CONDUCTING RESEARCH WITH HUMAN SUBJECTS

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- Respect for autonomy, informed consent
- Inducements
- Vulnerability, stigmatization, discrimination
- Minimizing risks, maximizing benefits
- Using secondary data, stored biological materials

Placebo brain surgery in Parkinson's (Freeman et al. NEJM 1999:341(13):988-92)

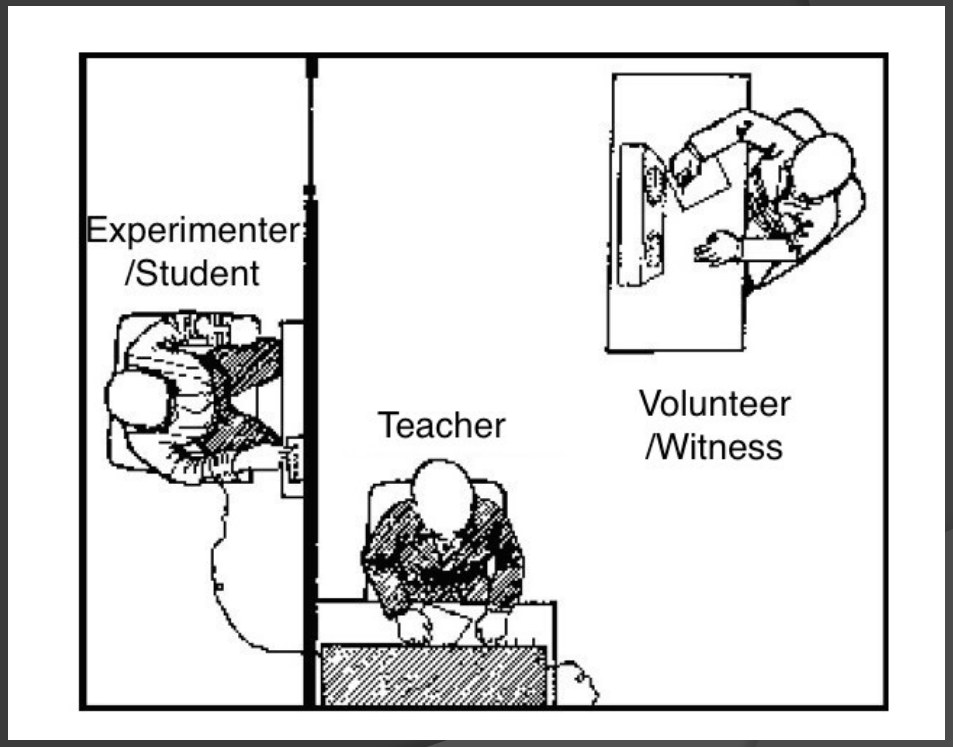
- Two surgical procedures separated by approximately one week
  - 12 bilateral transplantation of fetal substantia nigra 1 donor
  - 12 from 4 donors
  - 12 placebo
- Control group undergo two **placebo** surgical procedures equivalent experience for the subjects and their family members.
- **Placebo** procedure includes
  - placement of a stereotactic frame
  - target localization on magnetic resonance imaging
  - general anesthesia with a laryngeal mask
  - skin incision with a partial burr hole that does not penetrate the inner cortex of the skullL
- Low-dose cyclosporine for six months and continue to receive medical therapy.

Why research ethics?

- Research is an ethical obligation
- But… scandals: Tuskegee, research with prisoners etc.
- Basic issue: patients are vulnerable
  - Sick
  - Cannot make the difference between care or science
  - Dependency and pressure / seduction
- Conflict of duties >> ethics

Milgram (1963)

- Authority-following behaviour
- Presented as study of learning
- 1000 participants
- ‘Teacher’ – ‘learner’
- Separated rooms
- Error: electric shock 10 – 450 volts
- No real shocks were given



Beecher NEJM 1966

- 22 cases of unethical research from excellent journals:
  - Known effective treatment withheld (3x)
  - Hepatic side-effects tested in prisoners and juvenile delinquents
  - Effects of thymectomy in skin grafts, performed in children needing congenital heart disease surgery (3½ month-18yrs)
  - Conscious causing of severe side-effects for physiologic studies (7x)
  - Conscious causing of symptoms or disease (5x)
    - Ex: transplantation of melanoma to volunteering family member
  - Testing of new technologies (5x)
    - Ex: transbronchial heart catheterization in subjects with no heart disease

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Informed consent and autonomy

- When you ask a patient to articipate in research, you are asking a service from the patient >> we need to be humble
- Informed consent even more important than in care relation
- Give patient information on the level of education of the least educated patient
  - so NOT a 20-page document full of tables and medical language / jargon
  - simple language empowering the patient to make a decision

Informed and free consent

- Genuine choice
- No duress or inducement
- Comprehensible information about:
  - Equipoise
  - Risks and burdens
  - Realistic expectation of personal and general benefits

Problematic situations related to consent

- Incompetent patients
  - Children up to 18
  - Acutely ill
  - Permanent incompetence (Alzheimer's, intellectual disabilities)
  - Research with incompetent patients only acceptable if impossible with competent patients

Consent for incompetent patients

- Given by representative
  - Spouse
  - Parents
  - Children
  - Brothers/sisters
- Sometimes deferred consent in emergency situations

Problematic situations related to consent

- Realistic hopes?
  - ‘therapeutic misconception’: participants believe experimental arm is always better
  - Phase I oncology trials

Phase-I-study in oncology

- New chemotherapeutic drug Vorinostat (HDAC-blocker)
- Phase-I-study: safety, tolerability, pharmacokinetics
- Inclusion: patients with treatment refractory solid tumors or leukemia
- Negligible chance of benefit for patient
- Probable disadvantages: possible side-effects, risks (mainly haematological)

Phase-I-study in oncology

- New chemotherapeutic drug Vorinostat (HDAC-blocker)
- Phase-I-study: safety, tolerability, pharmacokinetics in children (1-22 yrs)
- Inclusion: patients with treatment refractory solid tumors or leukemia
- Negligible chance of benefit for patient
- Probable disadvantages: possible side-effects, risks (mainly haematological)

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Inducements and seducing

- Inducing: giving patient an extra reason to participate; seducing: persuade or attract someone to participate
- Can we offer patients money or other privileges to participate?

Inducements and seducing

- Inducing: something that gives you a reason to participate; seducing: persuade or attract someone to participate
- Can we offer patients money or other privileges to participate?
- Not above acceptable compensation for time loss and travel costs
- Should not be used to seduce people into participation
- Subtle inducement: ‘you will get better if you participate’

Moral obligation to participate?

- Harris, J Med Ethics. 2005 Apr;31(4):242-8. “Patients have a *prima facie* obligation to participate in scientific research”

Moral obligation to participate?

- Harris, J Med Ethics. 2005 Apr;31(4):242-8. “Patients have a *prima facie* obligation to participate in scientific research”
- 3 premises
  - Research is good
  - Obligation to help those in need (“rescue principle”)
  - If you refuse participation in research but you want to benefit from the participation of others, you are a free rider

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Vulnerable groups

- Children
- Cognitive impairments
  - Either inborn or acquired
- Some categories of psychiatric patients
- The very sick (for instance, after a heart attack)
- The terminally ill
- People in a dependent position (prisoners, soldiers, employees, poor people, children, etc etc….)

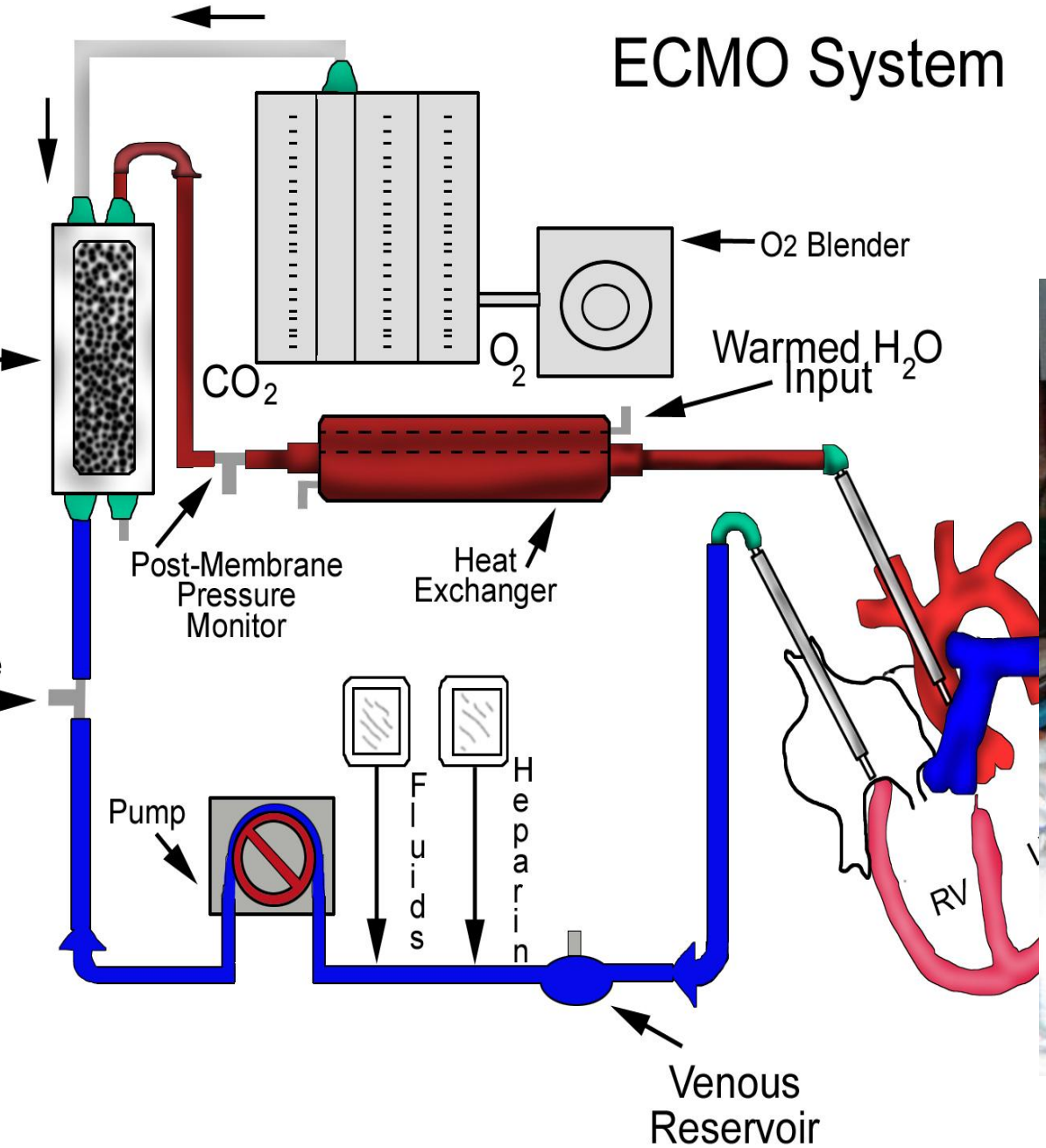
Declaration of Helsinki about vulnerable groups

- Should receive specifically considered protection
- Only justified if responsive to health needs of the group
- And if research cannot be carried out in a non-vulnerable group
- Should stand to benefit from the results

Resarch among the most vulnerable: premature infats

- ECMO in premature infants
- ExtraCorporeal Membrane Oxygenation
- ± 1990: Bradley, surgeon Boston starts using ECMO in premature infants <36wks with respiratory insufficiency

ECMO System


O2 Blender
O_2
CO_2
Warmed H_2O Input
Post-Membrane Pressure Monitor
Heat Exchanger
Pump
Fluids
Heparin
RV
Venous Reservoir

ECMO in premature infants

- ± 1990: Bradley, surgeon Boston starts using ECMO in premature infants <36wks with respiratory insufficiency
- Survival with ECMO in series of about 50: 90%
- Survival with normal ventilation ± 20%
- Is this sufficient evidence?

ECMO in premature infants

- Bradley performs trial in 10 children with ‘adaptive design’:
  - Child 1 randomised to ECMO or conventional ventilation
  - If child 1 survives: child 2 gets same treatment
  - If child 1 dies: child 2 two gets alternative
  - Etc, etc…

ECMO in premature infants

- Child 1 randomised to conventional treatment and died
- Following 9 got ECMO and survived
- Is this enough evidence?

ECMO in premature infants

- NIH: classic RCT necessary
- Researchers propose Zelen design:
- Informed consent only with experimental intervention *after* randomisation; control group no informed consent
- Acceptable?

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Minimization of risk and burden

- As little burden as possible
  - For instance, no special blood draw if a blood draw is already performed in care
  - Diminish the amount of blood drawn in vulnerable patients
- As little risk as possible
  - For instance, as little radiation risk as possible: guidelines for the acceptabel amount of radiation in mSievert

Maximization of benefits?

- Study participants should receive as much benefit from participaitng as possible >> ‘inclusion benefit’
  - Participation in research may be beneficial even for the control group
- May be tricky if benefit can be used as an inducement
  - For instance: study in cancer patients with a very short life expectancy (1-3 months) saying that the duration of the study is several years

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Using secondary data and stored material

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- Secondary data: only justified when approved by the patient and when annonymized
- Storage of material (biobanking)
  - Special attention for use in the same disease: material from GE-research can only be stored for future GE-research
  - Special attention for sharing agreements
    - Can material be sold to commercial parties?
    - Can it be shared with US researchers (less protection)?

Conclusion

- Ethics of research not delegated to IRB / REC, but responsibility of researcher
- Core ethical question: balance between benefit and risks/burdens
- Informed consent should really help patients choose
- No moral obligation to participate (as yet)

- Terimah kasih!!