International Human Subjects Research

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President's Dream Colloquium on Traveling for Health,
SFU, Fall 2015
15th October 2015
Talk

• Not an exhaustive look at international human subjects research
• An exploration of (part of) my own journey in bioethics and global health
• Focus on ‘travel’ as a central theme of the SFU Dream Colloquium Series
• Happy to structure it as a conversation
• Tweet- #SFUPDC2015
  @AnantBhan @jeremycsnyder
Talk outline

• History- brief
• Reiterate the importance of research
• Trends in research
  - outsourced research Vs underfunded research
• Research at times of disaster
• Community engagement in research
• Some concluding thoughts
History
Yellow Fever Experiments

• In 1900, Surgeon General George Miller Sternberg organized a medical commission headed by Dr. Walter Reed to investigate Yellow Fever in Cuba.

• No animal model, so members of the board decided on human experimentation.

• ‘Contract’ established with soldiers.
February 8, 2015

A mother's plea for thalidomide compensation and peace of mind
By INGRID PERITZ

Women who took the drug that led to their babies being born with deformed limbs in the 1960s are now watching their adult children deal with growing health problems and constant pain. Their fondest wish is that Ottawa pays the promised compensation soon so they know their sons and daughters will be provided for
“Without representation in the research community, developing countries become the object of research and not participants in it.”

Sarah Cummings

Trends in Research Outsourcing
### Average profit margins of five main industrial sectors, 2013

<table>
<thead>
<tr>
<th>Sector</th>
<th>Highest</th>
<th>Lowest</th>
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<tbody>
<tr>
<td>Pharmaceuticals</td>
<td>42</td>
<td>10</td>
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<td>Banks</td>
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<td>Oil and gas</td>
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<td>2</td>
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<td>Media</td>
<td>18</td>
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Note: Highest/lowest profit margins achieved by an individual company

Source: Forbes

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**Pharmaceutical industry gets high on fat profits**

Richard Anderson. BBC 2014 November 06

Global spending on medicines

2007: $731bn
2012: $965bn
2017: $1,170bn-$1,200bn (projection)

Source: IMS Institute for Healthcare Informatics

Pharmaceuticals industry facing fundamental change
Richard Anderson. BBC. 2014 Nov 07
Outsourcing of Clinical Trials

- Cost compulsions- pharma companies-shareholders and investors wanting high and quick returns.

- Focus on blockbuster drugs—development of one could increase share prices, failure in development process could lead to fall.
Eli Lilly & Co. said it will stop development of evacetrapib, an experimental cholesterol drug with blockbuster potential, because it failed to benefit patients with heart disease.

Lilly shares fell 7.1 percent to $80.05 at 9:52 a.m. in New York. The drug’s failure builds on a series of disappointments for medications that inhibit a molecule known as CETP, which results in higher levels of HDL. Also called good cholesterol, HDL is known to ferry fatty lipids out of the arteries. Merck & Co., which is still developing a CETP inhibitor, slid 1.6 percent to $50.11.
Commercial Pressure

• PriceWaterhouse Coopers: To keep levels of profitability: 23-35 successful drugs/year necessary

• 1999: > 450 heart, cancer & stroke drugs under development; 191 drugs for Alzheimer’s, arthritis & depression
Developing Countries: Increasing Clinical Research

• Globalization and economies opening

• Strict(er) regulatory standards in the west → Shift of clinical trials to LMICs

• Mushrooming of CROs- multiple sites, efficient, faster, better patient recruitment
INDIA

• Rising economy
• Mix of public and private sector in health
• Rich scientific pool
• Diverse and large patient population- both communicable and non-communicable diseases
• Patients not often aware of the physician-researcher divide (therapeutic misconception).
Increasing Trend of Research

- Pai et al – 400% ↑ in filing of IND applications: 1999 to 2000
- Lower costs of conducting trials
- Faster patient recruitment
- Availability of well trained medical and computer professionals
- High tech hospitals and language fluency
- Role of CROs, CREBs and clinical research courses.
- Government encouragement
Controversy

• Recruitment of Patients
  Who? What kind of information/consent? Rights?

• Lack of/poor regulation

• Standard of Care
  - AZT Clinical Trials in Africa in 90s
  - Use of placebo (acceptable/not acceptable)

• Post Trial Obligations
Conditions on the Ground

• Many subjects, undergoing trials, were either illiterate or semi literate

• Crowded Conditions in Public healthcare institutions

• CRO inducement to participate in CTs.
LMICs: a context in transition

• Many countries progressing economically (L→MIC)

• Become producers, sources of products and knowledge (domestic biotech, generics firms)
  - external sponsors?

• A clamor and citizen action for stricter regulatory controls, increased transparency, better oversight
NEWS

doi:10.1038/nm0504-440a

Outsourcing clinical trials to India rash and risky, critics warn

K S Jayaraman
Hyderabad

In Mumbai, a small firm that used to translate legal documents is making a fortune translating informed consent forms into a dozen local languages. Contract research organizations (CROs), which compete with each other to
A New Colonialism: Conducting Clinical Trials in India

- Samiran Nundy, C M Gulhati NEJM April 21, 2005

• India’s drugs’ regulator DCGI understaffed; technical staff just 3 pharmacists; no physician

• Fewer than 200 investigators trained in GCP.

• India makes more money in a day by software out sourcing than in would in a year by allowing it to be a site for MNC pharma research.

• Need to strengthen the regulatory system
Clinical trial participation

• A form of labour—bodies of research participants as vehicles for generating capital/physicians involved contractors rather than clinician-scientists actively involved in drug development

• Parallels: (transnational) surrogacy—patients coming to India to ART clinics and using surrogate Indian women

• Stem cell treatment ‘clinics’: taking advantage of lax regulations—offering magic cures.
Kumar, R., “Evolving Clinical Trials,” *Pharm Exec, October 1, 2008.*
Controversies

• HPV vaccine trials- participation of adolescents, concerns around consent and adverse events

• Involvement of vulnerable patients in trials- lack of information, participation for private gain by physicians

• Court cases– multiple PILs filed.
Clinical trial ethics in India: One step forward, two steps back

Anant Bhan
Researcher, Bioethics and Global Health, Pune, India

CONCLUSION

India, as an emerging economy needs to continue to promote a strong culture of research and development, including in the health sector. However, attention needs to be paid to ensuring that stringent quality checks are built in, and that investigators conduct research in an impeccable manner. Failure to do so will dent the credibility of the research enterprise, affecting not just investigators or institutions conducting research, but also those planning to do so.
India’s new policy to protect research participants
Urgent need to deal with its unintended consequences

Jeremy Sugarman Harvey M Meyerhoff professor of bioethics and medicine¹, Anant Bhan senior research consultant², Robert Bollinger professor of medicine³, Amita Gupta associate professor of medicine³

A drop in research activity might also reduce India’s research capacity. Moreover, global research efforts will suffer as a result of limited participation of Indian clinical research experts. The relevance, impact, and quality of global health research have been greatly strengthened by engagement of Indian scientists and participation of Indian research volunteers. Advances in health research need India’s leadership and participation.
Global health research trends: Under-funded research
Deaths attributable to antimicrobial resistance every year compared to other major causes of death

- Tetanus: 60,000
- Cholera: 100,000 - 120,000
- Measles: 130,000
- AMR in 2050: 10,000,000
- Road traffic accidents: 1,200,000
- Diarrhoeal disease: 1,400,000
- Diabetes: 1,500,000
- Cancer: 8,200,000

Source: Review on Antimicrobial Resistance 2014
TREATMENT TRENDS
The first comprehensive, global report on antibiotic use shows that the drugs are increasingly popular in low- and middle-income countries.

Justice and bioethics

Bhopal Gas Tragedy

- Corporate complicity, outsourcing, poor standards, lack of accountability
- Failure to conduct quality research
- Compensation for harm; attribution/causation
While we argue for food supplements for about 1.5 million people who develop TB annually in India, preventing TB in those 350 million Indians who have latent TB is possible only if they get adequate food. Undernutrition is a risk factor for the development of TB in at least half of the people and thus ensuring adequate and balanced food for all makes sense so that, among its many benefits, fewer people get TB.

Fig 1. Images of patients with tuberculosis at Jan Swasthya Sahyog, October 2014

India has only 6.5 Doctors for every 10,000 people vs global avg of 13.9 @india_maps bit.ly/1MBpTMB #data
The Atlantic @TheAtlantic · 10m
In Focus: Wrapped in Plastic, Waiting for Ebola theatl.ntc/1C5uAsm
↩ Reply  🎥 Retweet  ★ Favorite
Number of doctors & nurses per 100,000 population (WHO)

- Sierra Leone: 2.2 doctors, 16.6 nurses/midwives
- Guinea: 10 doctors, 51.1 nurses/midwives
- Liberia: 1.4 doctors, 27.4 nurses/midwives
- OECD average: 320 doctors, 890 nurses/midwives
Globalized world: research

• With international travel/migration, now public/global health threats are ‘glocal’ in nature
  – Ebola
  – AMR

• Difficult for countries to cope unless there is a sense of solidarity, sharing of health resources (personnel) and sharing of data (challenges- flu)
Improving Ethical Review of Research Involving Incentives for Health Promotion

Alex John London¹*, David A. Borasky Jr.², Anant Bhan³ for the Ethics Working Group of the HIV Prevention Trials Network

¹ Philosophy Department and Center for Ethics and Policy, Carnegie Mellon University, Pittsburgh, Pennsylvania, United States of America, ² Office of Research Protection, RTI International, Research Triangle Park, North Carolina, United States of America, ³ Researcher, Bioethics and Global Health, Pune, Maharashtra, India

Summary Points

- Advances in behavioral economics are driving efforts to use material or financial incentives to promote health-related behavior in international development, public health, and clinical medicine.
- Current ethical frameworks for human research assume that material or financial incentives are provided to participants either as compensation for their time and expenses, or as an inducement to participate in research.
- We argue that some common concerns about using incentives to increase participation in research, such as that attractive incentives will undermine participant autonomy, are misplaced when incentives are used to overcome economic obstacles or a lack of effective motivation, and when recipients are incentivized to engage in health-related behaviors or practices with which they are already familiar and which they regard as beneficial or worthwhile.
- We offer additional guidance to research ethics committees aimed at improving the evaluation of research in which incentives are used as an intervention intended to promote healthy behavior.
Research During Disasters: Ethical Concerns
When communication with communities goes wrong. Not #commisaid
The tsunami that marked a solemn end to 2004 left behind unprecedented devastation. The world was shocked at the increasing casualty figures and the real-time images of the disaster brought by the news media. These included clips and photographs of dead bodies, grieving relatives, and suffering patients admitted to makeshift emergency wards.

The photographs did help in organizing a quick response from the rest of the world, as societal pressure
Key point

• In disasters, the affected are often left with almost nothing and with negligible negotiating power. They might be left with only their pride and dignity, and they must not be robbed of that. Patients or affected families might not be in a condition to respond to encroachment on their rights. While health professionals want to facilitate recognition of their unidentified patients and also facilitate more aid to affected areas, they also have an enhanced responsibility to protect their patients’ dignity and rights. We should not need to be voyeurs into the grief of vulnerable victims to launch an effective and humane response to any disaster.
Ethical Issues in Post-Disaster Clinical Interventions and Research: A Developing World Perspective. Key Findings from a Drafting and Consensus Generation Meeting of the Working Group on Disaster Research and Ethics (WGDRE) 2007

ATHULA SUMATHIPALA, AAMIR JAFAREY, LEONARDO D. DE CASTRO, AASIM AHMAD, DARRYL MARCER, SANDYA SRINIVASAN, NANDINI KUMAR, SISIRA SIRIBADDANA, SLEMAN SUTARYO, ANANT BHAN, DANANJAYA WAIDYARATNE, SRIYAKANTHI BENERAGAMA, CHANDRANI JAYASEKERA, SARATH EDIRISINGHA, AND CHESMAL SIRIWARDHANA

Human Subject Research Following Disasters

Disasters cause destruction, death, disease/disorders, displacement, disappearance, and disarray, all of which have implications for mental health, public health, ethical/human rights and social policies.\(^4\) There is a growing collection of empirical evidence about best practices in responding to post-disaster health needs; however this needs to be buttressed through more field research. Hence, research pertaining to human subjects is crucial in the disaster context.\(^5\) Such research can range from clinical trials involving medical interventions to social science research involving focus group discussions.\(^6\)
Criteria

- Relevance to disaster situations
- Informed consent and voluntariness
- Community consultation and participation
- Non-exploitation
- Dignity, privacy and confidentiality
- Risk minimization
- Institutional arrangements; Professional competence
- Public interest and distributive justice
- Dissemination of results
- Ethics review
- International collaborative research
Ethical Issues Arising in Responding to Disasters: Need for a Focus on Preparation, Prioritisation and Protection

- Preparing for disasters
- Prioritization once disaster strikes
- Protection for those affected by the disasters
Research in this area

• Growing area of attention—also due to focus on related area of ethical issues in response to pandemics (SARS, H1N1, H5N1)

Hunt, Matthew (PI) 11/01/2012-10/31/2015
Sponsor: Canadian Institutes of Health Research
Investigation of the ethics of disaster research in low resource settings
This project aims to identify the processes and ethical principles that can reliably guide ethics review for research in low-resource disaster settings, and use these to develop a tailored normative framework. The final phase of the project will include knowledge transfer and exchange activities targeted at disaster researchers, and Research Ethics Boards that review disaster research.
Community Engagement in Research
GCGH enterprise

Grand Challenges in Global Health: The Ethical, Social and Cultural Program

Peter A. Singer*, Andrew D. Taylor, Abdallah S. Daar, Ross E. G. Upshur, Jerome A. Singh, James V. Lavery

PLoS Medicine | www.plosmedicine.org

September 2007 | Volume 4 | Issue 9 | e265
"Without community engagement and empowerment, the behavioural changes required to stop the outbreak would not have occurred." Our Chief Helen Clark applauded Sierra Leonean communities during her visit to Sierra Leone, where UNDP is leading the UN’s response on Ebola recovery.
Community engagement in global health/research

• Global health research often involves working in unfamiliar cultural and geographical settings

• Besides the science part, how can we do a better job at the ‘human’ aspect of the research that we conduct.
AMERICANS and Europeans stand out from the rest of the world for our sense of ourselves as individuals. We like to think of ourselves as unique, autonomous, self-motivated, self-made. As the anthropologist Clifford Geertz observed, this is a peculiar idea.

People in the rest of the world are more likely to understand themselves as interwoven with other people — as interdependent, not independent. In such social worlds, your goal is to fit in and adjust yourself to others, not to stand out. People imagine themselves as part of a larger whole — threads in a web, not lone horsemen on the frontier. In America, we say that the squeaky wheel gets the grease. In Japan, people say that the nail that stands up gets hammered down.
Working with communities

• Is a way of applying the principles of respect, beneficence and justice beyond individuals to communities

• Came into focus (in the west) after the Belmont Report was criticized for being too individual focused.

• Initially promoted extensively in HIV-AIDS research especially larger trials after activists protested about non-participation in decision making.

• Now extending to other forms of research
Problems can arise if communities not involved

• Controversy around Tenofovir prevention trials and suspension of research (Cambodia/Cameroon; 2004)

• Microbicide trials which were stopped early in South Africa (2007): allegations that participants had been used as "human guinea pigs"
Community Engagement- definition

- a process of working collaboratively with and through groups of people affiliated by geographical proximity, special interest, or similar situations to address issues affecting the well-being of those people

US CDC 1997
Operationalization of CE

• community outreach, including gatekeepers
• working through community educators
• hiring community members as staff members
• community member of the IRB
• civil society organizations
• setting up of Community Advisory Groups
Working through Civil Society Organizations

- Present extensively in LMICs, including India
- Maintain presence on the ground and often know communities
- Can have research capacity and help in advocacy and scaling up
Techniques

• 1) INFORMING, to explain the problem, alternatives and opportunities
• 2) CONSULTING, to obtain feedback on analysis, alternatives and decisions
• 3) INVOLVING, to work directly with the public throughout the process in order to ensure that concerns are constantly considered
• 4) COLLABORATING & PARTNERING in each aspect of the decision including identification of questions and development of methods and
• 5) EMPOWERING, to “place final decision-making in the hands of the public” and enable the community of using and benefiting from outcomes.

from International Association for Public Participation
<table>
<thead>
<tr>
<th>Outreach</th>
<th>Consult</th>
<th>Involve</th>
<th>Collaborate</th>
<th>Shared Leadership</th>
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<tbody>
<tr>
<td>Some Community Involvement</td>
<td>More Community Involvement</td>
<td>Better Community Involvement</td>
<td>Community Involvement</td>
<td>Strong Bidirectional Relationship</td>
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<tr>
<td>Communication flows from one to the other,</td>
<td>Communication flows to the community and</td>
<td>Communication flows both ways, participatory</td>
<td>Communication flow bidirectional</td>
<td>Final decision-making at community level</td>
</tr>
<tr>
<td>to inform</td>
<td>then back, answer seeking</td>
<td>form of communication</td>
<td>Forms partnerships with community on each</td>
<td>Entities have formed strong partnership</td>
</tr>
<tr>
<td>Provides community with information</td>
<td>Gets information or feedback from the</td>
<td>Involves more participation with community</td>
<td>aspect of project from development to</td>
<td>structures</td>
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<tr>
<td>Entities coexist</td>
<td>community on issues</td>
<td>on issues</td>
<td>solution</td>
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<tr>
<td>Outcomes: Optimally establishes</td>
<td>Entities share information</td>
<td>Entities cooperate with each other</td>
<td>Entities form bidirectional</td>
<td>Outcomes: Broader health outcomes affecting</td>
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<td>communication channels and channels</td>
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<td>communication channels</td>
<td>broader community; strong bidirectional trust</td>
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<td>for outreach</td>
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<td>Outcomes: Visibility of partnership</td>
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<td>established with increased cooperation</td>
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**Figure 1.** Community Engagement Continuum, developed by the Clinical and Translational Science Awards Consortium (2011).
Value of Community Engagement!

• Intrinsic Value
  – **Respect** the community’s values, culture, traditions, and social practices
  – Recognition that *communities* themselves might suffer collective harm
  – To ensure the **relevance** of research (*NBAC, Nuffield*)
  – **Protective** measure to limit harm to *individuals*
Value of Community Engagement!

• **Instrumental value**
  – Supports consent process by providing information over time
  – Ensures that research and consent processes are culturally appropriate, identify appropriate terminologies and analogies
  – Maximize opportunities for stewardship/ownership/control by community
  – Feedback of research findings
Value of Community Engagement

– Provide ongoing channels of communication between communities and researchers

– Address local fears, anxieties and rumours e.g. About blood sampling

– Establish relationships, build trust, seek commitments from formal and informal authorities
Model of CE: Community Advisory Board?

• CABs “provide a mechanism for community consultation that contributes to protecting communities and fostering meaningful research”.
Its important to understand

- Communities:
  - are complex
  - are not homogeneous or static
  - are wary
  - need to be respected (could mean learning to expect no for an answer)
  - often expect long term relationships
Evaluating community engagement in global health research: the need for metrics

Kathleen M. MacQueen¹, Anant Bhan², Janet Frohlich³, Jessica Holzer⁴, Jeremy Sugarman⁵ and the Ethics Working Group of the HIV Prevention Trials Network

Summary: There is a critical need to enhance efforts in evaluating community engagement to ensure that the work on the ground reflects the intentions expressed in the guidelines, and to investigate the contribution of specific community engagement practices for making research responsive to community needs and concerns. Evaluation mechanisms should be built into community engagement practices to guide best practices in community engagement and their replication across diverse health research settings.

MacQueen et al. BMC Medical Ethics (2015) 16:44
Conclusion

• Snapshot at some issues in international human subject research

• Choice and focus of research
  - outsourced research Vs need in LMICs

• Research during disasters

• Community engagement in research-role and challenges
Acknowledgments

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THANK YOU

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