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Beyond the informed consent procedure: continuing consent in human research

Para além do consentimento informado:
consentimento contínuo em pesquisa com seres humanos

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Abstract *An ethnographic field study about informed consent in hepatitis C clinical trials provides insight into how changes in protocol requirements and patient health status triggered the actions and decisions of researchers and human subjects during the conduct of these trials. U.S. federal guidelines recommend that informed consent should be conceptualized as more than a one-time event. Rather, a process of continuing consent should be the standard but little is understood about how exactly this process should unfold. We used a proposed typology of continuing consent to frame our analysis and were able to document that only some of the proposed types took place at the site of our study. The most frequent practice involved the researchers' re-consent of their subjects for major protocol revisions. Only one subject dissented and chose to withdraw even though he was technically eligible to continue in the study. Two other types of continuing consent were not observed. We discovered an additional type of continuing consent not described in the typology whereby subjects gave implied consent through their cooperation and adherence to the on-going requirements of the protocols. Implications for the informed consent process and the need for further research are presented.*

Key words *Informed consent process, Clinical trials, Hepatitis C disease*

Resumo *Um estudo etnográfico sobre o consentimento informado em pesquisas clínicas sobre Hepatite C permite compreender como as mudanças no protocolo e estado da saúde do paciente influenciam as ações e decisões dos pesquisadores e sujeitos durante estas pesquisas. As diretrizes federais americanas recomendam que o consentimento informado deva ser entendido como algo mais do que um evento único. Mais precisamente, deve-se seguir um processo de consentimento contínuo como padrão, mas pouco se sabe sobre como exatamente esse processo deve ser desenvolvido. Usamos uma tipologia de consentimento contínuo para nortear a análise e documentamos que só alguns dos tipos propostos ocorreram em nosso campo de estudo. A prática mais frequente tratava do re-consentimento dos sujeitos para as principais revisões do protocolo. Só um sujeito não consentiu e escolheu sair da pesquisa, apesar de ser tecnicamente elegível para o estudo. Dois outros tipos de consentimento contínuo não foram observados. Descobrimos um tipo adicional de consentimento contínuo, não descrito na tipologia, no qual os sujeitos deram um consentimento implícito por meio de sua cooperação e adesão aos protocolos em andamento. São apresentadas algumas implicações para o processo de consentimento informado e a necessidade de outras pesquisas.*

Palavras-chave *Processo de consentimento informado. Pesquisa clínica. Hepatite C*

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Introduction

The significance of informed and voluntary agreement to participate in human research is almost universally acknowledged. In the United States informed consent has been institutionalized to protect human subjects from harm and to safeguard their right to self-determination. The informed consent procedure, the focus of considerable scholarly attention, has come to be regarded as a socially situated and interactive event wherein research-related information is conveyed, choices are made, documents are signed¹, and status passage from potential to actual “human subject” is achieved². Informed consent long has been regarded as a continuous “process” that takes place between researchers and subject participants throughout the research enterprise^{1,3,4,5}. Moreover, it has been suggested that consent ought to be a continuous feature of human research⁶. A recently published article by Wendler and Rackoff⁷ seems a response to this suggestion. There, a typology of four types of continuing consent is proposed that includes: re-consent, in which “significant” changes to research are presented and documented by an impartial witness; on-going consent, in which minor changes to research are presented; reaffirmation, in which researchers periodically invite reflection on research participation; and dissent, in which voluntarily withdraw from research occurs⁷. Wendler and Rackoff assert, however, that while the timing of and warrant for continuing consent will depend on various contextual, personal, and research-related factors, changes in the nature of the investigation itself and or alterations in the health condition and interests of research subjects should lead to petitions for continuing consent. To date, however, whether and the extent to which informed consent is “triggered” as an on going feature of human research has not been empirically demonstrated.

In this paper we seek to shed analytic light on this phenomenon. We draw on data collected as part of a larger ethnographic field study of hepatitis C clinical trials research to examine the informed consent “process” during the protocol implementation phase of the clinical trials trajectory. We show how this process is set in motion through the interactions and involvement of researchers and trial participants in two clinical trial related practices: research protocol modification and health status surveillance. The first practice refers to alterations of research studies. Field data revealed that HCV clinical trial protocols

were revised to reflect new knowledge and or changes in study procedures, and that informed consent documents were amended to reflect protocol changes. When protocols were amended, researchers apprised participants of the changes, presented them with revised informed consent documents, and elicited their signed “re-consent” to continued research involvement. The second practice, health status surveillance, refers to activities of seeking and evaluating health information. Field data revealed that this practice was a function of protocol requirements, in that protocols directed attention to participant-related clinical indicators. It also revealed that researchers and participants sought to make sense of, or interpret, health status indicators, and that as a consequence of health surveillance, both parties rendered implicit and explicit judgments on trial continuation. We argue that the practices discovered in our field study – protocol modification and health status surveillance – correspond to the “triggers” to continuing consent identified by Wendler and Rackoff⁷. Our findings explicate the relationship between these practices and the informed consent process.

Study and method

In the early years of this decade, we conducted an ethnographic field study of informed consent and work practices of hepatitis C virus (HCV) clinical trials research. The study took place at Mountainview, a research-oriented tertiary health center that specializes in the care of adults with gastrointestinal and liver disorders. An aim of the study was to identify and describe the actions of research professionals (physician-investigators, nurse trial coordinators, support personnel) and research participants during the protocol implementation phase of the clinical trial trajectory, that is, after subjects were enlisted, had completed the informed consent procedure, and were enrolled into a clinical trial. Institutional Review Board approval for the study was granted from Mountainview and our host institution. Informed consent was sought and obtained from the research professionals and subject trial-participants of this study. Such measures as the de-identification of data and the use of pseudonyms in written reports were implemented to ensure the confidentiality of study participants and study site.

While both of us were involved in the study’s conceptualization and on-going data analysis, one of us (MRM) served as the on-site field research-

er. The field portion of the study spanned 17 months. Data were collected through participant-observation, informal and formal interviews, and review of documents. The study was designed along two somewhat overlapping phases of data collection: an initial period of observing Mountainview research activities and the procedure of informed consent; and a focused, prospective phase involving the recruitment of a cohort of trial participants and the strategic collection of observational and interview data on research professional and research participant related interactions and activities of clinical trials and protocol implementation. Nineteen trial participants constituted the study cohort. All cohort participants were enrolled in one of four double blind, placebo controlled clinical trial protocols: a phase one study of the safety and pharmacokinetics of an investigatory drug for chronic infection (N=3); a phase two study to assess the safety and efficacy of a drug on an HCV-related liver disorder (N=9); a phase two study on the effects of a medication to accompany standard HCV therapy (N=3); and a phase three study of the effects of a drug on advanced HCV liver disease (N=4). The research professional participants (physician-investigators, nurse trial coordinators, and support staff) in this phase of our study were involved in protocol implementation.

In the analysis reported here, we draw on field note observations of clinical encounters devoted to protocol implementation, tape-recorded and transcribed formal interviews with researchers and cohort participants, and a review of informed consent documents. Field notes and transcripts were coded and categorized, and analytic themes were conceptualized in accordance with accepted methods of qualitative data analysis⁸. Codes and categories were derived inductively, from the data, as well as deductively, from extant social science and biomedical concepts as well as from Wendler and Rackoff's typology of continuing consent^{9,7}.

Background to the study: hepatitis C and clinical research

Before the findings of the analysis are presented, we describe the clinical and organizational context of the study. The hepatitis C virus (HCV) is regarded as "a major public health problem" as well as "a leading cause of chronic liver disease"¹⁰. The Centers for Disease Control and Prevention (CDC) describes HCV as the most common blood-borne infection in the United States and

estimates that approximate 3.9 million Americans are infected with the virus¹¹. Yet this number may be an underestimate because of the high incidence of hepatitis C among persons not usually surveyed, such as the incarcerated and institutionalized¹¹. Hepatitis C is transmitted primarily through exposure to infected blood, blood products and transplanted organs¹¹. In the U.S., intravenous drug use is the main source of new infections, and viral transmission via organ transplantation and blood and blood product transfusions has been nearly eliminated since the 1992 development of laboratory tests to screen for viral antibodies; sexual transmission is rare¹¹⁻¹³.

Natural history studies of HCV demonstrate that the clinical course of the condition is usually long and protracted, with symptoms in the early post exposure or "acute" phase uncommon and or mild, and that chronic infection occurs in 60-85% of those exposed^{11,14}. Chronic illness may go undetected for two to three decades; as such, infected persons may unwittingly transmit virus and go onto develop such serious complications as liver cirrhosis, liver failure and hepatocellular carcinoma^{11,15}. It is estimated that approximately 5-20% of chronically infected individuals progress to develop HCV complications^{10,11,15}. The annual cost of available medical treatment varies, from \$10-90,000 per year¹⁶. Cure rates from available treatments vary, with estimates of 42-46% for persons infected with genotype 1 infection and estimates of up to 80% for those with genotypes 2 and 3 infection¹³. The modest cure rates associated with available treatment have led to the development of clinical trial protocols for unproven therapies against HCV infection. Just as some individuals with other chronic and or life threatening conditions seek to participate in clinical research studies¹⁷⁻²⁰, HCV infected individuals may come to regard clinical trials as desirable alternatives to standard medical care options²¹. It is for these clinical and social reasons that HCV clinical trials research was selected as a suitable case for exploring the informed consent process in the implementation phase of the research trajectory.

Mountainview's HCV clinical trial activities occurred on-site, during frequent clinical appointments. Field data revealed that clinical visits were similarly organized and structured. Here, we briefly describe the flow of a typical encounter. Trial participants arrived in the research unit at the appointed date and time, checked in with a receptionist, and proceeded to an on-site laboratory for trial-related blood and urine tests. Nurse

trial coordinators sought out and greeted patients after lab work was completed, and escorted them to exam rooms. Once situated, nurses and trial participants attended to non-protocol related issues, exchanging social pleasantries on topics like health, family, work, and weather. Nurses then informed participants of the activities to be accomplished during the appointment. In some cases, other research personnel (physician-investigators and support staff) took part in protocol implementation activities, attending to physical examinations, consultations, and clerical work. The interactions of researchers and participants involved reviews and or assessments of health indicators, and discussions of and instructions on trial procedures. In addition, protocol implementation encounters sometimes involved exchanges on aspects of the clinical trial and research participation. For instance, it was not uncommon for researchers to remind individuals as to clinical trial objectives, as is apparent in the following remark made by one nurse: “now remember, this study is not designed to attack the virus.” In some cases, researchers suggested that participants “review” their consent forms periodically, and to contact them with questions or concerns that emerged between scheduled visits. Frequently, researchers recalled study aims and procedures. For example, after reviewing laboratory results, an investigator said, “again, this is not a study to eliminate the virus.” Protocol encounters usually concluded after arrangements had been made for follow-up appointments.

Protocol visits were guided by clinical trial documents, specifically the protocols and case report forms. Protocols are written representations of research plans and activities^{22,23}. In human subject research, they detail study purposes, duration, participant recruitment strategies, inclusion and exclusion criteria, procedures, timelines, and methods of data collection. Protocols are dynamic documents, in that they are likely to be amended over the course of a research study; they are also study specific. Other research documents, such as informed consent forms and case report forms, are derived from protocols. Whereas informed consent documents reflect much of the information contained in protocols, case report forms reiterate protocol requirements for the collection of study related information, or data²⁴. These forms are also the repositories for the data collected over the course of a study. As such, case report forms serve as written accounts of participant involvement in the clinical trial. This field note excerpt illustrates the role of case

report forms in the actions of research professionals and clinical trial participants.

The nurse takes out the CRF [case report form] and tells the patient that a center physician will perform a physical examination during the visit. She asks if he is having depression or irritability. They talk about his feelings and what can be done to allay them. The nurse asks the patient for his diary, and he hands it to her. She looks through the diary and comments that one of the pages is blank. They talk about what is missing. The nurse said to the patient “let’s put that down,” and assists him in completing the record.

Towards the end of this encounter, the nurse left the exam room to photocopy the diary. Upon returning, she advised the participant to continue using the diary and to bring it to the next scheduled visit. She then appended the photocopied diary entry to the case report form record.

Clinical trial data collected and recorded in individual case report forms were prospectively aggregated and analyzed by researchers and or research sponsors to monitor study effects; they were also retrospectively aggregated and analyzed by researchers and or sponsors to determine study outcomes. In the sections that follow, we shall see that protocols feature prominently in the activities leading to and involving the process of continuing consent.

Results: “triggers” of the informed consent process

Protocol modifications and the formalized practice of “re-consent”

As Wendler and Rackoff⁷ note, “the nature of the research itself, as determined by its purpose, risks, potential benefits, requirements, and alternatives” should trigger the elicitation of continuing consent from human subjects. Field data revealed that a formalized approach to continuing consent, the “re-consent” procedure, was instituted when changes were made to the protocols and informed consent documents of on-going clinical trials. As we shall see, this form of continuing shares some similarities with Wendler and Rackoff’s concept of “reconsent.”⁷

Over the course of our field study we observed that the abovementioned HCV clinical trial protocols underwent numerous modifications; we also observed that informed consent documents were amended 5 times in one study and 3 times in the others. While it is beyond the scope of this

paper to detail changes made to these protocols and consent documents, field notations reveal that amendments reflected participant related procedures, such as the collection of additional clinical data, and trial administration related issues, such as enlistment practices or investigator responsibilities. But protocol revision is not peculiar to HCV clinical trials. The U.S. Code of Federal Regulations (45 CFR 46.116) requires that “a statement that significant new findings during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”²⁵ This regulation holds for all forms of human research, including biomedical, social, and behavioral. “New findings” that signal the need to reappraise subjects may involve changes in research procedures, number of subjects to be enrolled, and information learned in the course of the study or outside the study. When “new findings” arise, researchers amend study documents (protocols and informed consent forms) and submit them for review to their local Institutional Review Board. Once IRB approval has been secured, researchers inform and seek approval from current study participants.

We observed that when protocols were revised, researchers purposely sought participant agreement on continued clinical trial involvement. Such agreement seeking was formalized in a procedure referred to as “re-consent,” and enacted during scheduled protocol implementation encounters. We also observed that most (17/19) cohort participants were re-consented between 1 and 4 times during trial enrollment without the presence of an unbiased witness. Indeed, as a nurse trial coordinator told a patient, “you’ll get a lot of [amended consent forms] to sign” because with “big studies it’s not unusual to have up to 6 or 7 revisions.”

Just as the procedure of signed informed consent to enter research studies proceeds in a near ritualistic fashion², re-consent unfolded in almost routine manner as well. Re-consent is also organized to facilitate information transmission and decision-making. The exchange of information was evident in the remarks and actions leading up to the re-consent offer. Just as in the example above, researchers emphasized that revised consent documents reflect protocol changes. In addition, they provided participants with hard copies of amended consent forms and pointed to pre-highlighted sections of the text as they described changes to the original or previously amended (and signed) document. The following field note excerpt describes the enactment of this practice.

The nurse took out the new consent form and told the patient “now I know you signed a revised consent form before. But every year our studies get reviewed by the ethics committee, the safety committee.” [...] ***The nurse said that the current version addresses the financial compensation awarded to one of the study’s investigators by the research sponsor. The nurse looked at the patient and said “you need to know that.”***

In most cases, the discussion leading to the re-consent offer focused on the effects of protocol changes for individual trial participants. An illustration of personalization is apparent from the nurse’s comment, “you need to know that”, from the field recording above. Two other examples of this phenomenon are worth mentioning. For example, a nurse instructed a participant that additional laboratory data would be collected for the duration of the study stating, “this is what’s going to affect you.” In the other example, a protocol amendment highlighted an approved increase in trial enrollment. In explaining this change to a trial participant, a nurse said, “some patients say this is good, others say I’ll be too busy to take care of them.” The nurse then offered assurances that quality research care would be provided to all enrolled study participants.

Prior to inviting signatures on amended consent forms, nurses elicited comments and questions from research participants. Responses centered on points of clarification, such as the scheduling of the future appointments, or the impact of additional procedures. An example of such a response is evident in the following exchange. After a participant read through the amended consent form, he asked the nurse if the newly added health survey would need to be completed right away, stating “so you’re going to have me do the questionnaire at weeks 16, 20, and 24?” The nurse replied “Right. Today is week 16, so [you’ll fill it out] today.” Participant responses to protocol revisions also centered on declarations of confidence in the research staff and trial procedures. While signing an amended consent form, a participant relayed to the nurse, “I trust you guys. You tell me everything I need to know.”

Thus, the procedure of ‘re-consent’ involved information exchange and decision-making. Yet it appears that the interactions surrounding this practice were limited to the conveyance of information on and the facilitation of participant agreement to protocol amendments that were deemed relevant and significant by the researchers. It seems re-consent did not involve a thorough-going review of the general merits or draw-

backs of continued involvement in clinical trials research or the involvement of an impartial witness who might have facilitated such a dialogue. We explore these points in the discussion section of this paper.

The practice of health status surveillance and continuing consent

Wendler and Rackoff⁷ suggest that participant-related changes that come about during a research study, such as alterations in physical and or psychological conditions or individual circumstances, should trigger a reevaluation of research involvement. Field notations showed that much of the interactions that took place during protocol implementation encounters focused on the relationship between the health condition of research participants and the effects of the study drugs under investigation. Such interactions involved seeking out and making sense of, or interpreting, the clinical data collected over the course of the research study. We termed this practice “health status surveillance.” This practice resonates with Fox’s 1959 description of physician-investigator and patient related “guessing” and “wagering” on the therapeutic effects of medical investigations²⁶. We observed that seeking and evaluating health information seemed to prompt evaluations of research participation. In some cases, health status surveillance led to what we term “implied” continued consent; in other cases, it led to explicit decisions to end, or terminate, research involvement.

As previously indicated, the trial participants in this study were enrolled on double blind placebo controlled clinical trials. That means that individuals were just as likely to be randomly assigned to receive an ‘active’ agent as they were to be dispensed an inert substance, or placebo; it also means that neither parties were made aware of the assignment. Nevertheless, we observed all cohort trial participants, at one time or another, ventured a guess on their assignment to placebo or investigatory drug arms of the trial. For example, following a nurse’s review of recent blood tests, one person mused, “I’m assuming I’m on the drug. I haven’t felt this well for a long time, and my labs seem to show steady improvement.” Another participant offered: “I think I’m in the 50% [getting the drug]. I know I am not supposed to know, but when I take the medication I get diarrhea.” The nurse assured the participant that she would con-

sult with the investigator about the diarrhea. This field note example illustrates interactions leading to participant self-surveillance.

Today is the patient’s first visit since starting the study medication. The nurse asked him, “Did you feel little side effects”? He said he’d been tired “but that’s good in a way.” The nurse nods and the patient continues, “I think I must be getting something. But I know the mind can play tricks on you.” He laughs. The nurse replied, “It can, so don’t feel embarrassed if we find out later that you’ve been on the placebo.” She then went into a rather lengthy description of the ‘placebo effect.’

We also observed that researchers sometimes ventured a guess on the participant’s assignment to placebo or investigatory arms of the trial as well. The following field note excerpts illustrates this phenomenon.

After reviewing the patient’s lab results, the nurse remarked, “I’m pretty sure you’re on the medicine because it tends to” act on blood cells and reverse anemia. The participant retorted, “I know I’m on the drug. No doubt about it.”

During a discussion on health changes, a participant told a physician of having experienced various symptoms. A nurse, who was also present in the encounter, added that several other trial participants had reported similar symptoms. The investigator then commented, “I wouldn’t be surprised if it was the study medication [causing the problems],” implying that it was unlikely the patient was taking a placebo.

Here we see that both study participants and researchers viewed health status indicators in beneficial terms and that they attributed health benefits to the trial medication, even though they had no knowledge of trial group assignment. But in some cases study participants offered interpretations on receiving placebos. One man told a nurse, “I am pretty sure I’m on placebo because I have no side effects.” When such interpretations were voiced, researchers usually reviewed options that may be available to participants once the trial was complete, such as the receipt of active drug and or clinical trials. In the example mentioned above, the nurse replied, “The sponsor is going to make the drug available” to when participants complete the protocol.

In these case examples, parties set appointments for upcoming protocol implementation visits. That such arrangements were made suggest that both researchers and study participants agreed to continue trial involvement; it also suggests that this tacit agreement occurred in the absence of overt discussions on research participation. Thus, it

seems that the interpretation of positive health benefits resulted in *de facto*, or what we term “implied” consent to continue trial involvement.

As mentioned, health status surveillance triggered explicit decisions to terminate trial participation as well. We observed that such decisions followed interpretations of health status changes that fell outside of defined acceptable protocol criteria and or were deemed by researchers and or participants as unbeneficial. Two cases illustrate this phenomenon.

One participant experienced a life-threatening event, which required hospitalization and surgery. As mentioned, research protocols define the conditions under which health status changes are to be reported and or managed. Upon learning of this hospitalization, researchers consulted study protocols and determined that the condition constituted a “serious adverse event” and as such warranted trial withdrawal from the study. The participant was advised to stop taking the study medication as well as provided with information on the procedure for study termination. In addition, researchers made arrangements for the patient to pursue therapeutic options with a local hepatitis C disease specialty center.

Another participant sought out researchers and initiated discussions on laboratory reports. This individual had been carefully monitoring lab data and interpreted recent changes as indicative of HCV disease progression. He questioned the wisdom of continuing trial involvement and running the risk of remaining on a protocol in which he was assigned to a placebo. And while laboratory indicators fell within the protocol specified range of acceptability, researchers supported the participant’s decision to “dissent”⁷ by initiating termination procedures and withdrawing him from the study. The participant was referred to a Mountainview hepatology specialist for follow-up medical evaluation and clinical care.

Our data suggest that while researchers and subjects speculated as to whether the onset of new symptoms or a change in laboratory findings could be attributed to the drugs under investigation or the lack thereof, we found no evidence that a more comprehensive reappraisal of a trial’s merits was initiated by the researchers in the same way that protocol amendments required. A more thorough re-assessment of research aims and objectives was promised by the researchers only after the trial concluded. Furthermore, unlike the participant above who methodically scrutinized his test results and decided to withdraw, we found that a similar re-evaluation of the risks and bene-

fits by other participants did not occur; rather, subjects relied on the researchers to determine whether continued trial participation was in their best interest. Thus, the surveillance conducted by the research staff served primarily to gauge the subjects’ health status within the defined limits of the protocols. That is not to say, however, that researchers did not monitor clinical indicators and inform subjects of minor changes that fell within “acceptable” limits of a protocol. Wendler and Rackoff argue that researchers are obligated to inform subjects about these kinds of worsening health status indicators when they are only obvious to the research team. What we did not observe, however, were other instances when less dramatic clinical indicators that might have prompted some subjects to consider withdrawing even though the measurements remained within “acceptable” limits of a protocol.

Discussion

Despite the consensus that informed consent should be conceptualized as a process, Wendler and Rackoff observe, “neither the [governmental] regulations nor the research ethics literature explain how to implement informed consent as a process rather than as an event.”⁷ Their typology provides the first roadmap for how the process of informed consent might proceed throughout all phases of a clinical trial. Our data revealed that three types of continuing consent took place at Mountainview.

Throughout the data collection phase of our study, we did not record situations when researchers verbally informed subjects of variations in the conduct of the study that did not merit a formal reconsent. Wendler and Rackoff labeled this type of continuing consent as “on-going.” We did observe, however, that participants were frequently invited to “re-consent” by nurse trial coordinators when minor and major changes in the protocols were made. This may be explained, in part, by Mountainview IRB policies that require that any and all protocol changes be reviewed, approved and presented to study participants. That the practice of re-consent was institutionalized suggests that the Mountainview IRB officials and research staff were mindful of U.S. federal guidelines regarding the subjects’ right to be notified about amendments to clinical trials. However, the presence of a witness, someone without a vested interest in whether the participant continued in the study or not, was not observed during the

encounters we documented. It may be that witnesses were present during other visits. We can only speculate that the added presence of an unbiased witness might have prolonged the re-consent process and complicated an already complex, labor-intensive procedure, especially with the shortage of Mountainview research nurses that existed at the time of our study, a finding we have documented elsewhere²¹.

As we have said, the re-consent procedures that we documented at Mountainview were focused on the specific protocol amendments at hand. A more global appraisal, or “reaffirmation of willingness to participate” was not observed⁷. In this type of continuing consent, researchers periodically encourage their subjects to consider whether the interests and expectations that originally motivated them to enroll in the trial exist beyond the initial phase of enrollment. They argue that this kind of continuing consent is particularly necessary in studies where a prolonged commitment is required (all of the participants in our study were enrolled in Mountainview clinical trials of 12 to 52 weeks duration). In the context of a “reaffirmation” encounter, Wendler and Rackoff propose that subjects should be reassured that they are at liberty to withdraw at any point during the trial. It is possible that this is what was intended when the trial participants were encouraged to periodically review the aims of the study spelled out in their original informed consent documents. However, by creating opportunities for participants to re-examine the overall risk and benefits of trial participation in the manner proposed by Wendler and Rackoff, fewer subjects might choose to re-

main enrolled, potentially threatening the integrity of the investigation.

The subjects we observed complied with protocol requirements such as adherence to study drug regimens, schedule of appointments, and laboratory testing, implicit evidence of their continuing consent. We have coined this *implied consent*, a form of agreement by subjects to continue in the study that Wendler and Rackoff did not elucidate. Only one of the subjects we observed dissented and withdrew on his own volition. We cannot say whether the others complied with the requirements of their trials because they lacked an explicit understanding or awareness of their health status or because they did not realize that dissent and withdrawal were possible. These contingencies were not addressed in our investigation and therefore merit careful exploration in future studies.

It is clear that empirical evidence is needed for how continuing consent should unfold. The informed consent process we observed during the hepatitis C clinical trials at Mountainview revealed that *implied* consent and *re-consent* were regularly practiced by the subjects and researchers we studied, however *dissent* by subjects was uncommon. We did not observe encounters when *reaffirmation* or *on-going* consent might have taken place thus we cannot say how these practices could have influenced the conduct of the clinical trials had they been enacted. Further research is clearly needed to better elucidate and evaluate the entire range of practices that constitute continuing consent. Such knowledge may provide policymakers, researchers, and bioethicists with empirically-grounded insights for the development of specific standards in the conduct of clinical trials.

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Collaborators

MR Mueller and S Instone equally took part in all phases of the writing of the paper.

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