Informed Consent
Progress Toward an Improved Process

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“The ethical approach to experimentation in man has several components...the first being informed consent.” Henry Beecher

In 1900, physician Walter Reed was conducting human experiments in Cuba to determine the route of transmission for yellow fever. Subjects who agreed to participate in that study signed a one-page document giving their consent to take part in the experiment. Written in English (see page 12) and translated into Spanish, the one-page, single-spaced typewritten document contains most of the elements of informed consent required in the current FDA and Common Rule regulations. Potential subjects were told that participation in the study was voluntary, that it involved serious risks including death, and that there would be financial remuneration. Although an Institutional Review Board (IRB) of the 21st century would not approve this consent form and would have serious questions about a research design that included intentional exposure to mosquitos infected with the then-untreatable yellow fever, even this rudimentary document indicates thought about the implications of informing research participants, and represents an early stage in the development of an informed consent process. However, decades later, Henry Beecher published his groundbreaking article titled “Ethics and Clinical Research.” In this 1966 paper, Beecher cited several examples to indicate his concern that experimentation was being performed with insufficient informed consent.

By 2015 the chorus of voices critical of the state of informed consent documents had reached a crescendo. The consensus opinion being expressed by stakeholders from all facets of research – IRBs, regulators, sponsors, subject advocates, researchers and advisory committees – was that informed consent documents
had become too lengthy and too complex. The documents no longer served as a relevant source of information for potential subjects considering participation in research, or as a guide for the researchers conducting the informed consent process. It is not unusual to see an informed consent form (ICF) for a randomized clinical trial reach 20 or 30 pages. Critics are concerned about both the length and the complexity of consent documents. In addition to a thorough description of the elements of informed consent that are required by federal regulations, (8 required elements and 6 additional elements), and by Good Clinical Practice (GCP) guidelines (20 required elements), the contemporary consent form often contains additional information about research-related injuries, content related to institutional research policies, ClinicalTrials.gov, data-sharing language, and disclosures required by the Health Insurance Portability and Accountability Act (HIPAA).

In response to these broad concerns there have been several initiatives developing on parallel tracks that aim to improve informed consent documents. These initiatives include work by the U.S. Department of Health and Human Services Secretary’s Advisory Committee on Human Research Protections (SACHRP), the Clinical Trials Transformation Initiative (CTTI), a partnership between the Food and Drug Administration (FDA) and Duke University, and proposals outlined in a Notice of Proposed Rulemaking (NPRM) that would represent the first significant changes to the federal regulations governing human subjects research, typically referred to as the “Common Rule,” since their publication in 1991. Common to these initiatives is a goal of producing informed consent documents that are shorter in length and easier for potential subjects to read and understand.
SACHRP Recommendations

SACHRP was established in 2003 to provide expert advice and recommendations to the Secretary of Health and Human Services (HHS) on issues pertaining to the protection of human subjects in research. SACHRP meetings include representatives of all federal agencies operating under the Common Rule as well as representation from the FDA Office of Good Clinical Practice and the Office of Civil Rights, which oversees HIPAA. The SACHRP work on informed consent has involved numerous recommendations focused on discrete components of informed consent, including the elements of informed consent, interpretation of the regulatory requirements for consent, and the way information is presented during the consent process. In 2011 SACHRP produced “Guidance on Applying the Regulatory Requirements for Research Consent Forms: What Should and Should Not be Included?” The guidance includes recommendations on regulatory requirements for informed consent, and provides suggestions for how the

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elements of informed consent might be addressed and when they may be excluded without a formal waiver of consent. In 2015, SACHRP approved “Recommended Guidance on Minimal Risk Research and Informed Consent.” SACHRP developed that guidance to address the concern that consent forms have become unwieldy even in the context of low-risk research. To further address that concern, SACHRP subsequently developed models of consent forms for minimal risk research that incorporated the 2011 and 2015 guidances. However, these recommendations are not completely applicable in the context of greater-than-minimal-risk clinical research (which includes essentially all clinical trials), where the length of consent forms is a recognized issue.
CTTI established a working group in 2013 to examine the problem of very long informed consent documents in clinical trials. In 2015, CTTI published their recommendations for improving informed consent. In addition to recommending training research staff on how to conduct an effective informed consent process, CTTI recommended a significant change in the way information is presented. Described as a “tiered” consent process, the CTTI model divides the information into two or three separate tiers. The first tier would contain only the elements of informed consent required by federal regulations. In a larger second tier, additional information would be included as deemed necessary by the researchers, sponsors, IRBs or institutions. CTTI also suggests that for complicated studies a third tier could be provided consisting of a short (1-2 page) summary of the study. All tiers of this revised format would require IRB review, as the ICF does now.
In 2015, the U.S. Department of Health and Human Services (HHS) issued a highly anticipated Notice of Proposed Rulemaking (NPRM). The proposed rule regarding informed consent documents is similar to the CTTI recommendations. Under the proposed rule the main informed consent document would only be permitted to include information from the federally-required elements of informed consent, much like the brief consent document used by Walter Reed at the start of the 20th century (see page 12). All other information would be moved to an appendix, similar to the tiered model proposed by CTTI. In addition, the NPRM would require the posting of informed consent documents on a public-facing website. This posting would occur after enrollment is closed, and only one form would be posted regardless of the number of changes made to the consent form over the life of the clinical trial or the number of clinical sites with forms that may have modified the ICF to include site-specific wording. The authors of the NPRM have suggested that knowing that the informed consent document will be made public may motivate researchers and sponsors to put more effort into producing better consent forms.
While all of these initiatives are laudable for their goal of improving informed consent, there are some challenges with each. SACHRP recommendations have generally received little attention and poor uptake by the regulatory community. This would likely improve if the Office for Human Research Protections (OHRP) were to take the step of transforming the Committee’s recommendation into official guidance or revised regulations.

The formats endorsed by CTTI and the NPRM have been described as “rearranging the deck chairs on the Titanic.” The main concern raised about this approach is that the overall amount of information provided to potential study subjects is not changed. Skeptics have noted that this approach may even lead to more information being put in front of potential subjects, because the second tier may serve as a repository for all of the information of interest to the various stakeholders with a perception that there is no need to put a check on length of the document. These proposals also do not address the additional elements required under International Council on Harmonisation (ICH) GCP guidelines, the standard

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for industry sponsored clinical trials. In addition, subjective decisions would need to be made regarding what is moved to, or included in, the supplemental information; and all of it would still require IRB approval and be considered part of the informed consent document. At the same time, if the ability of subjects to absorb information really is limited, then there could be a benefit to starting the consent discussion focused on a concise primary consent form.

The public posting of consent forms may cause more confusion than it resolves. Significant implementation questions—Who is responsible for posting the forms? Where would they be posted?—were not resolved in the NPRM, and it is not clear who would access or use these forms or for what purpose. It is also not certain how or that this requirement would lead to an improvement in consent forms. Consent forms are not confidential documents, and sponsors and researchers are already aware that they may become public; it is not uncommon for study participants to post copies of their consent forms online. This growing trend has not appeared to result in any improvement in the forms.
Conclusion

Informed consent is one of the key underpinnings of ethical research, and an effective informed consent process is supported by the written information presented to potential subjects. At its best, informed consent documents help provide potential subjects with the information needed to make a voluntary and truly informed decision about participation in clinical research. At their worst, they can confuse potential subjects, obscure truly important information and lay the entire burden of communication of essential information on the skills of the researcher conducting the consent discussion. The consent forms of today are a far cry from the single page of information provided to subjects in Walter Reed’s yellow fever experiments, but not all of the evolutionary steps to today’s informed consent documents are necessarily for the better. Having many interested stakeholders involved in the process to improve informed consent is essential, but genuine progress will require the collaboration and coordination between the various parties and projects.
References


About the Author

David Borasky, MPH, CIP is Vice President of Quality Management at the Copernicus Group IRB, a WIRB-Copernicus Group company. He also serves as Co-Chair of the Subpart A Subcommittee of the Secretary’s Advisory Committee on Human Research Protections (SACHRP) and sits on the Board of Public Responsibility in Medicine and Research (PRIM&R).
The undersigned, Nicanor Fernandez, being more than twenty-five years of age, native of Cienfuegos in the province of Oriente, the son of Jose Fernandez and Dominga Beterez, here states by these presents, being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $500 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Guamasos, Cuba, on the 8th day of December nineteen hundred.

On the part of the Commission: Nicanor Fernandez
Walter Reed
Maj. & Surg., U.S.A.

The contracting party,