Responsiveness to host country needs and reasonable availability of interventions

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Case 1: Access to antiretrovirals

- Improved access to antiretroviral therapy (ART) in many low- and middle-income countries (LMICs)
- Many patients are now failing second-line ART regimens due to resistant HIV strains

Trial design

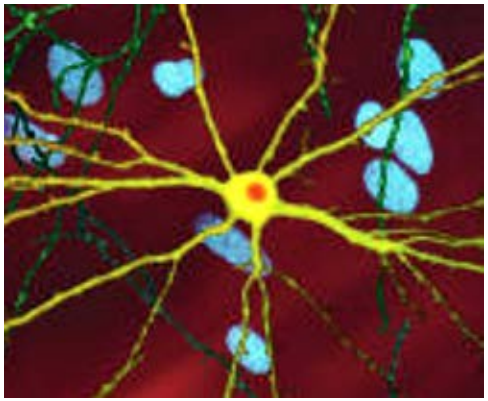
- Open-label phase IV, prospective interventional study
- Enrolling 500 HIV-1-infected adults currently failing a second-line regimen containing a protease inhibitor
- Testing novel method for assessing resistance and assignment to new treatment regimen
- Sites in Brazil, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda

Treatment after the trial

- Some of the therapeutic agents being evaluated in the study were not available outside the trial in host countries
- Researchers hoped that this data would encourage countries to start providing the drugs
- Participants who needed them would leave the trial without access to these life-saving drugs

Case 2: Huntington's test

- Huntington's disease is a hereditary brain disease
- Caused by an autosomal dominant mutation – children have a 50% chance of inheriting Huntington's
- Symptoms usually start between ages 30 – 50
- Most Huntington's patients die within 20 years of onset



Research in Venezuela

- A rural community on Lake Maracaibo, Venezuela has the highest concentration of Huntington's carriers in the world
- In 1993, U.S. researchers used blood and semen samples from the community to identify the gene causing Huntington's
- A genetic test was developed
- No one in the community has access to the test

- “In the U.S. or Europe whoever has the disease in their family has the option to decide. I want to get the test, or I don't want to know. The people of Maracaibo don't have that option, even after they collaborated in the research.”

  (Ernesto Solis, Maracaibo physician)

Two ethical issues

1. Post-trial access: What care should participants receive after a study?
2. Responsiveness and reasonable availability: Should host communities have access to study interventions or other benefits after a study?

International guidance

International guidelines

- “Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.”

  (WMA, Declaration of Helsinki, Paragraph 20)

International guidelines

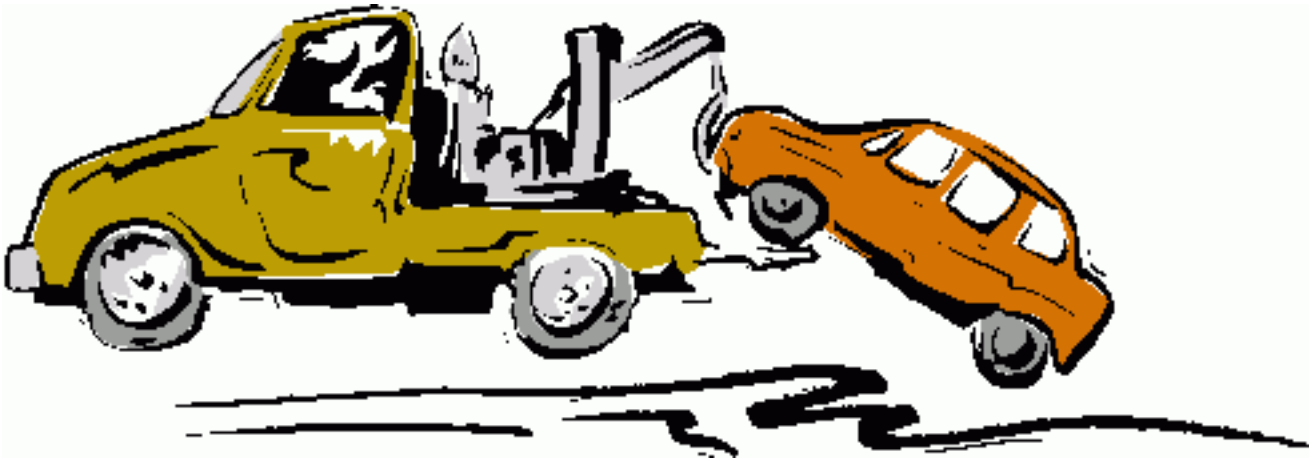
- “Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
  - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
  - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”

(CIOMS, 2002, Guideline 10)

Ethical analysis

Exploitation

- X exploits Y when X takes unfair advantage of Y's situation



The nature of exploitation

- Does it have to be harmful?
  - No
- Does it involve a problem with consent?
  - No
- It is possible to have mutually advantageous consensual exploitation

Burdens to host communities

- Using scarce clinical facilities
- Attracting physicians, nurses, and other clinicians away from the public health system
- Crowding out more valuable research

Benefits to host communities

- Answer questions about local health problems
- Develop new interventions for the population
- Expand and improve health care and research facilities
- Train health care workers

Criticisms of reasonable availability

- Not relevant to some research, e.g. Phase 1 trials, epidemiology studies
- Sometimes provides no benefits, e.g. interventions not shown effective
- Excessive burden on researchers and sponsors
- Exploitation is about the *amount*, not the *type* of benefits

Revised international guidelines

- “As part of their obligation, sponsors, and researchers must also:
- make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity.”

(CIOMS, 2016, Guideline 2)

“Fair Benefits” framework

- Wide range of benefits count, e.g. additional clinical care, clean water
- Communities must agree that the level of benefits is fair
- Transparency about benefit agreements to allow comparisons

Criticisms of “Fair Benefits”

- Lacks a theory of fair transactions
- Possible “race to the bottom” in practice

An interpretation of “responsiveness”

- *Responsive* research is research that has sufficient *local social value*
- The expected benefits of the knowledge to the host community prevent it from being exploitative

Conclusions

- Agreement that communities that host clinical trials should benefit
- Disagreement about type and extent of benefit
- Hard to justify requirement of reasonable availability of study product
- But, also hard to justify research that is not relevant to the health of host communities in LMICs

Case 2: Huntington's test

- Most people in Maracaibo do not know about the test and none have access to it
- The original goal of finding a cure has not been achieved
- But the researcher who led the project has raised more than $6 million for a Huntington's disease clinic in Maracaibo
- Sufficient benefit?

Case presentation: reasonable availability concerns surrounding a clinical trial

Case 1 again: Access to antiretrovirals

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Discussion

1. What obligations did the researchers/sponsors have to ensure that drugs would become available?
2. What would be an appropriate timeframe?
3. Should research sites be chosen depending on whether drugs were available outside of trials?
4. (What obligations did the researchers/sponsors have to participants?)

What happened…

- Manufacturers agreed to provide drugs for free
- Trial sponsor designed an extension study to test whether participants would remain virally suppressed two years after return to clinical care
- Two years thought to be long enough for countries to license the drugs and provide them through national programs