Online Pediatric Research: Addressing Consent, Assent, and Parental Permission

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Introduction

Research with children lags far behind research with adults, even though research conducted with pediatric participants is critical to developing scientific knowledge that can benefit children. This is particularly apparent in the realm of pharmaceuticals. In a recent study, physicians prescribed an off-label medication to children in 18.5% of pediatric ambulatory care visits. In 74.6% of these cases, the medication was prescribed to treat a condition for which it did not have FDA approval, and in 17.6% of cases the medication was approved for the condition but not in the child's age group.[1] This widespread practice of using unapproved, and thus potentially ineffective and unsafe, medications in children continues due to longstanding challenges in stimulating pediatric research.[2]

Numerous factors have contributed to delays in the pursuit of pediatric research. Economics has clearly played an important part in delays in pharmaceutical trials. Prior to 1997, drugs approved for adults rarely underwent clinical trials with children due to the high costs of pediatric clinical trials and lower potential for profits in the pediatric market. It is particularly telling that in order to incentivize drug companies to conduct pediatric clinical trials, it was necessary to promulgate regulations to make their medications more profitable in the adult market.[3]

In other domains of research, however, different challenges seem to drive delays in pediatric research. Longitudinal cohort studies, for example, struggle with logistical issues raised by pediatric research consent. One such study, the All of Us Research Program, delayed its efforts to enroll children while it sought to address logistical and ethical issues specific to children.

Unfortunately, pediatric research has long been ensnared by this catch 22. When the Nuremberg Code was published in 1947, it specified that informed consent for research participation could only be obtained from individuals who are capable of giving consent for themselves.[4] Since children were considered incapable of making such decisions,[5] the inclusion of children in research was regarded as unethical under this code. It was not until 1964 that the Declaration of Helsinki modified this requirement, specifying that proxy consent could be given for research participation and thus that children could be included in research with their parents' permission.[6] Debate about the ethical appropriateness of research with children, and in particular research with healthy children, persists to this day.[7]

The case of the All of Us Research Program, however, demonstrates that these debates need to be revisited in the digital age. All of Us adopted an approach to enrollment and data collection that takes place primarily through online and mobile platforms, raising important questions about how existing solutions for ethically appropriate pediatric research conducted face-to-face can be adapted to ensure that online research meets the same ethical standards.

As discussed throughout this special issue, unregulated research adds an additional twist to this digital-age challenge. Unregulated researchers ranging from

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individuals and patient advocacy groups to for-profit corporations are not subject to human subjects protections in the U.S. unless they accept federal funding or they wish to seek FDA approval for their products. This means that they are not legally obligated to meet conventional standards for the conduct of research with children. In theory, this might mean that such individuals and organizations could proceed with pediatric research without needing to address the relatively complex regulatory challenges that regulated researchers face. However, the lack of regulatory guidance might, paradoxically, create even more uncertainty for investigators about how best to pursue online research with children. This lack of regulatory guidance could cause them to take the same approach that other researchers have taken since the time of the Nuremberg Code: not conducting pediatric research at all.

Although this special issue focuses on unregulated researchers, we intend our guidance to address the challenges faced by both unregulated researchers, like the patient advocacy groups that play such an important role in addressing pediatric rare diseases, and regulated researchers, like the All of Us Research Program. Although many ethical and regulatory issues are raised by pediatric research, challenges related to consent are often the most difficult for researchers to address. For that reason, our guidance will center primarily on issues related to the involvement of both children and their parents in the decision to participate in online research.

In this article, we seek to provide practical guidance for researchers who wish to enroll and collect data from pediatric research participants through online and mobile platforms. Although this special issue focuses on unregulated researchers, we intend our guidance to address the challenges faced by both unregulated researchers, like the patient advocacy groups that play such an important role in addressing pediatric rare diseases, and regulated researchers, like the All of Us Research Program. Although many ethical and regulatory issues are raised by pediatric research, challenges related to consent are often the most difficult for researchers to address. For that reason, our guidance will center primarily on issues related to the involvement of both children and their parents in the decision to participate in online research.

Pediatric Research Consent

Before focusing on issues specific to online enrollment and data collection, it will be helpful to briefly review some of the concepts that underlie pediatric research ethics, and in particular consent for pediatric research. The most important of these concepts is that children typically develop the capacity for decision-making over time. While it is certainly true that infants do not have the capacity to make such decisions, children tend to develop the ability to understand information and make clear decisions as they mature. However, children do not all develop at the same rate.[8] Some children, especially those with rare diseases that affect neurological function, will never develop the ability to understand information about a research study and make a voluntary decision about participating. But even among children whose development is considered typical, the capacity to weigh this type of information develops at somewhat different rates.

Ideally, our solutions for including children in research would fully account for the complex dynamics of child development. Unfortunately, the relevant legal frameworks by necessity make distinctions that elide much of this complexity. Under these frameworks, minors rarely attain legal independence until they reach the age of majority (18 years of age in most U.S. jurisdictions). Until that time, their parents or guardians retain the legal authority to grant permission for their children to participate in research.

In order to address this incomplete fit between the real-world complexity of child development and the rigidity of parents' legal authority, the consensus framework for ethical pediatric research emphasizes the importance of including children in the decision-making process in a way that is appropriate to their current stage of development. For typically-developing adolescents, this means that they should be offered the opportunity to decide for themselves whether they wish to participate in research; adolescents are said to give *assent* to their research participation. Their

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parents, who retain legal authority for such decisions, grant their *permission* for the adolescent to participate. If the child is capable of giving assent, then both assent and permission are required in order for the child to be enrolled in a research study. For children at earlier stages of development, it would not be developmentally appropriate to ask them for assent. However, children should be given as much information about the research as they are able to understand, even if this is mainly just an explanation of what will happen next: "Now I am going to give your arm a hug with this blood-pressure cuff." We posit that this framework applies in all pediatric research contexts, regardless of whether a particular organization or a particular study is subject to the requirements of the Common Rule.

Online Pediatric Research Consent

With this conceptual framework in mind, we can now examine the practical challenges of obtaining ethically appropriate consent for pediatric research through online or mobile platforms. It will be useful in this discussion to consider two general scenarios. In the first scenario, it is possible that researchers may wish to collect information about children by interacting exclusively with their parents or guardians. We call this the *parent report model* for online pediatric research. In the second scenario, researchers may want to collect information directly from children using on-screen interaction (such as survey questions) and/or through the sensors built into a device (such as location information using global positioning system (GPS) sensors). We will refer to this as the *direct data-collection model*.

In both models, we have in mind research that involves interaction between a research team and at least one participant (parent or child). This interaction could involve active participation such as the administration of surveys or text-based instant messaging, or more passive means such as the use of sensors on the participant's phone. The fact that this type of research involves interaction between the participant and a researcher means that it would generally require explicit consent in regulated settings.

As discussed elsewhere in this special issue, one model of unregulated research is so-called "self-experimentation" in which individuals try out interventions on themselves. Websites like Crohnology.com have made this into a group activity, with patients exchanging information about their experience with treatments, diet modifications, and nutritional supplements. If disease advocacy groups or other researchers were to apply this model to pediatrics, parents might directly interact with one another or with researchers, but they would then test interventions on their children.[9] We believe this model for pediatric research is unethical outside of a formal research protocol and should be strongly discouraged. The discussion below is not meant to be applicable to this type of research.

For research limited to actively or passively collecting information online, however, the distinction between the parent report model and the direct data-collection model is important for a number of reasons. For example, the parent report model allows for parents to restrict the amount of sensitive information available to researchers. If asked about the child's physical location, parents can decide whether such information can be safely shared. With the direct data-collection model, however, researchers might obtain permission for longitudinal access to a child's location.

For the sake of this discussion, however, we will focus on one particular difference between the parent report model and the direct data-collection model: which individuals are actually interacting with the study. In the parent report model, the parent may be asked to reveal information about the child, but the parent is the individual who is actually participating in the research. In the direct data-collection model, the child is directly interacting with the researcher and is thus a direct research participant.

The Children's Online Privacy Protection Act (COPPA) and Parental Verification

In the sections that follow, we will explore a number of implications that are raised by the direct interaction between a child and research study. As a starting point, it is important to recognize that when an organization interacts with a child through an online interface, the provisions of the Children's Online Privacy Protection Act (COPPA) may apply. The federal regulations based on this statute are not research-specific, but rather apply to any online service that meets one of the following criteria:

1. "commercial websites and online services (including mobile apps) directed to children under 13 that collect, use, or disclose personal information from children"
2. "general audience websites or online services with actual knowledge that they are collecting, using, or disclosing personal information from children under 13."[10]

Websites that collect information about children under 13 years of age but interact directly only with parents (i.e., the parent report model) are not subject to the provisions of COPPA.[11] Non-profit organizations like disease advocacy groups also are not subject to COPPA's provisions.

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A comprehensive discussion of COPPA is beyond the scope of this paper. In short, however, these regulations mean that for-profit companies conducting online pediatric research under the direct data-collection model would be required to obtain permission from parents to collect this information, even if they are not subject to the consent requirements of the Common Rule. Specifically, it would require researchers involved in this type of research to obtain "verifiable parental consent" before collecting personal information from a child, allow the parent to opt out of sharing the collected data with third parties, give parents access to the information collected about their child, and provide a process for withdrawal from future data collection. Information collected under COPPA also must be stored in a location that meets certain security standards, and can only be retained "as long as necessary to fulfill the purpose for which it was collected."[12] In the context of research, this last provision would assumedly require that data collected for a specific research study would need to be deleted at the end of that study.

Some commercial researchers may view the consent provisions of COPPA as an unwarranted impediment to research, especially given the potential opportunities mobile devices create for conducting research with children who are underrepresented in conventional research. However, it is also possible to view COPPA as a boon to all researchers — regulated and unregulated, commercial and non-profit — who want to collect research information directly from children using online or mobile platforms. This is because ethical research in all of these domains should (according to our analysis) require parental permission, and the introduction of COPPA has led to the development of numerous options for obtaining verifiable parental consent without the requirement for a face-to-face encounter. Several of these options include:

- Sign a consent form (submitted by U.S. mail, fax, or digital scan)
- Complete a monetary transaction using a credit card, debit card, or other online payment system
- Talk with trained personnel on a toll-free telephone call or video-conference
- Submit a form of government-issued identification[13]

However, we should not assume that "verifiable parental consent" obtained using the procedures approved under COPPA is necessarily equivalent to "parental permission" ethically required in the context of pediatric research. For example, the procedures for parental consent under COPPA do require that parents verify their identity by, for example, physically signing a consent form or using their credit card to make an online payment. However, COPPA does not require that parents verify their relationship to the child whose information is being collected. Have researchers fulfilled their obligation to obtain parental permission for research if the adult who signed the informed consent document is not the child's legal parent or guardian? COPPA does not address this possibility, but researchers may be held to this higher standard.

One possible argument against using this higher standard is that pediatric research conducted in-person typically does not require that parents provide written documentation that they are a child's legal guardian. In fact, it is not clear that most parents would even be able to provide this kind of documentation. After all, adults who have become a child's guardian through a legal process, such as adoptive parents or foster parents, often do have written documentation of this relationship close at hand. A child's birth parents, on the other hand, could use a child's birth certificate for this purpose, but presentation of this kind of documentation is required so rarely in everyday life that few parents keep this document close at hand.

This seems to highlight a key distinction between in-person research and research conducted via online platforms: researchers who conduct face-to-face research tend not to require written documentation of the parent-child relationship because they have access to a number of implicit cues. First, the fact that an adult is present in a clinical setting with a child and that the child tends to treat that adult as a source of support and protection lends validity to the adult's claim to be the legal parent of the child. Second, research staff probably also pick up on a number of cues that we tend not to talk about: Is the parent's age (or apparent age based on their appearance) appropriate for what we would expect for the birth parent of a child this age? Do the parent and the child look alike? Do they have the same last name? When research staff, using these cues, perceive that the adult might not be the birth parent of the child, they will often ask about the adult's legal authority to make decisions: "Are you the legal parent or guardian of this child?" If it turns out the adult is not a birth parent but became the child's legal guardian through another process (like adoption), then the research staff members might ask for documentation of that relationship. Frequently, that documentation is already present in the child's medical record, because clinical staff go through a similar process to obtain consent for clinical treatment. On the other hand, if the adult states that they are the child's birth parent, and none of the implicit cues raise

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doubts about this, researchers rarely request documentation like a birth certificate.[14]

The point here is that when pediatric research is conducted exclusively online, the researchers are not able to take advantage of the implicit cues that are used in in-person settings. Perhaps even more importantly, it is clear that minors regularly circumvent online measures intended to restrict access, such as by lying about their age.[15] It is therefore foreseeable that when parental permission for research participation is obtained online, in some small proportion of cases the person granting this permission will either not be an adult, or will be an adult who is not legally authorized to grant permission for the child to participate. The former problem is addressed by the verification procedures developed under COPPA. The latter problem, however, lacks well-established solutions.

There are at least two workable solutions, however, that will allow both regulated and unregulated researchers to verify the legal authority of an adult to grant permission for a child to participate in online research. First, researchers can request that adults upload documentation of the parent-child relationship. Adults who claim to be a legal guardian of the child but not a birth parent could be asked to upload legal documentation (such as by using a scanner or taking a picture of the document). As noted above, guardians in this situation are frequently asked for this type of documentation, and thus typically have it readily available. However, birth parents who have always been a child's legal guardian rarely have documentation of this relationship close at hand. They could therefore be asked to sign an affidavit stating that they are the birth parent and their parental rights remain in effect.[16] The procedure for uploading images of signed documents is already an option for verifying the identity of an adult under the requirements of COPPA, so this procedure offers the advantage that a single procedure could be used to verify both the adult's identity and their legal authority as a parent or guardian.

Second, researchers could ask that a child and their parent complete an in-person visit before proceeding with research under the direct data-collection model. From an ethical perspective, this is the superior option. Not only would an in-person visit allow researchers to use the typical procedures and implicit cues to verify the parent-child relationship, it would also allow researchers to engage in a direct conversation about the risks and benefit of the research, answer questions from the parent and that child, and assess their understanding of this information. This is similar to the procedure that the All of Us Research Program adopted for adult participants, and it would make sense for online pediatric research projects in both the regulated and unregulated space to utilize this procedure whenever possible.

Many of the benefits realized through an in-person visit could also be realized through an online research visit conducted via video. This approach is particularly attractive because it could enable online research with families who are unable to complete an in-person visit, such as those who live in rural areas or who face transportation challenges. This approach could also be useful for conducting online research with children who have rare diseases. Because these families are literally few and far between, it is typically impractical to bring them physically to a participating research site.

Even though the completion of a research visit via telehealth technology is a promising option, the associated technical and practical challenges would need to be addressed. Participants' access to an appropriate device and network connectivity could pose challenges, especially since video communication tends to require more bandwidth than other routine research procedures, like filling out an online survey. Privacy and security protections also need to be a top priority when this approach is used. Given that many healthcare systems have successfully implemented clinical consultations via telehealth technologies,[17] it seems likely that these technical challenges can be solved in the research context as well.

Adolescent Assent to Online Pediatric Research

Researchers conducting online pediatric research also need to adopt appropriate strategies for obtaining adolescent assent for research participation. Regulated researchers clearly have a legal obligation to obtain adolescents' assent whenever they conduct online pediatric research that requires parental permission. Unregulated researchers do not have this same legal obligation, but they still have a strong ethical obligation to ensure that adolescents' participation in research is voluntary. For this reason, we believe that unregulated researchers should generally opt-in to meeting the same requirements that the Common Rule places on regulated researchers.

There are certainly important questions, however, about how the Common Rule's requirements for adolescent assent should be met in the context of online pediatric research. After all, the regulations that came to be known as the Common Rule were first promulgated in the 1980s when digital technologies were not being widely used, and a 2019 update to the Common Rule did not address procedures for obtaining adolescent assent.[18] The Common Rule therefore does not directly address how adolescent assent should be obtained in the context of online pediatric research.

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However, we can make several helpful observations by revisiting the concept of child development.

As discussed above, the ability for children to engage in decision-making tends to develop over time. However, this ability does not develop at the same rate in all adolescents, and some adolescents do not develop this ability due to developmental challenges. The obligation to obtain an adolescent's assent for research participation therefore hinges on the adolescent's developmental stage: if an adolescent is developmentally mature enough to give assent, his or her assent should be sought during the consent process. In pediatric research conducted in-person, the assessment of an adolescent's capability to provide assent is generally made based on a combination of the parent's report and the researcher's observations. In many cases, this decision is mostly implicit because it is readily apparent to the parent, the adolescent, and the researcher that the adolescent is capable of participating in the conversation about research participation and should therefore be offered the opportunity to provide his or her assent. In some cases, formal assessment tools are used to determine whether a child has the capacity to participate in an assent process for research participation.[19]

A child's capacity to engage in decision making grows over time, so their ability to understand the implications of research participation may change. Changes in understanding may affect their feelings about participation. Even if they remain willing to participate, it is important to ensure that their understanding of the research is updated to fit their changing capacity, particularly when the direct data-collection model is being utilized.

In the context of online pediatric research, however, the researcher will only have an opportunity to directly assess the adolescent's ability to engage in decision-making if the study involves an in-person or telehealth visit as described in the previous section. If an online-only enrollment strategy is utilized, then the researcher will not have an opportunity to directly assess the adolescent's decision-making capacity. In this case, the distinction between the parent report model and the direct data-collection model comes into play.

When the direct data-collection model is used to collect data from adolescents, the enrollment process can utilize strategies for directly assessing their capability to participate in the assent process. An adolescent's choice to use an app or website cannot be used alone as a surrogate for affirmative assent prior to the adolescent's participation. However, information about the research study can be provided directly via their device, and then their understanding of this information can be assessed using interactive tools like quiz questions. Methods for implementing an interactive consent process via digital device are described elsewhere in this special issue;[20] such a process for obtaining adult consent can easily be adapted to instead obtain adolescent assent.

For online research studies utilizing the parent report model, formal assent would typically not be required. While parents have broad latitude to report information about their children, they should be encouraged to discuss this with their children. They should also be informed during the consent process that reporting sensitive information may be harmful to their children in the case of a data breach.

Readdressing Consent in Longitudinal Pediatric Research

One important benefit of online pediatric research is that these platforms can allow researchers to remain in contact with parents and children over time. When pediatric research is conducted in a longitudinal fashion, however, it is crucial that researchers accommodate the changing developmental and legal status of pediatric participants. As we have discussed, a child's capacity to engage in decision making grows over time, so their ability to understand the implications of research participation may change. Changes in understanding may affect their feelings about participation. Even if they remain willing to participate, it is important to ensure that their understanding of the research is updated to fit their changing capacity, particularly when the direct data-collection model is being utilized.

As in other types of longitudinal pediatric research, researchers developing online studies need to plan for how and when they will update children on the details related to their research participation and offer them opportunities to revisit their decision to participate. In the U.S. and many other jurisdictions, adolescents who will continue to participate in research after they reach the age of majority (typically 18 years old) need to pro-

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vide their own consent for their research participation. Parents are legally authorized to give permission for research participation for children, but their permission is no longer legally effective for research interactions with adolescents that will take place after they reach the age of majority.[21] This is not the only time, however, when it may be important to revisit research participation with a child. The information provided to children when they enroll in a research study may have been developmentally appropriate at the time, but it will become outdated and inadequate as they mature. For this reason, pediatric researchers conducting longitudinal research need to view consent as an ongoing process that needs to be revisited periodically.

Online research approaches can make revisiting consent relatively straightforward. In conventional pediatric research, it may be difficult to locate children years after their initial enrollment. For online research approaches, and in particular mobile platforms, it is easier to stay in touch with participants even through geographic relocations and other life changes. Readdressing consent via online platforms is also likely to be preferable to participants, since it may help avoid travel for an in-person meeting. On the other hand, interactions that take place exclusively through online platforms may make it more difficult for research teams to assess when a child's capacity has changed sufficiently to justify revisiting consent. As longitudinal research projects increasingly adopt online strategies, as the All of Us Research Program has, it will be important that they proactively establish policies and practices for both assessing when children may be able to participate in decisions about their participation and the potential need to obtain their consent when they reach the age of majority.

Rare Disease Research

As we noted above, online pediatric research is a promising strategy for researchers who want to reach populations who are underrepresented in research, such as families who face transportation or other challenges or families who live in rural areas. Online research is also attractive to researchers who study rare diseases, defined in the U.S. as a condition that affects less than one in 200,000 persons.[22] Although some rare diseases occur with higher frequency in localized areas due to unique exposures or genetic founder effects, many occur sporadically in individuals or families spread across large geographic areas, including in multiple countries. This pattern makes it difficult to recruit enough participants to effectively study such conditions, even with multisite study designs. Online research offers the opportunity to recruit participants across the country (or even around the world) and collect important information about their condition without the need for face-to-face visits. In fact, mobile platforms have already been utilized by a number of rare disease networks as an approach to identify, contact, and consent families into studies related to rare pediatric diseases.[23]

Rare diseases represent one of the most important potential applications for online pediatric research. Even though each of these conditions is individually rare, combined they represent a significant source of morbidity and mortality. As many as 8000 rare diseases have been recognized, and worldwide these conditions affect about 400 million people.[24] Although rare diseases can affect both adults and children, much of the research focused on rare diseases is conducted with children. Many of these conditions are life-limiting, and some have profound effects on child development. As a result, a significant proportion of online research focused on rare diseases will involve pediatric studies utilizing the parent report model.

For parents, online research is attractive because it helps address a number of barriers that have previously prevented children with rare disease from participating in research. For families who live in rural areas, geographic distance from a major medical center may pose significant barriers to research participation, especially when the child has a condition that limits mobility. For families with limited resources, research participation may be difficult due to transportation challenges, even for those who live close to major medical centers. Online and mobile research platforms are also frequently combined with social features to connect with other families whose child has the same condition or tools that connect families to physicians who specialize in a specific rare disease. Families may find these tools useful, and thus they may be more likely to stay engaged with the research taking place through these platforms.[25] Parents also frequently comprise the disease advocacy groups that support research on rare diseases, including the development of studies based on mobile or online platforms.

For researchers, online research facilitates the recruitment of larger numbers of children with a particular rare condition. This is important because rare disease researchers face ongoing challenges of identifying a robust enough sample to conduct studies, and may even struggle to identify enough children with a rare disease to understand the typical course of these conditions. Online research can also reduce costs by eliminating the need for research staff and other resources at multiple geographic locations. These resource barriers are especially problematic for research on rare diseases,[26] where it may be harder to find funding opportunities for researchers. Advocacy

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groups and citizen scientists, who are often responsible for driving research on rare diseases, also face resource barriers, since they are typically self-funded.

Despite the numerous opportunities that pediatric online research strategies offer for research on rare diseases, researchers also need to address several concerns specific to consent in this setting. Parents who have a child with a rare disease often search for years before finding an explanation for their child's condition. Parents who have been on this diagnostic odyssey, or who are desperate to find an effective intervention for their children, may be willing to take on higher degrees of risk when participating in a research study. While this is rarely a reason to exclude families from a research study, it is important for research staff to address the intentions and expectations of parents enrolling their children in such a study. This may be difficult without direct interaction with families.

In addition, studies have shown that rare disease families often have distinctive perspectives on data sharing or privacy.[27] There is some evidence, for example, that parents of children with rare conditions may be less willing to share information about their children because they recognize their children are more identifiable, and thus more susceptible to discrimination, as a result of having a rare disease.[28] Other studies have shown that some parents with rare disease are more likely to share because they are desperate for answers, and that patients with more serious conditions may also be more willing to share data.[29] In either case, it may be difficult to assess how these special considerations are affecting decisions to participate in research or have data shared through online research platforms without face-to-face conversations with children and their families.

Conclusion

In the preceding sections, we have examined a number of challenges related to consent that arise in online research with children. And we have only scratched the surface. There are numerous issues that also need to be addressed by researchers who wish to utilize this innovative approach to studying pediatric health and disease: how to handle changes in guardianship, what to do with existing data if pediatric participants cannot be reached once they reach the age of majority, whether to return individual research results, and many others. We hope, however, that this analysis will provide a starting point for both regulated and unregulated researchers to begin including children in their online research. There are numerous important issues that need to be addressed, but the potential rewards for understanding and improving the health of children could be significant.

Perhaps the most important message, however, is that effective approaches to many of these complex challenges have already been developed in traditional, regulated research settings. Pediatric research efforts like the Adolescent Brain Cognitive Development (ABCD) study and the Gabriella Miller Kids First Pediatric Research Program have found ways to conduct innovative research while carefully and deliberatively developing strategies to address pediatric-specific ethical, legal, and regulatory issues. Online pediatric researchers can and should do the same. While there is room to disrupt conventional models of pediatric research, thoughtful application of ethical principles to innovative research can help us avoid the catch 22 that has held back pediatric research since the publication of the Nuremberg Code.

Note

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