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RESEARCH ARTICLE

How voluntary consent may be overlooked in gene editing clinical trials.

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ABSTRACT

In the United States, advocates have successfully fought for accelerated pathways for FDA approval of novel promissory technologies to address severe unmet medical needs. These pathways can blur the distinction between clinical trials as experiments vs. treatment. In addition, a recent focus on developing individual therapeutics through small clinical trials for people with rare diseases has not included early phases to test safety with healthy human volunteers. Rather, the clinical trials are offered as a therapeutic intervention for those with the targeted genetic condition.

This lack of clarity about the distinction between early-in-human trials and treatment is compounded by the unknowns of innovative promissory technologies, impairing the ability of researchers to convey an accurate and thorough picture of the risks and benefits of participation. In addition, researchers are responsible for ensuring that the potential research subject has understood the information provided about the study and for obtaining informed consent, which is considered valid only under conditions where a person makes a voluntary decision about participation. Scientists' belief that research subjects may not appreciate what is involved in clinical trials and incentives to recruit participants despite this may create a context in which voluntariness is not fully considered.

When physicians recruit their own patients for clinical trials, the dual role of patient care and trial recruitment may create a communicative context that undermines voluntariness. Physicians may be unaware that the patient's consent is not truly voluntary for several reasons. One is the normalization of their dual role - both scientists and physicians know they are influential in patients' decisions. Another is when the physician is convinced of the trial intervention's benefit as a treatment, despite its experimental status.

In this study, we used qualitative interviews to explore whether and how genome editing scientists and physicians are taking care to ensure research subject voluntariness in the face of potentially irresistible enticements to participate in testing unproven interventions. Moreover, we sought to understand whether the connection between one's professional role and enrollment of clinical trial subjects influenced how scientists and physicians saw the benefits of trial participation as in the subject's best interests.

INTRODUCTION

Patient advocacy groups, among others, have successfully fought for accelerated pathways for FDA approval of novel promissory technologies to address severe unmet medical needs. These pathways both benefit from and enable the blurring of the distinction between clinical trials as experiments vs. treatment or therapy. Recent meetings between the FDA and its stakeholders have focused on developing individual therapeutics through small clinical trials for individuals with rare diseases. Such trials do not involve early phases to test safety with healthy human volunteers; instead, they are offered as a therapeutic intervention for those with the targeted genetic condition. Further, the changing nature of small and large clinical trials is reflected by modified trial designs and the combination of phase 1 and phase 2 trials. This has facilitated quicker pathways for clinical applications of novel promissory technologies like CRISPR. Federal law requires that companies whose drugs have been granted accelerated approval based on preliminary studies confirm the drug's effectiveness *after* going to market. However, a 2022 study found that 42% of these confirmatory studies had not begun a year or more after approval.[1]

A lack of clarity about the distinction between early-in-human trials and treatment is compounded by the unknowns of innovative promissory technology, impairing the ability of researchers to convey an accurate and thorough picture of the risks as well as benefits of participation. Additionally, the complexity of the technology can make it challenging to translate risks and benefits into language easily understood by non-scientists. In public forums, some genome editing scientists have expressed concern that it is virtually impossible for research subject-patients to give valid informed consent if they have no background in genetics or the treatment approaches being tested in the study.

Despite the challenges of doing so, researchers are responsible for ensuring that the potential research subject has understood the information provided about the study, even if they believe that the individual is incapable of or uninterested in comprehending details. In addition, researchers are obligated to obtain informed consent, which is considered valid only under conditions where a person makes a voluntary decision about participation. Our previous work focused on the influence that CRISPR / gene editing research scientists have on the expectations of potential trial participants. The influence derives partly from new roles as spokespersons for cures and founders of companies that perform clinical trials. Overseeing clinical trials is accompanied by recruitment and communication with physicians about referring their own patients to the trials. Scientists' belief that research subjects cannot truly appreciate what is involved in their clinical trials and the strong incentive to recruit participants despite this may create a context in which voluntariness is not fully considered.

For physicians who recruit their own patients for clinical trials, the dual role of patient care and trial recruitment creates a dangerous communicative context that further threatens voluntariness. Voluntary consent requires understanding and freedom from undue influence. Physicians may not be attending to whether the patient's consent is voluntary for

several reasons. One is the normalization of their dual role–both scientists and physicians know that physicians are influential in patients' decisions. Another is when the physician is convinced of the trial intervention's benefit as a treatment, despite its experimental status. While this is an altruistic motive for enrolling patients, it may conflict with ensuring that each patient makes their own choice that reflects the voluntary nature of their consent.

In the United States, research ethics standards are codified by the Federal Policy for the Protection of Human Subjects ("Common Rule")[2] and FDA regulations[3,4] and guided by the 1979 Belmont Report, which are applied in specific contexts by Institutional Review Boards (IRBs). Each Belmont principle - respect for persons, beneficence, and justice - establishes specific duties owed to human research subjects.[5] The current study focuses on respect for persons, which includes a duty to recognize individual autonomy and the right to self-determination. The exercise of autonomy rests on two criteria: understanding and voluntariness.[5] This principle lies at the heart of informed consent, requiring that research participation is voluntary and based on receiving adequate information to make an autonomous decision. An autonomous decision reflects the patient's own values, free of undue influence.

Despite the importance of voluntariness, Belmont gives little specific guidance about ensuring understanding or voluntariness. It offers a narrow approach to applying the principle of respect for persons at a discrete point in the clinical trial timeline – obtaining informed consent. Thus, *agreement to participate*, demonstrated by signing a consent form or giving verbal consent, is the putative indication of voluntariness. However, agreement and voluntariness are separate and distinct concepts, related but not entirely congruent to each other. In fact, an emphasis on written documentation may serve primarily as liability protection for institutions and researchers, rather than "proof" of voluntary consent.[6]

Simply agreeing to participate in a clinical trial does not indicate that a person has understood what is involved in that participation, much less that they have made a decision free from undue influence, both internal and external. A systematic review and meta-analysis found that trial participants' understanding of the components of informed consent had changed little over 30 years. Importantly, participants in early phase trials were less likely to understand the purpose of the study, or even that this was a research endeavor serving the good of future patients and not a clinical intervention aimed to help the person enrolling.[7] And if significant attention to the problem of subject understanding has not moved the needle, concerningly, there has been almost no attention to ensuring voluntariness to participate in research.

This is unsurprising, at least in part, because of a lack of clear consensus about what voluntariness entails or how to measure it.[8] A traditional view is that consent can be considered voluntary if it is given intentionally and without "substantial" outside influence, distinguishing between persuasion, manipulation, and coercion.[9] However, this echoes Belmont's limited concept that "undue influence (e.g., coercion)" is primarily a concern for a narrowly defined set of "vulnerable" subject groups. Moreover, this reflects an "empirical" definition of coercion based on actual threats

and omits the notion that potential research subjects may perceive or experience coercion even if it falls short of explicit threats of harm.[10] Some have argued that a necessary component of voluntariness is "authenticity," determined by whether a decision aligns with an individual's sense of what is best for them.[11,12] Another view posits that what one does not know is central to voluntariness.[13] Being ignorant of facts necessary to decision-making thereby renders one incapable of giving consent. Still another view is that the choice to participate in a clinical trial cannot be considered voluntary when it is a person's only option (if there are no other acceptable options available to treat the condition).[14]

It has long been known that research subjects often do not understand that the purpose of an early-phase clinical trial is not to benefit them directly.[15] This therapeutic misconception (TMc) may prevent individuals from seeing the potential disadvantages of trial participation.[16] Similarly, it is well acknowledged that even when research subjects understand that a trial is an experiment and not clinical treatment for their benefit, they may expect more benefit than is likely to occur, which is described as therapeutic misestimation (TMe).[17] Our previous work has emphasized the importance of appreciation, which refers to understanding the personal significance of both the medical facts and the experience of trial participation.[18]

The links between TMe and TMc and voluntariness are apparent, yet examinations of these links and why they occur are limited. Though there is a large literature describing such therapeutic misconception and/or misestimation, much of it has traditionally focused on these as internal processes of "cognitive error" or other individual risk factors.[19,20] These explanations fail to consider the larger context within which therapeutic misconception and therapeutic misestimation occur.

There is increasing interest in moving beyond an atomistic focus on the individual research subject to the communicative context of the informed consent process. International guidelines have highlighted the communicative context in light of a potential cultural shift toward dual-role consent.[21,22] Recent bioethics debates about whether voluntariness is compromised when a potential research subject has been encouraged by their physician to participate in a trial reveal varying opinions, with some arguing that the physician's dual role may further blur the line between experimentation and treatment and create a context of therapeutic misconception and misestimation. Yet some argue strongly that the physician's dual role is necessary for clinical trial recruitment generally, especially to create "equity" in clinical trial participation.[23–27] Increasingly, clinical trials are moving toward small (n of one) trials and studies that combine research phases 1 and 2 in an effort to quickly bring treatments to market for individuals with unmet medical needs. In the process, there is often no clear line between patients and research subjects.

While regulators, scientists, and physicians engage in discussions about the meaning of informed consent in this rapidly evolving context, their focus is primarily on improving "information provision,"[28] less on comprehension (which some leading scientists see as virtually impossible because of the biological and technical complexity of genome editing), and very little on voluntariness, or even on achieving a shared understanding of the meaning of voluntariness.

Obtaining informed consent from research subjects is required, yet federal regulations fail to provide clear guidance for how this should occur. While numerous studies and related literature address the documentation of informed consent, we are concerned here with the process and whether it is clearly understood by those responsible for conducting clinical trials--the physician-scientists who initiate, design, and are responsible for how enrollment proceeds for human subjects. The concept of understanding or comprehension is not clear in the regulations, which creates a concern for scientists about whether informed consent is even possible. We wondered how voluntariness can be established if understanding cannot, and how well voluntariness is understood by those conducting clinical trials.

In addition, with the advent of innovative promissory technologies like CRISPR, we see a new role for bench scientists who have become involved as spokespersons for associated treatments and cures, interfacing directly with physicians, patients, and their families.[29] We wondered how this creates an ambient environment for the communicative context of therapeutic misconception and misestimation even further upstream. At what point might the framing of scientific experiments as treatment, especially for individuals who scientists view as unable to grasp what is involved enough to give "truly informed consent" constitute a new form of undue influence? This is especially a concern when people with conditions for which there is no treatment feel desperate to find a treatment, however experimental. [8] Are scientists and physicians taking care to ensure research subject voluntariness in the face of potentially irresistible enticements to participate in testing unproven interventions? Moreover, we wondered whether the connection between one's professional role and enrollment of clinical trial subjects influenced how scientists and physicians saw the benefits of trial participation as in the subject's best interest. How might the "irresistible enticement" of this process complicate the communicative context by creating TMe and TMc for physicians and scientists? Finally, how might subtle forms of manipulation enter into the communicative context, however unintended?

METHODS

This paper focuses on a study of basic scientists, physicians, and physician-scientists (total n=47). We used qualitative methods to gain an understanding of scientists' and physicians' perceptions of the voluntary nature of consent to participate in clinical trials. We relied primarily on interview data but also incorporated observation and contextual background from academic literature and popular media sources. These additional data aided interpretation by contributing to our understanding of the context of CRISPR somatic genome-editing research.

Participants and procedures

After obtaining approval and a certificate of confidentiality from our University's Institutional Review Board, we used purposeful sampling to recruit participants nationally through email. Eligible participants were US residents, held an M.D., Ph.D., or equivalent degree, and were involved in gene editing research or in treating patients who may be candidates for gene editing trials.

Most participants (n=19) were university faculty members, and two were biotechnology employees. Modest department store gift cards were provided to medical doctors as compensation for their time involved in the interviews; no compensation was provided to bench scientists.

The research team conducted 47 in-person, telephone, or videoconference interviews lasting 45-70 minutes, with two of us present at most interviews. The semi-structured interviews focused on how participants described their experiences and beliefs regarding the informed consent process with individuals who might participate in clinical trials. While one of us took a primary role in conducting the interview, the second interviewer observed non-verbal communication. Observing the dynamics of the interview was essential for noticing what seemed important to the interviewees and how each of them grappled with situations that might raise ethical concerns or questions. We avoided asking directly about ethical obligations to lessen social desirability bias and capture spontaneous thoughts rather than rote repetition of regulatory or ethics rhetoric. Instead, we asked about their experiences of challenging situations, probing for detail when necessary.

The authors work in bioethics with backgrounds in public health, psychiatry, and philosophy. Both were knowledgeable about the biological science of CRISPR, which was necessary to conduct in-depth discussions of the scientific issues raised during the interviews. As bioethics scholars, our work focuses on the rights of research subjects while bench scientists focus on cell biology and scientific methodology, and physician-scientists on treating diseases, disciplinary differences we kept in mind. Our approach was based on cultivating empathic curiosity towards the interviewees' (the scientists and physicians) positions within the interviews, seeing the world as much as possible from their perspective, and noting our gaps as reflecting our biases.

Analysis

After transcribing the interviews, we used abductive analysis to familiarize and defamiliarize the data using memos, field notes, and coding. We used a multi-step coding process to move from data to claims. We first used open coding, attending to how informants reported their own experience and how that experience may be influenced by contextual elements such as professional versus popular cultural exposures to CRISPR. We then identified larger themes by making connections between the code categories. Throughout the process, the research team discussed the codes to ensure the internal validity of our interpretations. We used collaborative interpretation to reflect on individual interpretations and build more robust analysis through research team members' contributions, existing literature, and ongoing contextual observation. We also attended to the variations across scientists' responses and to code categories and themes that emerged from the data. We strove for reflexivity about our own bioethics assumptions in interpreting our observations of the scientists. Writing was the final step of the analysis, with iterative reviews to ensure the integration of the data, the analysis, and the relevant theory. To protect participants' anonymity, we switched some gender

pronouns, omitted institutional or corporate names, and used some composite quotes. In addition, we identify participants as "scientists," "physicians," and "physician-scientists" and use S1, P1, and PS1, for example, to indicate the order in which individual participants were interviewed.

RESULTS

We sought to understand how physicians and scientists perceived the perspectives and experiences of potential research subjects as they experienced the informed consent process. We wondered whether scientists and physicians would focus on the voluntary nature of consent by considering whether subjects could truly appreciate how their lives would be affected by participating in a gene editing clinical trial.

We have divided the results into two parts: physicians' and scientists' views of individuals who may become subjects of clinical trials; and physicians' and scientists' views of professional roles in the informed consent process. Various categories and themes emerged from the interviews that shed light on the communicative context of the informed consent process for engaging subjects in gene editing clinical trials. In particular, the themes reported here represent how beliefs and attitudes about the nature of true consent and the value placed on clinical trial participation may underlie reasons for scientists' and physicians' limited focus on voluntariness as a necessary part of consent. Each category and theme are described below, and representative quotes are presented in Tables 1-4.

Part 1: Scientists' and physicians' beliefs about what potential research subjects understand and want.

In our interviews with physicians, scientists, and physician-scientists, we found several themes which we have categorized as 1) views that obscure the absence of voluntariness; 2) views that demonstrate awareness about challenges in getting truly informed consent; and 3) views that demonstrate a merger of the physician's or scientist's needs with the research subject's.

1.1 Views that obscure the absence of voluntariness (Table 1).

Subjects cannot fully understand complex details of the trials in which they agree to participate.

Many interviewees expressed the concern that potential subjects could not understand the science involved in genome editing or the purpose of the clinical trials. Their concerns echo a gene-editing scientist in a public forum: "How do you give truly – and how do you get truly informed consent from patients who don't have any background in genetics? You can explain it to them until you're blue in the face. What do they get?" However, this lack of ability to understand was not seen by most scientists and physicians we interviewed as precluding participation in clinical trials, or even affecting the research subject's voluntariness.

Patients/subjects do not want so much information in order to consent.

Some interviewees suggested that because potential research subjects cannot understand what is involved in the research trial, they do not want detailed information, preferring instead to be told what to do.

Signing the informed consent form indicates voluntariness.

For some physicians, voluntariness is assumed because patients/subjects/parents sign the consent form and are given a chance to ask questions and get their questions answered. The signed form is the "proof" that consent was voluntarily given. Some suggested that subjects or family members were so anxious to sign the form that they had to be persuaded to wait until they had heard all the required information.

TABLE 1: Physicians' and scientists' views that may obscure the absence of voluntariness.

Theme and Representative Quotes	Participant ID
Subjects cannot fully understand complex details of the trials for which they agree to participate	
I guess, for consent like that, I'm not sure that the patient is going to be able to process what I know, and what the physician knows.	S9
I mean, on the one hand, of course they should be told, on the other hand I think they don't have a background in which to contextualize that information.	S3
I mean informed consent is really challenging because it's so complicated now. And it's very hard to really feel that patients actually understand everything to where you can say, "is it truly informed?"…" Are they really rationally thinking about the options?	P5
I think that people have to be very knowledgeable about what people are doing for the gene editing…So, I don't know that patients can understand that…and how will they choose between that? I don't know.	P6
But I think very rarely are those patients actually able to listen and hear and ask questions and really take on that information in any kind of meaningful way…a lot of it is deep in the technical weeds and that that's not their area of expertise.	P20
The academic research around informed consent. is pretty scary. When you read about how little patients really, you know, are able to verbalize and recite back what the physician has thought that they just said.	PS11
Patients/subjects do not want so much information in order to consent	
You end up in these two, three-hour conversations. And you just see the families sometimes, like, it's too much. At the end of the day, they're just like, "Tell me what to do." Right? Yeah, that's probably going to keep getting worse.	P5

Theme and Representative Quotes	Participant ID
Subjects cannot fully understand complex details of the trials for which they agree to participate	
Well, in a lot of cases, the patients have a serious health predicament, and they have very limited understanding of the science. So, I would think that when you present an option of something that could be potentially better than the standard of care, most people, a lot of people accept it, right?	S15
Anecdotal evidence says people don't really pay attention, because it's so much information at a time where they are overwhelmed often by literally existential risk.	S20
Signing the informed consent form indicates voluntariness	
We forced the families to sit down and hear…the families approach it as we're doing this, it doesn't matter what the toxicities are. It's our responsibility to make sure they hear that, because later down the road…they have long term toxicities. It's important that they remember or have a piece of paper that we went through all that stuff.	P5
I think that the patient has signed an informed consent. And they generally understand that this can happen, possibly- So, the complications may indeed happen. Granted, we always hope they don't…	P6

1.2 Views that demonstrated awareness about challenges in getting truly informed consent (Table 2).

Some physicians and scientists we interviewed acknowledged that there are challenges in getting truly informed consent. There was variability among these responses, as some interviewees demonstrated subtlety in their reflections about this challenge. None of them indicated that voluntariness would be undermined by this challenge. Almost no respondents said that the lack of truly informed consent should prevent a research trial from going forward, or a potential subject from participating in the trial.

Subjects/patients are susceptible to therapeutic misconception (TMc) and misestimation (TMe)

Physicians recognized that their patients experienced therapeutic misconception and misestimation and expressed feeling unable to prevent or control it.

Table 2: Scientists and physicians' views that demonstrated awareness of challenges in obtaining truly voluntary consent.

Theme and Representative Quotes	Participant ID
Subjects / patients are susceptible to therapeutic misconception (TMc) and misestimation (TMe)	
And even though we always tell them that 9/10 patients are not going to respond. So that that is clear. There are people who think their kid is the 1/10 no matter what we tell them.	P12
I don't think you can control what the patients believe. They are going to participate usually because they think they're going to get a benefit. No matter what, I believe they think they're going to get a benefit. The early phase- even the late phase trials, they all think they can get a benefit.	P6
And the patient's going to say 'I don't want to hear any more, I know these [CAR-T cells] are great, I want, I want it. I'm so happy you have a slot for me.	P3
People are going to line up to be part of the first clinical trials, right? Even if you were to say, you know, you might not benefit from this at all.	S3
In our experience, the patients typically hear what they want to hear. So, it doesn't matter how many times that we may downplay something…it doesn't matter how many times I say that to a patient that has a child that's suffering, they still say hey I learned about this thing that says you can switch a piece of DNA around. And they're gonna hold onto that.	S4

1.3 Views that demonstrated a merger of the physician or scientist's needs with the research subject's needs (Table 3).

Subjects'/ patients' / parents' motives are altruistic.

Several interviewees expressed the belief that patients are willing to offer themselves or their child as trial subjects for altruistic reasons, in the interest of science "to make their lives mean something" or to be "part of the research team."

Subjects/patients are eager to participate in trials.

Many of the interviewees viewed people with genetic conditions as not just willing/voluntary but eager to participate in trials, often because they are desperate and willing to try anything. Support for this belief was the fact that patients contact scientists and physicians directly to volunteer as subjects for clinical research.

Subjects/patients believe that doing something is better than doing nothing.

Most interviewees saw prospective research subjects as truly desperate, and willing to try anything to alleviate their suffering or that of their child.

Table 3: Scientists' and physicians' views that demonstrated a merger of the physician or scientists needs with the research subject's.

Theme and Representative Quotes	Participant ID
Subjects' / patients' / parents' motives for entering trials are altruistic	
There are families who participate and are willing to take the risk associated with phase one trial knowing that they are potentially contributing to medical knowledge. And that gives meaning to their child's purpose. It feels like 50/50 [those who believe their child will benefit /those who want to contribute to medical knowledge] to me.	P12
Lives are being saved as we speak. And that's the point. The participants in the phase one trial are not there to get cured. They're there as volunteers. Part of the team, if you will, to help patients down the line receive a benefit.	S1
So, some of the early patients who sign up for these drugs who have failed all other therapies are doing it just for the goodness of their heart. That they want to help someone later on. Because they know it's not going to work for them.	P3
Subjects/patients are eager to participate in clinical trials	
Some of these patients that have, you know, no potential treatment and certainly no cure, I think they're going to jump at the chance.	S2
I have a lot of patients who would do any trial. They're just like, 'Give me a trial, anything.' So those patients can be hard to turn away. That's what makes them different than a normal, sort of real-world practice, is that they're not normal patients. And they're super motivated.	S12
I can't help but draw my memories of knowing about sickle cell patients who would give anything in a lot of cases from, from what I understand, to have an opportunity to escape this burden, right?	S2
Subjects / patients believe that doing something is better than doing nothing	
They love it. They're just happy to have people care about them.	S19
I think that it would be very difficult for them to really honestly assess risk versus benefit because there is such a need to do something. To try to save their child. It's the action of doing something that gives them a sense that they have done everything they could do to change their child's life for the better and, that doing something becomes more important than whether or not they think about the potential of a bad outcome.	PS9
The fact is they were going to die anyway.	P4

Part 2: Views of professional roles in the informed consent process

We also sought to learn how physicians and scientists viewed their respective roles in the informed consent process.

Physicians are influential in decisions to enter clinical trials.

Physicians and scientists recognized that the trust that patients place in their doctors has weight in decisions to participate in clinical trials. Physicians can influence decisions about entering clinical trials.

Physicians are giving people what they need/want.

Reflecting on their own responsibility to patients, physicians believed that they were acting on the wishes of their patients as well as their own. Sentiments like "at least we can offer something" were not uncommon.

Scientists assume that physicians are making sure that research subjects/patients are getting everything they need to give informed consent.

Scientists saw clear distinctions in roles in the work related to clinical trials. While some of them had occasion to speak directly to individuals, groups, or families about the possibility of gene editing clinical trial opportunities, they did not consider it their role to obtain informed consent from potential participants. Relying on a "division of labor" approach, they assumed that physicians and responsible others were conducting all necessary protocols and processes for ensuring informed consent. This was true even if scientists were involved in meeting with potential subjects through patient advocacy organizations etc.

Physicians and scientists may have multiple motivations to enroll patients in trials.

Both physicians and scientists stressed the importance of finding gene editing treatments for unmet medical needs to reduce suffering. They understand clinical trials as a critical step on the path to addressing those needs. With patient health of paramount importance, some physicians saw clinical trial enrollment as in the best interests of patients' current medical needs, while others stressed the need for clinical trials to help future patients. For some of the physicians, enrolling patients in clinical trials was one of the duties of their practice. Scientists saw clinical trials as an essential part of research to further scientific knowledge and its resulting translational outcomes.

TABLE 4: Physicians' and scientists' views of professional roles in the informed consent process

Theme and Representative Quotes	Participant ID
Physicians are influential in decisions to enter clinical trials	
And culturally, there are some cultures where whatever I say, they will do.	P12
Many people will just trust their doctor, and presented with a document that's a little challenging to read, they'll just be like, 'Yeah, where do I sign?'	S14
What I would really want to emphasize is…you're sacrificing a lot. But it's exciting. And gosh, can you imagine how you'd feel to be part of such a thing?	P6
Physicians believe they are giving people what they need / want	
I'll say, we think in a couple months we're going to have a CAR-T cell for you that's going to be really effective. So, while we're waiting, would you be willing to take a chance on this one? And they almost always say yes.	P3
Many times, patients will come to me and say, "Oh, I heard about this trial. I want to be in it."	PS4
Scientists assume that physicians / others are making sure that research subjects/patients are getting everything they need to give informed consent	
Well, I guess the responsibility of the clinician is to try to communicate as much and as well as possible the risk and rewards	S15
I guess the responsibility of the scientists is to communicate clearly with the physician. I would never imagine a scientist directly communicating with a would-be patient	S2
Physicians and scientists may have multiple motivations to enroll patients in trials	
What is our primary motivation for enrolling this patient? Is it because we have this trial open, and we want to fill some spots and we have to support our research program? Or is it because 100% believe that this could be beneficial?	P5
I am a firm believer that you can't push science forward if you don't have patients that are willing to take a risk and try something new. If we're doing Phase 2 and Phase 3, it's kind of easy to convince them to consider it heavily…if you're developing a new drug or even a genetic therapy, and you want to compare it to standard of care, they get standard of care for free if you randomize them…and they get transportation. And those incentives are very strong motivators for our elderly population.	P7

DISCUSSION

The results of this study reveal a context among our interviewees that is multi-layered. First, we found that physicians and scientists revealed their own form of therapeutic misconception or misestimation about clinical trials involving innovative, promissory technologies. This was evident in the many comments about the desire to offer patients "something," even when unlikely to have direct clinical benefit, or the stories of remarkable improvement in a condition after a trial, especially among children. It was also clear that physicians know and accept that they have influence over whether their patients participate in clinical trials due to several factors, including the knowledge/ information gap between patients and physicians, a trusting therapeutic relationship built over time, and the ways in which physicians frame trial participation as a form of "treatment." We also learned that physicians have multiple motivations for encouraging trial participation, including their interest in healing present or future patients, furthering their own research toward a disease cure, or an assigned role within their organization to oversee recruitment and retention of clinical trial subjects.

In addition, the communicative context and confusing messaging occurs within the ambient environment upstream. Bench scientists have become spokespersons for "breakthrough technologies," and speak about the potential for curing disease as if it has already been accomplished in professional papers, interviews, social media and in direct conversations with individuals with targeted conditions. They directly influence both physicians and patients, creating influence that has the potential to undermine voluntariness. We found that physicians and scientists did not express concern about research subjects' voluntariness. Instead, they saw subjects as clamoring to receive new "treatments" through their participation in clinical trials.

Distinct factors may have affected physicians and scientists' abilities to see the complexity of undue influence and voluntariness and appreciation. Upstream, scientists' beliefs that CRISPR is a breakthrough technology that will be ultimately successful in medicine and other fields, and their comfort in doing non-human experiments seems to promote an attitude that almost reduces clinical trials to a required "formality." Further, because scientists are several steps removed from obtaining consent or discussing barriers to participation with potential research subjects, most of their responses to our questions about informed consent were theoretical. Thus, the desire to make new treatments widely available to humanity in the abstract by expediting clinical trials omits consideration of the sacrifices and other lived experiences of specific patient-subjects. [29]

Physicians' failure to investigate or protect research participants from undue influence may arise for even more complex reasons. First, because the role they have with their patients is inherently beneficent, physicians want to be able to offer something to help ease suffering and may unknowingly place higher trust in developing but unproven treatments. Second, physicians, seeing scientists as experts and leaders in biotechnological advances and legitimate sources of scientific progress, are inclined to accept positive framing of innovative, promissory technologies that may finally help their patients. Third,

physicians may be comfortable with their influence on patients' decisions to participate in research because they are already accustomed to having a strong influence on patients' personal medical decisions. However, a decision to volunteer based on altruism versus a decision based on seeking personal benefit is quite different from an ethical standpoint. It seems highly likely that some patients who were seeking personal benefit were viewed as altruistically motivated by physicians who did not see such benefit as likely. Collectively our data suggest that as physicians pass on their positive views of clinical trials to inform or even recruit patients for innovative trials, they may lack self-awareness of the extent to which their dual role may compromise their interest in identifying if the patient's decision meets the criteria for genuine voluntariness.

For different reasons, both scientists and physicians assume that people with certain genetic conditions would be happy to receive anything with promise, even if it is thus far unproven. Among both groups in our sample, assumptions that altruism plays a primary role in decisions to enter clinical trials may specifically mask any signs of unclear voluntariness. Among the pathways for these assumptions is a possible therapeutic misconception or misestimation about the trials. These views reinforce each other as scientists influence physicians, and physicians, through scientists' role with patient advocacy groups, influence scientists.

The generalizability of this study's findings is limited by non-representative sampling. In addition, social desirability bias may have influenced physicians and scientists to answer the interview questions by presenting themselves in the best possible light. Despite these limitations, this study provides key insights that may help in developing strategies to help physicians attend more fully to their responsibility to safeguard participants' voluntariness in the informed consent process, especially with their own patients. Future research can focus on the perspective of research participants.

CONCLUSION

We found that the communicative context has moved upstream, creating an influence that has the potential to undermine voluntariness. As spokespersons for new "treatments," some genome editing scientists are influential in shaping beliefs and trust among physicians and their patients in experimental procedures. Scientists and physicians can unknowingly experience therapeutic misconception and/or therapeutic misestimation and may unintentionally introduce this into the informed consent communicative context. This is exacerbated by the influence that can be created by the dual role that some physicians have as primary care providers and recruiters in genome editing clinical trials. In addition, both scientists and physicians may have multiple motivations for recruiting trial participants, including beneficent and scientific goals.

This study has identified a need for reflective awareness of therapeutic optimistic biases in both scientists and physicians to create a less manipulative communicative context. This is especially important in the case of clinical trials using innovative technologies like genome editing that have a high degree of uncertainty. The authors see an opportunity for self-reflection within the research community to further explore potential conflicts of interest and unconscious bias that may be communicated to potential research

participants. We recommend that scientific gatherings related to genome editing include a focus on developing appreciation for what trial subjects may experience as a result of their consent to participate and building on that appreciation as a path to ensuring truly voluntary consent.

Author Contributions:

Sharon E. O'Hara made substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work. As the primary author, she drafted the work and revised it critically for important intellectual content and approved the version to be published.

Jodi Halpern made substantial contributions to the conception and design of the work, analysis, and interpretation of data for the work, revised the work critically for important intellectual content, and approved the version to be published.

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The authors have no conflicts of interest to declare.

Human Subjects Protection Statement:

The authors subscribe to the ethical principles underlying the conduct of research involving human subjects as set forth in the Belmont Report and codified in the Code of Federal Regulations (45 CFR 46) on the Protection of Human Subjects. Prior to conducting this study, the authors received ethical approval and a certificate of confidentiality from the University of California, Berkeley's Institutional Review Board.

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