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# Should Informed Consent Forms Have Black-Box Warnings?

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## Black-Box Warnings on Drug Labels

Drug labels include black-box warnings to ensure that prescribers are aware of very serious risks to their patients.

The FDA "Guidance for Industry: Warnings and Precautions, Contraindications and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format" states the following:

> A boxed warning is ordinarily used to highlight for prescribers one of the following situations:
>
> > There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug
> >
> > ***OR***
> >
> > There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug, or managing patient in a specific manner, avoiding use in a specific clinical situation)
> >
> > ***OR***
> >
> > FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

Black-box warnings can also be useful for nurses, pharmacists, patients and caregivers.

## Black-Box Warnings on Informed Consent Forms

The investigator's brochure is the equivalent of a drug label for a clinical investigator. The informed consent form is the equivalent of a drug label for a potential study participant. If black-box warnings are necessary for some drug labels, why aren't they necessary for some investigator's brochures and informed consent forms?

Informed consent forms are notorious for their inability to communicate information to potential study participants. In theory, the informed consent discussion addresses the gaps, but successful communication and correct emphasis are far from guaranteed.

Potential study participants might not notice an important piece of information in the avalanche of words we call informed consent. If an important piece of information is presented at the beginning of the consent process, the patient might forget it by the end; if it is presented in the middle of the process, the patient might have lost focus by then; if it is presented at the end, the patient's cognitive facilities might already be overloaded.

The person obtaining consent might not duly emphasize the importance of a particular piece of information. He or she might not consider that piece of information supremely important, might consider the point self-evident, might not want to overstress the point to the detriment of other points, or might not want to discourage the patient from participating in the study.

If an IRB believes that potential study participants must understand a particular piece of information, it could require that it be presented as a black-box warning, with its own place for the patient's initials. In this way, the information will not get buried in the avalanche.

The following information might qualify for block-box warnings:

- This is a high-risk study for the following reasons…
- This is a new drug with a mechanism of action that has never been tested on humans.
- This study will likely cause you significant pain and discomfort.
- Given the risks, other treatment options should be seriously considered.
- While you are in this study, you will not be able to take other treatments for your condition.
- If you participate in this study, you might be foreclosed from other treatments later.
- This study might reveal genetic information about you or your relatives that you or they might not want to know.

When an IRB reviews a clinical research study, it should consider whether any points of information merit black-box warnings in the informed consent form. An IRB that mostly reviews oncology studies will likely have a different perspective on this question than an IRB that mostly reviews sociobehavioral research. IRBs must use their own judgment, but some consistency across studies should emerge over time.

The severity of black-box warnings on drug labels vary. A block-box warning of a severe risk can have very negative consequences for a drug's prospects. The content of the warning(s) in a black box on an informed consent form should, accordingly, generate the appropriate level of caution to patients considering the study.

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