

## Informed Consent: Why and How?

Domestically and internationally, informed consent is recognized as a critical element of conducting ethical scientific research and ensuring public confidence in the process and outcomes. Pfizer has remained committed to conducting research in accordance with the International Conference on Harmonisation (ICH)/WHO Good Clinical Practice standards and in accordance with the principles in the Declaration of Helsinki.

### ***Informed consent***

*A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.*

– ICH Guidance for Industry,  
Good Clinical Practice Consolidated

## The Cornerstone of Every Trial

One of the oldest standards for medical care is the Hippocratic Oath, best known for commanding physicians to “first, do no harm.” Very different from standards today, the Oath also encouraged “*concealing most things from the patient, while you are attending to him... turning his attention away from what is being done, to him... revealing nothing of the patient's future or present condition.*”

Ideas around informed consent began to coalesce in the aftermath of World War II as Nazi crimes came to light during the Nuremburg Trials<sup>1</sup>.

Requirements of informed consent ensure those who might be considered vulnerable to pressure from doctors or researchers are given the opportunity to be informed of the risks and benefits of the research, to ask questions, and provide completely voluntary agreement to participate in the process.

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<sup>1</sup> The National Cancer Institute, “A Guide to Understanding Informed Consent” <http://www.cancer.gov/clinicaltrials/conducting/informed-consent-guide/page4>

## Five Step Process

Regulations at the local, national and international levels detail the various elements necessary to obtain informed consent. Generally, there are five steps in the process of obtaining consent:<sup>2</sup>

- 1) **Assess** decision-making capacity or competence of the prospective subject
- 2) **Disclose** relevant information about the proposed research
- 3) **Ensure** the subject understands the information
- 4) **Ensure** the subject is positioned to make a voluntary decision
- 5) **Authorize** a decision by the subject and sign a consent form (if affirmative)

This case considers issues related to steps two and three – how to disclose relevant information about the study, and how to ensure the potential subject understands the information.

## Barriers to Consent

Allegations of abuse and improprieties, for example the Tuskegee trials in the U.S.,<sup>3</sup> have created an atmosphere of increased scrutiny, intensified standards of practice, and a larger sense of accountability in the international research community. Yet, practical challenges – like education and literacy, differing cultural values, influence of local community leaders, or having adequate opportunities to review information with patients – can make the process more complicated.

Conveying information *effectively* is a challenge. In the *South African Journal of Science*, a researcher explained evaluating what is disclosed by the researchers can be transparent, evaluating what is understood by the subject can be much harder to assess.<sup>4</sup> An editorial in the *New England Journal of Medicine* states the problem bluntly. "Obtaining a signature on a paper does not ensure that a participant understands the proposed research."<sup>5</sup>

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<sup>2</sup> Lavori, PW, Sugarman, J, Hays, MT and Feussner, JR, "Improving informed consent in clinical trials: a duty to experiment," *Controlled Clinical Trial*,(1999) 20:187-193.

<sup>3</sup> Powe, N et al., "Race, medical researcher distrust, perceived harm, and willingness to participate in cardiovascular prevention trials," *Medicine*, Jan 2008.

<sup>4</sup> Lindegger, R et al., "HIV vaccine trials: critical issues in informed consent," *South African Journal of Science* 96, June 2000, <http://www.cancer.gov/clinicaltrials/conducting/informed-consent-guide/page4>

<sup>5</sup> Angel, M. "Is academic medicine for sale?" *NEJM* (2000) 342:1516–1518.

## Lessons from Tanzania

How can a research investigator take steps to ensure a potential participant understands and consents to participate in a study? A recent trial in Tanzania sponsored by Pfizer provides some lessons. Pfizer was following standard operating procedures in writing an informed consent document based on the research protocol. In order to develop a consent form for trial participation, ICH-GDP guidelines require 17 distinct informational elements be incorporated into every form. In the case of the Tanzania trial, the result was a 25-page consent form generated by investigators, for review by every prospective trial participant.

When, in accordance with ICH-GCP guidelines, Pfizer investigators submitted the 25-page consent form for approval, the local IRB overseeing the research rejected the form, indicating it did not meet the spirit of informed consent.

“People will not read a 20+ page form,” explained the review board. According to their own knowledge and expertise of the local population, including patients, physicians and other research staff, “the consent form shouldn’t be more than six pages,” in order to actually inform potential subjects about the research protocol.

An excerpt from the guidelines for clinical research published by the Tanzania National Health Research Forum gives some insight:

“The consent form was originally introduced to protect surgeons from allegations of assault by patients who came to regret the surgical interventions, which, had been carried out upon them. This is still seen by some researchers as the function of the consent form. With regards to the consent form an eminent judge has said,

‘There seem (sic) to be some confusion in the minds of some as to the purpose of seeking consent from a patient. It has two purposes, the one clinical and the other legal. The clinical purpose stems from the fact that in many instances the cooperation of the patient and the patient’s faith or at least confidence in the efficiency of the treatment is a major factor contributing to the treatment’s success. ...The legal purpose is quite different. It is to provide those concerned in the treatment with a defence to a criminal charge of assault or batter or civil claim for damage for trespass to the person.’”<sup>6</sup>

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<sup>6</sup> Guidelines on Ethics for Health Research in Tanzania, Publication of the Tanzania National Health Research Forum, First Version 2001, p 22.  
<https://webapps.sph.harvard.edu/live/gremap/files/Guidelines-2001-TZ-full.pdf>

## Creating Comprehension

One key challenge in properly consenting study participants has been the readability of consent forms.<sup>7</sup> ICH-GCP stipulates “the language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject...”

The information required to be covered by ICH-GCP guidelines is broad-ranging – from foreseeable risks and benefits, to treatment alternatives and confidentiality.<sup>8</sup> Communicating risks and benefits in a trial is particularly difficult. There are likely to be known risks, and those are communicated. But there are also likely to be risks that can be foreseen, and those that cannot. Each level of risk is increasingly difficult to explain. While consent requires knowing about material risks, it may not be possible to communicate every possible risk.

Further, the amount of information to be provided is dependent on the type of research being conducted. If what happens medically in the study is complicated, the informed consent document becomes more complicated. It is much more difficult to explain a lung biopsy than it is to explain a blood draw, for example.

As seen in the Tanzania trial, in efforts to be thorough and completely transparent with patients, consent forms can become onerously long and in turn become a barrier to an informed consent.

*“... no matter how comprehensive the disclosure, there is no guarantee that everyone’s interests and needs will be served. Finally, . . . because of certain problems with information overload, overdisclosure is as likely under most circumstances to lead to inadequate understanding as is underdisclosure.”<sup>9</sup>*

The question of how to simplify consent forms, but still give participants adequate information about the research is an area receiving significant attention in clinical studies.. One innovative approach involves the use of an “information sheet” which is a one or two page document that accompanies a longer consent form. Core elements of consent are included on the cover sheet which includes answers to questions such as:

- What are the risks?

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<sup>7</sup> Beyer, D et al., “Readability of Informed-Consent Forms,” *NEJM*, (2003) 348:2262-2263.

<sup>8</sup> *ICH* Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, April 1996.

<sup>9</sup> Faden R. & Beauchamp, T, *A History and Theory of Informed Consent* (Oxford University Press: New York, NY; 1986) pp. 306-7.

- What will be done to me as a patient in the trial?
- How long will I participate in the trial?
- Why is the study being conducted?
- How will my private data generated in the trial be protected?

Some sponsors such as The University of Wisconsin-Madison Human Research Protection Program has been using the information sheets in some of its studies and now provides templates for sponsors interested in this approach. An official from the university's Health Sciences Institutional Review Board Office says the sheet is helpful in bringing terms and concepts from the clinical trial to a conversational level, usually with someone who has little medical or scientific background.

### **Committed to Comprehension**

In the case of the trial in Tanzania, the Pfizer team reassessed the consent form it submitted to the IRB. "We thought we had to exactly translate the U.S. informed consent document, but now we know we don't." Because of Pfizer's vast research experience across the world it was able drawing on lessons from experiences in other countries where they had received similar feedback and fashion a new document that would better perform the function of the informed consent document – to ensure understanding, not simply obtain a signature.

As part of Pfizer's ongoing commitment to ensure trial participants are treated ethically and are positioned to give informed consent based on true comprehension of the study, a new, shorter consent form is in design to make the consent process more practicable and accessible to potential participants.

In this case, Pfizer has recognized the challenges of effectively engaging with a study population to ensure that they are well-positioned to convey meaningful consent. The firm is applying their long-standing tradition of innovation and solution-seeking to address issues that arise, and work closely with IRBs and local resources to effect positive change.

## Discussion Questions

1. How have past allegations of failing to obtain informed consent affected the current guidelines and standards set forth by ICH-GCP?
2. How might existing guidelines be altered to ensure key information is conveyed without overwhelming participants or inadvertently obfuscating trial information?
3. How will the shifting international preference toward shorter, more comprehensible consent forms impact the way consent is obtained in the U.S.?
4. What kinds of information about a trial are the most important to know about a study and should be discussed in informed consent?
5. Should "informed consent" be seen as a contract between the investigator and the patient?