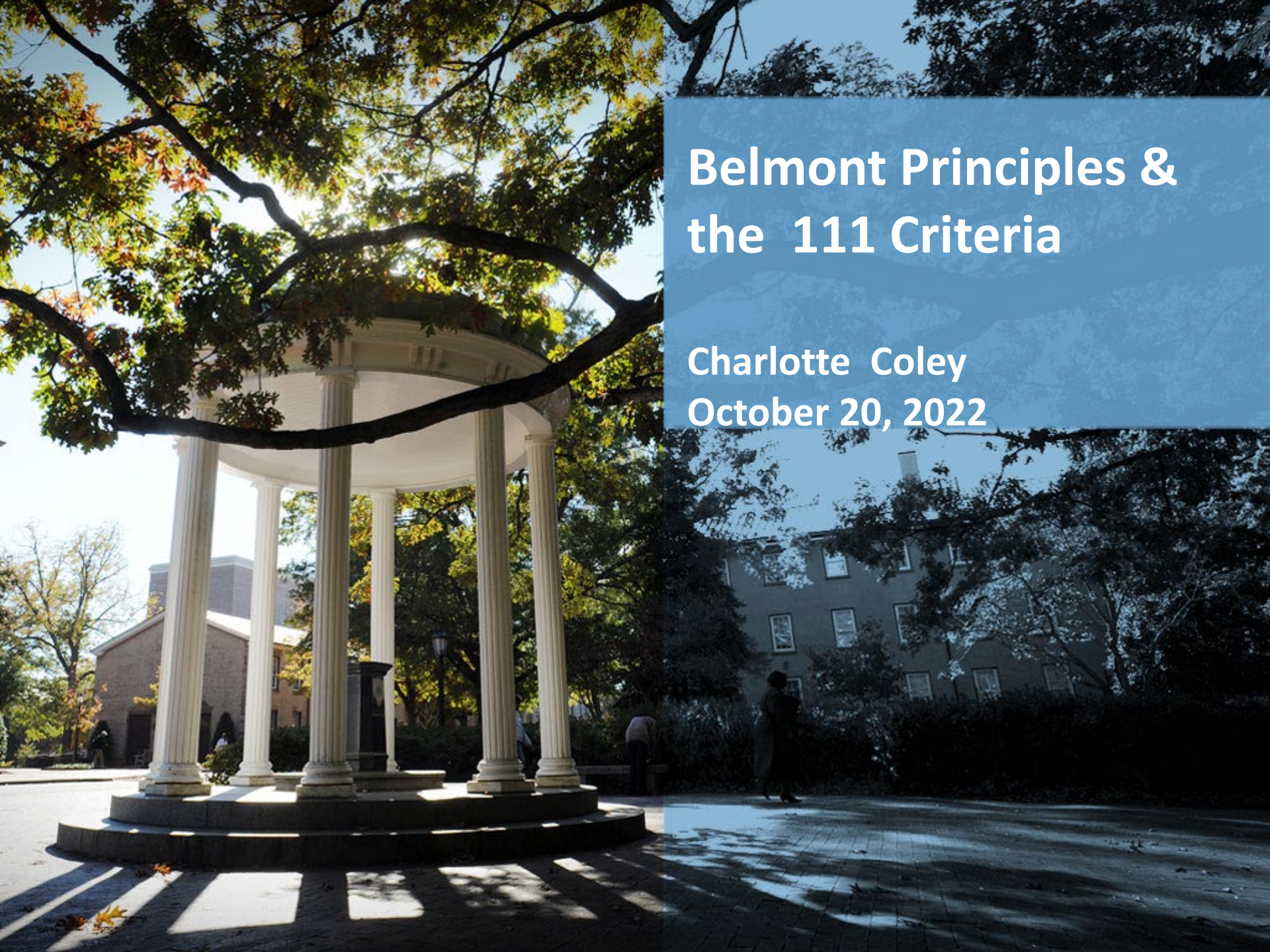

Belmont Principles & the 111 Criteria

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The IRBs **ONLY** Job is….

To protect research subjects & minimize study risks.

And is based on the honor system

IRB Regulations: Risk:Benefit a constant theme

RISK

Benefit

Minimal Risk

- *45 CFR 46.102(i)* defines minimal risk as: "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves *than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."*

- ***The IRB makes the determination of risk level.***

- Minimal risk studies may qualify for exemption or expedited review.

Risk:Benefit

Risk: *not just physical risks*

- **criminal** or
- **civil liability** or
- **financial standing**,
- **employability**, or
- **reputation**

Benefit

- NOT any reimbursement or renumeration
- Direct Benefit
- Benefit to advancement of science

Belmont Principles & 111 Criteria

- Respect for Persons
  - Risks are minimized
  - Favorable risk:benefit ratio
  - Informed consent is sought
  - Informed consent is documented
  - Privacy & confidentiality protected
  - Additional safeguards for vulnerable populations
- Beneficence
  - Monitoring plan for safety
  - Additional safeguards for vulnerable populations
- Justice
  - Equitable selection of subjects
  - Additional safeguards for vulnerable populations

Belmont 1st Principle:

Respect for Persons

- Risks minimized
- Favorable risk : benefit ratio
- Informed consent sought
- Informed consent documented
- Privacy & confidentiality protected
- Add'l safeguards for vulnerable populations

First things first: Is this a well-designed study that will be able to answer the research question?

1. Is there evidence of through preparation?
2. Is this the best design for this study & population?
3. Does the design allow for the most diverse cohort?
4. Does the consent ***really*** inform?
   - Any coercion, renumeration appropriate, too much jargon, too long, ….

For Example…

- Relabeling of Ambient to include dosage for women.
- Dangerous heart issues & Vioxx resulting in withdrawal of the drug.
- John Hopkins Asthma trial: wrong administration of study drug resulted in healthy subject death.

Criteria 2: Favorable Risk:Benefit Ratio

(Most challenging of the list!)

Risk for sick & healthy children? Well Child standard.

Which Vulnerable Group?

Why?

Really??

CAPA: Y/N?

Cat 9?

SAE?

Benefits? What? To Whom?

How many parental signatures?

§46.111 & §56.111 (2)

Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In evaluating risks and benefits, the IRB should consider **only those risks and benefits that may result from the research** (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

The ***IRB should not consider*** possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Informed Consent sought & documented

- #1 it is an On-Going Process NOT an event or 1-time action
- "in language understandable to the subject": Foreign Language Consents, Braille, Illiterate subjects
- Emergency Care Research & Emergency Research
- HIPAA & Research
- Competency: temporary, permanent, on a continuum
- Legally Authorized Representatives
- Special Requirements for Vulnerable Populations

When the Consent Process Doesn't Work…..

- Tuskegee Experiment
- Havasupai Tribe
- SUPPORT, PROMISE, CHEER Studies, titles confused subjects

45 CFR 46.111(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- **Privacy:** ***Individual private information***
  - "the state or condition of being free from being observed or disturbed by other people.
  - the state of being free from public attention. "(Google search)

- **Confidentiality:** ***protection of private data***
  - "the state of keeping or being kept secret or private." (Google search)

Privacy & Confidentiality Protections

- **UNC SOP 1901: Information Security--*Provisions for Data Security must be described in applications to the IRB and updated as necessary.***

- **UNC SOP 2601: Certificate of Confidentiality(CoC)--**Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have ***adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.*** ***(remember OHRPs definition of minimal risk)***

- NIH research meeting the following criteria is now covered automatically by a COC:

- Funded by NIH, in whole or in part, **and** Commenced or ongoing on or after December 13, 2016,

- The 21st Century Cures Act, requires all federally funded research in which **identifiable, sensitive information is collected or used to be issued a Certificate.**

Examples of Sensitive Data

1. Research on HIV, AIDS, and STDs;
2. Information about sexual attitudes, preferences, practices;
3. Information about personal use of alcohol, drugs, or other addictive products;
4. Information about illegal conduct;
5. Information that could damage an individual's financial standing, employability, or reputation within the community; ***(remember OHRPs definition of minimal risk)***
6. Information in a subject's medical record that could lead to social stigmatization or discrimination; or
7. Information about a subject's psychological well-being or mental health.
8. Genetic studies, including those that collect and store biological samples for future use;
9. Research on behavioral interventions and epidemiologic studies.

Belmont 2nd Principle:

Beneficence

- *Risks Minimized (again, sense a theme?)*
- *Favorable risk:benefit ratio (again, sense a theme?)*
- *Monitoring plan for safety*
- *Safeguards for vulnerable populations*

Belmont & Safety Plan (Beneficence)

45 CFR 46.111(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

How to Monitor & Who Does It ?

Safety Plan should match the risks posed.

Range of options

- Data Monitor--independent reviewer
- Data Monitoring Committee
- Chartered Data Safety Monitoring Board

[***NOTE:*** NIH funded trials require a Data & Safety Monitoring Plan & some a DSMB]

THE BUCK STOPS WITH THE IRB!

The IRB's mandate is the protection of the research subject,

- Minimizing research risks
- Ensuring the subject or their LAR are fully informed & consent to join the study.
- **ONLY** then can the IRB approve a study to include human subjects in a study.

Belmont 3rd Principle

Justice

- *Equitable selection of subjects*

- *Safeguards for vulnerable populations*

§46.111 & §56.111 (3) "Selection of Subjects is Equitable"

- IRB responsibility
  - Purpose of research
  - Research setting
  - Does it include subjects vulnerable to coercion or undue influence?
  - And could the research be done without including the vulnerable population?
    - Children
    - Prisoners
    - Impaired decision-making capacity
    - Economically or educationally disadvantages

Factors to consider

- Sex of animals & people
- Ethnic Groups
- Genetic factors
- Age differences
- What is the target population for this drug/device?

Considerations for the IRB

- Appropriate balance of male & female subjects
- Provisions for consent in other languages & staff with those same abilities to answer questions
- Will minors be enrolled? Appropriate?
- Recruitment strategy appropriate & through?

Consequences of Lack of Subject Diversity

- Limited knowledge of who the results apply to
- No knowledge of potential SAEs
- Waste of limited research resources
- Potential serious harm to patients

More Americans die from adverse effects of prescription drug medications than from illegal drugs.

- Source: **8 FDA Approved Drugs That Were Pulled From The Market - Drugsdb.com http://www.drugsdb.com/blog/fda-approved-drugs-pulled-from-market.html#ixzz6Wvlzoox8**

10 Recalled Drugs

1. Valdecoxib (Bextra)	2001 – 2005	4 Years
2. Pemoline (Cylert)	1975 – 2010	35 years
3. Bromfenac (Duract)	1997 – 1998	1 year
4. Levamisole (Ergamisol)	1989 – 2000	11 years
5. Rofecoxib (Vioxx)	1999 - 2004	5 years
6. Isotretinoin (Accutane)	1982 – 2009	27 years
7. Sibutramine (Meridia)	1997 – 2010	13 years
8. Terfenadine (Seldane)	1985 – 1998	13 years
9. Troglitazone (Rezulin)	1997 – 2000	3 years
10.Efalizumab (Raptiva)	2003 – 2009	6 years

Post approval SAEs

- Heart attacks; heart valve issues; HBP & stroke
- Deaths
- Severe kidney damage
- Stomach & intestine tears
- Stevens-Johnson syndrome
- GI Bleeding,
- Liver damage & transplants
- Suicidal ideation

Consequences

- Unknown health needs,
- Unable to improve health of some populations
- Guinea Pig Complex,
- distrust of science
- Distrust of medicine
  - Avoiding care
  - Health Issues become more severe
  - Avoid immunizations

45 CFR 46.111(8)—Vulnerable Populations

b) When some or all of the subjects are likely to be *vulnerable to coercion or undue influence,*

such *as:*

children,

prisoners,

individuals with impaired decision-making capacity, or *economically or educationally disadvantaged persons*, (situational too)

additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Vulnerable Subjects -- Across Several of the 111 Criteria

- Valid Study Design: to include or not include, what are the risks?
- Subject Recruitment: easy or robust & diverse?
- Informed Consent: really informed?
- Safety Plan: does it match the risk level of the study?
- Validity of Results: will results be appropriate for all populations?
- Harms: Does this proposal results in harms to any cohort?

Why is this included as a criteria?

- What are the consequences of not including vulnerable populations?
  - Good: protected
  - Bad: excluded from benefits of research

Where are the scales

In either situation?

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OHRP Resources

- Regulations & Guidences on Consent
  - FAQs: https://www.hhs.gov/ohrp/regulations-and-policy/index.html
  - Consent: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/informed-consent/index.html
  - Vulnerable Populations: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/vulnerable-populations/index.html