The pregnancy resulted from rape or incest.

- He is unable to consent because of unavailability, incompetence, or temporary incapacity.
- The father's consent not required.

Assent and permission will be obtained in accord with the provisions of 546.408 procedures involved in the research (i.e., "children" as per 546.420) who are pregnant.

For persons who have not attained the legal age for consent to treatments or

By any other means that cannot be obtained.

Research seeks Minimal risk to fetus.

All other requirements, plus:

Woman Consents

Both Benefit

If Woman or

Grant Consent

Father

Woman &

Benefits

If Neither

Only Fetus

Determining the termination

Regarding any decisions

Researchers will have no
terminate pregnancy

No inducements to

objectives achieving research

Risk is minimal for

Previous studies have been conducted & provide risk

45 CFR 46 Subpart B: Additional Protections for Pregnant Women & Fetuses (§46.204)
Is There an Ethical Obligation to Disclose Controversial Risk? A Question From the ACCORD Trial

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Is There an Ethical Obligation to Disclose Controversial Risk? 
A Question From the ACCORD Trial

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Researchers designing a clinical trial may be aware of disputed evidence of serious risks from previous studies. These researchers must decide whether and how to describe these risks in their model informed consent document. They have an ethical obligation to provide fully informed consent, but does this obligation include notice of controversial evidence? With ACCORD as an example, we describe a framework and criteria that make clear the conditions requiring inclusion of important controversial risks. The ACCORD model consent document did not include notice of prior trials with excess death. We develop and explain a new standard labeled risk in equipoise. We argue that our approach provides an optimal level of integrity to protect the informational needs of the reasonable volunteers who agree to participate in clinical trials. We suggest language to be used in a model consent document and the informed consent discussion when such controversial evidence exists.

Keywords: informed consent, research ethics, institutional review board, biomedical research, professional ethics

New paradigms of clinical research have continued to require us to develop new ethical guidance on risk disclosure. Researchers designing a clinical trial may know of uncertain or controversial evidence of serious, even life-threatening, risks described in previous studies. These researchers in developing their own research protocols must make a difficult decision regarding whether and how to describe in the informed consent process this uncertain or controversial risk. The ethical obligation to provide fully informed consent entails providing subjects with the important and necessary information on which to make an enrollment decision.

Using the Action to Control Cardiovascular Risk in Diabetes (ACCORD) protocol and model consent document as an example, we propose a new standard that will help researchers better meet the ethical obligation of good disclosure. In particular, in analyzing the ACCORD research protocol we argue that there is sufficient evidence to require the disclosure of a controversial risk of mortality for those in the tightly controlled blood glucose arms. The example of ACCORD illustrates how and when uncertain or controversial evidence of risk should be included in informed consent processes.

In this article, we develop a framework and criteria that make obligatory the inclusion of a controversial risk in the model informed consent document while avoiding the absurd need to list every conceivable harm that could befall a person. In developing the framework and criteria we employ an extended notion of equipoise together with a call for full transparency. We argue that our approach provides an optimal level of integrity to protect the informational needs of the reasonable volunteers (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979) who agree to participate in clinical trials.

We begin with an account of research integrity, heavily relying on government regulations and foundational documents such as the Belmont Report. This account supports our stated approach to reporting evidence of risk. Next we provide an overview of the ACCORD study and include an examination of the way prior evidence of the risk of excess death is handled in the ACCORD protocol. Finally, we propose a specific example of what should be included in a model consent document and in the consent discussion.

INFORMED CONSENT AND INTEGRITY IN RESEARCH
A therapeutic clinical trial typically entails unexpected risks. A volunteer for research may freely accept risk, but in doing so gains a special right to be informed about possible harms. This right to be informed about possible risks is based on the additional informational requirements of the reasonable volunteer as articulated in the Belmont Report.
Obligation to Disclose Controversial Risk

The Belmont Report asserts that the right to information about risks in research goes beyond the ordinary informational need in a purely therapeutic context (National Commission 1979). This right is also articulated in a variety of other codes and regulatory requirements, including the Nuremberg Code (1949–1953) and the Declaration of Helsinki (World Medical Association 1964–2008).

Regulatory requirements in the United States are included in the federal policy for the “Protection of Human Subjects” (Code of Federal Regulations Title 45: Section 46–116: CFR n.d.). This regulation, known as the Common Rule, requires “a description of any reasonably foreseeable risks or discomforts to the subject” (CFR n.d.).

Together these codes and regulatory requirements describe a general burden on researchers to present information about possible harms, but with varying descriptions of what should be disclosed, the threshold for disclosure, and characterization of the participants in the study. Evidence about a risk may be disputed. When this occurs, it is problematic whether the disputed risk should be included in the informed consent process. We offer a standard that provides a specification to the criteria of the Common Rule of “reasonably foreseeable” risk by using a conception of risk in equipoise. A serious risk of harm from a medical intervention is a risk in equipoise when disputed evidence of risk has not been accepted as disproven by a consensus among specialists in the appropriate medical field.

The risk in equipoise standard follows the lead of the classical clinical equipoise concept, involving balance as well as the notion of communal consensus, as presented by Freedman (1987). His concept of equipoise is based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of ‘clinical equipoise,’ the requirement is satisfied if there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment. (Freedman 1987, 141)

As the term is used in the risk in equipoise principle, equipoise indicates that the disputation of the evidence is balanced by lack of consensus on the status of the evidence. The use of “balance” is meant to be suggestive of lack of consensus, and is not meant to convey a sense of equality in weight of opinion between those who reject the evidence and those who do not. The research ethics use of clinical equipoise, as developed by Freedman, also represents a rough balance among arms of a trial. The judgment that two or more arms are in equipoise is typically based on lack of knowledge and so cannot support the expectation of equality in outcomes. Instead it indicates that there is no consensus that any arm will prove to be superior or inferior to the others.

Our risk in equipoise standard is rigorous—more rigorous than Freedman’s use of clinical equipoise. Our standard puts a heavy burden of proof on those who wish to disregard disputed evidence in the informed consent process; that is, the decision not to include the evidence requires supporting argumentation that a consensus among investigators has established the invalidity of the evidence of a serious risk. When there is reason to believe that no such consensus exists, the disputed evidence ought to be included in the informed consent document. The purpose of the risk in equipoise standard—to determine the appropriateness of exclusion of evidence of risk from the informed consent document—justifies its rigor. A reasonable volunteer would use such information in making a decision about participation. The risk in equipoise standard is supported by full transparency in the informed consent process.

A research volunteer places him- or herself at risk, in a way that benefits the general population. When serious risks are clear and known, current guidelines require that information about these risks be conveyed to the prospective research volunteer. However, the risk in equipoise standard involves a disputed risk about which the guidelines provide no guidance. The risk in equipoise standard provides a specification of when a rational volunteer should be told about such a risk. It is not enough to argue from the researchers’ perspective that the risk does not rise to the level of probability that would require disclosure. Reliance on the researchers’ perspective makes the reasonable volunteer dependent on the judgment of lead investigators who have designed and argued in favor of the trial. The reasonable volunteer relying on the lead researchers’ judgment lacks protection offered by the community of relevant experts who may not have come to a consensus rejecting the evidence of risk. The risk in equipoise standard provides a way to indicate when a prospective volunteer should be informed about a disputed risk without depending on the view of the researcher. The standard also offers guidance to institutional review board (IRB) members: IRB members, after reading a protocol such as that in the ACCORD trial, should attempt to determine whether the evidence constitutes a risk in equipoise.

Risk in equipoise is similar to the precautionary principle in environmental ethics. The “Wingspread Statement on the Precautionary Principle” includes a definition of the principle:

When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. (Wingspread Statement 1998)

The precautionary principle, as interpreted in the Wingspread Statement, places a high burden on those who propose actions that may harm people or the environment, and the Wingspread Statement explicitly assigns the burden of proof: “In this context the proponent of an activity, rather than the public, should bear the burden of proof” (Wingspread Statement 1998). In applications of the precautionary principle other than the Wingspread Statement, placement of a burden of proof may not apply or may only apply implicitly. Unlike the precautionary principle, risk in equipoise is intended to ensure appropriate action by way of information provided in an informed consent process, rather than to preclude significant risk.
The risk in equipoise standard is not designed to evaluate the ethical appropriateness of the design of a clinical trial. For example, the standard does not rule out the use of a therapy involving risks, whether disputed or not. Evaluating risk versus benefit is simply not in the domain of the standard. Instead, the rigor of the standard is designed to protect research subjects by providing transparent information that the patient may use to consent or reject inclusion in a trial.

Table 1 contains a summary of the elements of the codes relevant to our analysis and the elements of our suggested approach based on equipoise.

In what follows, we apply the risk in equipoise standard in evaluating disputed evidence of risk described in the ACCORD protocol and to show the need to disclose the risk in the model consent document.

**ACCORD’S QUESTION AND DISAPPEARING OUTCOME**

The ACCORD trial was designed to test whether intensive blood sugar control (targeting HbA1c of <6.0%) reduces cardiovascular disease (CVD) events more than standard control (targeting HbA1c of 7.0% to 7.9%) (ACCORD Study Group 2009, 1) The target for intensive treatment was ambitious; other studies, including the UK Prospective Diabetes Study (UKPDS), had not been successful in reaching an HbA1c as low as 6.0%. In UKPDS the intensive therapy group’s average achievement was an HbA1c range of 7.0–7.4% (UK Prospective Diabetes Study [UKPDS] Group 1998a, 837). The expectation in ACCORD that such low targets would be achieved was based on the level of drug intervention planned for ACCORD’s intensively treated group (ACCORD Study Group 2009, 54). The ACCORD protocol allowed doctors to choose from a menu of drugs, and to mix and match those drugs to achieve the target range for an individual subject.

ACCORD participants undergoing intensive blood sugar treatment experienced high all-cause mortality compared with those receiving less intensive blood sugar control (Ismail-Beigi et al. 2010, 420). The intensive therapy arm ceased operation in February 2008 based on a recommendation of the independent 10-member Data and Safety Monitoring Board (DSMB) after a median participation in the intensive therapy arm of 3.7 years (Ismail-Beigi et al. 2010, 420). Cessation of the intensive therapy arm occurred 17 months before ACCORD was slated to end. Following cessation, the intensive therapy arm participants were moved into study arms using less intensive treatment. No overall CVD benefit had accrued when the intensive arm was halted, although nonfatal myocardial infarction was reduced by 24% (p = .004) (Ismail-Beigi et al. 2010, 420). Before the intensive arm of the ACCORD study was terminated, there was a difference of 54 deaths between the intensive arm, in which there were 257 deaths, and the standard group, in which there were 203 deaths, with just over 5,100 subjects enrolled in each arm (Gerstein et al. 2008, 2551; National Heart Lung and Blood Institute 2010).

**QUESTIONING EVIDENCE OF HIGH ALL-CAUSE MORTALITY**

Before beginning its clinical trial, the ACCORD group had access to evidence that cardiovascular death or overall death may be associated with intensive blood sugar control. This evidence is from three studies whose results were available before ACCORD began, and the ACCORD protocol references these studies: UKPDS (UK Prospective Diabetes Study [UKPDS] Group 1998b), Veterans Affairs (VA) diabetes feasibility trial (VACS-DM) (Abraira et al. 1997), and University Group Diabetes Program (UGDP) (University Group Diabetes Program 1970). Table 2 contains information about outcomes from the three studies, as well as results from ACCORD.

The ACCORD protocol notes that in UKPDS there was an unexpected increase in death among those in an intensively treated arm in a substudy of the trial. Two drugs were involved: sulfonylurea to increase insulin release, and metformin to reduce glucose production:

Obese and non-obese intensive group participants in which metformin was added to a sulphonylurea... led to a 96% increase in diabetes-related deaths, and a 60% increase in all-cause mortality. This surprising observation was not apparent after a combined analysis with the treatment group starting with metformin and with epidemiologic analysis of the data, and remains unexplained. (ACCORD Study Group 2009, 7)

These findings from UKPDS included in the ACCORD protocol are based on the UKPDS results included in Table 2.

The authors of the UKPDS study expressed the view that these unexpected results “could be extremes of the play of chance” (UKPDS Group 1998b, 863). Consequently, UKPDS initiated further study. The additional inquiry first involved a combined examination of subjects who had an early addition of metformin to sulfonylurea with subjects who received metformin alone (UKPDS Group 1998b). This combined group was compared with those who had conventional therapy or sulfonylurea alone. The difference in death rate was no longer apparent, but the conclusion of this combination of differently treated subjects does not contradict the finding that the early addition of metformin to sulfonylurea led to a statistically significant increase in death.

Second, an epidemiological study was undertaken using 4,416 people to determine if a combined use of metformin and sulfonylurea led to excess death. This study concluded in a finding of a 5% decrease in risk of death, but the result was statistically unreliable, with a wide risk reduction confidence interval of −33% to 32% (UKPDS Group 1998b, 854). This interval is consistent with the UKPDS results of an increase in death, albeit not as large a risk as UKPDS found. In fact, with p = .78 (UKPDS Group 1998b), the result of the epidemiological study was essentially by chance. Furthermore, epidemiological studies are typically not considered as reliable as prospective controlled trials (Glantz 1992, 49, 54; Gillinov and Nissen 2012, 196).
Table 1. Positions on disclosure of harms in international research ethics codes and authors’ proposed standard

<table>
<thead>
<tr>
<th>Ethics code</th>
<th>Type of potential harms to disclose</th>
<th>Threshold for inclusion of risk disclosure</th>
<th>Characterization of participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuremberg Code1</td>
<td>a. Inconveniences and hazards</td>
<td>All reasonably expected</td>
<td>Voluntary</td>
</tr>
<tr>
<td></td>
<td>b. Effects upon health or person</td>
<td>Possible</td>
<td></td>
</tr>
<tr>
<td>Declaration of Helsinki2</td>
<td>Risks and discomforts</td>
<td>Potential</td>
<td>Voluntary</td>
</tr>
<tr>
<td>Belmont Report3</td>
<td>Risks</td>
<td>Report range of risks*</td>
<td>Reasonable volunteer</td>
</tr>
<tr>
<td>Common Rule4</td>
<td>Risks or discomforts</td>
<td>Reasonably foreseeable</td>
<td>Voluntary</td>
</tr>
<tr>
<td>Authors’ proposed (2012)</td>
<td>Risk of harms and burdens, especially mortality or serious morbidity</td>
<td>Reasonably foreseeable including those in equipoise**</td>
<td></td>
</tr>
</tbody>
</table>


∗ The Belmont Report provides no further guidance for determining the threshold for risk disclosure.

∗∗ Equipoise refers to risks for which there is a lack of definitive evidence.

Despite the fact that the best evidence of risk came in the initial UKPDS study with its statistically significant results (UKPDS Group 1998b, 864), the additional inquiry in UKPDS led to the technically true but weak and misleading claim in the ACCORD protocol that the increase in death was not corroborated. Failure to corroborate might lead to uncertainty, but it does not rise to the level of disproof.

The ACCORD protocol statement that the deaths “remain unexplained” (ACCORD Study Group 2009, 7) indicates that the protocol authors chose to accept the combined and epidemiologic analyses of the data that did not corroborate the findings of excess death. Even though the protocol authors labeled the finding of excess death as “unexplained” they added a note of caution: “It increases uncertainty regarding the best treatment approach for patients with type 2 diabetes” (ACCORD Study Group 2009, 8). The ACCORD protocol authors themselves explicitly identified uncertainty in the risk (i.e., risk in equipoise).

The ACCORD protocol treats another study showing worsened CVD outcomes associated with intensive blood sugar control with more caution. A Veterans Affairs (VA) diabetes feasibility trial (VACS-DM) reported a nonsignificant increase in risk from intensive treatment:

There were 61 new cardiovascular events in 24 patients (32%) in the intensive treatment arm and in 16 patients (20%) in the standard treatment arm ($P = .10$). There was no difference in total and cardiovascular mortality ($n = 5$ and $n = 3$ in the intensive and standard treatment arms, respectively) or in new events in patients with cardiovascular history ($n = 10$ in each arm). (Abraira et al. 1997, 181)

Table 2. Glucose-lowering trials considered in ACCORD trial protocol with respect to all-cause mortality and ACCORD results

<table>
<thead>
<tr>
<th>Study</th>
<th>Total participants</th>
<th>Intensive blood glucose-lowering arm (n)</th>
<th>Mean age (in years)</th>
<th>Percent male</th>
<th>Type 2 diabetes duration</th>
<th>HbA1c achieved (%)</th>
<th>All-cause mortality (number/group size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ACCORD UGDP1</td>
<td>613</td>
<td>408</td>
<td>52</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
<td>64/408/21/205</td>
</tr>
<tr>
<td>VACS-DM2</td>
<td>153</td>
<td>75</td>
<td>60</td>
<td>100</td>
<td>7.9 years (mean)</td>
<td>7.1</td>
<td>57/57/57/57</td>
</tr>
<tr>
<td>UKPDS3 (1998b)</td>
<td>537</td>
<td>268**</td>
<td>59</td>
<td>60</td>
<td>7.0–7.4</td>
<td>7.8–8.0</td>
<td>47/268/31/269**</td>
</tr>
<tr>
<td>ACCORD 4</td>
<td>10,251</td>
<td>5128</td>
<td>62</td>
<td>39</td>
<td>10 years (mean)</td>
<td>6.4</td>
<td>257/5128/203/5123</td>
</tr>
</tbody>
</table>


∗ VACS-DM not a randomized clinical trial.

∗∗ Metformin added to sulfonylurea.

*** Sulfonylurea alone.
The findings from VACS-DM included in the ACCORD protocol are based on the VACS-DM results included in Table 2. The ACCORD protocol labels these events “unexplained,” pointing to the short duration of the trial, the use of a sulfonylurea-class drug only in the intensive arm, and the relatively few adverse events associated with treatment (ACCORD Study Group 2009, 8). Nevertheless, the VA feasibility trial raised a cautionary warning among the ACCORD researchers, with explicit mention of the uncertainty raised by the results. The ACCORD protocol notes that “the results [an increased risk of CVD events] highlight residual uncertainty regarding the potential CVD benefits of glycemic control, and the importance of testing if glycemic control with various strategies prevents CVD events” (ACCORD Study Group 2009, 8). This statement in the ACCORD protocol appears to indicate recognition that there is risk of death from intensive glycemic therapy. Such a recognized risk should be conveyed in a consent document.

A third report of increased death from intensive glycemic therapy was noted in the ACCORD protocol. This report originated with the 1970 University Group Diabetes Program (UGDP). Results from UGDP are included in Table 2. The only comment in the ACCORD protocol about adverse events in UGDP is in a paragraph mainly about lowering risks: “This controversial study reported an increased CVD mortality in a tobutamide arm after 6 years, which was therefore discontinued” (ACCORD Study Group 2009, 8). Tolbutamide is a first-generation version of a sulfonylurea.

Although lead researchers in the ACCORD study commented in the protocol on three studies involving excess death associated with intensive blood sugar control, no mention of the possibility of excess death in the intensively treated arm was made in the model consent form.

The risk in equipoise standard indicates that the risks discussed in the ACCORD protocol should have been included in the model consent document. The evidence from three prior studies available to the researchers as they planned the ACCORD trial was enough to conclude that a risk of excess death from intensive treatment was an anticipatable outcome, or at least one that deserved an explicit notice. Although there was uncertainty about excessive mortality, the chance of risk was there and was known. It would be difficult to show that the evidence of risks covered in the ACCORD protocol was not in equipoise. To show lack of equipoise, the risk in equipoise standard indicates that there must a consensus that the evidence of the risk has been disproved. There was no such consensus. As Byron J. Hoogwerf succinctly states,

In earlier trials in type 2 diabetes, concerns had been raised about an increased risk of cardiovascular events and possibly death associated with glucose-lowering drugs, hypoglycemia itself, or both, and these were well known when ACCORD was convened. (Hoogwerf 2008, 729)

The ACCORD protocol did point out the uncertain nature of the risks, but it failed to show a consensus that the risks were debunked.

RISK NOTIFICATION IN THE ACCORD MODEL CONSENT DOCUMENT

The ACCORD Model Consent Document is contained in Appendix I of the ACCORD protocol, dated January 5, 2009 (ACCORD Study Group 2009). In general, the researchers in ACCORD provided an exhaustive and robust model consent document that adhered to the standards of regulation and research ethics. The model consent document explains the nature, purpose and organization of the study.

The model consent document also specifies a long list of participant risks in a section entitled “POTENTIAL RISKS OF PARTICIPATING IN THE ACCORD STUDY” (ACCORD Study Group 2009, 155–159). Many common and sometimes rare side effects are listed for a variety of blood sugar treatments, blood pressure treatments, and lipid treatments. Risks from blood draws and hypoglycemia are covered.

The list of risks from intensive treatment in ACCORD does not include death from CVD or all-cause mortality but does include death from hypoglycemia. Given the extent of the risk information provided in ACCORD’s model consent document, a prospective participant might reasonably assume that there are no indications of increased risks of death or, more importantly, any competing evidence to support such an indication. Despite the ACCORD researchers’ characterizing as “unexplained,” “uncorroborated,” or “controversial” the increase in death in three previous studies, the evidence of risk was great enough to be included in the model consent document; its absence was a significant oversight by the investigators. We can learn from that oversight and improve the consent process.

The main investigators in ACCORD bore primary responsibility for including notice about the risk of death from intensive therapy in the model consent document. Because the notice of risk was not included by the main investigators, the IRBs of all institutions participating in the ACCORD trial did not receive the guidance from the ACCORD protocol to assure its inclusion in the consent process. If local IRBs relied on the model consent, prospective and actual subjects did not receive information in the consent process they might have valued in making their decision to participate. Recent studies of IRB modification of consent forms suggest it is unlikely that local IRBs made changes in the consent form to include this risk (Stair et al. 2001; Ravina et al. 2010). Whether or not local IRBs in ACCORD made this change, it remains the responsibility of the main investigators to disclose the risk in the model consent.

RECOMMENDATIONS ON RISK NOTIFICATION IN A CONSENT DOCUMENT

Emerging data continue to tell us that consent documents are already too long and onerous for research participants
To accord with best ethical practice, model consent documents ought to adopt greater transparency, and this requires informing prospective research subjects of risks in equipoise.

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REFERENCES


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Can We Keep It Simple?
Mark S. Schreiner, MD

For more than 30 years, investigators, institutional review boards (IRBs), and editorialists have been decrying the deficiencies with consent documents. Most subjects sign documents that they can neither completely read nor fully comprehend. Despite numerous studies to improve the consent document, the goal of ensuring informed participation seems more elusive than ever. Instead of simplicity and plain language, subjects face an overwhelming deluge of information written in technical and legalistic terms. Instead of brevity, consent forms remain verbose, increasing in length by approximately 1.5 pages per decade, with some well in excess of 20 pages.

While it is feasible to simplify long, technical consent forms to create concise documents written at a fifth- to eighth-grade
reading level, the evidence demonstrating that this improves subject comprehension has been disappointing at best. A meta-analysis of interventions to improve consent forms found that multimedia, enhanced consent documents, and extended discussion failed to result in significant improvement. Only use of test/feedback as part of the consent process showed consistent improvement in subject comprehension. Others have advocated teach-to-goal as a better means to ensure that subjects sufficiently comprehend the requisite information before being permitted to enroll in a clinical trial.

A previous editorial in the Archives of Pediatrics & Adolescent Medicine written in response to a previous study by Tait et al noted that enhancement of the interactional component of the consent process was more likely to improve greater gains than just attention to simplifying the consent form. Given that consent forms do not achieve the objective of achieving informed consent by themselves, if the federal regulations continue to require their use, they should be simple as possible.

Toward that end, Tait et al in this issue of JAMA Pediatrics have examined the simultaneous impact of factors that might impede subject comprehension of the material presented in research consent forms. They simultaneously examined 5 factors that might improve subject comprehension including shorter length, readability at lower (eighth-grade vs higher-grade) level, high processability (improved formatting using typographic and layout design), verbal disclosures to augment the consent form, and graphical decision aids. While all factors contributed to improved comprehension, the 3 most important factors were eighth-grade reading level, improved formatting, and use of graphical elements. A number of important limitations should be mentioned. The consent forms tested explained a very simple, simulated trial and not an actual study; the subject population was highly educated, with 46% of the subjects having graduated from college or graduate school (compared with 27% of the US adult population); and the verbal discussion used was brief and did not use test/feedback.

The Office for Human Research Protections recently issued an Advanced Notice of Proposed Rulemaking (ANPRM) that included, among many proposed changes to the federal regulations, changes to improve the consent process by improving the consent documents. This would be accomplished by:

(1) prescribing appropriate content that must be included in consent forms; (2) restricting content that would be inappropriate to include; (3) limiting the acceptable length of various sections; (4) prescribing how information should be presented, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form; (5) reducing institutional “boilerplate” in consent forms; and (6) making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions.

While there is much to dislike in the ANPRM, this aspect could be a real advance. The Tait et al group 8 consent document (available as Appendix 1 in Tait et al Supplement) provides a concrete example of what a consent form might look like if simplified using the goals of the ANPRM.

After having served off and on as a member of the IRB of a major teaching hospital since 1980, including the last 7 years as a full-time chair, I have reviewed literally thousands of consent documents. My own conclusions are that without the substantive guidance proposed by the ANPRM, any IRB will have a limited ability to insist on concise, well-formatted forms that use graphical elements, in other words, the factors that Tait et al found most relevant. The consent form templates used by the IRB at many institutions already include many of these features but there are obstacles in moving from an IRB’s template to an approved consent document.

The first is that investigators do not appear to spend much effort to create consent documents that follow the guidance information. Investigators participating in multicenter trials typically base their consent documents on the sponsor-provided sample form. Many investigators outsource the task of creating the consent form to their study coordinators, who may not have the necessary writing ability. Some IRBs rely heavily on their office staff to edit consent documents. Given the volume of submissions (our IRB receives >500 items per month), most do not have the resources to totally rewrite them. It is not even clear whether an IRB’s efforts actually improve consent forms.

Even when the IRB devotes the energy to rewriting a consent document, study sponsors and study groups frequently refuse to allow many of the requested changes to be implemented. When a rewritten consent form is approved, if it deviates from the sponsor template too drastically, other problems ensue. Each protocol amendment that changes the sponsor-provided consent form results in the need to revise an IRB’s approved version as well. If the forms deviate greatly, integrating the changes becomes a time-consuming task for both the investigator and the IRB.

To make consent forms as simple as possible, the ANPRM proposes to develop explicit guidance and create concrete examples; both efforts would prove more helpful than revising the regulations. To be effective, the resulting guidance and examples would need to be adopted by both the Office for Human Research Protections and the Food and Drug Administration to address both National Institutes of Health–sponsored and Food and Drug Administration–regulated research.

To achieve brevity, the description of procedures and the risks of common procedures that subjects already understand need to be shortened or omitted. Describing basic procedures such as a physical examination, interviews, and blood draws in detail adds no value. Extensive discussion of less familiar procedures should also be omitted and replaced by information sheets or even verbal instructions.

The risk information in consent documents can be particularly overwhelming. When every possible adverse drug reaction is listed, it obscures the most important risks of study participation by burying them among the extensive laundry list of other risks. I propose that the risk section provide a brief description of the overall risk of study participation by focusing on the most important harms. For example, an oncology
chemotherapy trial consent could inform participants that taking part could result in death, life-threatening infection, serious bleeding, and toxic effects to organ systems. Risks related to the quality of the subject’s daily life, such as loss of hair, appetite, and energy, should also be included. Frequently, these risks are similar to care outside of the research setting. Specific important risks for an experimental drug might also be added to the general risks of participation. All other potential intervention-related harms should be provided in supplemental handouts—1 per drug or procedure—attractively and professionally designed. If the handouts were consistent across all study group trials, it would be easy to keep all studies up to date.

To further shorten the risk section, all minimal-risk procedures could be lumped together and their risks and discomforts described as no greater than minimal. Our IRB was once cited by the Office for Human Research Protections for failure to disclose that electrocardiogram pads and the gel for an ultrasonography might feel cold. The trial involved fetal surgery, a procedure that had major serious risks that needed to be disclosed. It is not that a subject should not be told that the ultrasonography gel might feel cold, but is it necessary in the consent document?

The confidentiality section of the concise version of the consent form used by Tait et al was more likely to be read than the standard version, probably because it was not fully compliant with the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The mandatory HIPAA authorization language lengthens consent forms by at least 1 or 2 pages. Institutional review boards could shorten and simplify consent documents considerably by insisting on the use of stand-alone HIPAA authorizations instead of using a combined form. The confidentiality information in the consent document could be reduced to a few sentences that explained the possibility that a subject’s personal information would be used during the research and that that the investigators would do their best to protect it and prevent it from being shared with others. The main downside to using a separate HIPAA authorization is that 2 separate signatures are required; the upside includes shortening the length of the consent form, inclusion of simple understandable explanation, and removing the IRB or privacy board from the HIPAA process altogether since IRBs do not review stand-alone HIPAA authorizations.

Many consent forms involving genetic research now include extensive optional choices for return of results and contact about future research. The consent document could inform participants that they would complete a questionnaire to indicate their preferences rather than adding several pages to the consent form. The research procedure would become completion of a questionnaire rather than wading through pages of complicated choices.

Making these changes will not be enough. Everything we know about consent documents indicates that regardless of how much they are shortened, simplified, or enhanced, many subjects will not be able to comprehend the material presented to them. And if they do, they will not be able to precisely recall the information later on. At this point, it would be more productive to explore methods to improve the consent process, using techniques such as test/feedback, teach-to-goal, or new methods of presentation, such as interactive computerized methods, rather than continuing to pursue consent document enhancement.

The consent document should represent the culmination of the subject’s informed agreement to take part in the research rather than serving as an end in itself. To serve that purpose, the consent document should be reimagined to become as simple and concise as possible.

### ARTICLE INFORMATION

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### REFERENCES


SEC Charges Two Clinical Drug Trial Doctors With Insider Trading

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Washington D.C., May 19, 2014 — The Securities and Exchange Commission today charged two California-based doctors with illegally trading on inside knowledge that the Food and Drug Administration (FDA) had halted the clinical trials of a new prostate cancer drug developed by biopharmaceutical company GTx Inc.

The SEC alleges that Dr. Franklin M. Chu and Dr. Daniel J. Lama were medical investigators in the drug trials of Capesaris and avoided significant trading losses by selling their GTx stock after being informed by the company that the FDA had halted the trials due to patient safety concerns. After GTx publicly announced the negative development a few days later, its stock dropped more than 36 percent.

Dr. Chu and Dr. Lama, who practice at the San Bernardino Urological Associates Medical Group in San Bernardino, Calif., made more than $45,000 in illicit profits from their alleged insider trading. They have agreed to settle the SEC’s charges by paying a combined total of $116,864.

“Dr. Chu and Dr. Lama were promptly notified about the FDA hold so they could safely remove patients from the drug trials. It’s disheartening that they immediately misused that information for personal financial gain,” said Scott Friestad, associate director in the SEC’s Division of Enforcement. “Clinical drug trial information often is critical to investors in this sector, so we will continue to vigorously investigate and prosecute those who illegally trade on this information before it’s available to the market.”

According to the SEC’s complaints filed in U.S. District Court for the Central District of California, the purpose of the clinical trials was to test the safety and efficacy of Capesaris in anticipation of GTx applying for approval of the drug by the FDA. Beginning in early 2011, GTx and

San Bernardino Urological Associates Medical Group entered into a series of clinical trial agreements (CTAs) in which GTx paid compensation to the medical practice for each patient it enrolled in the study. The CTAs contained strict confidentiality provisions that prohibited Dr. Chu and Dr. Lama from using nonpublic information about the trials for any purpose other than rendering services.

The SEC alleges that on Feb. 17, 2012, Dr. Chu and Dr. Lama each learned from GTx that the FDA was placing a hold on the Capesaris clinical trials because of concerns about an increased risk of blood clots in participating patients. Immediately after learning this material, nonpublic information, Dr. Chu and Dr. Lama breached their duty to GTx and sold company stock held in their personal accounts. Dr. Chu sold 16,000 shares and Dr. Lama sold 5,400 shares at an average sale price of $5.82 per share. After GTx’s public announcement on Feb. 21, 2012, the stock price dropped sharply to close at $3.69 per share. Dr. Chu and Dr. Lama avoided trading losses of approximately $34,081 and $11,502 respectively.

The SEC further alleges that when Dr. Lama was initially contacted by SEC investigators, he provided false information and claimed that he had no knowledge of the FDA hold at the time of his trading.

The SEC’s complaint charges Dr. Chu and Dr. Lama with violations of Section 10(b) of the Securities Exchange Act of 1934 and Rule 10b-5 as well as Section 17(a) of the Securities Act of 1933. To settle the SEC’s charges, they consented to a final judgment permanently enjoining them from future violations and ordering them to pay financial sanctions without admitting or denying the allegations. Dr. Chu agreed to pay disgorgement of $34,081, prejudgment interest of $2,014, and a penalty of $34,081. Dr. Lama agreed to pay disgorgement of $11,502, prejudgment interest of $680, and a penalty of $34,506. Dr. Lama’s penalty is three times the amount of his illicit trading profits.

The SEC’s investigation was conducted by Daniel Weinstein and Brian Vann. The case was supervised by Brian O. Quinn. The SEC appreciates the assistance of the Financial Industry Regulatory Authority.

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