International Research and Standards of Care

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Disclaimer

- The opinions expressed are my own and do not reflect the policies or positions of the NIH, USPHS, or DHHS

Short-course AZT trials

- Without treatment 15 - 30% of newborn children of HIV-positive mothers are HIV-positive
- 076 regimen reduces this by two-thirds
- Could not be implemented in many low- or middle-income countries
  - High cost
  - Lack of healthcare infrastructure

Short-course AZT trials

- Researchers wanted to develop a “short course” AZT regimen that could be implemented
- Expected to be worse than 076 regimen
- Comparison to 076 regimen was expected not to produce meaningful results

Ethical controversy

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Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries

Peter Lurie, M.D., M.P.H., and Sidney M. Wolfe, M.D.

N Engl J Med 1997; 337:853-856 | September 18, 1997 | DO

f double standards

Defense of short course AZT trials

- Active controlled trial not expected to produce meaningful results
- Urgent need for intervention:
  - 076 regimen could not be implemented
  - HIV prevalence very high in host countries

International research of concern

- Sponsored by high-income country institutions
- Carried out in low- and middle-income countries
  - Resource-limited settings
  - Vulnerable participants
  - Lack of access to good quality healthcare outside of clinical research

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vascular disease, it will be important to test drugs and devices on a global scale. However, among the ongoing phase 3 clinical trials that we examined that were sponsored by U.S.-based companies in developing countries, none were trials of diseases such as tuberculosis that disproportionately affect the populations of these countries. In contrast, we found a variety of trials in developing countries for conditions such as allergic rhinitis and overactive bladder. Developing countries will also not realize the benefits of trials if

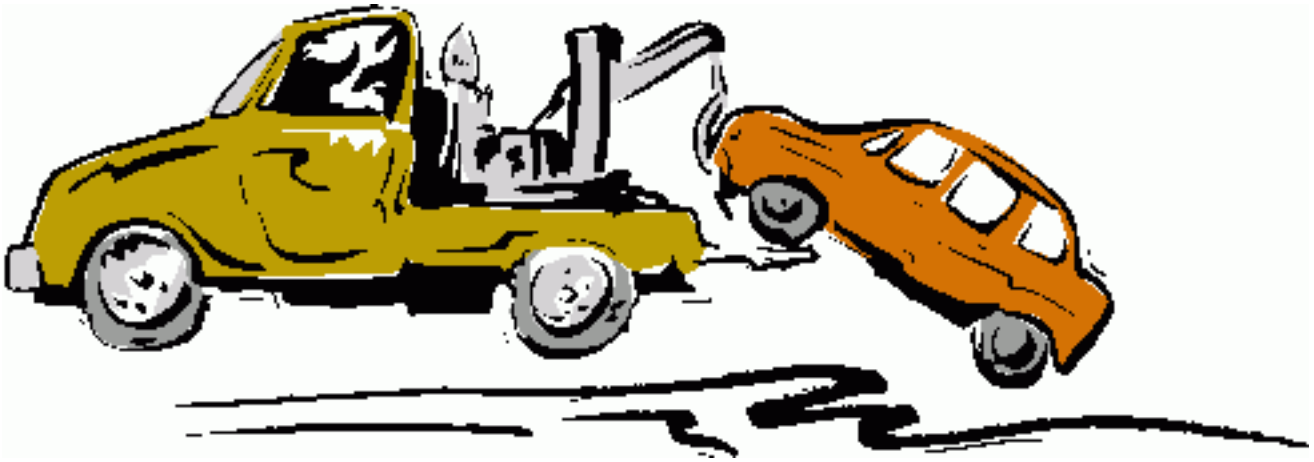
A (fictional) study

- Placebo-controlled trial of new anti-hypertensive
- Enrolling treatment-naïve patients diagnosed with hypertension in urban clinics in India
- Free physical examination, education, monitoring
- 50/50 randomization to experimental drug or placebo
- No plans to market drug in India

Exploitation

Exploitation

- A exploits B when A takes unfair advantage of B's situation



How to avoid exploitation

- Ensure that the distribution of benefits and burdens is fair

The standard of care debate

- Concerns what care should be provided in the different arms of a trial
- This determines what interventions the trial compares
- The interesting clinical question is usually whether an experimental intervention is better than the best proven intervention

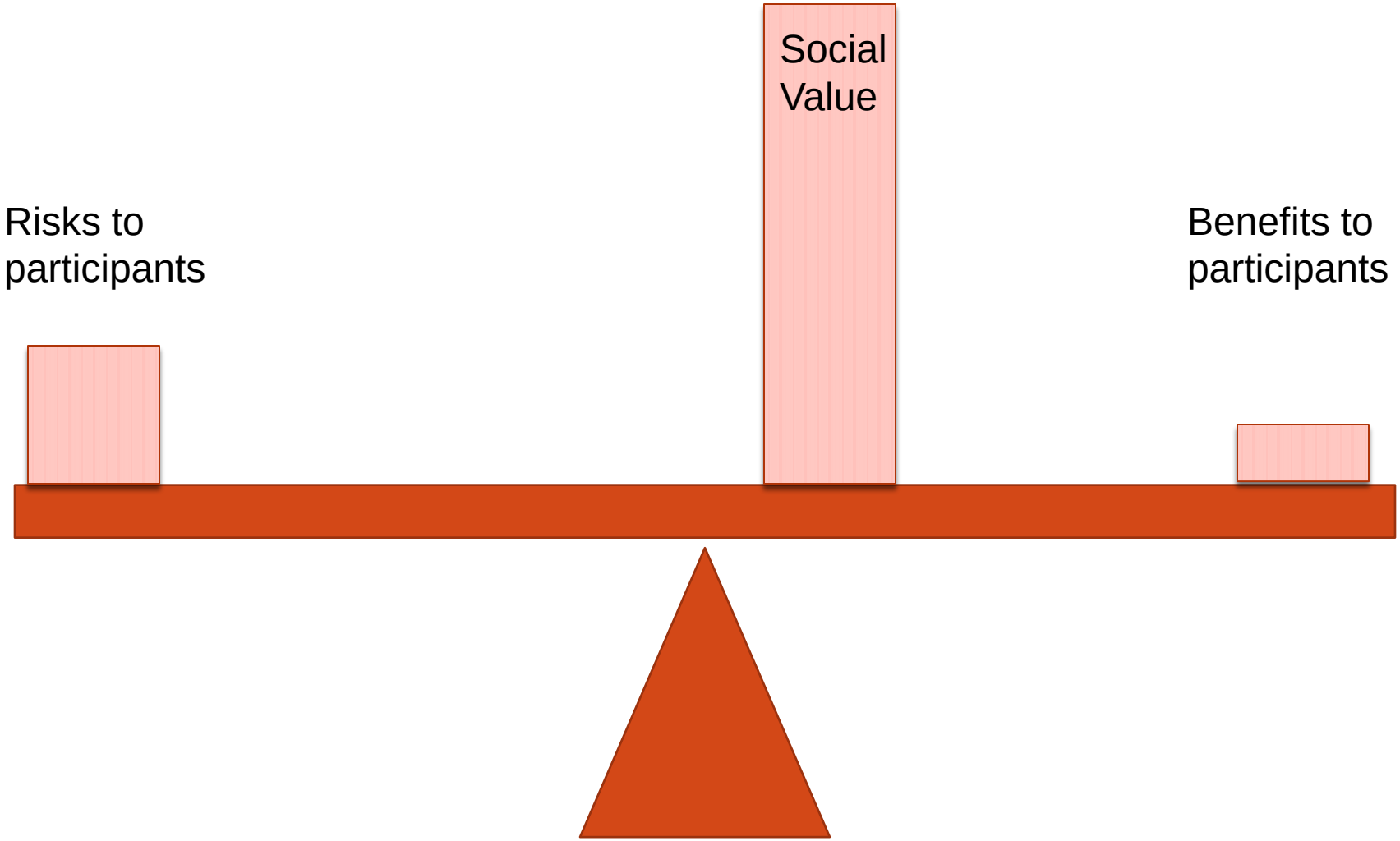
Standards of care

- Local standard of care
  - De facto
  - De jure
- Global best standard of care

Risk/benefit analysis

1. Minimize risks consistent with the goals of the research
2. Risks should not exceed a threshold
3. Risks to participants should be balanced by the benefits to participants and society

Balancing risks and benefits



The “no loss” view

- It is permissible to provide less than the global best standard of care if participants are not deprived of treatment that they would otherwise receive

The “no double standards” view

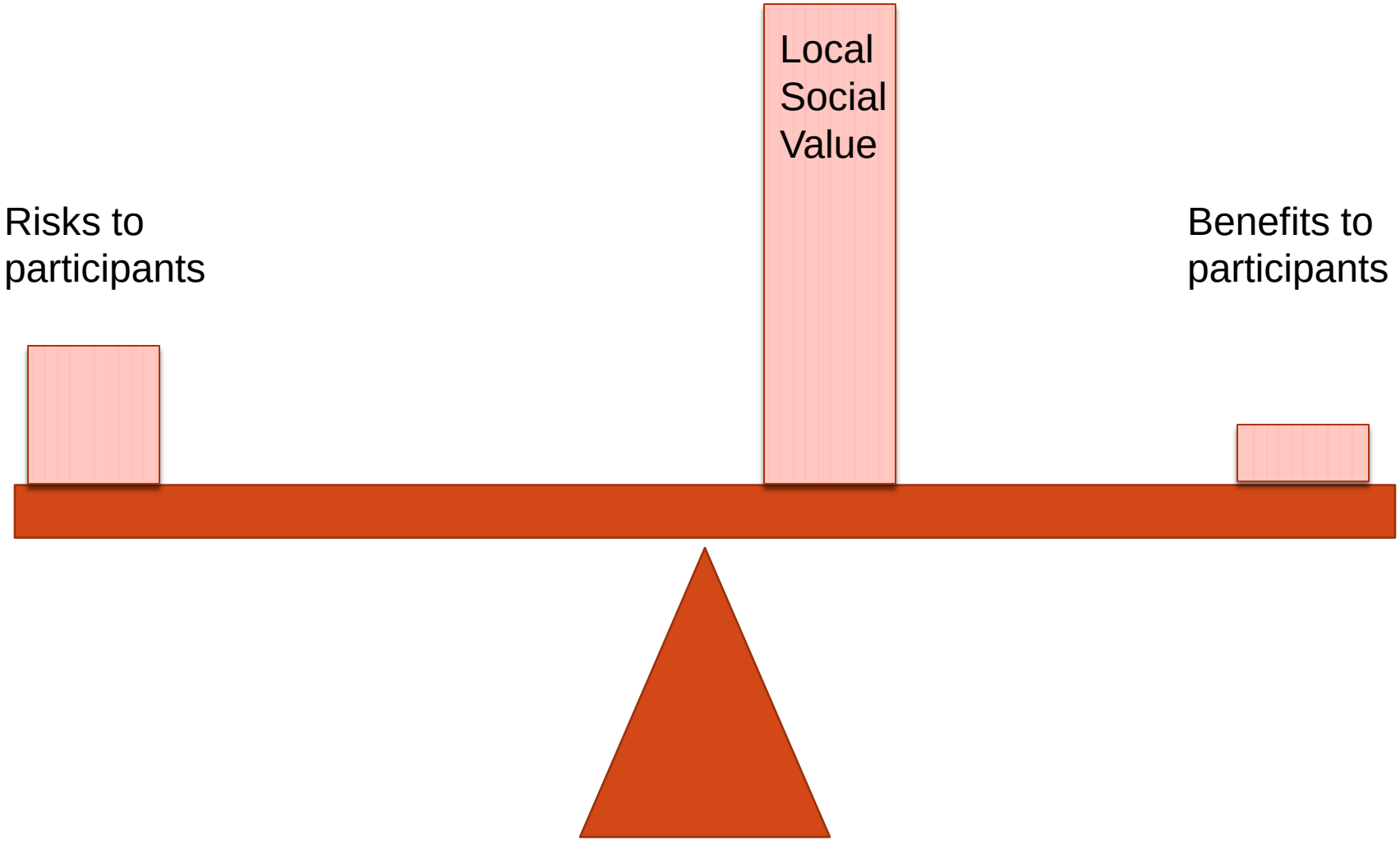
- It is permissible to provide less than the global best standard of care if the same trial would be permissible in a developed country

The “responsiveness” view

- It is permissible to provide less than the global best standard of care if:

1. Lower standard of care scientifically necessary
2. Participants not deprived of treatment they would otherwise have received
3. Research is responsive to the needs of the host communities

Balancing risks and benefits



Outstanding questions

- Who ought to benefit from the research?
- What sorts of benefits should people receive?
- What should happen after the trial?
- Who is responsible for providing benefits?

Summary

- International research conducted in resource-limited settings raises complex ethical questions
  - Exploitation of poor participants and host communities
  - Risks of providing less than the best standard of care
- These ethical considerations are intertwined