing interests. The nihilistic resolve to burn it down and build something new does not benefit from that kind of transparency and accountability.

Heather Douglas's (2009) work on science, values, and democracy is helpful in the attention she gives to scientific decision-making in the face of uncertainty. This surely is more helpful for practicing clinicians working with sub-optimal evidence than medical nihilism. Their duties to help and heal are not removed when poor evidence surfaces. Medical nihilism, as much as evidence purism raises the possibility of justifying abandoning patients and denying care.

Douglas follows Rudner (1953) in characterizing scientific reasoning as a value-laden exercise insofar as determinations of evidentiary justification (Which evidence? How much of it?) are qualified by determinations of inductive risk: what is the consequence of wrongly accepting or rejecting a hypothesis? (Rudner, 1953).

Inductive risk situates science socially by connecting the standards of evidence used within science to the downstream social consequences of science. Induction refers to the inference from what we can directly observe to broader conclusions, such as the move from observable data to broader generalizations to explain the data. For example, the move from clinical trial data to the conclusion that the experimental therapeutic works. This conclusion must account for the data points, but the data is always incomplete. Instead the universalizing tendency is mediated by perceptions of risk: what follows from being wrong, and how do we balance competing wrongs between false positives and false negatives?

This focus on inductive risk pushes non-epistemic or social values to the centre of scientific reasoning because, according to Douglas, assessing the social consequences that can result from error necessitates the inclusion of social values. This can happen in many internal stages of science: choice of methodology, characterization of data, and interpretation of results (Douglas, 2000). Like Longino, Douglas presents

[3] This characterization of Longino's position comes from Reiss and Sprenger (Reiss & Sprenger, 2017).

value-free science as untenable.

Douglas argues that the appropriate balance of false positives and false negatives should depend, in part, on what those potential effects are. If the social consequences of a false positive error are about as bad as the consequences of a false negative error, then it makes sense to balance the two kinds of error within the research process. But if one kind of error is much more serious, then researchers should take steps to reduce the risk of that kind of error, even if that means increasing the risk of committing the other kind of error. Determining risk is a socially mediated exercise—determinations of what harms we can live with and what risks are intolerable are value judgments.

These sorts of risk considerations do not only arise in the later application of research findings to practical problems. They shape the research itself, with research design incorporating considerations of the high risk contexts in which the research will be applied. Scientific research is thereby not value-free. Douglas's view on how values should be mediated in science is different from Longino's. Rather than collapse the division between contextual and constitutive values, and subject them to a community of inquirers, Douglas sketches out different roles for values in science: direct roles and indirect roles. Douglas thinks that limiting the place of social values to *indirect roles* in key points of scientific inquiry protects science against "wishful thinking", the problematic event where our values may predetermine the scientific findings that we desire. A full articulation of this framework, and comparison with Longino on values in science, is beyond the scope of this paper.

Even without full articulation and evaluation of the framework, Douglas's work is revealing. In addition to acknowledging the social nature of science and the interplay of contextual and constitutive values in scientific reasoning, it offers a framework for working through uncertainty—a condition of scientific reasoning—rather than trying to overcome it. This exercise in parsing out values (epistemic and non-epistemic) and characterizing their roles in science (direct or indirect) situates the way values, both ethical and epistemic, contribute to the production of science. This framework is well suited to the task of medicine as medicine itself is quite value imbued as the ends it seeks to achieve relate to human aspirations and goals. The very idea of human health itself, with concern for well-being, morbidity, mortality, suffering, function and the language of care are intertwined with value-oriented goals we seek to achieve for individuals and populations. It is surprising that values became disconnected from the process of evidence production in the first place.

Douglas's concern for inductive risks and the possibility for error resonates particularly strongly for medical science. As she notes:

Once these values (epistemic) have been utilized to assess how much uncertainty we think there is, the other values (social, ethical, and cognitive) must compete to help weigh whether the evidence (and its relationship to the theory) is enough. It is here that inductive risk is crucial, that the indirect role is central, and that a direct role is prohibited (Heather Douglas, 2016).

However, in medicine, these values do not so much compete, but are critical to the weight of evidence itself. The central task is to understand the extent to which uncertainty has been characterized and how good the evidence is at delimiting or describing the uncertainty. Medicine has been slow to accept the honest disclosure of the extent of uncertainty in clinical medicine in particular. Showing that the process of creating evidence is an uncertainty-managing rather than truth-assuring process is a significant way forward.

Inductive risk calculus is a useful tool for clinicians confronting the often urgent needs of patients in the face of suboptimal evidence. While medical nihilism can direct some aspects of medical practice, i.e. by inviting more skepticism and humility among practitioners instead of overconfident prescribing of the latest magic bullet therapeutics for their patients (Stegenga, 2018, p. 185), physicians still remain with an incomplete evidence base to justify therapeutic options, and patients who often urgently need care. While the evidence in support of aggressive pharmacological and surgical intervention are likely to be overestimated, "gentle medicine" alternatives are also frequently unsupported due to low investment in research into gentle (lifestyle, etc.) care options (Stegenga, 2018, p. 191). Inductive risk is useful for balancing considerations of the risks involved with overestimating and underestimating any therapeutic option in order to make treatment recommendations that support the interests and goals of the patient in improving health (however conceived) and avoiding harm.

Stegenga employs inductive risk calculus not for clinical decision-making, but rather to improve drug regulation, which he (and many others) find deficient in ensuring that only the most beneficial products are approved and ineffective and harmful products are excluded. The FDA, by his account, under-regulates drug development because the approval process: allows for loose standards regarding the outcomes measured in trials (chapter 3) and what instruments could make such measurements (chapter 8), and permits poor statistical measurements of effectiveness (chapter 8) and harm (chapter 9). The FDA also does not adequately guard against admitting evidence from trials that suffer from biases (chapter 10). From his conclusion that current inductive risk calculus is unacceptably tilted towards unwarranted drug approval (a false positive error), we again glimpse the (unarticulated) non-epistemic values that guide the medical nihilism project—all tied to a commitment to more effective medicine and less drug-related harms—but those values, as discussed earlier, are not articulated explicitly nor are they defended such that they could be open to democratic scrutiny, revision, and debate.

7. Moving forward

So what does the analysis suggest so far? The idea that EBM helps explain the world as it is, and that healthcare is *based* on evidence, is problematic. First, as we have argued, the concept of a fact is complex in and of itself. How facts become facts is the result of measurement processes that have a certain conventional or arbitrary nature. They may be assembled and validated by methodologies prone to certain biases and communicated in a diverse and difficult to access system of knowledge production. In essence, there is an evolving plasticity to facts and evidence and an enduring and perhaps increasing amount of uncertainty. We ought not be surprised by this state of affairs and fallibilism supplies an account for why this is the case. Those distressed by claims that most medical knowledge is false should perhaps reassess their beliefs and assumptions about what emerges from such research in the first place.

The larger concern relates to medical nihilism and countering its withering claims about confidence. Low confidence is not the same as no confidence and faulty evidence is still evidence of a sort. Humans have always needed to use whatever imperfect knowledge instruments they have at their disposal to manage significant challenges posed by suffering and finitude. Pseudo-confidence and epistemic arrogance are poor substitutes for honesty and epistemic humility. There are indeed significant consequences to the challenges outlined above in terms of whether the social resources poured into medical systems and health research are, all things considered, worth the costs, and whether future promise from breakthrough technologies warrant waiting further still for these promises to be fully realized. But the opposite response of collective despair and nihilism are equally unwarranted.

Recognizing the entanglements of facts and values in health care is the first step in addressing the numerous challenges facing medicine and countering the morose view that medicine is broken. Opening up the discussion about what sorts of questions *should* be pursued would at least bring some discursive legitimacy to the process. This is indeed envisioned by Kelly et al. in their account of how values inform EBM (Kelly et al., 2015). Longino's process of transformative criticism would be helpful in this regard (Longino, 1990, p. 280).

More explicit articulation of epistemic values may help clarify matters by encouraging greater focus on the nature of inductive risk associated with the delivery of health care. There is room for more than just investigators' views on what questions should be answered with

research dollars, what the consequences of error are, and what the harms associated with clinical encounters would be.

In medical research, the need to trade off evidence related to benefits and harms in terms of the sample size required to detect an effect in clinical trials to favour detecting benefits over harms (Stegenga, 2016; 2018). This makes a certain amount of sense given the interests behind clinical trials. For a therapeutic agent to be approved, there must be a demonstration of benefit in a clinical trial, but such trials underestimate the possibility of harm, and once released into the general population, detecting harms becomes considerably more difficult. This means that much of the weighing of benefits and harms in clinical decision-making is asymmetrical giving greater weight to study architectures that are oriented to demonstrating benefits. Thus, issues of inductive risk are systematically underrepresented, despite most patients wanting a full account of risks attendant to initiating therapy. That such choices are value based related to epistemic values has not hitherto been sufficiently recognized and is not appreciated in the account of Kelly et al. (Kelly et al., 2015). One benefit of the proposed new standard for statistical significance is that with larger sample sizes, the capacity to detect relevant harms will also be increased (although asymmetry between detecting benefits and harms will still persist). This may mean a smaller number of trials are convincing and more merely suggestive, but it would be more protective of both the ethical and epistemological interests of medicine. This line of reasoning supports arguments for having fewer RCT's, and by parity of reasoning, fewer meta-analysis as well (Borgerson, 2016).

Recognizing how facts and values are entangled opens up the possibility of facing these challenges in an open and transparent manner. There is a vigorous literature on the interaction between democratic values and science to inform this effort (Heather Douglas, 2016; Kitcher, 2011; Longino, 1990, p. 280). This literature has not yet informed the debates on evidence in health care, yet they can bear directly on the above considerations of why fewer RCTs might be warranted, and why more stakeholders ought to have a voice in establishing research priorities and agenda setting.

8. Conclusion

We have argued that the facts and values are deeply entangled in medicine, and that this is not something that should be lamented. The complexities of what constitutes a "fact" in health research require a fallibilist orientation as a hedge against nihilism. Values enter into both the epistemic and ethical domains of medicine and acknowledging this explicitly will open up a more robust discourse over the goals of medicine. Kelly et al. (2015) rightly attend to how values play a role in EBM, but fail to see the deep fact-value entanglement that occurs in health research. The work of Putnam (2002), Longino (1987, 1990, 1996), and Douglas (2000, 2016) help to structure an understanding of the licit and illicit ways in which values can play a role in health care. How values enter science, and the extent to which they influence our notions of objectivity, is as complex as the notion of factuality. Investigating these entangled relations of facts and values brings the processes of scientific knowledge production under closer scrutiny, especially the social forces shaping inquiry. Additionally, acknowledging the social process of science would better ground some of EBM's claims to legitimacy. Douglas's attentive treatment to decision-making under uncertainty is also useful for clinical reasoning; it is surely more helpful for practicing clinicians working with sub-optimal evidence than medical nihilism. Their duties to help and heal are not removed when poor evidence surfaces.

Fundamentally, we find ourselves in accord with Peirce that all inquiry, whether in science, medicine, or in ethics, is normative, that is, striving for the best possible ways in which we ought to conduct human affairs, without any guarantee that we will be in possession of such ways in any given historical horizon.

Authors statement

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Appendix A. Supplementary data

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