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.

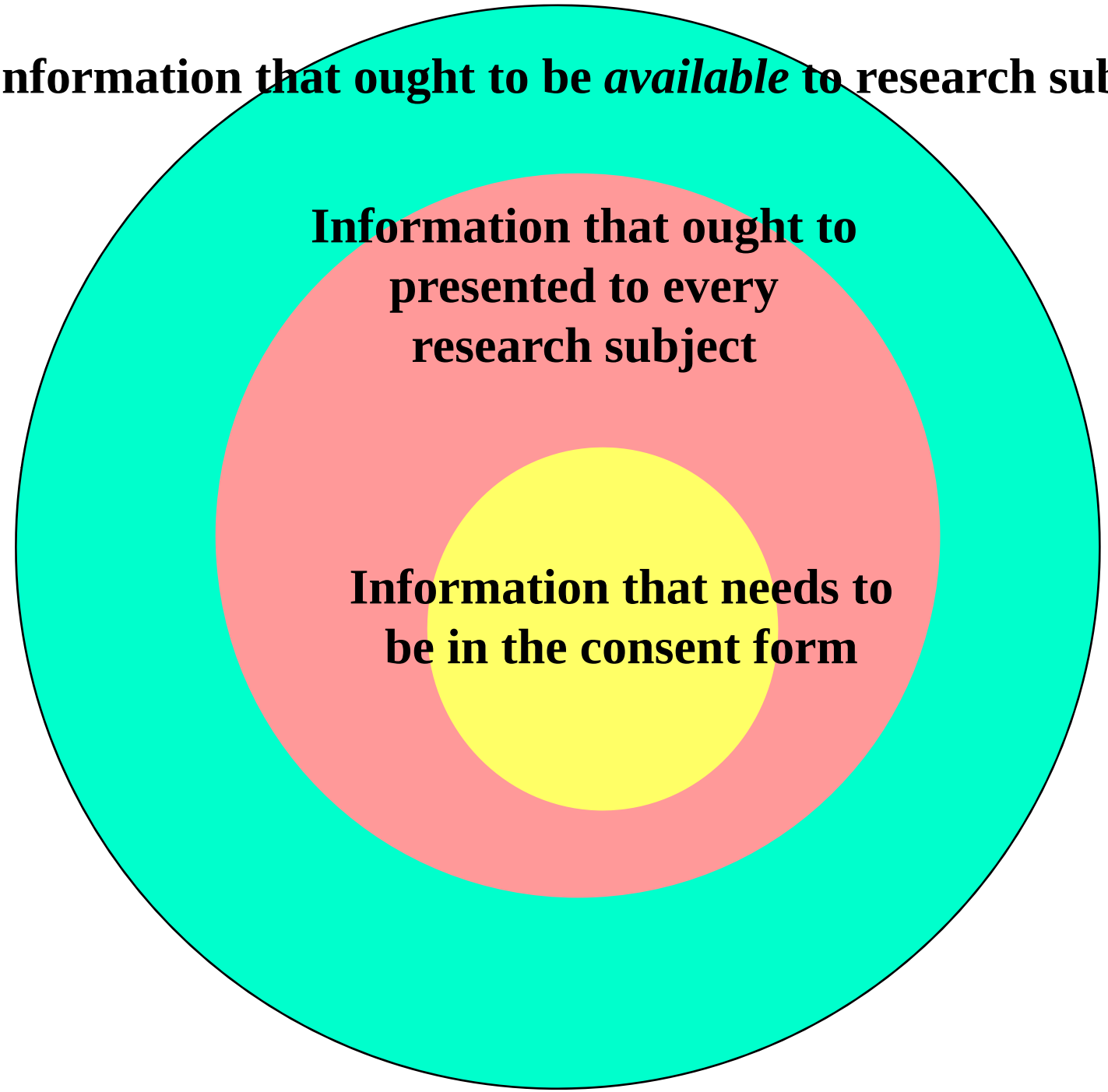
In order to be that ultimate arbiter of the risk/benefit balance…

…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 about describing 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 …

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 = 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?

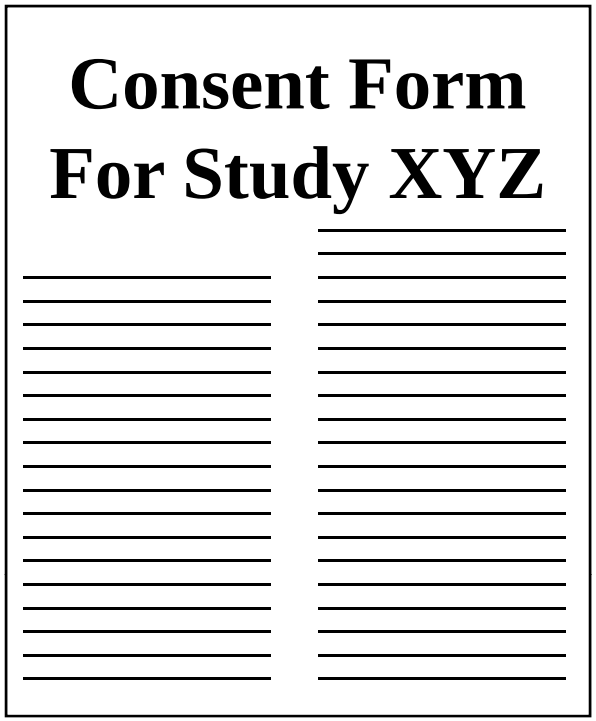
- **A subject/patient in this study has developed leukemia and has required treatment;**
- **We think that the gene transfer made the leukemia more likely to happen;**
- **It's too early in the study to know if this will be a rare event or a common one;**
- **It's too early to know how well the child 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.**



If we present the information in the consent form in simple terms …

… and if we make fuller background information available to anyone who wants it …

… and if we admit that we're trying to do our best in the face of a potload of uncertainty and ambiguity …

Maybe the "fairy tale" of informed consent will be just a little one (with a happy ending)!

1968: David Camp