

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,
and Janet Woodcock, M.D., *Editors*

Informed Consent

Christine Grady, R.N., Ph.D., Steven R. Cummings, M.D.,
Michael C. Rowbotham, M.D., Michael V. McConnell, M.D., M.S.E.E.,
Euan A. Ashley, F.R.C.P., D.Phil., and Gagandeep Kang, M.D., Ph.D.

This multipart review provides an overview of innovative approaches to improving and expanding the informed consent process for researchers and participants, along with short essays covering specific areas of innovation.

The Changing Face of Informed Consent

Christine Grady, R.N., Ph.D.

In the classic interaction in which informed consent is obtained for research, an investigator presents the potential participant with information regarding a new therapeutic, diagnostic, or prophylactic intervention and then asks the participant to read and sign a detailed written consent document. This traditional prototype is becoming outdated. Informed consent, which is ethically essential in most clinical research, respects persons' rights to decide whether participation in the research is compatible with their interests, including their interests in protection from exploitation and harm.^{1,2} In the process of informed consent, participants are given an opportunity to understand relevant information about research participation and to make a voluntary choice.³ Required by ethical guidelines and regulations unless explicitly waived by institutional review boards,^{4,7} informed consent is thus a means of protecting the rights and welfare of participants while they contribute to the advancement of knowledge.

Over the past 50 years, the informed consent process has become increasingly regulated and standardized, while the challenges remain persistent and hard to overcome.⁸ Consent forms are increasingly long and complicated, obscuring important details, and are often designed to serve the interests of institutions and sponsors. Data show that participants often have a limited understanding of study information even when they have

signed a consent form.⁸ Technological advances driving changes in research methods and information practices have influenced how we think about informed consent for research, which raises the possibility of new approaches to informed consent and innovative options for obtaining it.

CHANGING RESEARCH METHODS

Unprecedented opportunities to answer important clinical research questions are available through the analysis of massive amounts of data ("big" data) in commercial, health care, research, and government databases, in social media and mobile devices, and in growing collections of biologic specimens and clinical and genomic data. Data are amassed quickly and easily, sometimes through passive technologies such as location-based mobile devices, through registries, or through systems of electronic health records or data and biospecimens collected for other purposes. Innovative studies are being developed that are conducted entirely through the Internet, as described below by Cummings and Rowbotham, or through the use of smartphone apps, as described below by McConnell and Ashley. Such research allows "access" to participants remotely without the constraints of time or location. Powerful technologies enable data mining and analytics, as well as the integration of data from multiple sources.

Is the classic written informed consent process and document appropriate for these research paradigms? The level of risk to participants is low and is usually thought to be primarily informational,⁹ which differs from the risks associated

with traditional interventional clinical research; the researcher–participant relationship also differs. Some argue that although informed consent allows participants to decide about acceptable risks, it may be unnecessary for research that involves the mining of large data sets or the analysis of deidentified biospecimens, because risks are low, especially as compared with the risks of research on previously untested treatments. In addition, deidentification and privacy protections further attenuate any individual informational risk.^{10,11} Moreover, there is concern that requiring consent for low-risk research of this type could impede or make infeasible otherwise valuable research or could result in selection bias — that is, a situation in which persons who are willing to consent differ fundamentally from those who are not willing, thus jeopardizing the science.^{12,13}

In the commercial marketplace, people use social media and mobile devices and contribute their data to large databases in innumerable ways, and they may be unaware of the multiple entities gathering and storing their data for future use. Persons are sometimes notified in general terms about various uses of their data, yet “[r]esearchers are rarely in a user’s imagined audience.”¹⁴ Reactions to certain research studies, such as the Facebook emotion experiment or OkCupid research,¹⁵⁻¹⁷ as well as empirical data, such as that gathered in association with Twitter’s population-level depression monitoring,¹⁸ provide evidence that some people feel strongly about being asked and may not consent to certain research uses.¹⁹

Research with biospecimens may pose risks that are different from those posed by research with either actively or passively gathered data, yet public and private researchers often use deidentified clinical biospecimens without consent.¹² Requiring consent for the use of such samples could result in smaller, more highly selective pools of participant samples, which may impede publicly beneficial research or limit its validity. The debate about the need for and form of informed consent for research with stored biospecimens was revived by recent international discussions and proposed changes to the U.S. Common Rule (changes that were not ultimately accepted) that would have required written consent for all research use of biospecimens.^{20,21} Even those who favor requiring consent for biospecimen research disagree about whether consent should be broad

for a wide range of future possible research or specific for each use, one-time or ongoing, and opt-in or opt-out.²²⁻²⁷

Other emerging clinical research paradigms, including pragmatic trials and learning health care systems — that is, systems in which interventions that are within the scope of standard practice are tested and data are gathered passively in an attempt to improve outcomes — have also provoked debate about appropriate methods of informed consent.²⁸⁻³¹ Although more similar to the prototypical clinical trial, some of these studies pose low research risks, are more similar to quality-improvement studies than to interventional clinical research, and depend on collective participation for scientific validity. Features of some of these trials arguably permit less formal consent procedures, perhaps notification with opt-out and, in some cases, even waiver.³¹

In survey after survey, however, people report that they prefer to be asked and given a choice about research even if there is little risk to them.^{27,32-39} The challenge is finding practical, nononerous ways to respect persons’ choices that have minimal negative effects on the science. Information technology may provide new opportunities to implement informed consent with minimal intrusion.

CHANGING INFORMATION TECHNOLOGIES AND PRACTICES

Digital technology has transformed how people communicate, learn, and work; information is increasingly acquired and communicated online or through mobile devices. Society is gradually becoming paperless, and information is constantly at our fingertips. Health information is stored in electronic health records. Small tablet computers and smart phones are multiplying five times faster than the global population.⁴⁰ Technological and societal changes in information practices present fresh opportunities for innovative implementation of informed consent. Apps, tablets, video, interactive computers, robots, personal digital assistants, mobile phones and smartphones, and wearable technology could help to modernize, alter, and improve methods of informed consent. Technologies permit broad standardization and easy updating of information, ready use of creative graphics, the means for remote interactive discus-

Table 1. Components and Challenges of Informed Consent with Traditional Paper Forms and Electronic Methods.

Component	Traditional Paper Informed Consent	Electronic and Digital Informed Consent	Challenges and Areas for Research
Disclosure	Information is written, usually on paper Discussion with investigator takes place, usually face to face	Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces Investigator can be remote in time or place from participant	All types of disclosure require determining the appropriate content (amount and complexity of information) for disclosure User-friendly disclosure is needed Amount and style of information tailored to electronic platforms need to be determined
Understanding	Investigator and participant discuss information Participant asks questions Investigator assesses understanding, in some cases using questions, structured quizzes, other methods	Questions and assessment of understanding are easily built in Ongoing engagement is enabled Links to additional information can be included	Evidence indicates that people do not read click-through agreements on computers and mobile devices Information should be engaging and user-friendly to promote reading and understanding It may be difficult to assess capacity and understanding Empirical evidence to date indicates that video and multimedia consent strategies have not resulted in consistent advantages or disadvantages with regard to participant understanding ⁴⁷
Voluntariness	Investigator asks participant to make a choice in a setting free from coercion and undue influence Research team observes participant's body language and any hesitation	Some electronic systems facilitate participant control Participant can easily sign off or disengage Participant can decline	It may be difficult to assess voluntary choice without the clues of body language and tone It may be difficult to verify the identity of the person consenting Some data collection is passive In some cases, contributing data is a required part of the arrangement
Authorization	Paper consent document is signed Copies of document are kept in records	Options might include clicking agreement or an electronic signature Records of agreement are kept electronically	It may be difficult to verify the identity of the authorizing person

sions, and documentation of the process. Investigators can use technologies to provide information, interact with participants, answer questions, and assess understanding on an ongoing basis. Available consent tool kits featuring visual interactive approaches aim to make informed consent more participant-centered and less focused on signing legal documents.⁴¹ Other tool kits allow researchers to create apps for medical research and include customizable visual consent templates.⁴² Technologies allow for methods of informed consent that are modern, green, interactive, and dynamic.⁴³⁻⁴⁶

Along with providing opportunities, adoption of digital and electronic methods of consent requires deliberation, evidence, and recognition of challenges (Table 1). Investigators and oversight bodies must still determine the appropriate content for disclosure. Replacing long, complex, technical written forms with long, complex, technical or legalistic electronic information pages would not represent progress. Indeed, very few persons read click-through agreements, a common notice-and-consent feature of computer and mobile device use, before clicking “agree.”^{48,49} Clicking an agreement box without engaging with the information would be the equivalent of signing a consent form without reading it. This approach to consent would probably do more to protect investigators and sponsors than to inform participants. Important additional challenges in digital consent interactions include verifying that the people who are consenting have the capacity to consent and are who they say they are (authentication). If informed consent aims to provide information that participants can use to make decisions, promoting informed consent will require the creative use of electronic technologies that are simple, easy to use, and in widespread and common use. The interactions need to be brief, engaging, informative about risks and benefits in a way that users can easily appreciate, and equipped with methods for authentication, as discussed below by Cummings and Rowbotham. Such approaches to obtaining consent could also reduce worries about possible selection bias.

Information technologies enable new ways of presenting information and transferring some control to participants even in research in which investigators and participants never meet, yet they do not resolve questions related to the necessity or adequacy of informed consent. As described

below by Kang, regulations in India require consent interactions to be videotaped in order to enhance accountability, with the hope of improving the consent process and ensuring its adequacy.

Informed consent as a process that serves to respect autonomous choices and protect people from risks is not “one size fits all” and should be tailored to context. One-on-one interactive informed consent with detailed information about the purpose of a study as well as about its risks, benefits, and alternatives is necessary for high-stakes gene-transfer research, for example; however, in my view, it is unnecessary for studies that involve deidentified aggregate clinical data. For the latter, educating the public and notifying persons whose data will be used might sufficiently show respect without impeding the science.

Broad dialogue and empirical research should inform decisions about adopting new methods of obtaining informed consent and tailoring models of consent to changing research paradigms. Research is needed to examine whether and when any progress made through low risk–high reward research outweighs other issues, including the ethical reasons behind obtaining prototypical in-

formed consent. Researchers should also investigate public views about informed consent for the use of big data and electronic consent methods, as well as methods promoting engagement with and comprehension of digital study information, methods of authentication and capacity assessment as part of digital consent, and the extent to which there is selection bias in research in which digital consent technologies are used. The ethical goals of informed consent and the importance of considering research context should guide us as we assimilate technology into research and the informed consent process and develop creative and effective evidence-based practices.

The views expressed are those of the author and do not necessarily reflect those of the Clinical Center, the National Institutes of Health, or the Department of Health and Human Services.

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

I thank Frank Miller, Dave Wendler, and Carl Runge for their helpful comments.

From the Department of Bioethics, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Grady at the Department of Bioethics, National Institutes of Health Clinical Center, National Institutes of Health, Bldg. 10, 1C118 Bethesda, MD 20892, or at cgrady@nih.gov.

Electronic Informed Consent and Internet-Based Trials

Steven R. Cummings, M.D.,
and Michael C. Rowbotham, M.D.

Informed consent for a research study brings to mind a paper document with a handwritten signature completed at a clinical research site. However, the paper, ink, and clinical site are not necessary. Sufficient information to enable a participant to make an informed decision can be provided electronically, either on-site (when the investigator and the participant are at the same location) or remotely.⁵⁰

Informed consent by means of electronic devices (e-consent) often includes multimedia, such as graphics or video, about essential study features that may increase understanding of the study, particularly for people with a low educational level or limited literacy⁵¹⁻⁵³; for example, the ADAPTABLE trial (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; ClinicalTrials.gov number, NCT02697916) — a very

large pragmatic trial comparing two doses of aspirin — includes a video overview of what the study is about and what participation involves (<https://adaptablepatient.com/en/prescreen/watch-video>).⁵¹⁻⁵³ E-consent includes a display of the official document, but the document can be enhanced with pop-up definitions of unfamiliar terms and links to additional information or an audio version. Built-in quizzes assess comprehension and correct misunderstandings of key trial features; an example of an e-consent knowledge review questionnaire is shown at www.youtube.com/watch?v=HtLuqJdYuoQ.⁵⁴ A participant must be given the opportunity to have questions answered during the informed consent process through a telephone call, real-time video, or electronic messaging, and the discussion may be guided by review of a participant's errors. Most studies have shown that participants' recall of key facts about a study is better with the use of e-consent with these interactive features than with paper forms.⁵⁵⁻⁵⁸ Participants and staff usually prefer e-consent over informed consent on paper.^{56,57,59}

Participants can sign electronically using pass-

words known only to the participant or using a fingertip on a mobile device.⁵⁰ When e-consent is performed remotely, the identity of the person who is giving the consent can be confirmed in one of several ways, such as digital signature, username and password, or biometrics.⁵⁰ Participants receive a copy of the completed e-consent form, which can be provided electronically.⁵⁰ Signed e-consent records are stored securely (e.g., encrypted to protect privacy, with audit trails to track any changes).⁵⁰

E-consent is also used currently for the enrollment of participants in biobanks.^{58,60-62} The e-consent system can link a participant's consent electronically to all aliquots obtained from that participant; as a result, changes in a participant's informed consent for assaying a specimen are updated instantaneously, and participants can also track how their specimens are used. The e-consent process for an entire study can be tracked centrally to obtain information on time spent on steps in the form, queries of unfamiliar terms, and errors on quizzes, and these data can be used to improve the e-consent process.⁵⁷ Amendments to forms can be distributed immediately to all clinical sites.

E-consent has disadvantages. Videos and quizzes add time to reading the consent form.⁵⁵⁻⁵⁸ Initial development of an e-consent process can be costly, but reuse of templates can save money in subsequent studies. Although e-consent has been accepted by central institutional review boards in the United States, launching a multisite trial can be challenging because local institutional review boards may be unfamiliar with e-consent or may want unique modifications. For international trials, countries may have different requirements for e-consent.

INTERNET-BASED CLINICAL TRIALS

Freeing the informed consent process from physical clinical sites enables trials of drugs or supplements to be conducted entirely through the Internet. Trials conducted entirely through the Internet have several potential advantages over clinic-based trials.⁶³ Instead of recruiting patients from separate clinical sites with limited catchment areas, one center could reach all potentially eligible people who have Internet access; recruitment could be performed through online advertisements and so-

cial media campaigns, and with appropriate permissions, patients may receive e-mail messages with links to a study website. Since there are no face-to-face visits, the identity of potential participants can be confirmed by other means, such as online identity verification services, transmission of images of government-issued identification cards, or biometrics; participants can then use passwords or fingerprints to sign into their accounts, which minimizes the chance of duplicate enrollment or fraudulent participation under multiple identities.⁶²

Internet-based clinical trials also have potential disadvantages. Trials that require specialized assessments and treatments in clinical settings cannot be performed completely through the Internet. To overcome this problem, mobile research nurses can make home visits to draw blood, conduct tests (e.g., electrocardiography), perform assessments guided by video with a study physician, and verify identity.^{64,65} As is the case in standard trials, adverse events may be reported by telephone, e-mail, or text to the central staff or study clinicians, who record the adverse event data and, if appropriate, give advice or refer the participant to emergency care or follow-up with their physicians.

Treatments can be sent to participants through secure overnight delivery with signature confirmation of receipt; unused treatments can be returned by the same method. Participants can also be instructed to send an e-mail message that includes the number on the bottle to acknowledge receipt of the treatment. If necessary, mobile research nurses can also deliver medications and administer some types of parenteral drugs during a home visit. The Food and Drug Administration has allowed sending approved but not investigational treatments directly to participants.⁶⁶ State laws may require that the study treatments, including placebo, be prescribed by a physician licensed in that state.

Published examples of Internet-based trials include a simple (i.e., fewer steps for the participants and fewer exclusions) trial of nutraceuticals for insomnia and anxiety, in which 391 participants from 45 states were enrolled and underwent randomization over an 8-week period,⁶⁷ and a trial of omega-3 fatty acids for autism, in which 57 children from 28 states were enrolled and underwent randomization over a 6-week period.⁶⁸ In contrast, a complex clinical trial that was conducted un-

der an investigational new drug application for a urinary incontinence treatment used a protocol that mimicked previous clinic-based trials.⁶⁶ The online screening, informed consent, and data collection systems worked well. However, the protocol required multiple steps that included laboratory tests and 24-hour urine collections; consequently, less than 1% of women who entered the screening process continued to randomization.⁶⁶ The aforementioned ADAPTABLE study is being conducted entirely through the Internet, with the use of electronic medical records to recruit participants and ascertain end points (<http://theaspirinstudy.org>).

THE FUTURE

We believe that freeing informed consent and clinical trials from the fetters of paper forms and physical clinical sites has the potential to improve the informed consent process, expand participation, and reduce the costs of trials. E-consent and Internet-based trials should also be studied with the goals of improving their performance and increasing the confidence of patients, investigators, and regulatory authorities in these new methods.⁶⁹

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

From the California Pacific Medical Center Research Institute (S.R.C., M.C.R.), the San Francisco Coordinating Center (S.R.C.), and the Departments of Medicine, Epidemiology, and Biostatistics, University of California, San Francisco (S.R.C.) — all in San Francisco. Address reprint requests to Dr. Cummings at the San Francisco Coordinating Center, Mission Hall, Box #0560, 550 16th St., 2nd Fl., San Francisco, CA 94143, or at scummings@sfcc-cpmc.net.

Mobile Health Research — App-Based Trials and Informed Consent

Michael V. McConnell, M.D., M.S.E.E.,
and Euan A. Ashley, F.R.C.P., D.Phil.

The use of smartphones to conduct health research allows investigators to reach a large population, including participants who may not be in close proximity to a research center. Mobile device subscriptions in the world now exceed the world population (>7 billion), and smartphones

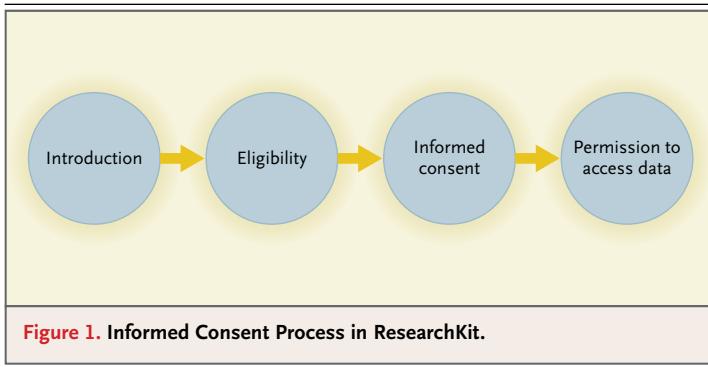
account for 75% of all mobile phones sold.⁷⁰⁻⁷² Almost half the population in the developing world has a mobile device, with the largest growth in mobile device use in India, Africa, and Asia-Pacific, and mobile access worldwide now exceeds desktop access to the Internet. Thus, “apps” (i.e., software programs designed to run on smartphones) are the natural evolution in facilitating clinical and population health research.

ADVANTAGES AND CHALLENGES OF APP-BASED RESEARCH

App-based research has multiple additional advantages. Principal among them is that all or most of the research study can be conducted through the smartphone — from obtaining informed consent to collecting data. A powerful feature of smartphones is that they now contain multiple sensors, such as accelerometers, global positioning system receivers, cameras, and microphones, which can be used for passive or active collection of data (e.g., the 6-minute walk test)⁷³ without requiring a person to visit a facility for testing. Indeed, the ability to collect data on a more frequent and continuous basis in a more real-world environment with a device people have with them throughout the day may expand the wealth of research data and the potential for insights. The smartphone has also become a hub for importing and aggregating a wide range of health data, such as data from other apps, wearable devices (e.g., fitness trackers and smartwatches), and connected medical devices. Furthermore, the majority of smartphone users keep their device with them throughout the day and interact with it multiple times per hour,⁷⁴ which offers opportunities for more interactive research, such as reporting and tracking symptoms or testing behavioral interventions.

Conversely, conducting health research and obtaining informed consent on smartphones raise several unique challenges and limitations. The most important limitation is that there is no face-to-face confirmation of identity. For example, it is possible that one person could sign in to confirm identity and another could carry the device. Therefore, app-based research is most suitable for low-risk studies in which electronic informed consent (e-consent) is appropriate (discussed by Cummings and Rowbotham above).

INTRODUCTION OF APP-BASED RESEARCH STUDIES



The major introduction of app-based research studies occurred in March 2015 with the launch of five institutional review board–approved study apps that were created with ResearchKit (<http://researchkit.org>) on the Apple iOS platform; the study apps, which have been described previously,⁷⁶ include MyHeart Counts (cardiovascular disease), mPower (Parkinson’s disease), Gluco-Success (type 2 diabetes), Asthma Health (asthma), and Share the Journey (breast cancer). MyHeart Counts enrolled more than 10,000 participants in the first 24 hours, and the total enrollment in all five studies in the first 7 months was more than 70,000 participants. The open-source ResearchKit platform is a software toolkit to enable building apps for smartphone-based medical research. ResearchKit includes an e-consent process (Fig. 1),⁷⁷ with a visual consent flow (see the Video) composed of animated screens of consent elements, links to “learn more,” and a full consent form for review. In addition, the participant is given a screen to review and “opt-in” to allow access to each element of health or demographic data through the smartphone and a screen to choose whether the data can be shared with researchers worldwide. MyHeart Counts updated its informed consent process to enable enrollment outside the United States and, along with other ResearchKit-based studies, has added a consent module to incorporate personal genomic data.⁷⁸ ResearchKit was initially limited to iPhone users, but similar software tools (e.g., ResearchStack [<http://researchstack.org>]) have now been made available for app-based informed consent and research on the Android operating system,⁷⁹ a system that runs on more than 80% of smartphones worldwide.⁷²

The smaller screen size of smartphones adds a considerable challenge to the e-consent process in that multiple consent screens are required to review all the key consent components. However, the interactive nature and multimedia capabilities of mobile phones provide potential advantages over the standard process of obtaining informed consent. These advantages include graphics and animation, explanatory audio and video clips, links to additional information, and interactive quizzes to ensure understanding.



A video showing the consent process in the MyHeart Counts study app is available at NEJM.org

Although smartphone use and familiarity with mobile technology are growing, they are certainly not evenly distributed across populations. This uneven distribution can cause selection bias with respect to which participants are able to download the app and complete the informed consent process and study tasks. Even more of an ethical challenge is the inability of segments of the population to participate in smartphone-based research studies because of issues related to access or cost of smartphones or data connectivity.

Another key challenge with respect to app-based research and informed consent is data security and privacy.⁷⁵ Modern smartphones have security features that exceed those of most computers, because they are enabled with biometric identification (e.g., fingerprint) for access, as well as data encryption. The mobile phone identification number and global positioning system location involve specific risks to privacy that should be safeguarded. International use and travel raise additional issues, because most countries have their own regulations regarding health data crossing borders; therefore, the language used in the consent process should be clear about who has access to the research study app and how the app can or cannot be used when the person is traveling internationally.

Initial data from the MyHeart Counts study showed both the challenges and the potential of app-based research.⁸⁰ The population that provided consent was predominately young (median age, 36 years) and male (82%), and although the nearly 5000 participants who completed the 6-minute-walk test at the end of 7 days was the largest such cohort reported, it represented only 10% of participants who provided consent. On the other hand, a cluster analysis of activity data in more than 20,000 participants yielded distinct activity patterns that correlated with cardiovas-

cular health status as reported by the participants, particularly more frequent transitions from an inactive to an active state. These findings will need prospective, longitudinal evaluation.

THE FUTURE

The growth in mobile access and device use heralds greater ability to conduct both personalized and population health research.⁸¹ Using mobile devices, people can participate and contribute their data to research more easily, and researchers can have broader access to populations as well as deeper access to individual activities. The wealth of “big data” that can come from this research offers the potential for new insights into health and disease.⁸² Indeed, the Precision Medicine Initiative launched by former President Barack Obama aims to leverage this potential by including mobile devices as part of its “phenotyping technologies” and empowering patient-centered research^{83,84}; this initiative uses novel approaches to enrollment, informed consent, and engagement in its plan to recruit more than 1 million volunteers in the *All of Us* research program.⁸⁵ Federal agencies are actively updating their approaches to research and mobile devices with guidance on e-consent, mobile medical applications, and low-risk devices.⁸⁶⁻⁸⁹ There is clearly a need — and an opportunity — to study and improve app-based informed consent processes as experience and technologies advance.⁹⁰ The overarching goal is to provide the research community of participants and researchers with better tools to enhance medical research in the 21st century.

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

From the Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford (M.V.M., E.A.A.), and Verily Life Sciences, South San Francisco (M.V.M.) — both in California. Address reprint requests to Dr. McConnell at the Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Dr., Stanford, CA 94305, or at mcconnell@stanford.edu.

Video Informed Consent

Gagandeep Kang, M.D., Ph.D.

In 2013, the Indian Supreme Court ruled on a case that highlighted the fact that patients enrolled in clinical trials had little or no under-

standing that they were participating in a research trial or of the nature of the trial; in the ruling, it was recommended that the informed consent process be recorded on video. During the previous year, widely reported issues with consent and participation had resulted in Supreme Court rulings that delayed or cancelled many clinical trials in India, including several that were supported by the National Institutes of Health.⁹¹

After the turmoil that followed the initial rulings of the Supreme Court, which threatened to stop all clinical trials in India unless higher standards were established, the directive regarding video recording of the informed consent process offered a path to permitting experimental studies involving patients to resume. Because it was a new requirement for clinical trials and researchers had no previous experience with the process, there was little clarity, much ambiguity, and intense discussion among researchers regarding the execution and standardization of processes.⁹² A 10-page guidance document issued by the Central Drugs Standard Control Organization (CDSCO, the equivalent of the U.S. Food and Drug Administration) in early 2014 provided instructions about the information to be given to participants, included the requirement that the faces and voices of participants and investigators or designees should be clearly recorded, emphasized confidentiality, and stated that recordings were to be archived for a minimum of 5 years.⁹³ After much experimentation and discussion in the past 2 years in India, there have been several lessons learned and standard operating procedures developed,⁹⁴ but clarity is still needed with regard to both process and some ethical issues.

Setting up video recording of the consent process in a busy clinical environment is not simple. It requires a quiet room that is large enough to accommodate at least four people: the prospective trial participant; the investigator or designee; a witness, in case the participant is illiterate; and a videographer, who despite being able to use small, high-resolution cameras still needs to have sufficient distance from those being recorded to record two or three people going through the consent documents, the discussion, and the initialing and signatures. In the case of children being recruited, the room also needs to be large enough to accommodate additional family members. The requirement of oral consent for



An example of video informed consent is available at NEJM.org

the recording and of the provision of initial information, followed by the discussion and the recording of the process of informed consent, results in multiple sessions for some studies, particularly when the participants need time for discussion with their families. (An example of video consent is available with the full text of this article at NEJM.org.)

Each recording has to be reviewed for quality, which results in more demands on the time of the study team and the need for backup equipment, since any poor recordings or equipment breakdowns will require obtaining consent again or lead to substantial delays in recruitment. Digital storage is not expensive in relation to the costs of clinical trials, but there is as yet no specific guidance on the acceptability of location (e.g., cloud storage) or the need for backup storage, level of encryption, and access.

Although the practical difficulties have solutions, two ethical issues need consideration. The directives require that only participants who consent to video recording may participate in a clinical trial. This may result in a lack of participation for religious, cultural, or social reasons that lead to a reluctance to be recorded on video, even though the potential participant understands the benefits and risks and would like to enroll in the study. Small studies have indicated that patients worry about the confidentiality of video recording, particularly when they have cancer or stigmatizing diseases. In a study in southern India involving 150 participants, up to a third, particularly women and younger persons, said that they would refuse to participate in a study because of the recording.⁹⁵ My own experience has been that video recording does result in some eligible persons refusing to go further, but the likelihood of refusal can be decreased with careful explanations from the investigative team in hospitals. Another approach that works well in community-based trials is the encouragement of discussion of the process with participants enrolled in other studies who have agreed to describe their experiences when asked by the investigators. Despite these approaches, denial of participation because of a refusal to be recorded goes against the principle of justice; the opportunity to share in the benefits and risks of research should be offered to all eligible persons. In an amendment issued by the CDSCO in August 2015, the issue

was partly addressed by permitting only audio recording for trials related to human immunodeficiency virus and leprosy.

A second unresolved issue is that of confidentiality: there is no clarity with regard to the control the participant has over the process. Opt-out clauses can ensure that biologic samples are destroyed after the original purpose of study is completed, but for video records there is no information on who can view the video — within the research team, within the institution, among members of the institutional review board, among regulatory or legal authorities — and whether the participant has the right to deny a viewing of the video to any of these authorities and at what time during or after the study.

Overall, video recording of informed consent has the laudable purpose of ensuring better conduct of the process of informed consent and should decrease the conduct of trials in which participants are insufficiently informed and do not understand the purpose and the risks and benefits of research. It requires planning, new processes, and substantial resources, but it is feasible if the resources are available.

The unresolved issues of processes for ensuring confidentiality and for addressing participation in trials when persons may not want to be recorded need attention and discussion. There is no empirical evidence as yet that the goals of truly informed consent are being met through the process of video recording, and there is no measure of the proportion of persons or communities who refuse participation because of their unwillingness to be recorded. The cost, complexity, and level of preparation required for video recording also mean that in certain emergency care and public health settings, it will not be possible to test interventions, given the logistic constraints. Overall, although the goal is to protect vulnerable populations, the costs in terms of resources and opportunities require regulatory authorities to carefully consider the populations, settings, and study designs that truly benefit from the requirement for video recording of consent.

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

From the Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India. Address reprint requests to Dr. Kang at the Division of Gastrointestinal Sciences, Christian Medical College, Ida Scudder Rd., Vellore, TN, 632004 India, or at gkang@cmcvellore.ac.in.

1. Miller F, Wertheimer A. The ethics of consent: theory and practice. New York: Oxford University Press, 2010.
2. Faden R, Beauchamp T. A history and theory of informed consent. New York: Oxford University Press, 1986.
3. Miller FG, Wertheimer A. The fair transaction model of informed consent: an alternative to autonomous authorization. *Kennedy Inst Ethics J* 2011;21:201-18.
4. U.S. Code of Federal Regulations. Title 45 CFR, Part 46 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>).
5. U.S. Code of Federal Regulations. Title 21 CFR, Part 50 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=50&sh>).
6. World Medical Association. Declaration of Helsinki — ethical principles for medical research involving human subjects. 2013 (<http://www.wma.net/en/30publications/10policies/b3/>).
7. International Conference on Harmonization. Guideline for good clinical practice: E6(R1). 1996 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf).
8. Grady C. Enduring and emerging challenges of informed consent. *N Engl J Med* 2015;372:855-62.
9. Pullman D, Etchegary H, Gallagher K, et al. Personal privacy, public benefits, and biobanks: a conjoint analysis of policy priorities and public perceptions. *Genet Med* 2012;14:229-35.
10. Mostert M, Bredenoord A, Biessart M, van Delden JJ. Big Data in medical research and EU data protection law: challenges to the consent or anonymise approach. *Eur J Hum Genet* 2016; 24:956-60.
11. Grande D, Mitra N, Shah A, Wan F, Asch DA. The importance of purpose: moving beyond consent in the societal use of personal health information. *Ann Intern Med* 2014;161:855-62.
12. Lynch HF, Bierer BE, Cohen IG. Confronting biospecimen exceptionalism in proposed revisions to the Common Rule. *Hastings Cent Rep* 2016;46:4-5.
13. El Emam K, Jonker E, Moher E, Arbuckle L. A review of evidence on consent bias in research. *Am J Bioeth* 2013;13:42-4.
14. Boyd D, Crawford K. Critical questions for Big Data. *Inform Community Soc* 2012;15:662-79.
15. Goel V. Facebook tinkers with users' emotions in news feed experiment, stirring outcry. *New York Times*. June 29, 2014 (http://www.nytimes.com/2014/06/30/technology/facebook-tinkers-with-users-emotions-in-news-feed-experiment-stirring-outcry.html?_r=0).
16. Zimmer M. OKCupid Study reveals the perils of Big-Data science. *Wired*. May 14, 2016 (<https://www.wired.com/2016/05/okcupid-study-reveals-perils-big-data-science/>).
17. Verma I. Editorial expression of concern: experimental evidence of massive-scale emotional contagion through social networks. *Proc Natl Acad Sci U S A* 2014;111:10779.
18. Mikal J, Hurst S, Conway M. Ethical issues in using Twitter for population-level depression monitoring: a qualitative study. *BMC Med Ethics* 2016;17:22.
19. Simon JR. Corporate research ethics: whose responsibility? *Ann Intern Med* 2014;161:917-8 10.7326/M14-1669.
20. Office for Human Research Protections. Revisions to the Common Rule. 2017 (<http://www.hhs.gov/ohrp/humansubjects/regulations/nprhome.html>).
21. Mascalzoni D, Dove ES, Rubinstein Y, et al. International Charter of principles for sharing bio-specimens and data. *Eur J Hum Genet* 2015;23:721-8.
22. Grady C, Eckstein L, Berkman B, et al. Broad consent for research with biological samples: workshop conclusions. *Am J Bioeth* 2015;15:34-42.
23. Wendler D. One-time general consent for research on biological samples. *BMJ* 2006;332:544-7.
24. Lo B, Barnes M. Federal research regulations for the 21st century. *N Engl J Med* 2016;374:1205-7.
25. Ballantyne A. In favor of a no-consent/opt-out model of research with clinical samples. *Am J Bioeth* 2015;15:65-7.
26. Vayena E, Mastroianni A, Kahn J. Caught in the Web: informed consent for online health research. *Sci Transl Med* 2013; 5:173fs6.
27. Tomlinson T, De Vries R, Ryan K, Kim HM, Lehpamer N, Kim SY. Moral concerns and the willingness to donate to a research biobank. *JAMA* 2015;313:417-9.
28. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. *Hastings Cent Rep* 2013;43:S16-S27.
29. Faden RR, Beauchamp TL, Kass NE. Informed consent for comparative effectiveness trials. *N Engl J Med* 2014;370:1959-60.
30. Kim SY, Miller FG. Informed consent for pragmatic trials — the integrated consent model. *N Engl J Med* 2014;370:769-72.
31. McKinney RE Jr, Beskow LM, Ford DE, et al. Use of altered informed consent in pragmatic clinical research. *Clin Trials* 2015;12:494-502.
32. Botkin JR, Rothwell E, Anderson R, Stark LA, Mitchell J. Public attitudes regarding the use of electronic health information and residual clinical tissues for research. *J Community Genet* 2014;5:205-13.
33. Moodley K, Sibanda N, February K, Rossouw T. "It's my blood": ethical complexities in the use, storage and export of biological samples: perspectives from South African research participants. *BMC Med Ethics* 2014;15:4.
34. Brothers KB, Morrison DR, Clayton EW. Two large-scale surveys on community attitudes toward an opt-out biobank. *Am J Med Genet A* 2011;155A:2982-90.
35. Kaufman D, Bollinger J, Dvoskin R, Scott J. Preferences for opt-in and opt-out enrollment and consent models in biobank research: a national survey of Veterans Administration patients. *Genet Med* 2012;14:787-94.
36. Simon CM, L'heureux J, Murray JC, et al. Active choice but not too active: public perspectives on biobank consent models. *Genet Med* 2011;13:821-31.
37. Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB, Burke W. Informed consent in genome-scale research: what do prospective participants think? *AJOB Prim Res* 2012;3(3):3-11.
38. Treweek S, Doney A, Leiman D. Public attitudes to the storage of blood left over from routine general practice tests and its use in research. *J Health Serv Res Policy* 2009;14:13-9.
39. Riordan F, Papoutsis C, Reed JE, Marston C, Bell D, Majeed A. Patient and public attitudes towards informed consent models and levels of awareness of Electronic Health Records in the UK. *Int J Med Inform* 2015;84:237-47.
40. Boren ZD. There are officially more mobile devices than people in the world. *Independent*. October 7, 2014 (<http://www.independent.co.uk/life-style/gadgets-and-tech/news/there-are-officially-more-mobile-devices-than-people-in-the-world-9780518.html>).
41. Sage Bionetworks. Participant centered consent toolkit (<http://sagebase.org/governance/pcc-toolkit-frequently-asked-questions>).
42. Apple. Introducing ResearchKit (<http://researchkit.org/>).
43. Kaye J, Whitley EA, Lund D, Morrison M, Teare H, Melham K. Dynamic consent: a patient interface for twenty-first century research networks. *Eur J Hum Genet* 2015;23:141-6.
44. Wee R, Henaghan M, Winship I. Dynamic consent in the digital age of biology: online initiatives and regulatory considerations. *J Prim Health Care* 2013;5:341-7.
45. Meslin EM, Alpert SA, Carroll AE, Odell JD, Tierney WM, Schwartz PH. Giving patients granular control of personal health information: using an ethics 'Points to Consider' to inform informatics system designers. *Int J Med Inform* 2013;82: 1136-43.
46. McCaughey T, Liang HH, Chen C, et al. An interactive mul-

- timedia approach to improving informed consent for induced pluripotent stem cell research. *Cell Stem Cell* 2016;18:307-8.
47. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics* 2013;14:28.
 48. Plaut VC, Bartlett RP. Blind consent? A social psychological investigation of non-readership of click-through agreements. *Law Hum Behav* 2012;36:293-311.
 49. Bakos Y, Marotta-Wurgler F, Trossen D. Does anyone read the fine print? Consumer attention to standard form contracts. *J Legal Stud* 2014;43:1-47.
 50. Use of electronic informed consent in clinical investigations: questions and answers — guidance for institutional review boards, investigators, and sponsors. Silver Spring, MD: Food and Drug Administration, December 2016 (<http://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf>).
 51. Tait AR, Voepel-Lewis T. Digital multimedia: a new approach for informed consent? *JAMA* 2015;313:463-4.
 52. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292:1593-601.
 53. Hockley WE. The picture superiority effect in associative recognition. *Mem Cognit* 2008;36:1351-9.
 54. Festinger DS, Dugosh KL, Croft JR, Arabia PL, Marlowe DB. Corrected feedback: a procedure to enhance recall of informed consent to research among substance abusing offenders. *Ethics Behav* 2010;20:387-99.
 55. Rowbotham MC, Astin J, Greene K, Cummings SR. Interactive informed consent: randomized comparison with paper consents. *PLoS One* 2013;8(3):e58603.
 56. Rothwell E, Wong B, Rose NC, et al. A randomized controlled trial of an electronic informed consent process. *J Empir Res Hum Res Ethics* 2014;9(5):1-7.
 57. Vanaken H. eConsent study provides insights to shape industry adoption. *Applied Clinical Trials Online*. August 1, 2016 (<http://www.appliedclinicaltrialsonline.com/econsent-study-provides-insights-shape-industry-adoption>).
 58. Simon CM, Klein DW, Schartz HA. Interactive multimedia consent for biobanking: a randomized trial. *Genet Med* 2016;18:57-64.
 59. Warriner AH, Foster PJ, Mudano A, et al. A pragmatic randomized trial comparing tablet computer informed consent to traditional paper-based methods for an osteoporosis study. *Contemp Clin Trials Commun* 2016;3:32-8.
 60. Boutin NT, Mathieu K, Hoffnagle AG, et al. Implementation of electronic consent at a biobank: an opportunity for precision medicine research. *J Pers Med* 2016;6:17-28.
 61. Simon CM, Klein DW, Schartz HA. Traditional and electronic informed consent for biobanking: a survey of U.S. biobanks. *Biopreserv Biobank* 2014;12:423-9.
 62. Karlson EW, Boutin NT, Hoffnagle AG, Allen NL. Building the Partners HealthCare Biobank at Partners Personalized Medicine: informed consent, return of research results, recruitment lessons and operational considerations. *J Pers Med* 2016;6:2-13.
 63. Dorsey ER, Venuto C, Venkataraman V, Harris DA, Kiebertz K. Novel methods and technologies for 21st-century clinical trials: a review. *JAMA Neurol* 2015;72:582-8.
 64. Wilson LS, Maeder AJ. Recent directions in telemedicine: review of trends in research and practice. *Healthc Inform Res* 2015;21:213-22.
 65. Tanner CM, Meng CC, Ravina B, et al. A practical approach to remote longitudinal follow-up of Parkinson's disease: the FOUNDED study. *Mov Disord* 2014;29:743-9.
 66. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp Clin Trials* 2014;38:190-7.
 67. Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An Internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore)* 2005; 84:197-207.
 68. Bent S, Hendren RL, Zandi T, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. *J Am Acad Child Adolesc Psychiatry* 2014;53:658-66.
 69. Lentz J, Kennett M, Perlmutter J, Forrest A. Paving the way to a more effective informed consent process: recommendations from the Clinical Trials Transformation Initiative. *Contemp Clin Trials* 2016;49:65-9.
 70. GSMA mobile economy 2016 (<http://www.gsma.com/mobileeconomy/global/2016/>).
 71. Ericsson mobility report. Stockholm: Ericsson, November 2016 (<https://www.ericsson.com/assets/local/mobility-report/documents/2016/ericsson-mobility-report-november-2016.pdf>).
 72. Meeker M. Internet trends 2016 — code conference. June 1, 2016 (<http://www.kpcb.com/internet-trends>).
 73. Brooks GC, Vittinghoff E, Iyer S, et al. Accuracy and usability of a self-administered 6-minute walk test smartphone application. *Circ Heart Fail* 2015;8:905-13.
 74. Newport F. Most U.S. smartphone owners check phone at least hourly. Gallup. July 9, 2015 (<http://www.gallup.com/poll/184046/smartphone-owners-check-phone-least-hourly.aspx>).
 75. Filkins BL, Kim JY, Roberts B, et al. Privacy and security in the era of digital health: what should translational researchers know and do about it? *Am J Transl Res* 2016;8:1560-80.
 76. Dorsey ER, Yvonne Chan YF, McConnell MV, Shaw SY, Trister AD, Friend SH. The use of smartphones for health research. *Acad Med* 2017;92:157-60.
 77. ResearchKit: obtaining consent (<http://researchkit.org/docs/docs/InformedConsent/InformedConsent.html>).
 78. Regalado A. 23andMe to share DNA data with researchers using Apple iPhone. MIT Technology Review. March 21, 2016 (<https://www.technologyreview.com/s/601082/23andme-to-share-dna-data-with-researchers-using-apple-iphone/>).
 79. ResearchKit study apps for both iOS and Android. New York: Applied Informatics (<http://appliedinformaticsinc.com/mobile-researchkit-study-apps/>).
 80. McConnell MV, Shcherbina A, Pavlovic A, et al. Feasibility of obtaining measures of lifestyle from a smartphone app: the My-Heart Counts Cardiovascular Health Study. *JAMA Cardiol* 2017; 2:67-76.
 81. Mega JL, Sabatine MS, Antman EM. Population and personalized medicine in the modern era. *JAMA* 2014;312:1969-70.
 82. Antman EM, Benjamin EJ, Harrington RA, et al. Acquisition, analysis, and sharing of data in 2015 and beyond: a survey of the landscape: a conference report from the American Heart Association Data Summit 2015. *J Am Heart Assoc* 2015;4(11):e002810.
 83. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;372:793-5.
 84. Ashley EA. The precision medicine initiative: a new national effort. *JAMA* 2015;313:2119-20.
 85. All of Us research program. Bethesda, MD: National Institutes of Health (<https://www.nih.gov/AllofUs-Research-Program>).
 86. Guidance for industry — use of electronic informed consent in clinical investigations: questions and answers — guidance for industry. Silver Spring, MD: Food and Drug Administration, March 2015 (<http://www.fda.gov/downloads/drugs/guidance-compliancereulatoryinformation/guidances/ucm436811.pdf>).
 87. Mobile medical applications — guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration, February 9, 2015 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf>).
 88. General wellness: policy for low risk devices — guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration, July 29, 2016 (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf>).

89. Federal Policy for the Protection of Human Subjects (AKA "The Common Rule"). Silver Spring, MD: Food and Drug Administration, January 19, 2017 (<https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects>).
90. Rothstein MA, Wilbanks JT, Brothers KB. Citizen science on your smartphone: an ELSI research agenda. *J Law Med Ethics* 2015; 43:897-903.
91. Bhattacharjee Y. Clinical trials paused as India adopts new rules. *Science* 2013;341:327.
92. Kulkarni NG, Dalal JJ, Kulkarni TN. Audio-video recording of informed consent process: boon or bane. *Perspect Clin Res* 2014;5:6-10.
93. CDSCO. Guidelines on audio-visual recording of informed consent process in clinical trial. New Delhi, India: Central Drugs Standard Control Organization, January 9, 2014 (http://www.cdsc.nic.in/writereaddata/Guidance_for_AV%20Recording_09-January.14.pdf).
94. SOP for audio visual recording of informed consent process. Faridabad, India: Clinical Development Services Agency (http://www.cdsaindia.in/sites/default/files/AV-Consent-FERCI-template_06_01_14-Final-1.pdf).
95. Chauhan RC, Purty AJ, Singh N. Consent for audio-video recording of informed consent process in rural South India. *Perspect Clin Res* 2015;6:159-62.

Copyright © 2017 Massachusetts Medical Society.