21CFR50.25(c) requires that informed consent documents and processes for applicable clinical trials contain a statement defined by the Food and Drug Administration Amendments Acts of 2007 (FDAAA). FDAAA is designed to promote transparency of clinical research to participants and patients.

According to FDA guidance

- The requirement began March 7, 2012
- Trial Sponsors and Investigators are responsible for determining if a trial is an “applicable clinical trial”
- The exact statement must be reproduced verbatim in informed consent documents for applicable clinical trials:
  “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”
  This statement is in the NU consent template
- The responsibilities of the IRB under this rule are to continue to review and approve informed consent documents.

Support for ClinicalTrials.gov at NU:
Barb Ferry (312-503-0792) is the liaison and administrator of the Protocol Registration System (PRS) for ClinicalTrials.gov. Contact her for:
- Inquiries on FDAAA Requirements for Applicable Clinical Trials, IRB & Journal (ICMJE) Requirements
- Application to request user name and password to access the PRS
- Assistance with: registering your study, submitting your results, biostatistical input, compliance, penalties
  Ms. Ferry's contact information is also part of the NU consent template instructions in case Investigators need assistance
Conceptions of Risk Regarding a Chronic Illness Survey: Perspectives of Participants, Researchers, and Ethics Review Board Members

Risk assessment is central to research governance. The ethical utility of risk assessment, however, may compromise human subject protections in certain research designs. Current regulatory systems require hypothesizing about risk, while a retrospective and systematic examination of what actually occurred during research is generally neglected. The burgeoning literature on the experiences of research participants offers insights into the research process and governance, this includes recent studies on informed consent and potential risks of participation that differ from concerns associated with the biomedical approach to human subjects protection. Over the last two decades, critics from the social sciences and bioethics have argued that the current biomedical model of protection for research participants emphasizes concerns about potential physical harms to participants and neglects to consider potential systemic or social harms that might be more difficult to quantify in a risk-benefit analysis. In addition, biomedical models of risk are inadequate for social and behavioral science research designs that involve interviews and surveys.

Many commentators have also highlighted crucial gaps in ethics oversight and identify a lack of capacity for reflexivity in the ethical review process. Ethics review boards are primarily responsible for protecting individuals who participate in research, yet rarely, if ever, are they informed about what happens to research participants during the course of a study. Some commentators question the efficacy of the research governance system and call for empirically driven research ethics. Evidence-based ethics would fundamentally challenge the current practice of ethics review boards (and their institutional equivalents) and their predictive risk assessment prior to the research, with no formal system devised to determine the accuracy of their assessments post research.

Integral to evidence-based ethics is an understanding of research participants’ experiences. Recent research examines participants’ experiences in clinical trials and their roles in biomedical research. Studies also show that the consent process is often ineffective because it fails to engage with individuals’ priorities and concerns. Others have reported about the perspectives of ethics review board members and about researcher standpoints. Yet very few studies, if any, have compared the perspectives of research participants, researchers, and ethics review board members regarding a single research study in which all three stakeholder groups played a role. We tackle this deficit by examining how these groups conceptualized risk regarding a recently completed Canadian survey study designed to identify how a chronic illness affects parenting roles.

In Canada, all research conducted at institutions receiving funding from Canada’s three federal research councils must conform to guidelines in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS). The TCPS states that risk is “a function of the magnitude or seriousness of the harm, and the probability that it will occur, whether to participants or to third parties.” An expedited review process is granted to research protocols deemed to be minimal risk, in other words, when “the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research.” In our experience, surveys are
generally classified as minimal risk research.\textsuperscript{14}

We report here the results of a case study whose purpose was to identify how research participants, researchers, and research ethics board (REB) members in British Columbia, Canada, conceptualized risk with regard to a survey about chronic illness. The case study is part of a larger project, Centering the Human Subject in Health Research: Understanding the Meaning and Experience of Research Participation. The overall goal of the larger project is to better understand and enhance human subject protections across the spectrum of health research. The case study we describe was one of four designed to recognize research participants as central to the research enterprise while also generating data on cogent ethical matters from multiple perspectives. In this paper we focus on the concept of risk as a major theme that emerged in our analysis of the data. We compare survey respondents' reflections on completing the survey with researchers' and REB members' reflections on how they had anticipated or imagined respondents' experience of survey completion. We compare the three standpoints, focusing on how they offer different perspectives on the utility of risk assessment in the chronic illness survey.

\section*{Study Methods}

The chronic illness survey we selected for our case study is an example of behavioral health research. Survey respondents were women with dependent children. The sample comprised mothers who had a diagnosis of the same chronic illness (ranging from less than 1 year to more than 20) and a healthy control group for comparative purposes. The 23-page questionnaire had several sections and included instructions to check boxes, circle numbers, or write out answers (e.g., explain "other" if checked). The survey respondents were told that other mothers had taken 30 to 90 minutes to complete the questionnaire. There was one opportunity for respondents to elaborate on a closed question. Three open questions concluded the questionnaire on the final page. The topics included parenting tasks, household work and support, physical and emotional health, and demographic information.

Crucially, the principal investigator (PI) of the survey was cooperative and allowed access to project documents, reports, and personnel. Relational aspects were key. We established trust with the PI and negotiated access to the study in a collaborative, respectful, and iterative process. The PI also permitted us to contact the REB members about the original protocol and facilitated our access to the sample of survey respondents and the research team, based on our assurance that we would maintain anonymity of the information we received. Building a trusting relationship with the PI was particularly important, as PIs may be reluctant to grant other researchers access to research participants and study materials due to privacy and confidentiality concerns.\textsuperscript{15} For our case study, we recruited a sample of survey respondents, members of the research team who designed and conducted the survey, and REB members who reviewed the survey protocol. To preserve anonymity, we do not identify the chronic illness the survey focused on.

We sent letters of invitation and recruitment documents to 99 survey respondents (living in British Columbia). All members of the research team (7) and REB members involved in the review of the study protocol (2) also received the documents. Interviews were arranged at a mutually convenient time and place. The University of British Columbia Behavioural REB gave permission to conduct the study, and all participants provided written consent.

Nineteen individuals (15 females, 4 males) participated in our case study. Ten of the individuals (all women) had been respondents in the survey; 8 self-reported a diagnosis of the chronic illness, and 2 reported being healthy. We included the healthy control group in our sample to reflect the original design of the survey. All survey respondents were mothers, lived with their spouses in British Columbia, Canada, and were 20 to 60 years of age. Some were homemakers, while others were employed part or full time. The seven researchers from the survey included the PI, who was a senior scholar and trained clinician; two senior clinician-researchers; one research associate; two research assistants (one of whom was involved in recruitment only); and one consumer-researcher. The REB members we interviewed had approved the protocol for the survey.

\section*{Interviews.}
Two of the authors (AT and SC) conducted semistructured, face-to-face interviews between December 2008 and August 2009. Four follow-up focus groups were held in November 2010. At least two of the three authors were present at the focus groups to facilitate discussion and take detailed notes. Nine interviews took place in the homes of the survey respondents, and one at the University. The research team and REB member interviews took place at the interviewer's or interviewee's workplace (university or hospital set-
The audiorecorded interviews lasted between 60 and 90 minutes and were transcribed verbatim.

The interview schedules comprised five sections: individuals' role in the survey, how individuals became involved in the research, issues of recruitment and consent, issues around the construction and completion of the survey, broad questions about ethical issues and how ethics related to the survey. Prompts and probes were used for elaboration and clarification. The participants were encouraged to express their views and discuss their priorities. Themes that emerged in early interviews were probed in subsequent interviews (e.g., issues of risk).

Analysis was iterative and informed by grounded theory; constant comparisons were made between and within transcripts. Two authors (AT and KT) read all of the transcripts and annotated and identified codes independently. They then discussed coding strategies and compared codes. Emerging themes were identified and discussed. The themes and codes were then discussed with the third author (SC), and final codes and themes agreed upon. Transcripts were revisited, and codes amended and refined.

Predominant themes from the five topic areas were presented to the focus groups. These themes included reasons for participating in the survey, method of recruitment, constructing and completing the survey, sharing the results, and ethical issues. The nature and degree of alignment between the three perspectives was included in the presentation of preliminary findings to the focus groups.

**Focus Groups.** After preliminary analysis of the interviews, four focus group discussions were conducted (two with survey respondents and two with researchers) at one of two educational or research institutions. The purpose of the focus groups was twofold: to report back initial findings from the interviews to the participants and to elicit discussion and reflections from the participants to further validate the initial findings and generate additional data about their responses. The focus groups of survey respondents involved 6 of the original 10 survey respondents (3 in each of the two focus groups), 1 of whom was healthy. One individual participated via teleconference. Five of the seven research team members participated in one of two focus groups, and the PI participated in both focus groups. The groups were comprised as follows: (1) the PI, one senior clinician-researcher, and one consumer-researcher and (2) the PI, one senior clinician-researcher, and one research associate. Participants were reminded of group confidentiality. All quotations were assigned identity numbers and identified as human subject, researcher, or REB member. Focus groups lasted approximately two hours and were audiodigitally recorded and transcribed verbatim. The transcripts were subsequently coded using the qualitative software NVivo 8, applying the same coding scheme developed for the individual interviews.

Preliminary analysis of the interviews identified a broad alignment between the three perspectives, about the role and importance of research, and general concerns about ethical practice. Quotations from the initial interviews were displayed to illustrate predominant themes related to the five areas identified above. These quotations were effective in engaging the group in discussing areas of interest or relevance to them based on their own experiences.

**Study Results**

Overall, survey respondents, researchers, and REB members shared positive views of the survey project. All were asked about reasons to participate, method of recruitment, the survey as research instrument, sharing results, and ethical issues. The three groups all highlighted the importance of inter-role trust and respect, and they conveyed a sense of community and reciprocity underpinned by common understandings, values, and research goals informing practice. There was strong agreement across groups about the importance of well-designed studies, reliability, and the practical goals of research. A dominant theme to emerge across perspectives was the notion of risk in health research regarding coercion during the recruitment process and concerns around confidentiality, privacy, and the safety of electronic data. All three groups agreed that the survey was well designed and likely to answer the aims of the study. There were, however, significant points of disagreement regarding the survey as a research instrument. In the sections below, we describe discussions about research risk related to the survey and its completion, turning first to the survey respondents, then to the researchers, and finally to the REB members.

**Chronic Illness Survey Respondents**

**Reflecting on Risk and Burden.** Respondents described the burdens of survey completion, reflecting on the time and effort they contributed in order to re-
spond honestly in the context of busy lives. Those who shared the chronic illness diagnosis (8) sought to avoid exacerbating their condition in their attempts to give valid and accurate responses to the survey questions. As one respondent said,

I was able to put my opinion out there. And if that can help anybody in any way, ... that's good ... The energy and fatigue ... were pretty severe ... I thought, “Well if I do [the survey], I've got to really mentally focus ... get ... engaged ... [H]ow much [symptom aggravation] will it give me after?” (HS 709)

These words highlight tensions between focusing on the task and remaining cognizant of the potential negative impacts of efforts to respond accurately to survey questions. Respondents with the chronic illness also described how completing the survey affected their illness management strategies. Several relayed how they faced illness with a positive attitude as a coping mechanism; they consciously avoided dwelling on symptoms, personal limitations, or disruptions to their daily lives. One respondent reflected on how exhausting it had been to give honest answers when her coping strategy was to “sugarcoat” how she felt:

When you do it [the survey], you try 'n do it exactly to what it was, but that's why it took me longer. Because I wanna sugarcoat, I wanna put, “How’re you feeling?” ‘I’m tired, but I’m okay, thanks,’” where I should have been putting down, “I’m exhausted!” ‘cause I know when I filled this out ... I remember thinking, “Okay, you’ve gotta give an honest answer.” But in giving the honest answer, you have to listen to the truth yourself ... I do remember thinking afterwards ..., “You're tired, because ... you’re mentally tired, because you’re having to answer honestly.” (HS 715)

The emotional cost of really engaging with the questions is evident. The tensions in this extract also reflect the reported experiences of others who described coping with their symptoms by adopting a positive attitude and avoiding disclosure of their suffering to others or even acknowledging it to themselves. This illustrates the “hidden” efforts people took to complete the survey and the more nuanced but significant impact of research participation. In answering survey questions, respondents focused on their symptoms and the impact chronic illness had on their daily lives and their parental roles.

**Reflecting on Risk: Tensions.** Acknowledging loss was a salient feature of the accounts of those with chronic illness. A core impact was how their self-identity as mothers was compromised by their illness. “The hardest part of filling it [the survey] in,” said one respondent, “was that I couldn’t be this supermom that I used to be before I got [ill], and so that affected my attitude as far as I just wanted that back” (HS 709). For some respondents, completing the survey meant making comparisons between a healthy past and a present characterized by illness. The following extract is an example of how one respondent reflected on her loss in terms of her life, role and identity as a mother:

When you break down ‘n analyze everything so much and you reflect on everything, “How much do you hurt? How fatigued do you feel? Do you feel like you’re being a good mom? Are you able to give everything you can to your kids?” Wow, after a while, yeah, you feel, “Am I? Do It? Wow, I am more tired than I used to be! Yeah, things hurt a lot more!” ... It surprised me how sad I felt after ... how fatigued ... how much things hurt ... how my life had changed. Reflective on how I was ... three years before when I didn’t have the disease. (HS 714)

This mother’s surprise at how sad she felt highlights the sensitizing and emotional impact of the survey for her. She elaborated,

When I finished the whole survey, if I recall, I cried. I had a couple cups of tea. And I don’t do that ... [M]y rule is I don’t have pity parties. It’s just the way my life is now. I move on from that. But I was very sad when I finished the survey. But the point is, I’m trying to maybe help ... That did surprise me. I wasn’t expecting to feel that way, but that’s just part of the reflective process. (HS 714)

Echoing the experiences of other survey respondents, this mother relays her stoicism and positive attitude in facing illness. Her reaction to completing the survey is unexpected and brings to the surface the emotional impact of her illness, how she deals with it and its consequences. The extract also illustrates the research participant’s moral agency and pragmatism: she regards the emotional impact of the survey (responding to the questions) as a necessary part of the reflective process. For this mother, contributing to research means hoping to help others who share her chronic illness experience, which means facing her suffering and loss. Reflecting the views of other mothers, this extract also reveals tensions between what should be done (volunteering for research) and the subsequent impact of research participation. Revealing a sort of inner calculus, one respondent said, “I guess my belief is deeper than whatever I’m going through physically” (HS 709). In sum, the experience of participating in and completing a survey about chronic illness is complex. Respondents acknowledged the burden it imposed on them yet also
trusted that the benefits of the research would outweigh any discomfort they felt in confronting losses and other difficult aspects of their illness.


Positive aspects of survey completion also featured in the focus groups as the mothers shared their reflections on risk. One respondent with debilitating symptoms expressed the overly negative connotations of the concept of risk and described feeling validated in her role as mother and homemaker:

"Risk" is a relatively negative term..."[I]mpact" is not... There was an impact... in terms of filling in a survey that allowed me to see, hey, wait a minute... it's valid for me to get less done, because it hurts to do it, you know? And so the people who're just telling me that I just don't get enough done can just... back off... So the impact was positive in that sense because it validated my experience. (HS 710)

Like other mothers in the focus groups, this respondent expressed how it would be more appropriate for REBs and researchers to consider the "impact" of the survey as opposed to anticipating any risks when assessing what survey completion might or might not mean for respondents: "[I]t could be negative for some people who... respond differently emotionally... So you can't predict whether the impact's gonna be positive or negative. But there will be an impact. It's a much more appropriate term for this form of survey" (HS 710).

Risk and Vulnerability. Respondents emphasized how some people may be more vulnerable than others, and there was no definitive way of knowing who such persons might be. They agreed that the survey could be more distressing for some than others and suggested ways of assessing the extent to which survey respondents were likely to be distressed or negatively impacted according to their illness trajectory. In this way, vulnerability was seen not as a fixed characteristic associated with specific groups or sensitive topics but as a fluid concept. Individuals may move through various stages of vulnerability depending on their personal circumstances. For example, in the focus groups, the survey respondents discussed levels of vulnerability associated with the timing of the chronic illness diagnosis, specifically whether a diagnosis had been given prior to or since having children. As one respondent pointed out,

"[I]t really strongly depends on where the individual person is in the... process of an illness, right? If you had this since you were five years old, and... doing a survey at 40[,]... this is not a surprise. But if you're someone who has been diagnosed two years ago with it, your life has changed drastically. And so it's a more emotional situation. But that's something that... the ethics board has to be aware that there are going to be people in situations of more emotional vulnerability. (HS 708)

The two respondents who were the healthy control group understandably differed in their reflections on completing the survey, as they reported being symptom free. They had no sense of loss on which to reflect. However, one described difficulties in finding "quiet time to complete the survey," illustrating efforts taken to respond in the context of a full life that involved parenting young children. Such efforts demonstrated a responsibility to the research enterprise. The other healthy respondent agreed that assessing potential impact was more appropriate than assessing potential risk when anticipating survey completion. Overall, respondents' reflections on survey completion included descriptions of their daily lives, illness trajectories, and identity issues and identified both concrete and nuanced impacts of research participation. This was in contrast to the hypothetical assessments of risk demanded by current approaches to ethics review.

The Research Team

Assessing Risk. All members of the research team agreed that the survey either held no risk or constituted minimal risk. They differentiated between severity and probability of potential harms, noting a risk of discomfort for respondents rather than distress (nonsevere) and a very low (probability of) risk of emotional harm. In formulating the survey, the research team had anticipated minimal risk on both counts. As one researcher explained,

We didn't think that there was any risk from... the survey, other than the time that [the respondents] committed... On the other hand, it's hard to anticipate if any of these kinds of questions would be uncomfortable or disturbing... and if they are, you're free to ignore those questions... [W]e probably... didn't anticipate any... in the survey. We thought if it was disturbing... they'd stop, and we don't actually know that it's occurred... I think that... any question has the potential... [T]here is a little bit of a risk that you stir up some memories that people would rather've left undisturbed. (RSCH 704)

The language "I think we probably," "hard to anticipate," and "we don't actually know" denotes uncertainty. Researchers "thought" that the questions asked may be ignored, consequently a "little bit of risk" was
a possibility. Another researcher reflected, “I don’t think you can really judge what risk is. Like what is risk? . . . It’s traditionally not risky, but in those 200 people . . . there might’ve been a question in here that caused emotional upheaval” (RSCH 711). The researcher continued to contrast the risk associated with clinical trials with the potential impact of completing a survey:

There’s a difference between filling out a survey and [being] a participant in a clinical drug trial. There’s a potential for serious side effects from a body . . . a medical perspective, there’s more risk there. But then from a psychosocial perspective or a relational or spiritual or an emotional, when you’re thinking in those terms . . . if you filled out a fatigue scale, and then thought, “Oh, I can’t exercise; I can’t walk; I can’t engage in the actual activity,” there’s an awareness there, and what does the person do with that awareness? . . . How does it make them feel? What resources do they seek out or not? So there’s an impact there. Would I call it risk? I don’t know if I’d call it “risk.” I might call it “impact.” (RSCH 711)

Illustrated here are the tensions that emerged for the researchers in assessing risk, which is more typically associated with physical harm, and assessing a more nuanced impact of survey completion. Focus group discussions further conveyed uncertainty about the inadequacy of the concept of “risk” in assessing survey completion and the more apt use of “impact.” As one researcher said, “I think ‘impact’ is a better word . . . . It’s more meaningful . . . . It’s not really a risk [but] . . . . it may have consequences” (RSCH 706). The salient point that the researchers emphasized is that risk assessment guidelines originally designed for biomedical models of research appear ineffective when researchers are attempting to identify potential harms—or impacts for the survey respondents.

The Ethics Review Board Members

Members of the REB agreed that the survey should be categorized as minimal risk. They mentioned the potential risk of emotional distress and physical harm when, for example, members of a group being surveyed could be vulnerable due to their interactions with professionals. One REB member commented on how he assessed risk in a survey study:

[I]n some cases [I ask myself] who the participants are going to be. . . . We would be worried about the safety of the participants. . . . If you wanted to do surveys with street youth, for example, . . . for them to be seen by their peers as answering the questions from an interviewer who they might think is a police officer, or something like that, that also would put them at risk. (REB 720)

The concern here is the potential for physical risk of a vulnerable group due to the context of research. This REB member also described how he tried to “make sense of risk” when reviewing a study involving a survey:

Some of the questions could’ve been anxiety-arousing, perhaps, or embarrassing or might have revived memories that people would prefer not have revived. . . . So it depended . . . [S]urveys, for example, if people who had been abused as children . . . ask them in detail about their experiences of abuse. That could help in disturbing, that kind of thing. . . . And what are you asking about? What are you asking people to recall, think about? (REB 720)

This comment underlines the way that risk may be associated with particular groups who share vulnerabilities around emotional distress and social isolation. Another REB member reflected the researchers’ views about the survey as posing no or minimal risk, “I would’ve said that . . . it would be very difficult to come up with a reason that there would be any risk involved in this kind of survey” (REB 719). Interestingly, one REB member stated that he had interpreted “risk” as impact:

I think the reasonable criterion for what is minimal risk is that there’s no risk greater than we’d encounter in normal day-to-day living . . . [P]eople can ask you, you know, “Is your husband helping you out with the kids?” So I don’t think it poses more than minimal risk to be asked those kinds of questions. . . . I think we interpreted the word “risk” as meaning “impact.” (REB 720)

Given this interpretation, and echoing the researcher in the previous section, the REB member notes that risk assessment for the survey involved imagining the impact the survey may have for respondents, rather than the risk of specific harms.

Both the researchers and the REB members attempted to put themselves in the shoes of the respondents. The researchers anticipated and the REB members imagined risk of harms that might emerge. In the words of an REB member interviewed during phase I of our larger project, Centering the Human Subject in Health Research, they engaged in an act of “protective imagination.” In so doing, they complied with particular guidelines of risk rooted in biomedical models of research based on assumption, common-sense understandings, and best guesses.
Discussion

We have reported the accounts of research participants, researchers, and REB members' regarding their involvement with a survey-based study on chronic illness and explored how they conceptualized risk associated with the survey study. Comparing the perspectives of three stakeholder groups offers an understanding of the difference between, on the one hand, attempts by the researchers who designed the study and the REB members who approved the protocol to anticipate the potential risks of survey completion and, on the other hand, the reflections of the research participants who responded to the survey. Our analysis suggests that although there are similarities across groups regarding perspectives on risk, the complex meanings of survey completion are best understood by examining the reflections of those who completed the survey. All three perspectives reflect difficulties with the concept of risk and its inadequacy regarding the chronic illness survey, which may have implications for research governance. It could be argued that assessing risk served to comply with guidelines of governance regulations rather than with the realities or lived experience of the research participants or with the realities of the researchers and REB members as they attempted to make meaning of the concept of risk in the context of the survey.

Based on the findings of this case study, we suggest that during the evaluation of the potential risk of harms a study poses, it might be productive to ask what impacts the study might have on participants. There would then be an alternative to pure reliance on "best guesses," which is to consider evidence systematically gathered from the experiences of previous participants in similar situations. Our findings echo Morse's claim that a risk approach that emphasizes physical well-being is likely to neglect more nuanced participant experiences and the emotional impacts of behavioral research such as unstructured interviews. We extend this proposition to survey completion. Risk in surveys has been explored in relation to vulnerable groups or sensitive topic areas, for example, in surveys about recent bereavement and palliative care. Guidelines for ethical review have also identified this dimension of risk (e.g., the U.S. Common Rule and the Canadian Tri-Council Policy Statement). This parallels the REB members' discussions in our study of particular groups as being vulnerable to risk. While it is clear that some individuals and groups are more vulnerable in regard to some topics than others, such a priori categorization is problematic, and an a posteriori approach is preferable. A group may be more vulnerable at one time and much less susceptible to adverse impacts at other times. For example, the survey respondents discussed how those who were diagnosed after becoming mothers or had a recent diagnosis would likely have been more affected by completing the survey than would mothers with a long-standing diagnosis.

Our findings also revealed feelings of ambivalence around survey completion (for the survey study participants) and around survey assessment (for the REB members and researchers). These tensions suggest that a binary risk-benefit assessment may be inadequate for certain research designs. An impact assessment fosters more nuanced considerations of both positive and negative aspects of research participation than the current model based on risks of concrete harms and benefits of morbidity and mortality. Assessing impact allows for considerations of both positive and negative impacts for respondents and allows for ambivalence around survey completion. We also note that researchers and REB members identified how they conceptualized risk as impact when creating and assessing the survey, illustrating that regulatory criteria proved inadequate.

We do not claim generalizability from this case study. Experiences of research participation vary, depending on context, meaning, and process. We recognize that the experiences reported are reflections given in interviews and focus groups with the attending limitations. Given that the aim of good governance is to protect and respect the experience of research participants, a strength of our study is to recognize the alignment and the differences in conceptualizations of risk and the gap between how it was assumed that survey completion would be experienced and how the respondents who participated in the survey reflected on their experiences.

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17. See ref. 4, Morse et al. 2008.
Ensuring Patient Privacy in Data Sharing for Postapproval Research

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Postapproval research is essential to address questions about safety and effectiveness that are not answered in the pivotal trials leading to approval of medical products by the Food and Drug Administration (FDA). There are many reasons why preapproval studies cannot answer all such questions, including the frequent exclusion of key segments of the population in these studies and the studies’ inability to detect rare but life-threatening adverse events. The need for methodologically robust and efficient postapproval research will grow more urgent as more investigational products are subjected to expedited preapproval studies.

Postapproval observational studies are both a practical and a necessary means to assess safety and effectiveness. Sharing electronic medical records and other secondary health care data sets facilitates observational studies by enabling rapid capture of a greater number of persons with exposures and outcomes of interest as well as by supplying a broader spectrum of study variables than would otherwise be possible if these resources were not shared. These enhancements improve statistical power, permit more rigorous adjustment for confounding, and enable more detailed subgroup analyses to better understand treatment-effect heterogeneity.

Important questions persist, however, about how data sharing can be best accomplished given patients’ privacy rights that are outlined under the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health (HITECH) Act. These rules limit the ability of covered entities — health care providers, insurers, and administrators — and their business associates to share individually identifiable health information for purposes not related to treatment, payment, or health care operations. Such protected health information can be critical for postapproval observational studies. In this article, we detail data-sharing pathways for research purposes under HIPAA and the HITECH Act, and we assess their usefulness and the associated risk of liability among investigators seeking to combine large data sets to conduct postapproval research.

PATHWAYS FOR SHARING INFORMATION FOR OBSERVATIONAL RESEARCH UNDER HIPAA

Enacted by Congress in 1996, HIPAA required the Department of Health and Human Services (DHHS) to establish national privacy and security standards for the use of protected health information and authorized criminal fines and imprisonment for covered entities who unlawfully obtained or disclosed protected health information knowingly, under false pretenses, or with the intent to secure commercial gain or inflict harm. Civil fines were reserved for cases of at least willful neglect and were capped at $25,000 per year. HIPAA did not, however, permit patients to sue covered entities directly.

Enactment of the HITECH Act in 2009 resulted in three changes to this enforcement system. First, it extended the reach of HIPAA to the business associates of covered entities. Second, it authorized state attorneys general to bring civil actions on behalf of their constituents. Finally, the HITECH Act significantly increased the range of possible civil penalties for a wider range of actions, including inadvertent HIPAA breaches, and it allowed fines of up to $1.5 million per year.

One way in which HIPAA regulations permit observational studies is by allowing covered entities to share protected health information for
“public health activities” conducted under the auspices of a public health authority. Such activities include current efforts by the FDA to develop a postapproval risk identification system for medical products. This Sentinel Initiative offers great promise to regulators, but it will not obviate the need for researchers to conduct independent studies of safety and effectiveness. HIPAA permits covered entities to share protected health information for observational research outside the auspices of a public health authority without specific patient authorization or waiver of authorization by an institutional review board under two circumstances: first, if there is conditional use of a limited data set stripped of 16 identifiers, including unique device identifiers and patient-specific addresses that are more specific than a ZIP Code, and second, if the data are deidentified (Table 1). Deidentification may be achieved by means of a “safe harbor,” which prohibits sharing of the same 16 identifiers — including increased restrictions on patient-specific addresses — in addition to all elements of dates except years and any other unique identifiable characteristic, or by obtaining an expert determination that “the risk is very small that the information could be used, alone, or in combination with other reasonably available information . . . to identify an individual.” Although HIPAA regulations authorize states to impose stricter safeguards for data sharing that does not involve public health activities, state privacy laws rarely appear to impose additional burdens on researchers. The data-sharing pathways generally still necessitate review of the research protocols by an institutional review board, but they can simplify the process, expediting review times and limiting the possibility that an institutional review board will request substantive protocol alterations. This streamlined process is particularly advantageous for ensuring the consistency of multicenter investigations.

**APPLICATION OF THE PATHWAYS FOR POSTAPPROVAL RESEARCH**

The three pathways — limited data sets, the safe harbor, and expert determination — have different strengths and limitations in facilitating postapproval research. The ideal pathway would maximize usefulness while minimizing invasion of the patients’ privacy and risks of liability among covered entities and expert certifiers.

Although enforcement for noncompliance with HIPAA has historically been limited, the DHHS imposed its first civil penalty for a HIPAA breach, a $4.3 million fine, in February 2011. Since that time, the DHHS has collected an additional $18.2 million from 17 other covered entities. State attorneys general have also brought independent civil actions for suspected violations in Connecticut, Massachusetts, Minnesota, and Vermont. These enforcement actions primarily involved nonsecure maintenance, movement, and disposal of protected health information. No charges have been filed for improper data sharing for research purposes or inadequate deidentification efforts under HIPAA.

**LIMITED DATA SETS**

The chief advantage of limited data sets in postapproval research is that they can contain precise, patient-specific dates of health care encounters. Specificity in the timing of events such as initiation of treatment, implantation of a device, and the onset of illness is necessary to establish temporal relationships that facilitate causal inference.

However, limited data sets have important constraints. Their restriction on supplying device identifiers could hamper device tracking and, thus, the identification of batch-specific manufacturing defects. It was the desire to enable such tracking that prompted Congress to require the FDA to develop a system of unique device identifiers. This system will soon require most medical devices to be affixed with a device identifier that details its specific model and a production identifier that provides the batch number, manufacturing and expiration dates, and the serial number of the device. Although it is clear that serial numbers on devices are precluded from limited data sets, it is uncertain whether batch or model numbers on devices are prohibited.

In addition, in limited data sets, the prohibition on providing patient-specific addresses more granular than ZIP Codes limits investigations of street-level disease burden and drug usage. Using a simulation model, Kamel Boulos et al. showed how data aggregation according to census tracts, which generally cover 1200 to 8000 people, can mask outbreaks of disease. Limited
<table>
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<th>Pathway</th>
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<tr>
<td>Limited data set</td>
<td>Cannot include 16 identifiers: names, postal addresses more specific than ZIP Code, telephone numbers, fax numbers, e-mail addresses, Social Security numbers, medical-record numbers, health plan beneficiary numbers, account numbers, certificate and license numbers, vehicle identifiers, device identifiers, Web uniform resource locators (URLs), Internet protocol (IP) addresses, biometric identifiers (e.g., fingerprints), and full-face photographs; may share only minimum data needed</td>
<td>Yes</td>
<td>Required (recipients must be named, and their receipt of data must be conditioned on limited disclosure, safeguards, notification of breaches, and nonidentification)</td>
<td>Ability to determine temporality through patient-specific dates; moderate geographic limitations (can mask areas of high disease burden or risk, results in loss of a tool to control for socioeconomic confounding); uncertain ability to use batch or model number for research in medical devices</td>
<td>Risks to covered entities if they fail to take corrective action when aware of a breach of the data-use agreement by the recipient party or if more than the minimum amount of data necessary to achieve research goals is shared</td>
</tr>
<tr>
<td>Safe harbor</td>
<td>Cannot include 18 identifiers, including 16 limited data set identifiers (with no postal addresses except the first three digits of a ZIP Code and then only when there are &gt;20,000 people in the region), all elements of dates except year, and any other unique identifying numbers, characteristics, or codes; must attest to lack of knowledge that the data are identifiable</td>
<td>No</td>
<td>Not required</td>
<td>Ability to determine temporality through date shifting; limitations related to date shifting (not useful for studies of short duration); moderate geographic limitations (can mask areas of high disease burden or risk, results in loss of a tool to control for socioeconomic confounding); uncertain ability to use batch or model number for research in medical devices</td>
<td>Risks to covered entities if identifiable data are knowingly shared</td>
</tr>
<tr>
<td>Expert determination</td>
<td>Expert certification that the risk of identification from the data, alone or in combination with other reasonably available information, is very low; documentation of reasoning leading to conclusion required</td>
<td>No</td>
<td>Not required</td>
<td>Investigation-tailored data sharing; lack of certifying standards</td>
<td>Risks to covered entities if deficiently certified data are knowingly shared; risks to expert certifiers if certifications are negligent</td>
</tr>
</tbody>
</table>
data sets may therefore prove to be suboptimal for postapproval research involving narrow clustering of outcomes, as in research on infectious diseases. They may also prove to be problematic if socioeconomic confounding is a concern, given that addresses can serve as proxies for income.21

Finally, the use of the limited-data-set pathway poses two risks of liability. First, a covered entity can be found to be in breach of HIPAA for failing to take corrective action if there is awareness of the recipient party’s noncompliance with the data-use agreement.10 Because limited data sets are protected health information, covered entities can also face penalties for sharing more than the minimum amount of data necessary. The “minimum necessary” standard remains vague, with no case law and only minimal guidance explaining it. In the HITECH Act, Congress specified that all limited data sets would be deemed to be compliant with the minimum necessary standard until the DHHS provided clarification.5 This guidance is overdue and, once issued, it may affect the applicability of this pathway for postapproval research.

SAFE HARBOR
Covered entities face a lower risk of liability under the safe-harbor pathway. Sharing is not subject to the minimum necessary standard, and covered entities are not responsible for acting on their knowledge of unpermitted transactions by the recipients of data. They are liable only if the shared data are not properly deidentified.

The data restrictions involved in meeting the safe harbor, however, impose substantial restraints on the usefulness of the resulting data set. Of primary concern is the prohibition on sharing components of patient-specific dates other than the year. In many instances, covered entities can mitigate the restriction by sharing temporal data that do not contain actual dates. For example, informing researchers that a patient had a myocardial infarction 45 days after receiving a newly approved drug is normally permitted. Such date shifting is currently used in deidentified electronic medical-records systems run by institutions such as Vanderbilt University Medical Center22 and in publicly accessible clinical trials data sets from GlaxoSmithKline.23

Date shifting is less feasible, however, for postapproval investigations of short duration or long-term collaborations involving routine data updates over short intervals, since the recipient party may be able to use the supplied data to infer the date of occurrence of events with greater specificity than the year. Figure 1 shows such a scenario in a postapproval observational investigation of the influenza A (H1N1) 2009 monovalent vaccine (Focetria) in Italy from October 15, 2009, through January 31, 2010. Data for the study were obtained from treating physicians in two periods: up to 3 weeks after vaccination and between 4 and 6 weeks after vaccination.24 If the study had been conducted in the United States and patient-specific data were obtained from primary care practices (i.e., covered entities) through date shifting, recipient researchers would know the date of vaccination with greater specificity than the year for many patients who had an adverse event in the second follow-up period. For example, if a physician reported that a patient had acute respiratory failure 40 days after vaccination, researchers could deduce (in violation of the safe harbor) that the patient was vaccinated in the latter half of 2009. Although many current postapproval studies of drugs and devices span a period of 3 years or more,25-27 there is a growing impetus to conduct these investigations within shorter time frames, increasing the chance that date shifting will contravene the safe harbor.

In addition, as compared with limited data
sets, the safe harbor imposes greater restrictions on sharing information about devices and addresses. Although both pathways preclude the transfer of device identifiers, the safe harbor requires that covered entities certify that they have no knowledge that the shared data are identifiable. Such certification will prove difficult if covered entities seek to share batch numbers when the quantity of devices per batch is small and the batch numbers implicate a creation date that implies the date of allocation. This information would narrow the population of possible recipients of data considerably. Covered entities can also share only the first three digits of a ZIP Code and only in circumstances in which the region they encompass has a population of more than 20,000 people. Thus, postapproval studies conducted with the use of safe harbors are subject to increased limitations on their ability to produce descriptive information and to perform adjustment for confounding. Such limitations make it unfeasible to conduct a study similar to the one by Brownstein et al., who mapped the frequency of abuse of specific prescription opioids according to three-digit ZIP Codes in New Mexico and adjusted for the availability of these drugs within these regions.

EXPERT DETERMINATION

Using the expert-determination pathway, covered entities can tailor the data they share to specific research needs, enabling transfer of otherwise precluded identifiers (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Expert determination can protect patients’ privacy as well as the safe-harbor pathway, which is generally considerably safer than limited data sets.

Widespread usage of the expert-determination pathway, however, requires the generation of additional standards and the existence of experts who are willing to certify that the risk of identification is very small. Risk assessment will need to be tailored to the specific data shared and account for the capabilities and trustworthiness of the recipient. At the same time, data protection must be based on real, evidence-based “threat scenarios.” For example, a systematic review revealed that although some safe-harbor data can be reidentified, the rate of such instances can be small, suggesting that the protections of the safe-harbor pathway are sufficient in many cases.

Expert certifiers face very little risk of liability under HIPAA. Although the HITECH Act expanded the requirements of HIPAA to the business associates of covered entities, it is usually covered entities, and not expert certifiers, who share data. Expert certifiers nevertheless could face possible tort action for negligence under state laws just as the developers of predictive analytics models may be subject to state product-liability claims. Given the infancy of the field, the standard of care required of an expert certifier and the cost of gauging the risk of identification incorrectly are unknown.

Objectively, deficient certification could in theory also lead to risks of liability among covered entities. These risks are small, however, because covered entities should be able to rely on certifications, unless they have definitive evidence that the certifications are inadequate or they do not exercise reasonable care in the selection of an expert. As of this writing, no negligence actions have been taken against covered entities for sharing data after deficient certifications.

CONCLUSIONS

Although long-term postapproval studies can be successfully conducted with data shared through the safe-harbor pathway, the pathway is not well suited for investigations involving short follow-up or small-scale geographic variation in exposures, covariates, or outcomes. Furthermore, until the DHHS clarifies whether batch and model numbers are considered to be device identifiers under HIPAA, the usefulness of safe harbors for postapproval research on devices remains uncertain. By contrast, limited data sets are more conducive for postapproval studies, but they require a data-use agreement, pose a moderate risk of liability among covered entities, and, like safe harbors, are potentially problematic for investigations of devices or studies in which narrow clustering of diseases is a concern. Expert determination is a promising alternative for cases in which the above limitations are prohibitive, but additional steps are needed to make this pathway more viable.

We think that the DHHS should foster the development of additional standards for expert determination, including model assessments across a sample of interventions and diseases.
One way to do so would be through the creation or designation of national deidentification centers of excellence. All parties would benefit if the DHHS clarified the risks of liability among expert certifiers and ensured that malpractice insurance is readily available to experts who are willing to offer their services. Greater attention to these issues may facilitate the ability of investigators to use shared data sets to conduct post-approval research of new drugs and devices.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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6. Uses and disclosures from for which an authorization or opportunity to agree or object is not required, 45 C.F.R. § 164.512(b)(1).
10. Other requirements relating to uses and disclosures of protected health information, 45 C.F.R. § 164.514(e).
11. Other requirements relating to uses and disclosures of protected health information, 45 C.F.R. § 164.514(b)(2).
12. Other requirements relating to uses and disclosures of protected health information, 45 C.F.R. § 164.514(b)(1).

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Facebook now says it will apply greater internal review to research projects, but it misses the ethical point by rejecting external review. With more than one billion users worldwide, the stakes are high for social media users.

Facebook Chief Technology Officer Mike Schroepfer admits that a research project filtering posts to study emotional content should have explored a non-experimental method as an alternative. Although this subject matter was important to research, we were unprepared for the reaction the paper received when it was published and have taken to heart the comments and criticism. It is clear now that there are things we should have done differently. For example, we should have considered other non-experimental ways to do this research. The research would also have benefited from more extensive review by a wider and more senior group of people. Last, in releasing the study, we failed to communicate clearly why and how we did it.

On his Research at Facebook blog Oct. 2, Schroepfer pointed readers to published research and areas of interest. The checks now include internal research guidelines, review, training and publication access:

• Guidelines: we’ve given researchers clearer guidelines. If proposed work is focused on studying particular groups or populations (such as people of a certain age) or if it relates to content that may be considered deeply personal (such as emotions) it will go through an enhanced review process before research can begin. The guidelines also require further review if the work involves a collaboration with someone in the academic community.
• Review: we’ve created a panel including our most senior subject-area researchers, along with people from our engineering, research, legal, privacy and policy teams, that will review projects falling within these guidelines. This is in addition to our existing privacy cross-functional review for products and research.
• Training: we’ve incorporated education on our research practices into Facebook’s six-week training program, called bootcamp, that new engineers go through, as well as training for others doing research. We’ll also include a section on research in the annual privacy and security training that is required of everyone at Facebook.
• Research website: our published academic research is now available at a single location and will be updated regularly.

Still, the fact that Schroepfer refused to be questioned by The New York Times and other media, demonstrates the shortcomings of reliance upon a for-profit technology giant to protect consumer rights.

Academic researchers, on the other hand, are bound by federal restrictions that require review of human subjects research. On my campus, we share an Institutional Review Board (IRB) with the

http://www.huffingtonpost.com/jeremy-harris-lipschultz/social-media-research-eth_b_5933052.html?utm_hp_ref=tw
University of Nebraska Medical Center. All faculty must complete an IRB training course and refresher modules every three years. Last week, IRB representatives met with our graduate faculty in the School of Communication to discuss updates to the review procedures.

The system is not perfect when it comes to social media research. For example, our UNO Social Media Lab has an interest in the Social Media Research Foundation’s NodeXL project that uses open source software to collect Twitter data and visualize social networks. From #Ferguson to #Ebola there are real-time research questions. If you have been an active Twitter user, you might find yourself among the NodeXL graph gallery images and data.

One interpretation is that Twitter collects data and essentially makes everything available to researchers performing secondary data analysis. This would be similar to historic use of the University of Chicago National Opinion Research Center survey data, in which the U of C is responsible for research ethics in data collection.

Another viewpoint, however, would be that most social media users neither read nor understand complex social media Terms of Service (TOS) agreements with the top sites. Users may not see themselves as research subjects, and ethics demands clear disclosure. Still, Twitter is a very public platform - often presenting clearly identifiable speakers.

IRB's, as well as national research agencies, need to take a stronger lead in balancing the privacy rights of social media users with our desire to research and understand behavior. The emphasis should be on development of clear definitions and procedures. We should not accept Facebook’s unilateral decision to be the lone reviewer of its human subjects research.