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Direct and Enhanced Disclosure of Researcher Financial Conflicts of Interest: The Role of Trust

Roy G. Spece Jr.

DIRECT AND ENHANCED DISCLOSURE OF RESEARCHER FINANCIAL CONFLICTS OF INTEREST: THE ROLE OF TRUST

Roy G. Spece, Jr.†

ABSTRACT

In earlier writing, I recommended direct disclosure of major researcher financial conflicts of interest in per capita funding arrangements—the practice of providing researchers with a fixed sum for each subject recruited and enrolled in a study. This Article adds a recommendation for *enhanced* direct disclosure. The enhancement in the disclosure is a summary of why per capita and excess payments are being discussed and further includes whether the sponsors of the research and the researchers have claimed that there are no excess payments. The reason per capita payments are being discussed is because of the risk—with special caution when sponsors and researchers are not willing to claim that there are no excess payments—of introducing bias into researchers' decisions regarding study design, implementation, and interpretation, as well as concerning whom to enroll or keep in studies. Researchers' claims that there are no excess payments do not vitiate the risk of such payments. Nevertheless, a special admonition when sponsors and researchers do not claim the absence of excess payments would hopefully encourage them to eschew excess payments.

My recommendations are required by the rights to bodily integrity and autonomy embedded in informed consent. Several arguments have been made against my recommendations, many of which relate to supposed effects on trust. My rights-based recommendations should not be rejected because of objections based on propositions that (1) are conceptually unclear because of a failure to unbundle different kinds and degrees of trust and (2) have not been empirically proven even where concepts are clarified. In some instances, the required strong empirical confirmation cannot be made because of practical or ethical restraints, including the fact that some of the necessary studies would require

† University of Arizona James E. Rogers College of Law; J.D. 1972, University of Southern California Gould School of Law. I would like to thank Michael H. Shapiro, Dorothy W. Nelson Professor of Law at the University of Southern California Gould School of Law and my University of Arizona colleague, Professor Christopher T. Robertson, for constructive criticism on earlier drafts of this Article. I also would like to thank participants in seminars at the 2012 Asian Conference on Ethics, Religion, & Philosophy, March 2012, Osaka, Japan, and at the 2012 ASLME Health Law Professors Conference, Phoenix, Arizona, who provided feedback on ancestor versions of this Article that were presented as discussion papers.

invasion of the right to informed consent. Finally, I suggest and partially apply an organizational method to generate empirical questions and guidance for future research in this area. Even the few hypothetical scenarios addressed demonstrate how complex—and sometimes practically or ethically impossible—the empirical studies must be to adduce proofs sufficient to overcome the imperative of informed consent.

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INTRODUCTION

I was among the scholars who early, over two decades ago, called for direct disclosure of certain researcher financial conflicts of interest to subjects in clinical trials.[1] "Direct disclosure" is defined here as disclosure to the subject as part of the informed consent process. "Indirect disclosure" means disclosure to third parties, such as by posting on a public website.[2] I argued in my earlier writing that subjects should be "told the mechanism [and source] of the funding (for example, capitation or block grant with a target enrollment), as well as the amount of funding." The mechanism of compensation I focused on was "per capita funding" of a set amount for each subject recruited and enrolled in a study. Per capita funding is troubling because it risks inclusion of compensation beyond fair market value of the resources, goods, and services supplied by the researchers. It is a bribe of sorts.[3]

1. David S. Shimm & Roy G. Spece, *Industry Reimbursement for Entering Patients into Clinical Trials: Legal and Ethical Issues*, 115 ANNALS OF INTERNAL MED. 148, 148 (1991) [hereinafter Shimm & Spece 1]; David S. Shimm & Roy G. Spece, *Ethical Issues and Clinical Trials*, 46 DRUGS 579, 579 (1993) [hereinafter Shimm & Spece 2]; David S. Shimm & Roy G. Spece, *Conflict of Interest and Informed Consent in Industry-Sponsored Clinical Trials*, 12 J. LEGAL MED. 477, 510–11 (1991) [hereinafter Shimm & Spece 3].

2. *See* discussion *infra* Part II regarding indirect disclosure.

3. Shimm & Spece 1, *supra* note 1, at 149; Shimm & Spece 3, *supra* note 1, at 511.

The problematic nature of per capita funding is apparent from an example. Thomas Parham was enrolled in a clinical study despite having a heart condition that should have excluded him.[4] His physician was paid a generous sum for each subject enrolled in the study.[5] Toward the beginning of the study, Parham had symptoms that indicated that his heart condition was deteriorating, but his physician ignored the problem.[6] Weeks later, Parham was hospitalized and required a pacemaker.[7] At least as far as appearance is concerned, it is easy to believe that a conflict in the form of per capita payments caused the physician to enroll and continue Parham in the study despite the risks to his health.[8]

My earlier recommendation that financial conflicts of interest (focusing on per capita funding) should be directly disclosed to subjects was based on historical aspects of human experimentation, the dynamics of privately funded human subjects research, and, primarily, rights to autonomy and bodily integrity embedded in and supported by the pertinent case law, statutory law, and commentary regarding informed consent in clinical practice and research.[9] In a legal context, this leads to the conclusion that direct disclosure is required by the right to informed consent. The core justification of the earlier recommendations was based on a nonconsequentialist moral framework concerning each subject's—indeed, all persons'—*presumptive* individual rights.[10] The present Article takes these rights as given and is based on the same moral foundation. But, being a moral pluralist of sorts, I believe that consequences are morally material. I agree that strong empirical proof demonstrating the high likelihood of significant harm and little good resulting from direct disclosure might overcome a presumption in favor of subjects' individual rights to bodily integrity and autonomy in decision making.[11] The strength of empirical proof required to overcome subjects' rights in this or any context is a normative question.[12] Thus, my necessarily normative answer to that question is that the required empirical proof must be established beyond a reasonable doubt. I also doubt that this level of proof can be achieved outside of direct or field studies, as opposed to experimental ones. The nature of the researcher-subject relationship and

4. Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at A1.

5. *Id.*

6. *Id.*

7. *Id.*

8. *Id.*

9. Shimm & Spece 3, *supra* note 1, at 510–11.

10. *Id.*

11. Here I do not address a possible "right to know."

12. ROBERT LAWLESS ET AL., EMPIRICAL METHODS IN LAW 21 (2009).

the subject's usual sick role cut against establishing empirical propositions beyond a reasonable doubt. Some of the primary arguments against direct disclosure are based on empirical assertions about the effects of disclosure on subjects' "trust" in researchers.

This Article will show that currently there is no strong empirical proof of direct disclosure's effects on subjects' trust in their researchers that would overcome the presumption in favor of individual rights. Direct (or "field") studies that would be needed to adduce strong proof of effects on trust that would overcome the presumption in favor of individual rights would require that up to fifty percent of subjects be denied the very information required by their rights to bodily integrity and autonomy. It seems that the only studies that can be ethically practically undertaken are vignette or mock studies, also known as "experimental studies," such as the one done by Weinfurt and his colleagues addressed later in this Article.[13] Whether experimental or field studies are in question, both are subject to the criticism here regarding the insufficient probing of "trust."

Disclosure is needed now more than ever. The amount of research and the percentage of it that is privately funded have increased tremendously during the last two decades. There is no reason that this growth is not matched by a proportionate increase in the number of conflicts. In fact, conflicts are now not only more numerous proportionately, but even more likely to occur as a percentage of all cases. For example, consider the probability that companies will be under more pressure to recruit and enroll subjects from what is now a proportionately smaller pool of candidates (given growth in research). This might lead them to use per capita funding more often and to offer compensation in excess of fair market value to entice researchers to stretch rules and norms past their limits when recruiting and enrolling subjects. They would surely attempt to hide any excess payments within seemingly legitimate budget items such as "administrative fees." Examples of researcher misconduct would include making misleading statements to recruit subjects or failing to honor protocols concerning who are proper subjects. Furthermore, much of the privately funded research has moved from the academic setting to the offices and clinics of physicians in private practice.[14] This arguably has exacerbated researcher conflicts of interest caused by exchanges of value between pharmaceutical companies and researchers. For example, payments in the academic setting are distributed through units having a

13. Jeremy Sugarman, *Data, Policies And Conflicts Of Interest in Research*, 6 ST. LOUIS U. J. OF HEALTH LAW & POL'Y 69, 74-75 (2012) (discussing a multi-year study funded by NIH in which it was found impossible to nest a study of disclosure of financial conflicts of interest in an actual clinical study).

14. KATHLEEN M. BOOZANG ET AL., CTR. FOR HEALTH & PHARM. LAW & POLICY, CONFLICTS OF INTEREST IN CLINICAL TRIAL RECRUITMENT & ENROLLMENT: A CALL FOR INCREASED OVERSIGHT 6 (2009) [hereinafter BOOZANG 1].

managerial structure and several professionals (thus diluting the effect of excess payments on any one researcher), and academic physicians are in a culture at least *intended* to be conducive to high ethical standards that should counsel against acceptance of excess payments. In contrast, in non-academic settings, physicians receive payments directly and may be under little "environmental" or "cultural" restraint.[15]

This Article has a circumscribed focus. It addresses researcher conflicts but does not examine associated institutional conflicts. It does not address the entire array of conflicts; it only considers disclosures of conflicts created by per capita payments.[16] And it does not develop all the arguments for and against direct disclosure. Rather, it focuses on direct disclosure's possible effects on subjects' "trust" in researchers and whether particular effects argue for or against direct disclosure. This Article goes beyond my earlier work in that it recommends *enhanced* direct disclosure: summarizing the relevance of the conflict to the subject, with additional emphasis on when sponsors and researchers are not willing to claim that there are no excess payments. It would seem that an enhancement of disclosure would add to the likelihood of effects on trust.

I. ENHANCED DIRECT DISCLOSURE

An example of an *enhanced* direct disclosure that might affect researcher-subject trust would be a requirement that subjects in studies funded on a per capita basis be told:

> This study is funded by Company X, which has paid Researcher Y $10,000 for each subject enrolled.
>
> [If true, add: "X and Y claim that these payments are not in excess of fair market value." If not true, add: "X and Y are not willing to state there are no excess payments."]
>
> This form of per capita funding (a set amount for each subject enrolled) risks payment to Y that exceeds the fair market value of resources, goods, and services supplied by Y to X. [If applicable,

15. *See generally id.* at 13–15; KATHLEEN M. BOOZANG ET AL., CTR. FOR HEALTH & PHARM. LAW & POLICY, THE LIMITS OF DISCLOSURE AS A RESPONSE TO FINANCIAL CONFLICTS OF INTEREST IN CLINICAL RESEARCH 5 (2010) [hereinafter BOOZANG 2]; Mark Hall et al., *Per Capita Payments in Clinical Trials: Reasonable Costs Versus Bounty Hunting Fees*, 85 ACAD. MED. 1554, 1554–1556 (2010) (discussing the greater risk of bounty hunting fees in the non-academic environment and calling for research on whether excess payments are in fact a problem).

16. The criticisms here regarding inadequate exploration and clarification of "trust" are nevertheless applicable to studies of institutional conflicts of interest and conflicts other than per capita payments (e.g., researcher equity interests in the research sponsor).

> add: "especially when X and Y or those in similar positions refuse to state that there are no excess payments."].
>
> Excess payments present the risk of biasing, in favor of X, Y's decisions concerning the design of the research study, whether and when to enroll or keep each subject, and how to determine whether the data from the study demonstrate [the studied intervention] is safe and effective.

The early recommendations for direct disclosure have been embraced to a limited extent.[17] For what it is worth, recommendations for indirect disclosures (e.g., to the public on a website) have fared better. For example, disclosure of basic data concerning virtually all exchanges of value from pharmaceutical companies to physicians in a broad array of contexts is required by portions of the Patient Protection and Affordable Care Act.[18] These disclosures are limited, however, to delineation of the nature and amount of consideration on a publicly available website.[19] For example, per capita payments to a physician-researcher would be posted by the amount of total payments without designating that the payments were made on a per capita basis. This "sunshine" legislation is not likely to serve subjects' rights to autonomy and bodily integrity except in speculative or remote ways although it will provide data useful to researchers. Consider the example above concerning Thomas Parham. If the total amount of per capita payments in that case had been posted on a public website without designation of the per capita mechanism of payment, it is unlikely that Parham would have both researched for this conflict and understood what it meant. Probably not even an expert could have understood it. Its significance would not have been apparent without possibly futile research for further information such as the per capita nature of the payments.

Scholarly commentary opposed to direct disclosure of conflicts is likely at least part of the cause of the limited support for including

17. Shannon Benbow, *Conflict + Interest: Financial Incentives and Informed Consent in Human Subject Research*, 17 NOTRE DAME J.L. ETHICS & PUB. POL'Y 181, 206–16 (2003) (discussing a proposed federal law requiring direct disclosure but only insofar as determined advisable by an Institutional Review Board); James A. Christensen & James P. Orlowski, *Bounty Hunting and Finder's Fees*, 27 IRB: ETHICS & HUMAN RES. 16, 18 (2005) (explaining that disclosure must be made to an Institutional Review Board which should then decide whether there should be direct disclosure to subjects); Jammi N. Rao & L. J. Sant Cassia, *Ethics of Undisclosed Payments to Doctors Recruiting Payments in Clinical Trials*, 325 BRIT. MED. J. 36, 37 (2002) (asserting that consent cannot be informed without disclosure of payments).

18. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 6002(a)(1)(A), 124 Stat. 689 (2010).

19. *Id.* § 6002(c)(1)(E)(i).

compensation information in the informed consent process even when there is growing acceptance of the need for indirect disclosure. This literature gives several arguments against direct disclosure, including claims that it would: (1) negatively "free" physicians from some ethical obligations through a conceit that disclosure itself is more than sufficient;[20] (2) *increase* trust so much that subjects would irrationally become too placid and would not sufficiently monitor researchers;[21] (3) *decrease* trust so much that subjects would overemphasize the risk and, presumably, forego participation in possibly beneficial studies;[22] (4) *decrease* trust so much that subjects who do enroll in a study would forego a chance to benefit from therapeutic effects inherent in the researcher-subject relationship;[23] (5) confuse subjects, except those from a wealthy, educated elite who least need protection;[24] (6) waste resources because subjects' decisions would not be affected;[25] (7) leave many subjects with no viable alternative, thus making disclosure gratuitous;[26] (8) cause institutions to be lax in their general oversight responsibilities related to financial conflicts on the assumption that the informed subjects themselves would make reasoned choices;[27] (9) cause information overload and lead to subject confusion or inattention to more pertinent information such as physical risks;[28] (10) not be necessary because of

20. BOOZANG 2, *supra* note 15, at 12.

21. *Id.* at 11.

22. *Id.* at 13

23. *Id.* at 11; Daylian M. Cain et al., *The Dirt on Coming Clean: Perverse Effects of Disclosing Conflicts of Interest*, 34 J. OF LEGAL STUD. 1, 5 (2005); Don A. Moore & George Loewenstein, *Self-Interest, Automaticity, and the Psychology of Conflicts of Interest,* 17 SOC. JUST. RES. 189, 196 (2004); DON A. MOORE ET AL., *Conflicts of Interest Challenges and Solutions from Law, in* MEDICINE AND ORGANIZATION SETTINGS 1, 1 (2004); MARC A. RODWIN, CONFLICTS OF INTEREST AND THE FUTURE OF MEDICINE: THE UNITED STATES, FRANCE, AND JAPAN 215 (2011); Marc A. Rodwin, *Physicians' Conflicts of Interest: The Limitations of Disclosure*, 321 NEW ENG. J. MED. 1405, 1405 (1989).

24. BOOZANG 2, *supra* note 15, at 14; Omri Ben-Shahar & Carl Schneider, *The Failure Of Mandated Disclosure*, 159 U. PA. L. REV. 647 (2011) (attacking mandated disclosure in an array of contexts including the clinical research and practice settings, e.g., consumer protection). For a criticism of Ben-Shahar & Schneider's article as based on (1) false premises that disclosure fails insofar as it seeks to honor disclosees' autonomy and to improve "naïfs'" decision making when dealing with "sophisticates" and (2) debatable normative assumptions that naïfs' interests should supercede others' interests, *see* Jeremy Sheff, *Disclosure as Distribution*, 88 WASH. L. REV. 475 (2013).

25. BOOZANG 2, *supra* note 15, at 10.

26. *Id.* at 10-11.

27. *Id.* at 12.

28. *Id.* at 13.

indirect disclosure or other protections;[29] and, (11) not have any beneficial effects.[30] Several of these arguments against direct disclosure relate to effects on trust, and this Article will examine them exclusively. But first, an obvious question: what is "trust?"

II. The Multiple Domains or Aspects of Trust, Conflicting Research on Trust, And Why, Given the Current Literature, Trust Concerns Should Not Guide Decisions about Enhanced Direct Disclosure

The central problem of analyzing direct disclosure's effects on "trust" is that the pertinent literature does not sufficiently define the aspects of trust addressed in each study. Here, I will stipulate a broad, tentative working definition of at least the core of trust: *trust is a favorable, subjective state of mind concerning another's expected motives, intentions, propensities, competencies, or behavior.* Beyond this working definition, I will expand on various aspects or domains of trust. I will not attempt a comprehensive analysis or taxonomy of trust. The existing disclosure literature's failure to adequately define and probe trust and its various dimensions alone erodes the power of any findings to a degree that eliminates them as guides for policy.

Trust is a multi-faceted concept that can be approached from many perspectives. For example, one can consider why a person trusts another person or an entity. Is it because of that person's membership in some group (such as doctors), or is it because that person has earned trust over time through what is perceived as sound performance? One can speak of particular dimensions of trust: faith in another's competence, veracity, or empathy. There are also levels of trust. For example, trust could be comprised of magnitudes of belief in the researcher's overriding concern for the subject's best interests. At its apex, trust might be a subject's willingness to unqualifiedly submit herself to a researcher. Conversely, the lowest level of trust might be characterized by a subject's complete mistrust in a researcher and consequent refusal to enroll. Above this nadir of complete mistrust could be ascending levels of trust: (1) that which a subject would grudgingly place in an adversary, probably causing a subject to carefully scrutinize each word and every action the researcher takes; (2) that which a subject would place in most people, probably motivating a subject to reasonably monitor a researcher; and (3) that which a subject would place in a close and respected family member, probably resulting in only a cursory monitoring of researchers' decisions, representations, and recommendations.

The best study relevant to the effects of direct disclosure of per capita payments on trust is a vignette or mock (i.e., experimental) study done by

29. *Id.* at 11.

30. *Id.* at 15.

Kevin Weinfurt and his colleagues.[31] This article is instructive even though it addresses financial conflict of interest in the form of per capita payments to *institutions* and the closely related conflict of interest inherent in significant *equity ownership* by individual *researchers*. Even Weinfurt is not clear concerning the forms of "trust" his study addresses. He writes that his study concerns "trust in medical research."[32] To establish a pre-study baseline of "trust in medical research," Weinfurt asked subjects to rate their agreement with the following statements: "'Doctors who do medical research care only about what is best for each patient'; 'Medical researchers tell people everything they need to know about being in a medical research study;' 'Medical researchers treat people like "guinea pigs"'; and 'I completely trust doctors who do medical research.'"[33] These questions suggest different aspects of trust. The first question addresses what motivates researchers. The second question speaks to what researchers will disclose to patients. The third question relates to the expected behavior of researchers. The fourth question suggests a global form of trust that presumably would encompass the aspects spoken to in the first three questions.

The question Weinfurt asked to reach conclusions about the effect of direct disclosure on trust in researchers and research institutions was: "How likely would you be to agree with the following statements: I completely trust Dr. Smith to do good medical research[, and] I completely trust University Medical Center to do good medical research." Here, trust is faith in doing good medical research, but it seems that distinct elements of trust have been collapsed into the phrase "doing good medical research." What does this phrase mean? It seems to relate most directly to the researcher's technical competence as opposed to concern with subjects, but one can only guess. Even "technical competence" bears major ambiguities—competence in choosing a project; competence in setting up methodology; competence in mechanical tasks; and competence in monitoring, recording data, doing statistics, and so forth. We could address even more specifically—and very importantly—competence to properly administer diagnostic tests and the intervention being studied; to properly enroll and maintain subjects in the study generally; to make enrollment, continued participation, and other decisions in the best interests of the particular subject whose trust is being measured; to fully inform subjects; to do all of the preceding; and more.

Different dimensions of trust or different aspects of a single meaning of trust are inherent in the questions above. All these dimensions or aspects of trust are relevant to subjects, but to different degrees, often depend-

31. Kevin P. Weinfurt et al., *Effects of Disclosing Financial Interests on Participation in Medical Research: A Randomized Vignette Trial*, 156 AM. HEART J. 689, 689 (2008).

32. *Id.* at 690.

33. *Id.*

ing on variations among individual subjects. These dimensions of trust concern strength of belief in whether researchers are (1) making decisions in the best interests of the particular subject (thus protecting the subject across the board); (2) fully informing subjects (thus allowing them to opt out of studies); (3) properly administering diagnostic tests and the intervention being studied (consequently protecting the subject from injury caused by substandard care and maximizing the possibility that the subject might benefit from the studied intervention); (4) properly enrolling subjects in the study generally (hence protecting fellow subjects and the validity of the study's conclusions); and (5) competently designing, conducting, and interpreting the study to obtain good data (thereby reaching correct conclusions regarding safety or efficacy of the studied intervention). Of course, a global conception of trust would include all the senses of trust and provide all the protections in (1) through (5). In all of these, there are problems of combining different degrees of different variables. It is impossible to determine which, or which combination, of these five dimensions or aspects of trust that participants in Weinfurt's study had in mind when they answered the questions regarding "doing good medical research." Again, the current literature does not sufficiently specify which dimensions or aspects of trust should be, or most often are, studied. Consequently, the best I can do in this Article is to speculate about enhanced direct disclosure's effects on various forms or aspects of trust.

The ambiguity concerning what facet(s) of trust are being studied is one of the reasons that direct disclosure's supposed effects on trust, as spoken of in the literature, should have little or no influence on decisions whether to implement direct disclosure. Because studies of direct disclosure offer no clear specification of which aspects of the complex mosaic of trust are being investigated, the findings about direct disclosure's supposed effects offer limited guidance at best and should have little or no influence on decisions whether to implement direct disclosure. This is a comment about the utility of the studies, not ultimately about the concepts being studied. A largely new set of studies and analyses is necessary before the literature achieves basic reliability. This is vividly illustrated by the fact that findings conflict as to whether direct disclosure of financial conflicts of interest *enhances* or *diminishes* trust.[34] This is a rather basic failure, and it is not merely empirical—it is conceptual. There has been a failure to recognize and sort through the serious systematic ambiguities of trust, which is reflected in its strikingly different—though obviously connected—dimensions. Thus, the utility of any supposedly "empirical" conclusions about direct disclosure's effects on trust is questionable. It is also ironic that there are conflicting views concerning whether enhancement of trust is good or bad. On the one hand, for example, it can be argued that enhancement of trust will contribute to

34. BOOZANG 2, *supra* note 15, at 13.

better subject participation or outcomes. Conversely, it can be argued that enhancement of trust will exacerbate the therapeutic misconception that the primary goal of a clinical study is treatment for the subject rather than scientific inquiry.

Empirical investigation of direct disclosure's effects on trust is also subject to the limitation that it is unethical to withhold disclosure from subjects in a control group. Obtaining consent to not being told would be impossible without either telling too little to obtain informed consent or too much to prevent biasing the study.[35]

III. FOCUS ON ENHANCED DIRECT DISCLOSURE OF PER CAPITA PAYMENTS

There is a working understanding among most policy makers and scholars that although per capita payments risk excess compensation and excessive or inappropriate enrollment, they should not be prohibited as necessarily involving such improper incentives in every case.[36] I take no position on prohibition. At the very least, however, per capita payments should be treated as generally suspect, because they risk excess payment and consequent negative incentives for at least three reasons. First, it is relatively easy to hide excess payment in complex budgets. There are many complex variables that can affect the appropriate funding of any particular study at a specific venue and a dearth of research on the costs of conducting clinical studies. This makes it very difficult to prove excess payment in a given case.[37] The risk is not vitiated even if the sponsors or researchers claim that there are no excess payments. Second, per capita payments also pose a high risk of excess compensation because they ignore the economic principle of economies of scale: the more subjects there are, the cheaper it will likely be to add each successive subject. When a study begins, it is uncertain how many subjects ultimately will be available. This uncertainty provides a ready excuse for not taking account of economies of scale when figuring actual costs. Third, as mentioned above, per capita payments can also improperly entice researchers to enroll subjects or keep them in a study when doing so is contraindicated. The allure of a

35. *But cf.* the American Medical Association's position that placebos cannot be ethically used without informed consent to their use. Anne Barnhill, *Clinical Use of Placebos: Still the Physician's Prerogative?,* 42 HASTINGS CTR. REP. 29, 29 (2012). Although the AMA accepts the possibility that one can consent to use of a placebo without vitiating its "efficacy," this possibility is not sufficiently strong, in light of the restriction on not disclosing matter that would bias the study, to overcome the presumption in favor of disclosure posited here to flow from the rights to autonomy and bodily integrity.

36. Mark A. Hall et al., *Per Capita Payments in Clinical Trials: Reasonable Costs Versus Bounty Hunting*, 85 ACAD. MED. 1554, 1556 (2010).

37. *Id.*

substantial set amount of money, say $10,000,[38] for each captured target of opportunity is especially strong.

In this context, my original call for direct disclosure of per capita payments remains important. I now also propose that direct disclosure include an explanation of how a conflict can harm a subject or the public. This is the *enhanced* direct disclosure mentioned earlier. Specifically, again, subjects should be told that per capita payments pose the risk of excess payments that might bias (in favor of the company funding the study) researchers' decisions concerning the design of the research study, whether and when to enroll or keep each subject, and how to determine whether the data from the study demonstrate that the studied intervention is safe and effective. I make this recommendation for enhanced direct disclosure because otherwise subjects might not understand why they are being informed about per capita payments and risk of excess compensation. The enhancement of disclosure adds a variable that is not addressed in the studies to date.

A. Five Variables Concerning Risks to Trust

Although the literature does not contain sufficient information to confidently predict the effect enhanced direct disclosure might have on particular forms of trust in any given study, it is useful to consider what actions might be best to take under a series of assumptions that enhanced direct disclosure increases or diminishes *specified* forms of trust. An adequate study requires attention both to the five dimensions of trust discussed above that are under investigation and to at least five variables that map onto the five dimensions of trust (or all of them together). These variables are: (1) the nature of the conflict; (2) the precise wording and method of disclosure; (3) the demographics of the subjects; (4) the setting; and (5) the magnitude of the impact on trust, if any (often itself the focus of empirical study). One can mix-and-match various combinations of these five variables in different hypothetical situations (sometimes with specific assumptions such as the subject's affinity or aversion concerning risk) to generate specific questions for research and analysis. This is a heuristic formulation to help isolate questions and guide further study.

I have just listed variables that need to be addressed in studies of trust and provided an organizational scheme to guide future research. Once the propositions that require empirical confirmation are identified, it can be determined whether some or all of them are amenable to proof

38. Shimm & Spece 3, *supra* note 1, at 482 (discussing $2,000 to $5,000 payments per subject in 1990 dollars); *see also* Benbow, *supra* note 17, at 210; Rao & Sant Cassia, *supra* note 17, at 37; Christensen & Orlowski, *supra* note 17, at 16 ("It is now fairly commonplace for clinical researchers to be offered large sums of money ($5,000 to $10,000) for each individual they enroll in a research study, even where the investment of time and expertise on the part of the researcher is relatively minor.").

in sufficiently powerful empirical studies that can be ethically or practically performed. If certain policy recommendations relating to trust can only be supported by proofs that either have not been made or cannot be made in the future because of practical or ethical restraints, those recommendations should not be pursued—at least not at this time. Consideration of the various dimensions or aspects of trust and the five variables identified above suggests the difficulty of adducing proofs of the effects of enhanced direct disclosure sufficient to overcome the rights to bodily integrity and autonomy that justify enhanced direct disclosure.

In the remainder of this Article, I will venture representative applications of my organizational scheme, having already explained that the current literature concerning direct disclosure's supposed effects on trust is insufficient to support any objections to direct disclosure. Before proceeding, however, I emphasize that the current literature is deficient because it neither specifies nor controls for *each* of the five variables above, and it fails to explain what dimensions or aspects of trust are involved or why researchers have reached contradictory findings as to whether direct disclosure enhances or diminishes trust. It is quite possible that, in some cases, "contradictory" results are not contradictory at all, because they involve different kinds of trust that are affected differently under different disclosure regimes in different settings.

B. Some Partial Applications of the Suggested Guide for Future Study

I will now apply my guide for further study to a few hypothetical scenarios involving the five variables and one of the many different dimensions or aspects of trust. The goal is to demonstrate how one might generate questions for study of the impact of enhanced direct disclosure on the various dimensions or aspects of trust. In each of these hypotheticals, assume the following: (1) that the conflict disclosed is the use of per capita payments; (2) that the wording, conveyed both verbally and in writing, is the enhanced direct disclosure delineated earlier; (3) that the setting is outside of academia; (4) that the demographic of subjects is primarily white, middle-class males; (5) that the aspect of trust to be studied is faith that the researcher will make all decisions with the subjects' best interests being of paramount concern; and (6) that we have done preliminary work to determine a baseline of trust (in the stipulated sense) that would exist without enhanced direct disclosure against which we will judge any increase or decrease in trust. These assumptions allow the study of each hypothetical to center on the direction and magnitude of any effects on trust from the trust baseline without enhanced direct disclosure.

For a first scenario, assume the subject has unqualified trust in the researcher's commitment to the subject's best interests to such a degree that the subject is prone to unqualifiedly submit himself to the researcher's representations and requests; the studied intervention is known to have serious albeit remote risks; and the subject is generally very guarded and risk-averse. A reasonable subject in this scenario might well decline participation, and without further probing resulting in information cutting in favor of participation, the subject will probably refuse

to enroll. Nevertheless, his form and level of trust in the researcher as specified in this hypothetical might well lead him to automatically consent. Based on these assumptions, it would seem that trust in the form and level assumed would be bad because it would likely lead to unquestioning participation on facts that call out for skepticism and scrutiny. The questions for research derived from this case include: (1) whether enhanced direct disclosure of per capita payments enhances or diminishes trust in the form of belief that the researcher will honor the subject's best interests; (2) if so, the amount trust will be enhanced or diminished and to what level will that put overall trust when computed along with any degree of trust without enhanced direct disclosure; and (3) how that will affect the subject's decision making—e.g., will an *increase* in trust cause the subject to be far more deferential and to forego reasonable (never mind strict) review of issues likely to be material within her own value framework, or will a *decrease* in trust engender a desired level of skepticism.

In the same vein, suppose that direct disclosure could, at least in some cases, attenuate trust with the effect of harming researcher-subject relationships and thereby lower the possibility of therapeutic benefits from a studied intervention as possibly potentiated by a high quality researcher-subject relationship. Probes of this possible deleterious effect would be extremely complicated and difficult even if one disregarded the ethical objection to withholding direct disclosure from persons in control groups. This is one reason that it will be very difficult for scholars to adduce empirical proofs concerning enhanced direct disclosure's various possible effects on specific facets of trust.

For example, assume that the positive quality of the researcher-subject relationship has been shown to improve subject outcomes through the same mechanisms that have been shown to improve outcomes when a placebo (inactive intervention) is prescribed.[39] In this sense, improved quality of the researcher-physician relationship would be analogous to a placebo. "Placebo" might be expanded to include relationship quality, or, better, relationship quality effects could be labeled "placebo-like." The common idea is that an element that is not therapeutically effective, independent from participation in the study, may affect outcome measures favorably. To be sure, a therapeutic relationship is not a medicine, device, or procedure and is not literally a placebo (unless perhaps we are discussing talk therapy and its accompanying relationships). Now assume the project is to answer the following

39. These are actually disputed questions. *See* Anup Malani, *Regulation with Placebo Effects*, 58 DUKE L. J. 411, 441 (2008). Moreover, the studies necessary to best establish the assumptions might be practically impossible or unethical. This is true for the same reasons that it would be practically impossible or unethical to judge the effects of disclosure on the quality of the researcher-subject relationship explained in the text following this footnote.

questions (put in the same form as before): (1) whether enhanced direct disclosure of per capita payments diminishes a specified form of trust; (2) if so, what is the magnitude of this effect; and (3) how the subject's level of trust as modified by the direct disclosure will affect the quality of the researcher-subject relationship and consequent therapeutic effects (i.e., will it harm the relationship so as to negate any placebo-like effect?).

Although the questions presented by the hypothetical study are important, answering them via the gold-standard of a double-blind study with placebo would require the following groups of subjects: (1) those receiving enhanced direct disclosure and receiving a placebo; (2) those not receiving enhanced direct disclosure but receiving an active experimental intervention rather than a placebo; (3) those receiving enhanced direct disclosure and receiving an active experimental intervention; and (4) those not receiving enhanced direct disclosure but receiving a placebo rather than an active intervention. It is questionable whether such a study would yield valid results. All these permutations of disclosure would threaten the overriding purpose of isolating the effects of the active intervention as opposed to placebo or placebo-like effects. In the traditional physician-patient relationship, one could (in theory) determine the effect of relationship quality on outcomes without the confounding variable of using a placebo. However, the best experimental design in the researcher-subject context requires use of a placebo. Scientific consensus and legal regulation demand that efficacy requires a therapeutic effect beyond the effects of placebo.[40] This would logically require that therapeutic effect from the studied intervention alone exceed effects from both a placebo and a quality researcher-patient relationship.

CONCLUSION

This Article explains that my recommendations are required by the rights to bodily integrity and autonomy embedded in informed consent. It also identifies several arguments that have been made against those recommendations. I have explained that many of the arguments against direct disclosure relate to supposed effects on trust. I have further argued that my rights-based recommendations should not be rejected because of objections based on propositions that (1) are conceptually unclear because of a failure to unbundle different kinds and degrees of trust and (2) have not been empirically proven even where concepts are clarified. In some instances, empirical confirmation in the required direct or field studies cannot be made because of practical or ethical restraints.

40. Jennifer Kulynych, *Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 127 (1999); 21 C.F.R. § 314.126 (2012).

These restraints include the fact that some of the necessary studies would require invasion of the right to informed consent. Finally, I have suggested and partially applied an organizational method to generate empirical questions and guidance for future research. Even the few hypothetical scenarios addressed demonstrate how complex—and sometimes practically or ethically impossible—the empirical studies must be to adduce proofs sufficient to overcome the imperative of informed consent.