

# Requirements for Ethical Human Research

- **A valid and important question**
- **Valid methodology**
- **Balance between risks/benefits**
- **Independent ethical review**
- **Informed consent**

*Thanks to Zeke Emanuel*

# Requirements for Ethical Human Research

- **Informed consent**

# **Informed consent is very important, because...**

- **It is the principal manifestation of the ethical principle of autonomy (respect for persons)...  
... and of the political principle of liberty.**
- **People simply have a right to a say in what is going to be done to them.**



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## **Beecher (1966):**

**... Consent in any fully informed sense may not be obtainable. Nevertheless, except, possibly, in the most trivial situations, it remains a goal toward which one must strive for sociologic, ethical and clear-cut legal reasons. There is no choice in the matter.**

**In order to be that ultimate arbiter of the  
risk/benefit balance...**

**...the subject or surrogate has to understand:**

- What's going to happen ...
- How that's different from what would happen outside of the study ...
- What risks the study brings to the table ...
- What benefits there might be to being in the study ...
- That participation is voluntary ...

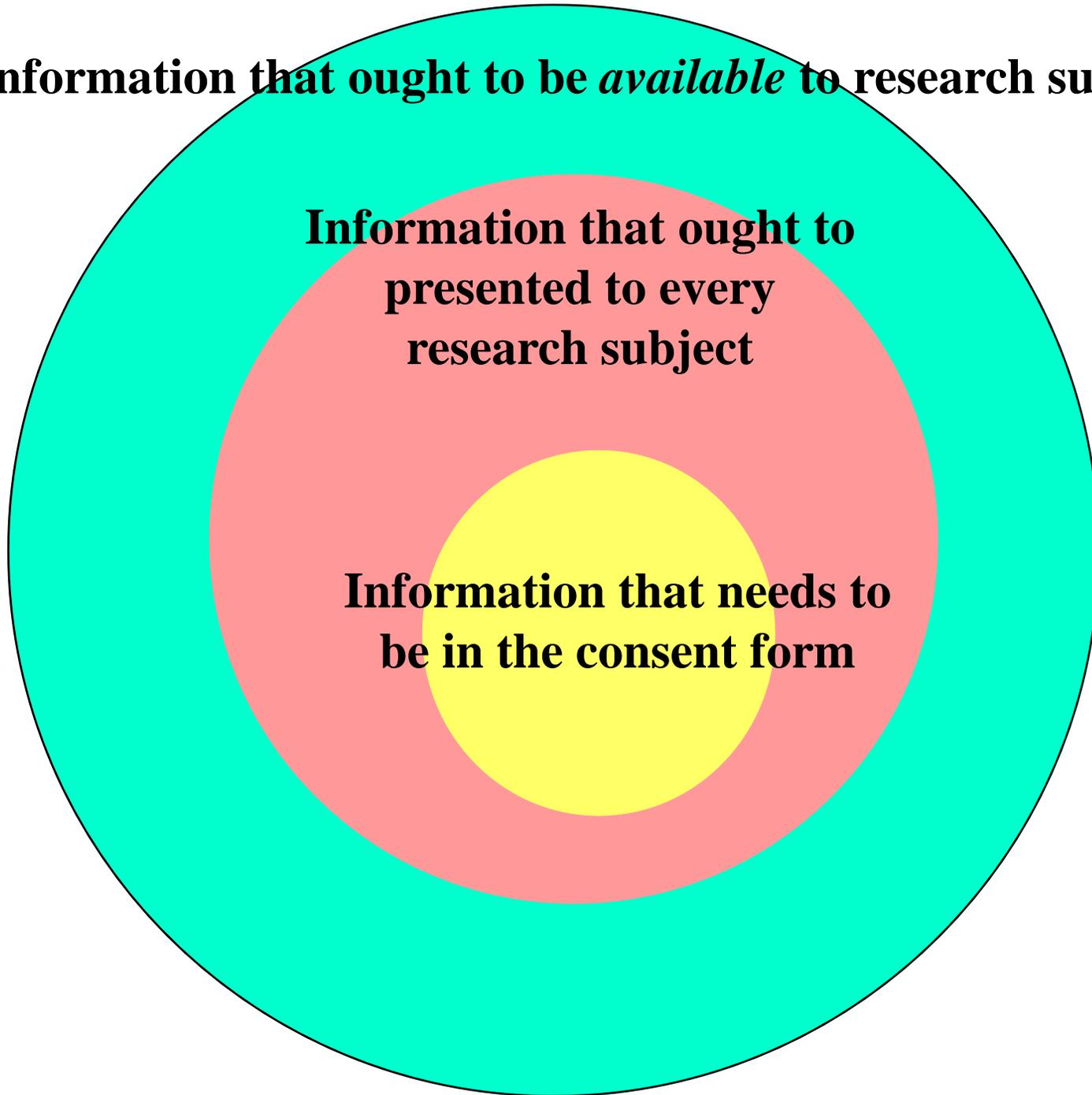
# **That hoped-for understanding may be impeded by many things:**

- **Complexity of information ...**
- **Complexity of presentation of information ...**
- **Dilution of important concepts in a well-intentioned sea of detail ...**
- **Conflating therapy and research ...**
- **Therapeutic misconception or desperate hope ...**
- **Unregulated information (such as websites, news stories, advocacy groups) ...**
- **Confusing consent *forms* with consent ...**

**Information that ought to be *available* to research subjects**

**Information that ought to  
presented to every  
research subject**

**Information that needs to  
be in the consent form**



# **Risk is an actuarial construct**

*It has several major components...*

**You don't really understand the risk under consideration if you don't have a sense of each of these components ...**

**If you don't understand the risk, you cannot assess the risk/benefit balance ...**

**If you cannot assess the risk/benefit balance, you cannot give informed consent**



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## **What do the regs say<sub>a</sub> bout describing<sub>r</sub> risks?**

*45 CFR §46.116 ≡ 21 CFR §50.25*

**(a) Basic elements of informed consent...**

**(2) a description of any reasonably foreseeable risks or discomforts to the subject**

**You have to go to guidance documents and educational materials to find that information about probability and likely severity are deemed important as part of “a description”**

# How about the RAC/NIH Guidelines?

## *Appendix M-III-B-1-e: Possible Risks, Discomforts and Side Effects*

There should be clear itemization in the Informed Consent document of the types of adverse experiences, their relative severity, and **their expected frequencies ...**

The Informed Consent document should provide information regarding the **approximate number of people who have previously received the genetic material under study ... warn ... that unforeseen risks are possible ...could be severe.**

# So what can we do??

**We want to do the right thing for the  
subjects/patients enrolled in these trials ...**

**Because the trials look promising, we want them to  
go forward ...**

**We're called to a high standard of risk description,  
both ethically and by RAC guidelines ...**

**We don't have enough information to meet that  
standard easily ...**

**We don't want a lot of cat-fights involving IRBs,  
local investigators, RAC and passersby ...**

*It's ~~OK to admit that we don't know all the answers ...~~  
~~OK to admit that we don't~~*

# Utility Pre-Test:

*Both asked how the consent process was improved by including (expletive deleted) details about terminology and possible mechanisms ...*

*(Michael had been reading a book about Watergate)*

*At least I had  $n = \underline{2}$  !!*

*I gave 'em each the “straw-man” language ...*

*They both found it tough going...*

# Dr. Dale's Bias

- Give the subjects/surrogates as much detail as they want and can understand;
- Give all subjects/surrogates fairly complete background information as part of the consent *process*;
- Keep the *required* story in the consent *form* short and to the point;
- Don't micromanage how the local IRBs present this; set minima rather than insist on specific wordings

# What's the Minimum?

- **A subject/patient in this study has developed leukemia and has required treatment;**
- **We think that the gene transfer made the leukemia more likely to happen;**
- **It's too early in the study to know if this will be a rare event or a common one;**
- **It's too early to know how well the child with leukemia will do;**
- **Enough children in the study have had improved immune function that we think it is still appropriate to continue the study.**

# And of course ...

- **If the monitoring is changed in a way that has an impact on the frequency of visits, blood draws, *etc.*, that has to be disclosed;**
- **If the follow-up is to continue until the kids have reached majority, the transition from parental permission to subject consent should be planned for;**
- **If data/sample archiving is done in a way that adds to confidentiality risk, that may also require consent/disclosure**

# For whom?

- **This information belongs in the CF and process for new enrollees in the trial(s) of retroviral gene transfer for X-SCID;**
- **This information belongs in a verified informational update for current enrollees in the trial(s) of retroviral gene transfer for X-SCID;**
- **With appropriate modifications, it should go in CFs and info updates for new and current enrollees in other trials of retroviral gene transfer;**
- **For some studies/diseases, it may not be as clear that the risk/benefit balance remains favorable.**

