FDA's Clinical Investigator Course

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A *Grimm* Reality

The Fairy Tale of Informed Consent

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The Over-Arching Consideration:

Informed consent won't fix the problem (and won't be truly informed) if the research is not well designed, well conducted, free from problematic bias and honestly reported.

The Responsible Conduct of Research

- **Rules are helpful reminders, statements of standards, and norms against which performance may be evaluated…**
- **… but what really matters is the integrity of the enterprise, in turn depending on the integrity of the people doing the research**

If you like "Text Bites":

- **Don’t get so focused on *compliance* that you forget about the ethical imperative**

A favorite quote:

“The first step in the evolution of of ethics is a sense of solidarity with other human beings.”

Albert Schweitzer

“Individual ethical behavior is likelier to flourish within a just society. So in order to lead an ethical life one should work for a just society. That is, if most of us will behave about as well as our neighbors, it is incumbent on us to create a decent neighborhood.”

-Randy Cohen

If Research Conduct is to be Responsible:

- Human Research Protections
- Research Protections for Animals
- Research Misconduct
- Conflict of Interest and Commitment
- Mentor/trainee Relationships
- Responsible Authorship
- Peer Review (An interest of mine)
- Data Management, Sharing and Ownership
- Collaborative Science

Pithy summary ---

"For a scientist, integrity embodies above all the individual's commitment to intellectual honesty and personal responsibility … For an institution, [integrity] is a commitment to creating an environment that promotes responsible conduct by embracing standards of excellence, trustworthiness, and lawfulness…"

-Integrity in Scientific Research

The National Academy of Sciences


Brüder Grimm
Kinder-Märchen.
Loewes Verlag Ferdinand Carl
Stuttgart.
No 318.

Opening Anecdote #1

- **Patient with newly-diagnosed CML; was wife of a family physician**
- **Heard about a new tyrosine kinase inhibitor with activity against CML**
- **Got web-based information from *the manufacturer*, from *the Wall Street Journal*, from patient chat groups, from investor advisory sites**

Opening Anecdote #1

- Decided she wanted the new drug
- Declined to enter into consent dialogue, claiming that she'd already gone through the difficult decision-making and didn't want to hear about any "alleged" reasons she might want to reconsider/reconfirm
- I found it difficult in conscience to enter her into the study

Opening Anecdote #2

- Patient with longstanding CML; getting harder to control on IFNα and hydroxyurea
- Heard about a new tyrosine kinase inhibitor with activity against CML
- Got web-based information from the manufacturer, from the Wall Street Journal, from patient chat groups, from investor advisory sites

Opening Anecdote #2

- Decided she wanted the new drug;
- Wanted to ask about reliability of the information she'd found; especially concerned that there might be a hidden "down-side";
- Her homework allowed us to have one of the best consent discussions I've ever had with a patient/prospective subject

Themes:

- 1) We're kidding ourselves if we think we have control over the information that is presented to a prospective subject
- 2) Information comes in a context and is delivered with a set of biases
- 3) Information — even if reliable — may distract or mislead rather than help a decision
- 4) Sometimes there's more chaff than wheat
- 5) It's hard to make complex information intelligible to a diverse audience

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

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.**

Early Rumblings:

William Beaumont (1833):

- Important question
- Information not otherwise available
- Consent (including right to withdraw)

Early Rumblings:

Berlin Code (1900):

- Prussian government demanded free and informed consent for medical procedures with intent other than diagnosis, treatment or immunization;
- Need for supervision.

Early Rumblings:

Walter Reed (1900):

- **Investigators as co-subjects in dangerous research;**
- **Written statement of risks and benefits and consequences of withdrawal**

Not-so-Early Rumblings:

Reichsgesundheitsrat Circular (1931):

- **Risk/benefit balance;**
- **Informed consent;**
- **Concern for minors, exploitation;**
- **Supervision;**
- **Respect for dignity and privacy**

These are the rules in effect during the Nazi era...

Nuremberg Code, 1947

***Ten points** (including):*

- **Informed Consent**
- **Need for Scientific Merit**
- **Right to Withdraw**
- **Risk/Benefit Balance**

- **Subsequent codes have allowed that consent may be waived when the research risk is vanishingly small …**
- **… and surrogate consent of one form or another may be allowable when the research activity is of direct benefit and the subject cannot give consent …**
- **… but for most circumstances, the ethical and regulatory norm remains that of getting the free, uncoerced, informed consent of a prospective subject before that person experiences any research-related risk.**

Pithy summary statement:

- Research participation is a gift and contribution by the subject.

- The invitation to participate in research must be extended so that the rights to be secure in one's person and body remain sacrosanct.

Jay Katz, 1994

Thanks to Steve Miles for this one

- **Informed consent is actually an elusive goal, which one tries to approximate but doesn’t always achieve;**
- **People seeking consent often are less than zealous and/or less than skilled in pursuit of the goal.**

The Process of Informed Consent

Three components/stages

- **Threshold**
  - **Ability to give consent**
  - **Circumstance requiring consent**
- **Information**
  - **What the subject needs to know**
- **Agreement**

Thanks to Jeremy Sugarman & Ruth Faden

The Process of Informed Consent

Threshold issues:

- **Incompetence to give consent**
- **Contextual incompetence to give consent**
  - **Nature of risk exotic, hard to understand**
  - **Context diverts attention (new diagnosis)**
  - **Too sick to think straight**

The Process of Informed Consent

Informational issues:

- **Informant knowledgeable about study?**
- **Informant skilled at layspeak?**
- **Informant knowledgeable about consent?**
- **Supporting information in language understood by subject**

The Process of Informed Consent

Informational issues:

- **Supportive information free of indirect messages?**
- **Presentation of information in a context that encourages questions?**
- **Dialogue structured such that understanding is tested?**

The Process of Informed Consent

Informational issues:

- **Information from unscrutinized sources?**
  - **Internet**
  - **Investment information**
- **Decision made before scrutinized process begun?**
  - ***Vide supra***
  - **Specifically referred for a study**

The Process of Informed Consent

Informational issues:

- **Is agreement given freely?**
- **Has half-hearted assent been accepted?**
- **Has lack of *dis*sent been accepted?**
- **Has context been coercive?**
- **Has a signature on a piece of paper been overvalued?**

Tired but True:

Informed consent is a process and is a goal one strives to achieve;

Informed consent is NOT a piece of paper.

(Nor is it a contract)

(Nor is it a quantum event at a single point in time)

Although the form is not the process...

… it is unfortunately common that consent for clinical studies is sought by trainees (sometimes at odd hours) …

… the trainees may not know the study well and may not be skilled in obtaining consent …

… so the consent form plays a bigger role than it ought to.

It is therefore important that the consent form be a good, complete and easily-understood document ... … it is unfortunately common that such is not the case.

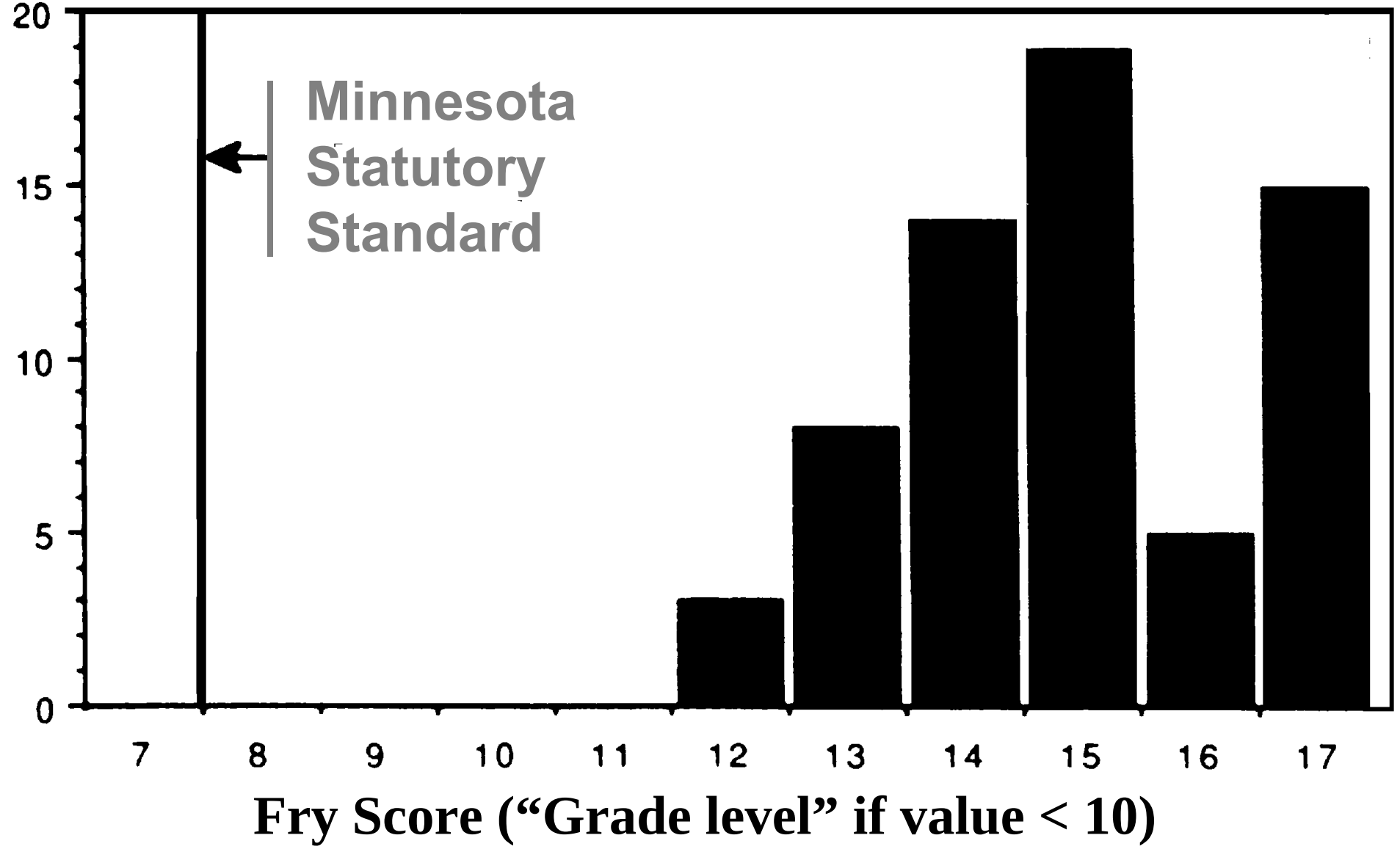
Major problems with CFs

- **In therapeutic trials, one CF is often asked to be both study CF and treatment CF: rôles get muddled**
- **CFs are written by and screened by highly educated people, often with "help" from lawyers: they may be impenetrable to laypeople**

We did a CF readability study at Minnesota

- **Random sample scored prospectively; corrected for a typicality of CF prose**
- **Scored before and after IRB review — which almost always asked for readability improvements**
- **Compared intramural/extramural; social/medical**
- **Compared with other med. info sources**

All CFs Failed Minnesota Readability Standard

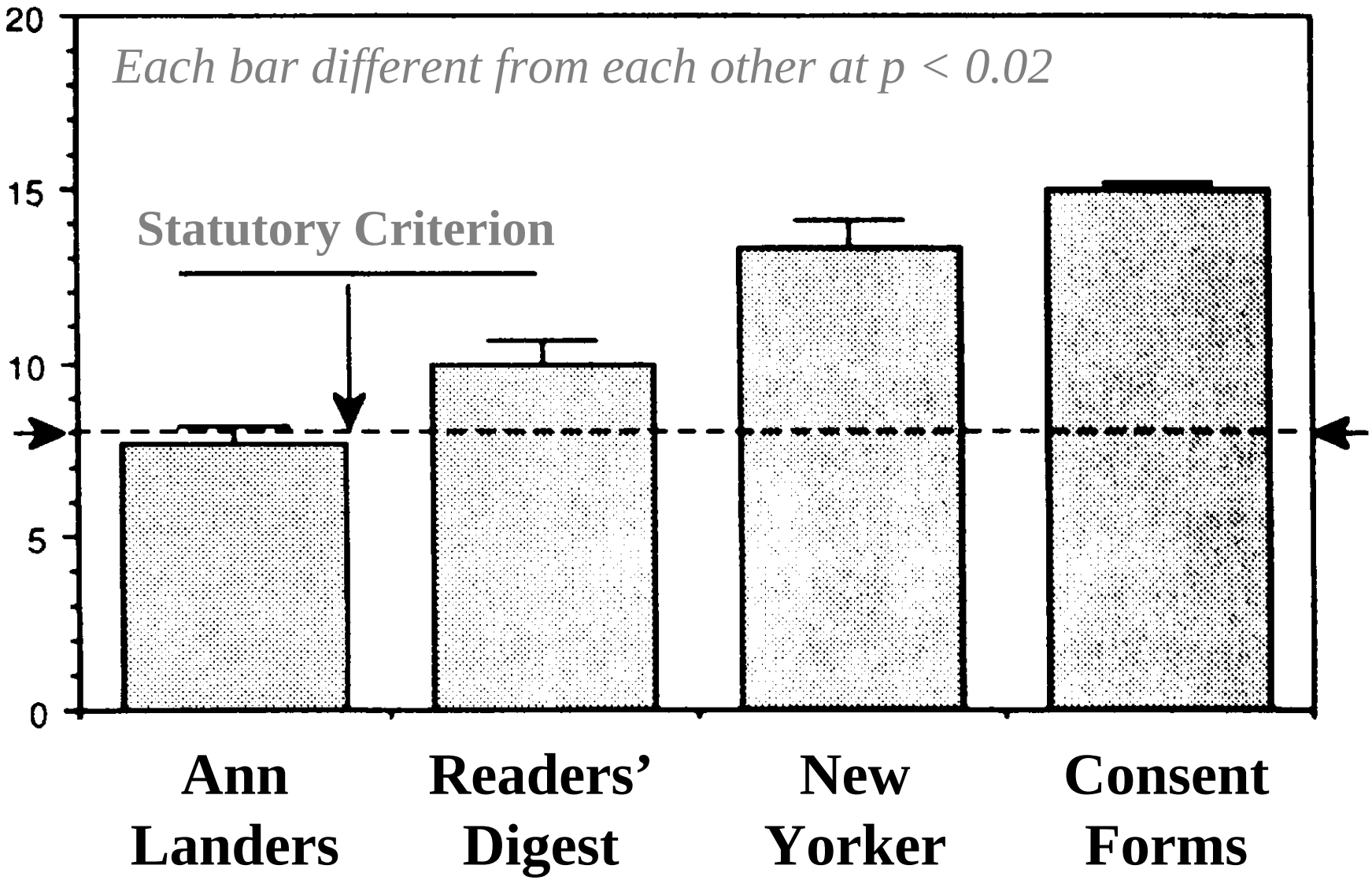


Comparisons:

- **IRB review: No significant change; rarely more than one "grade level" improvement**

IRB review probably improves clarity for the fully fluent, educated reader, but does little to make the documents more accessible to those of limited reading skill

That Doesn't Mean the Task is Impossible…



The most important thing about CFs

A consent form is an important aid, documentation and information source for obtaining informed consent

But it is NO substitute for a genuine consent *dialogue*, with someone who is knowledgeable about the study, knowledgeable about informed consent, and skilled at layspeak

The Process of Informed Consent

Another informational issue:

- **Language commonly used in consent forms and consent discussions may be understood differently by laypeople.**

- **Information may therefore be "understood," but not in a way that helps make consent effective.**

Advisory Committee on Human Radiation Experiments

- **Asked people if they had been subjects in research, then examined records.**
- **Depending on specifics, 8-15% of people had it wrong.**
- **Glass half full or half empty?**

Advisory Committee on Human Radiation Experiments

- **Asked people to respond to several different terms for research participation:**

Clinical Trial

Medical Study

Clinical Research

Clinical Investigation

Medical Experiment

Laypeople didn't see these as approximate synonyms

"Medical Experiment"

- **Evoked greater sense of risk and lesser sense of opportunity for clinical benefit.**

Laypeople didn't see these as approximate synonyms

"Clinical Research"

- **Sense of risk and benefit varied a great deal according to which of the other terms it was being compared to.**

Laypeople didn't see these as approximate synonyms

"Clinical Study"

- **Was seen as pretty innocuous.**

Laypeople didn't see these as approximate synonyms

"Clinical Trial" *and*
"Clinical Investigation"

- **Evoked mystery.**

Beecher (1966):

- All so-called codes are based on the bland assumption that meaningful or informed consent is readily available for the asking. As pointed out elsewhere, this is very often not the case. 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.

Beecher:

If suitably approached, patients will accede, on the basis of trust, to about any request their physician may make. At the same time, every experienced clinician investigator knows that patients will often submit to inconvenience and some discomfort, if they do not last very long, but the usual patient will never agree to jeopardize seriously his health or his life for the sake of “science.”

Beecher:

- **“In any precise sense statements regarding consent are meaningless unless one knows how fully the patient was informed of all risks... A far more dependable safeguard than consent is the presence of a truly responsible investigator.”**

That truly responsible investigator will:

- **Design experiments that minimize risk;**
- **Make sure that the information is available for the subject to make a sound decision about participation;**
- **Make sure that information is presented in a way that maximizes understanding;**

That truly responsible investigator will:

- **Make sure that the information is presented in genuine dialogue, both testing understanding and affording opportunities for questions;**

- **If possible, give the subject time for reflection and consultation before a decision is required;**

That truly responsible investigator will:

- **Make sure that the decision, when it is made, is made under the least coercive conditions that can be arranged;**

- **Make sure that the decision will be honored, even if contrary to the investigator's wishes;**

That truly responsible investigator will:

Perhaps most important of all --

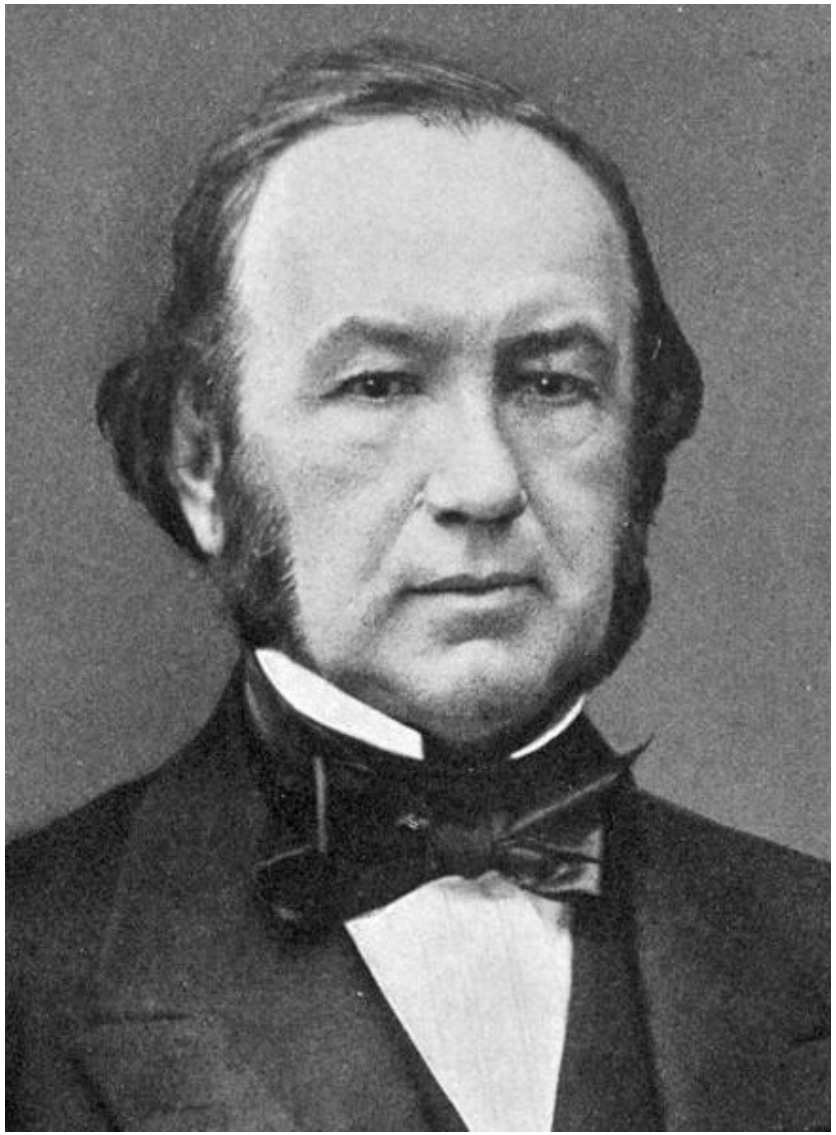
- **Continue the consent dialogue for the duration of study participation, so that:**
  - **new questions are addressed;**
  - **new information is shared;**
  - **continued presence of consent is assured;**
  - **opportunity to withdraw is genuine**

That truly responsible investigator will *also*:

- **Conduct the research in a responsible manner, so that the consent granted by the subject is given in support of research that is both ethically and scientifically sound.**

Epilogue: The academic emphasis on RCR may be recent, but the concept is hardly new …

Fairy tales can have happy endings, after all!!!



Claude Bernard

Paris, 1865

- **Commitment to a desired research result poisons the product**
- **Pride and ambition are just as bad as commercial prospect**
- **Keeping your data secret guarantees that they will be held suspect; deprives you of insights from others**
- **The researcher owes a duty of protection to the subjects (he called them “patients”)**
- **“Bad” experiments often aren’t; rules for data handling must be prospective**
- **It’s easier to be critical of research that challenges your own beliefs**