Ethics Dumping – Paradigmatic Case Studies; a report for TRUST

Research · October 2016

DOI: 10.13140/RG.2.2.17861.86243

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Citing suggestion: Schroeder D, Cook Lucas J, Fenet S, Hirsch F (eds) (2016) “Ethics Dumping” – Paradigmatic Case Studies, a report for TRUST, available: http://trust-project.eu/deliverables-and-tools/.

Report on Paradigmatic Case Studies

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Project full title:	Creating and enhancing **TRUST**worthy, responsible and equitable partnerships in international research
Project acronym:	TRUST
Type of funding scheme:	Coordination and support action
Work programme topics addressed:	Reducing the risk of exporting non ethical practices to third countries, GARRI-6-2014
Project web-site:	www.trust-project.eu/
GRANT AGREEMENT No:	664771
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Contents

Contents 3

Executive Summary and Introduction 7

Methodology 7

An Overview of the Case Studies 8

Conclusions and Recommendations 9

The Horizon 2020 Ethical Issues Table 10

Case Studies 11

1.1. Safety and Security Risks of CRISPR/Cas9 11

Abstract 11

Area of Risk of Exploitation 12

Analysis 12

Recommendations 16

1.2. CRISPR/Cas9 – Good Practice 17

Abstract 17

Area of Good Practice 17

Analysis 18

Lessons Learned 19

2. The Use of Non-human Primates in Research 20

Abstract 20

Area of Risk of Exploitation 20

Animal Research World-Wide 21

Specific Case and Analysis 23

Recommendations and Conclusion 26

References 27

3. ICT and Mobile Data for Health Research 29

Abstract 29

Area of Risk of Exploitation 30

Specific Case and Analysis 32

Recommendations 33

References 33

4. International Genomics Research involving the San People 35

Abstract 35

Area of Risk of Exploitation 35

Specific Case and Analysis 36

Lessons Learned 40
Recommendations 41
References 41
5. Social Science Research in a Humanitarian Emergency Context 42
Abstract 42
Area of Risk of Exploitation 42
Background 42
Specific Case and Analysis 43
Lessons Learned 45
Recommendations 45
References 46
6. Healthy Volunteers in Clinical Studies 47
Abstract 47
Area of Risk of Exploitation 47
The Problem 48
The Way Forward 48
References 49
7. Human Food Trial of a Transgenic Fruit 50
Abstract 50
Areas of Risk of Exploitation 51
A Proposed Human Food Trial 51
Lessons Learned 54
Recommendations 55
8. Hepatitis B Study with Gender Inequities 57
Abstract 57
Area of Risk of Exploitation 57
Case Description 57
Analysis 58
Outcome of the Application for Ethics Approval 61
Lessons learned and recommendations 61
9. A Controversial International Cooperative Genetic Research Project conducted by American and Chinese Research Institutes in Anhui Province, China 62
Abstract 62
Area of Risk of Exploitation 62
Background 63
Specific Case and Analysis 64

Lessons Learned 67
Recommendations 69
References 70
10. Sex Workers Involved in HIV/AIDS Research 71
Abstract 71
My Experience Visiting Majengo 71
About Majengo 72
The Majengo Clinic 73
Majengo Research 74
Majengo Research Participants 74
Ethical Concerns and Benefits 75
Conclusion and Looking Forward 77
References 77
11. Ebola Vaccine Trials 78
Abstract 78
Area of Risk of Exploitation 79
Specific Case 79
The Informed Consent Process 82
Conclusion 87
Supplement to the Ebola Vaccine Trial Case – The Importance of TRUST 88
12. Virus Sharing 90
Abstract 90
Area of Risk of Exploitation 90
Case Analysis 90
Lessons Learned 93
References 94
13. Cervical Cancer Screening in India 97
Abstract 97
Area of Risk of Exploitation 98
Context 98
Background on Cervical Cancer Screening in India 99
Study Design 100
Three cluster randomised controlled trials of VIA with “no screening” controls in India 101
Analysis 106
Recommendations 109
References 110

Short Notes on Remaining Areas in Horizon 2020 Ethics Review 112
Human embryos and foetuses 112
Health and Safety 113
Appendix 115
Case Study Resources 115
Contributors 116

Executive Summary and Introduction

The main goal of TRUST is to catalyse a global collaborative effort to improve adherence to high ethical standards in research around the world. To achieve this aim, the project develops three tools:

— A **global code of conduct** that can be used by the European Commission and funders world-wide to foster ethical research and equitable partnerships.
— A **fair research contract** - an on-line tool that gives power to vulnerable populations.
— A **compliance and ethics follow-up** tool for conditions of high vulnerability.

Standards
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All tools will be informed – amongst other things - by case studies involving North South collaboration. Case studies in the area of ethics in medical research are widely published, see also our short Resources section in the Appendix. However, the ambitious goal of the TRUST project is to cover *all* research efforts in North South collaboration and not only medical research.

Methodology

The structuring principle of this deliverable is the Horizon 2020[2] Ethical Issues Table[3] to ensure that we cover all foreseeable ethical issues. The table has just been assessed by an external review and was considered complete.[4] This approach ensures that the case studies developed for this deliverable are comprehensive and not merely a collection of cases the project discovered in an unsystematic manner.

The structuring principle of this deliverable is the Horizon 2020 Ethical Issues Table.

The case studies were sourced in five ways[5].

1. Experts from the partner organisations of TRUST wrote case studies in their specialist area of expertise.
2. The two NGOs involved in TRUST (working with sex workers in the Nairobi slums and with indigenous populations in South Africa) produced one case study each.
3. A bottom-up case study competition was launched to source additional cases from low and middle income countries.
4. Three TRUST external advisors were commissioned to write a chapter based on their unique expertise.
5. A case studies workshop was organised in India in March 2016.

[2] Horizon 2020 is the current research funding program of the European Commission.
[3] http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-msca-itn-2015/1620147-h2020_-_guidance_ethics_self_assess_en.pdf
[4] Julian Kinderlerer and Doris Schroeder with support from Paul Webb and team, Assessment of the Horizon 2020 Ethics Review Process, evaluation completed on 31 July 2016.
[5] In addition, short notes were added in some areas where no full case studies were available. Please see section: Short Notes on Remaining Areas.

An Overview of the Case Studies[6]

CRISP/CAS9

Non-human primates

Mobile data for health

Genomics - San Peoples

Social science in emergency setting

Healthy volunteers (* 2)

Genetically modified bananas

Gender case - Russia

Biosamples export - China

Sex workers - Nairobi

Ebola vaccine trials

Virus sharing

[6] References were handled as convenient by the case authors; hence there is a mix of footnotes and Harvard style.

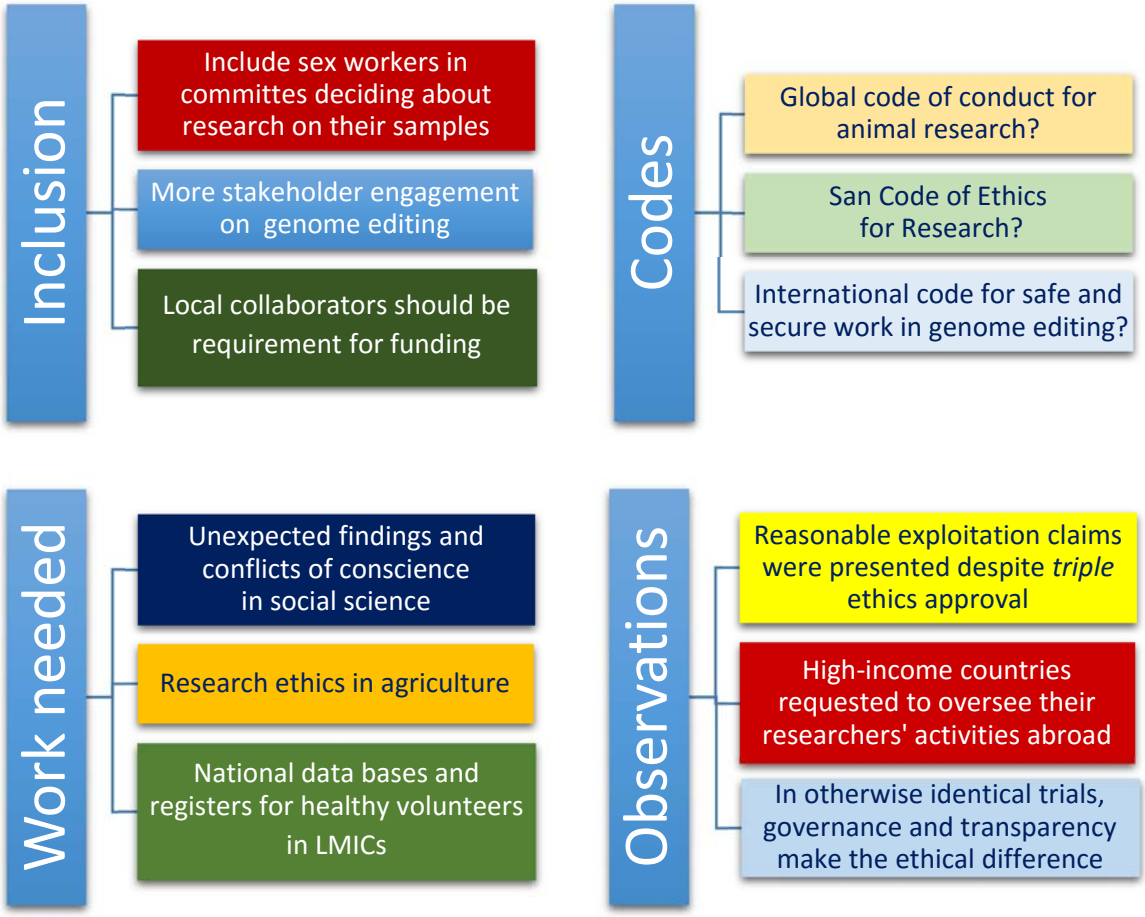
Conclusions and Recommendations

On purpose, no conclusions were drawn in this case study deliverable, which forms the basis of future deliverables and tools. Whilst, recommendations were presented by individual chapter authors, these are not recommendations from the TRUST project, as they will still need to be analysed for future work. Watch this space! http://trust-project.eu/

Shutterstock

However, we produced the following graphic overview of ambitious suggestions for equitable research partnerships plus some surprising observations as well as comments on future work needed. These are drawn from the recommendations of individual chapter authors.

Diagram 1 – Preliminary Overview of Report Results



The Horizon 2020 Ethical Issues Table[7]

Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020[8] notes in its Article 29:

> Research and innovation activities supported by Horizon 2020 should respect fundamental ethical principle … and the use of animals in research and testing should be reduced, with a view ultimately to replacing their use. All activities should be carried out ensuring a high level of human health protection.

To ensure that Horizon 2020 projects are carried out respecting fundamental ethical principles, an Ethical Issues Table is available to applicants and grant holders. The following table maps the Horizon 2020 ethical issues against case studies in this report.

Table 1: Horizon 2020 Ethical Issues Table mapped against Case Studies

Ethical issue	Ethical issue sub-category	Main case study no.
Human embryos and foetuses		++
Humans	Volunteers for social science research	5
	Persons unable to give consent, incl. minors	8, 11
	Vulnerable groups	4, 9, 10, 13
	Patients	6, 10
	Healthy volunteers in medical studies	6, 10, 11, 13
Human cells and tissues		9, 10, 12
Personal data		3
Animals		2
Third countries	Not applicable as all cases in this report involve third countries	
Environment and Health & Safety	Environment	1, 7
	Health & Safety	++ 1
Dual use		1, 12
Misuse		1, 12
Other issues	Perceived injustice between countries	12

++ the sections marked with a double cross are discussed in the "Short Notes on Remaining Areas".

[7] http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-msca-itn-2015/1620147-h2020_-_guidance_ethics_self_assess_en.pdf

[8] http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-establact_en.pdf#page=11

Case Studies

As noted before, the case studies were selected to cover all relevant areas of the Horizon 2020 Ethical Issues table and the Main Horizon 2020 sections. The match with both can be found in tables 1 and 2 above. We begin with an important case, for which we provide both potential exploitation risks and good practice. This is the case, because CRISPR/Cas9 is a new technology for which little ethics/safety/security advice exists. The two elements (exploitation risk/ good practice) were separated to ensure ease of reading.

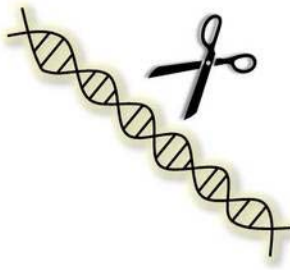
1.1. Safety and Security Risks of CRISPR/Cas9

Johannes Rath

Abstract

This case study looks into recent developments with regard to the CRISPR/Cas9 and other novel genome editing technologies that are becoming widely available due to their low costs and limited technological requirements.

Genome editing allows the specific modification of a genome; genes are modified within their respective location in the genome, making the changes often indistinguishable from natural mutations. Developments of this technology such as the use of gene drives, where specific genes are spread within populations, or the use of viral vector systems, are enabling additional applications in environmental engineering and disease treatment. There are substantial individual and societal benefits from applying genome editing; nonetheless the technology also poses significant risk to individuals, society as whole and the environment.



CRISPR/CAS9

The central focus of this case study is on the unresolved ethical issues related to safety and security that pose both short-term and long-term challenges to international research partnerships. As such, the case study focuses not on a single incident but on the risks of proliferation of a new and very powerful technology in a time where accepted and tailored ethical and legal frameworks at the international, national and local level are missing.

In the case study two areas of *safety* risks are mapped and existing governance approaches described: First, risks to humans e.g. in relation to therapeutic applications of genome editing; second, risks to the environment in relation to the use of genome editing on animals, plants and microbes. In addition, two aspects of *security* risks are also assessed: First, the creation of harmful agents relevant in the bioweapons' context; second, human enhancement in a military context and its medium and long-term implications for international security.

It is concluded that the rapid emergence of high-risk safety and security applications of genome editing not only challenge today´s safety and security risk assessment but also existing governance tools. In addition, missing international standards of governance may

result in transferring safety- and security-sensitive experiments to countries with less stringent oversight, which will have serious implications on trust in international research.

Area of Risk of Exploitation

The key area of risk relates to exploitation of international inconsistencies in biosafety and biosecurity with regard to the governance of genome editing experiments. This creates an environment where risky experiments might be carried out in countries with no legal framework[9], or in countries where although legal frameworks exist their implementation cannot be achieved due to limited resources[10]. This undercuts established European standards of safety and security while at the same time, due to the nature of some of these experiments, there is the potential to affect safety and security in Europe itself.[11]

Safety and Security

In everyday life, these terms are often used interchangeably. Here safety denotes protecting humans, animals, plants and the environment from unintentional harm, whereas security refers to intentional harm (e.g. in a military context).

Analysis

This case study on genome editing focuses on the safety and security implications in four concrete experimental settings that have either been carried out in laboratories to date, or are well within the range of existing technological capacities. These experimental settings are:

a) The use of genome editing in human inheritable disease, human enhancement, infectious disease and cancer treatment;
b) The use of genome editing in creating novel pathogenic organisms;
c) The use of genome editing in environmental engineering and disease vector eradication;
d) The use of genome editing in agriculture.

The controversy surrounding the publication of a research paper applying genome editing technologies to human embryonic stem cells (hESC) has brought to the attention of the international scientific community the varying international governance approaches regarding such research. Since then a broad discussion has emerged on how to use this technology in an ethically sound way. [12, 13,14]

[9] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/ethics
[10] P. Dickmann, H. Sheeley and N. Lightfoot; Biosafety and biosecurity: a relative risk-based framework for safer, more secure, and sustainable laboratory capacity building; Frontiers in Public Health (2015), Vol 3 Art 241
[11] Defensive Drives (Editorial) Nature (2015) 527, 275–276
[12] E Callaway. Embryo editing gets green light. Nature (2016) 530: 16
[13] D Cyranoski. Embryo editing divides scientists. Nature (2015) 519: 272
[14] E Lanphier, F Urnov. Don't edit the human germ line. Nature (2015) 519: 411

Although many of these discussions focus on the moral status of a human embryo and the permissiveness of human germ line enhancement, it has become generally accepted that a common ethical issue is whether or not genome editing can be carried out safely and securely.

The safety aspect was highlighted very early on in the discussion as a critical limitation that will need to be resolved before any application of genome editing on humans or the release into the environment can take place.[15] The security aspect on the other hand has only recently obtained attention as leading governmental officials identified genome editing as a national security threat.[16]

Therefore, resolving major safety and security concerns of genome editing will be of general importance not only as a pre-requisite for a reasonable discussion of the potential benefits, but also in fostering trust among stakeholders in international collaborative research.

Resolving major safety and security concerns of genome editing will be of general importance … in fostering trust among stakeholders in international collaborative research.

The use of genome editing in human inheritable disease treatment and human enhancement has huge potential. Research in this area is carried out with regard to the treatment of various genetic disorders, infectious diseases and cancer. Recent examples that are currently undergoing safety testing in clinical trials are the use of somatic gene therapies involving immune cell modifications to treat cancer[17]; the CRISPR based approaches to treat HIV;[18] or the proof of principle of genome editing in the treatment of heritable diseases like Duchenne muscular dystrophy.[19] Key safety concerns in this area have been the number of off-target changes, mosaicism and potential epigenetic effects.[20] These are not novel safety concerns, but have also been encountered in other gene therapeutic approaches. As such, the existing step-wise approach applied in clinical studies should be sufficiently robust to identify, assess and govern such risks.

[15] Akbari O, Bellen H, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P8, Edwards OR, Esvelt KM1, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA, O'Connor-Giles KM, Parks AL, Perrimon N, Port F, Russell S, Ueda R, Wildonger J. BIOSAFETY. Safeguarding gene drive experiments in the laboratory. Science (2015)349(6251): 927-9. doi: 10.1126/science.aac7932.

[16] KA. Oye, K Esvelt, E Appleton, F Catteruccia, G Church, T Kuiken, S Bar-Yam Lightfoot, J McNamara, A Smidler, JP. Collins. Regulating gene drives. Science (2014) 345 (6197): 626

[17] S. Reardon; First CRISPR clinical trial gets green light from US panel, Nature News (2016) doi:10.1038/nature.2016.20137

[18] S. Reardon; Gene-editing method tackles HIV in first clinical test, Nature News (2014) doi:10.1038/nature.2014.14813

[19] JR Mendell, LR Rodino-Klapac. Duchenne muscular dystrophy: CRISPR/Cas9 treatment. Cell Res. (2016) 26(5):513-4. doi: 10.1038/cr.2016.28.

[20] Editorial: Next-generation genome editing. Nature Biotechnology (2015) 33(5): 429

The relation of using genome editing in heritable disease treatment to human enhancement is fluid.[21,22] Genetic human enhancement has substantial security implications. Approving the use of genome editing for human enhancement (e.g. IQ, physical, endurance, etc.) in certain countries will have far reaching military and economic security implications at the national and international level. These security risks need to be included in risk benefit assessments of genome editing based human enhancement.

Certain genome editing techniques open the opportunity for the creation of a new class of infectious pathogenic organisms. A recent example has been the creation of cancer models in mice where the cancerous mutation was introduced through genome editing using viral vectors – in essence transforming cancer into a transmissible infectious disease.[23] This creates novel safety risks that will need to be included in current biosafety oversight schemes. In addition, such work has the potential to create new generations of biological and chemical weapons which might not be detectable by current diagnostics.

The use of genome editing in environmental engineering has been discussed in the pest control context with new ways to eradicate agricultural pests [24],[25] as well as in the context of disease eradication. For example, gene drive systems are developed to eradicate malaria[26] and contemplated for the eradication of the Zika[27] arthropod vector. Key safety concerns relate to the environmental harmfulness, controllability and reversibility of such environmental interventions. Key security concerns relate to their potential use as socio-economic and environmental weapons.

Disease-carrying-mosquito

[21] T. Ishi Germ line genome editing in clinics: the approaches, objectives and global society, Briefings in Functional Genomics (2015) 1–11

[22] DB Turitz Cox, RJ Platt, F Zhang. Therapeutic Genome Editing: Prospects and Challenges Nat Med. (2015) 21(2): 121–131. doi:10.1038/nm.3793.

[23] SH Chiou, IP Winters, J Wang, S Naranjo, C Dudgeon, FB. Tamburini, JJ Brady, D Yang, BM Grüner, CH Chuang, DR Caswell, H Zeng, P Chu, GE Kim, DR. Carpizo, SK Kim, MM Winslow. Pancreatic cancer modelling using retrograde viral vector delivery and in vivo CRISPR/Cas9-mediated somatic genome editing Genes Dev. (2015) Jul 15;29(14):1576-85. doi: 10.1101/gad.264861.115

[24] Huang, Y., Chen, Y., Zeng, B., Wang, Y., James, A.A., Gurr, G.M., Yang, G., Lin, X., Huang, Y., You, M., CRISPR/Cas9 mediated knockout of the abdominal-A homeotic gene in the global pest, diamondback moth (Plutella xylostella), Insect Biochemistry and Molecular Biology (2016), doi: 10.1016/j.ibmb.2016.06.004.

[25] PT Leftwich, M Bolton, T Chapman. Evolutionary biology and genetic techniques for insect control. Evol Appl. (2016) 9(1): 212–230. doi: 10.1111/eva.12280

[26] VM. Gantza, N. Jasinskieneb, O. Tatarenkovab, A. Fazekasb, VM. Maciasb, E. Biera, AA. James, Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi, Proc Natl Acad Sci U S A. 2015 Dec 8;112(49):E6736-43. doi: 10.1073/pnas.1521077112.

[27] J Heg. Is Intentional Extinction Ever the Right Thing? PLOS Ecology Community (2016) http://blogs.plos.org/ecology/2016/07/01/is-intentional-extinction-ever-the-right-thing/

In conclusion, the use of gene drives in an environmental context creates novel risks both with safety as well as with security, which are not limited to national boundaries. Current national and international risk management approaches to biosafety and biosecurity are incapable of mitigating these risks adequately.

The use of gene drives in an environmental context creates novel risks both with safety as well as with security, which are not limited to national boundaries.

The use of genome editing in agriculture for breeding purposes of plants and animals[28] creates unique and novel challenges to biosafety and biosecurity. Key safety concerns relate to the outbreeding and spread of these new varieties into natural populations, detectability of these new variants[29], and challenges to established co-existence provisions.[30]

Below some quotes from leading researchers address some of the relevant issues on biosafety and biosecurity: [31]

Leading Researchers	***Quotes***
J. Haber – on the issue of off-target effects:	*These enzymes will cut in places other than the places you have designed them to cut, and that has lots of implications.*
Jennifer Doudna - on biosafety/biosecurity of an experiment creating a human cancer model through a CRISPR engineered virus:	*It seemed incredibly scary that you might have students who were working with such a thing.… It's important for people to appreciate what this technology can do.*
George Church - - on the safety risks of gene drives in relation to the environment:	*It has to have a fairly high pay-off, because it has a risk of irreversibility — and unintended or hard-to-calculate consequences for other species.*
Jennifer Kuzma - on the detectability of genome edited GMOs in nature:	*With gene editing, there's no longer the ability to really track engineered products. It will be hard to detect whether something has been mutated conventionally or genetically engineered.*
Kenneth Oye - on governance:	*It is essential that national regulatory authorities and international organizations get on top of this — really get on top of it.*

[28] T Sovová, G Kerins, K Demnerová, J Ovesná. Genome Editing with Engineered Nucleases in Economically Important Animals and Plants: State of the Art in the Research Pipeline, Curr. Issues Mol. Biol. (2016) 21: 41-62

[29] Breeding controls. Nature (2016) 14;532(7598):147. doi: 10.1038/532147a.

[30] H Ledford, THE CRISPR DISRUPTOR, Nature (2015) 522: 20-22

[31] H Ledford, THE CRISPR DISRUPTOR, Nature (2015) 522: 20-22

Recommendations

There are four levels where recommendations can be made to avoid exploitation of safety and security weaknesses in genome editing in the future.

1. Level: Technical level

Recommendation 1: Reduce off target effects, mosaicism and epigenetic effects through further research in higher fidelity and better understanding of genome editing technologies.

Recommendation 2: Use safe virus systems or alternative less risky vector systems to transfer genome editing tools.

Recommendation 3: Develop reversal gene drives in parallel that can undo the effects of gene drives.

Recommendation 4: Provide technological assistance (e.g. detection capacities for modified organisms) in implementing international obligations like the *Cartagena Protocol*.

2. Level: Containment Level

Recommendation 5: Ensure adequate biosafety risk classification and implementation of adequate containment measures in biosafety sensitive genome editing experiments.

Recommendation 6: Develop "molecular containment" approaches when working with genome edited high risk pathogens.

3. Level: Governance and Oversight level

Recommendation 7: Provide international guidance or amend existing guidance documents in biosafety and biosecurity to cover risks from genome editing.

Recommendation 8: Map the status of existing biosafety and biosecurity legislation as well as its practical implementation in countries carrying out genome editing experiments.

Recommendation 9: Include stakeholders (e.g. funding institutions, research institutions, researchers) in the responsible governance of research involving genome editing.

4. Level: International Standardisation

Recommendation 10: In case of gaps in legal oversight, develop international codes and guidelines for safe and secure work in genome editing.

1.2. CRISPR/Cas9 – Good Practice

Johannes Rath

Abstract

The problems in governing safety and security concerns in current genome editing research are manifold. Ranging from inadequate risk assessment tools, through large degrees of uncertainty over risks, to missing legal frameworks at the international and often also at the national level to effectively assess and mitigate risks. In such an environment, individual and collective self-governance of the scientific community and/or co-governance approaches become of critical importance.

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As an example, the Ethics Appraisal for research funded under Horizon 2020[32] is discussed. The Ethics Appraisal can be understood as a co-governance approach where legislators have provided the legal base for such an assessment; however, most of the assessment and risk mitigation rests on the expertise of individual researchers and independent experts.

It is concluded that, if applied appropriately, the Ethics Appraisal scheme can provide a suitable approach to address safety and security concerns in international genome editing projects, overcoming the existing patchiness in national and international governance and being flexible enough to accommodate the fast pace at which the technology advances. Critically important will be, however, that adequate expertise capable of carrying out risk benefit assessment in biosafety and biosecurity will be available during the Ethics Appraisal. Furthermore, adequate financial resources need to be provided in order to ensure that implementation of the requirements for safe and secure work environments in various countries can be accomplished.

Area of Good Practice

1. The Role of Ethics Appraisals in the harmonization of missing international governance in safety and security

Today, the global situation with regard to the harmonization and standardization of safety and security legislation in relation to genome editing is non-existent[33]. Although there are non-legally binding general international guidelines available for biosafety, no such guidelines exist in the area of security. In this context, the Horizon 2020 Ethics Appraisal scheme has the capacity to fill gaps and contribute to international harmonization in the governance of genome editing-related safety and security concerns.

2. The Role of Ethics Appraisals in best practice development

In line with the previous point and underlined by efforts in other areas (*e.g.* Declaration of Helsinki[34]), ethics assessment has the potential to develop codes and guidance documents for

[32] http://ec.europa.eu/research/swafs/index.cfm?pg=policy&lib=ethics
[33] H Ledford, US rethinks crop regulation, Nature (2016) 5 3 2: 13-14
[34] http://www.wma.net/en/30publications/10policies/b3/

best practice models. Proposals for best practices have been made by leading researchers, for example, on how to apply gene drives more safely.[35] The Ethics Appraisal process in Horizon 2020 could be one of the entry points for such best practices.

Analysis

The introduction of novel genome editing technologies like CRISPR/Cas9 has not only brought about a powerful new tool set for genetic engineering it will also, due to its technological simplicity and low costs, lead to a "democratization" of capacities. This challenges national as well as international law-based safety and security arrangements.[36] Here we assess the potential of research ethics promoted through large funding institutions as a vehicle to increase safety and security in this specifically challenging environment.

Ethics is often considered a hindrance to scientific progress. The recent refusal to publish work done on hESC through genome editing by US- and UK-based top scientific journals might be interpreted as limiting scientific freedom based on ethical principles, especially as the work was finally published in a Chinese journal. Different ethical standards in different countries may therefore result in reduced trust, and potentially limit international collaborations in the research area.

Different ethical standards in different countries may therefore result in reduced trust, and potentially limit international collaborations in the research area.

A key ethical concern in relation to genome editing relates to safety and security. Different national standards and capacities to handle safety and security issues in research exist. The impacts on international security by diverging national standards with regard to genome editing, are however substantial. Furthermore, genome editing does not only affect classical biosecurity issues like the creation of deadly weapons, but may also have long term security implications through human enhancement and environmental engineering. Commonly accepted guidelines on how to handle these issues are currently almost completely missing.

In a situation like this much depends on bottom-up initiatives from individual stakeholders. In order to provide for a functional bottom-up governance approach, general guidance, individual project risk assessment and implementation of risk mitigation measures are needed. As for the aspect of gene drive applications of genome editing, the proposed principles for safety proposed by leading scientists can be seen as providing general guidance.[37] The mandate of the European Commission Ethics Appraisal scheme is of a

[35] OS Akbari, HJ Bellen, E Bier, SL. Bullock, A Burt, GM Church, KR. Cook, P Duchek, OR Edwards, KM Esvelt8, VM Gantz, KG Golic, SJ Gratz, MM Harrison, KR Hayes, AA James, TC Kaufman, J Knoblich, HS Malik, KA Matthews, KM O'Connor-Giles, AL Parks, N Perrimon, F Port, S Russell, R Ueda, J Wildonger. Safeguarding gene drive experiments in the laboratory: Multiple strategies are needed to ensure safe gene drive experiments
Department. Science (2015) 349(6251): 927–929. doi:10.1126/science.aac7932

[36] E Waltz, Gene-edited CRISPR mushroom escapes US regulation Nature (2016) 532: 293

[37] OS Akbari, HJ Bellen, E Bier, SL. Bullock, A Burt, GM Church, KR. Cook, P Duchek, OR Edwards, KM Esvelt8, VM Gantz, KG Golic, SJ Gratz, MM Harrison, KR Hayes, AA James, TC Kaufman, J Knoblich, HS Malik, KA Matthews, KM O'Connor-Giles, AL Parks, N Perrimon, F Port, S Russell, R Ueda, J

framework for co-governance to, *inter alia*, govern safety and security aspects. The work of independent expert panels to provide individual risk assessments of specific research activities and their outcome can also be seen as tailored risk mitigation mechanisms. Through this concept of co-governance, the Ethics Appraisal provides an inclusive framework for stakeholders which, if applied adequately, has the potential to safeguard ethical issues in relation to safety and security in genome editing.

Lessons Learned

Lesson 1: Although national and international legal standards in safety exist, fast evolving technologies like genome editing cannot be handled in a timely manner in a law-based top-down approach. In order to safeguard research, a bottom-up approach, building on ethics and including various stakeholders, has the capacity to mitigate safety and security concerns in international collaborative research.

Lesson 2: Since classical security safeguards, like export control of technologies, do not work in the context of genome editing because of its technological simplicity and low cost, alternative measures to increase security are needed. Research ethics has in the past complemented gaps that could not be filled through export control or information security mechanisms (e.g. application of the Responsible Research concept to the US Dual Use governance). Research ethics should be a critical element when developing a framework for the governance of security sensitive genome editing research.

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Lesson 3: Oversight regimes need to be sufficiently flexible to mitigate the rapidly emerging safety and security challenges posed by emerging technologies. Research funding institutions with established oversight mechanisms on safety and security like the European Commission therefore have not only a unique tool but also a strong responsibility in safeguarding genome editing research against safety and security risks.

Wildonger. Safeguarding gene drive experiments in the laboratory: Multiple strategies are needed to ensure safe gene drive experiments Department. Science (2015) 349(6251): 927–929. doi:10.1126/science.aac7932

2. The Use of Non-human Primates in Research

Kate Chatfield and David Morton

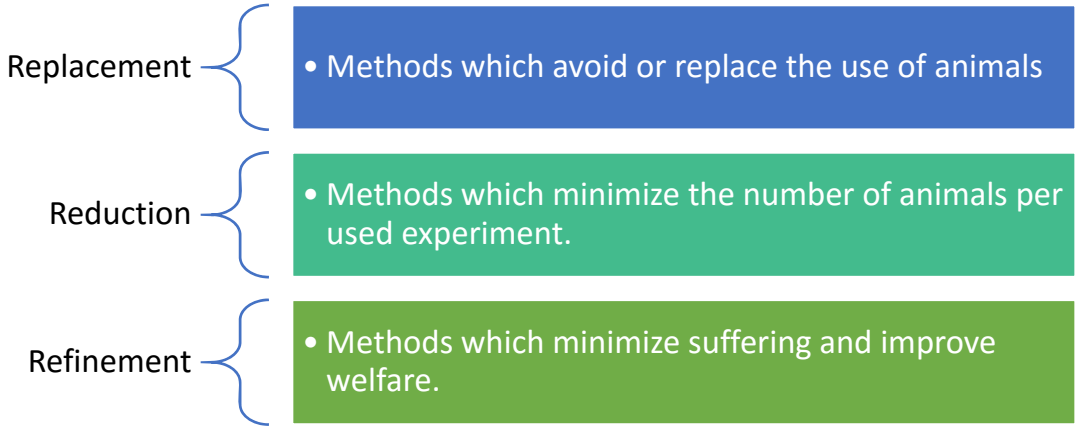
Abstract

The use of non-human primates in biomedical research is a contentious issue that raises serious ethical and practical concerns. In the EU, where regulations on their use are very tight, the number of non-human primates used in research has been in decline over the last decade. However, this decline has been paralleled by an increase in numbers used elsewhere in the world, with less regard for some of the ethical issues (e.g. genetic manipulations). There is evidence that researchers from high income countries, where regulations are strict on the use of non-human primates, may be tempted to conduct some of their experiments in countries where regulation is less strict, through new collaborative efforts. In collaborative ventures, equivalence in the application of ethical standards in animal research, regardless of location, are necessary to avoid this exploitation.

Area of Risk of Exploitation

This case study applies both to academic researchers and to political entities supporting such research. Many areas of research using animals cause public concern, but none more so than the use of non-human primates. The European Directive 2010/EU/63 imposed several stringent conditions on their use in research, including their acquisition, limited scientific reasons for their use, husbandry and housing conditions and record keeping, restricting the overall severity of the procedures carried out, and their care during an experiment. Non-human primates are used in a number of research fields, including neurological research that involves advanced brain responses which can be tracked in various ways; in safety testing for novel medicines and new batches of vaccines; in defence studies; and in studies that may be to the benefit of the wild population of animals. While in most areas of research the animals may not suffer extremes of pain, some of the work will cause significant mental distress for the animals concerned. Substantial human benefits can be envisaged by some types of work (e.g. defence strategies and antidotes) and this may drive some researchers to seek collaboration abroad to carry out work that might be limited or severely curtailed in their own countries.

Diagram 2: The Three Rs



Compromises could be made on the acquisition of experimental primates as wild caught animals, often seen as local pests, could be used instead of purpose-bred animals. Furthermore, the application of the Three Rs[38] is likely to be less stringent, particularly in refinement strategies in the housing and husbandry of the animals, and even more so for the experimental design of studies (for example, the implementation of severity limits and humane endpoints).

Animal Research World-Wide

Animal experimentation is used for many biomedical research activities, including pharmaceutical studies, basic scientific research, biotechnology and traditional medicine research. We cannot determine the exact number of animals used worldwide in research, but the global figure has been estimated at between 50 and 60 million animal procedures per year, with rats and mice by far the most commonly used species (Understanding Animal Research 2015).

It is estimated that non-human primates represent a very small proportion of the total number of animals used in experiments: less than 1 in 1,000 animals in the EU, and approximately 3 in 1,000 in the US (Scientific Committee on Health and Environmental Risks 2009). However, worldwide, the number may equate to more than 100,000 each year.

Worldwide, more than 100,000 monkeys and apes are being used in biomedical research each year.

A wide variety of non-human primate species are used in research and can be divided into New World species such as marmosets e.g. the Common marmoset (*Callithrix jacchus*), and Old World species such as the long-tailed or cynomolgus or crab-eating macaque macaque (*Macaca fascicularis*), and the rhesus macaque (*Macaca mulatta*). In addition, baboons, another Old World primate of the genus Papio, are occasionally used.

Non-human primates are highly valued in biomedical research because of their genetic similarity to humans[39] which means they can be especially useful for testing the safety of new drugs, studying infectious diseases, and in neurophysiology, where they can be trained to respond to external stimuli and their central nervous system responses monitored or followed in some way.[40] However, their similarity to humans also raises specific ethical concerns about

[38] Reduction, refinement and replacement – the underpinning requirements of most policies and regulations in animal research. See also Diagram 1.

[39] For example, baboons have a 91% DNA similarity (see also http://www.scientificamerican.com/article/tiny-genetic-differences-between-humans-and-other-primates-pervade-the-genome/).

[40] Safety testing of new drugs, substances and devices (especially those aimed for human medicine and dentistry) accounts for approximately 67% of the total number of non-human primates used in research. Fundamental biological research accounts for a further 14% and research and development of medical and dental products and devices for humans for about 13%. (Scientific Committee on Health and Environmental

their use in scientific experiments (Scientific Committee on Health and Environmental Risks 2009).

In the EU, animal experiments are governed by Directive 2010/63/EU on the protection of animals used for scientific purposes, and EU Member States were required to introduce the provisions of the Directive into their national legislation from 1 January 2013. According to this Directive, the use of non-human primates demands special attention and certain requirements have to be met.

> Due to their genetic proximity to human beings and to their highly developed social skills, the use of non-human primates in scientific procedures raises specific ethical and practical problems in terms of meeting their behavioural, environmental and social needs in a laboratory environment. Furthermore, the use of non-human primates is of the greatest concern to the public (Article 17).

Consequently, the use of non-human primates is strictly controlled and the purposes for which they can be used require rigorous scientific justification:

> Therefore, the use of non-human primates should be permitted only in those biomedical areas essential for the benefit of human beings, for which no other alternative replacement methods are yet available. Their use should be permitted only for basic research, the preservation of the respective non-human primate species or when the work, including xenotransplantation, is carried out in relation to potentially life-threatening conditions in humans or in relation to cases having a substantial impact on a person's day-to-day functioning, i.e. debilitating conditions (Article 17).

Furthermore, there are other requirements on the provision of life histories and severity monitoring that add further criteria to try to ensure that the science is of the highest quality and that animal welfare is not avoidably compromised (Articles 30, 39).

With increased scrutiny and regulation, and in reaction to public opinion, there has been a marked reduction in the number of non-human primates being used in research. Figures show that approximately 6,000 were used in scientific procedures in the EU in 2011, compared with almost 10,000 in 2008 (SCHEER 2016). Furthermore, some institutions are no longer using primates, like the Harvard Medical School which closed its affiliated primate facility in 2015. Others are reviewing their primate use; for instance, the US National Institutes of Health announced recently that it would review all non-human-primate research that it funds (Cyranoski 2016).

Some institutions are no longer using primates, like the Harvard Medical School which closed its affiliated primate facility in 2015.

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In light of this trend, the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) announced (June 2016) that it is seeking more information to update the EU Directive on the use of non-

Risks, 2009. Non-human primates in research and safety testing, available: http://ec.europa.eu/health/scientific_committees/opinions_layman/en/non-human-primates/index.htm).

human primate research. In particular, they are seeking opinion on areas of research and testing where non-human primates continue to be used, possibilities to replace their use, and the potential implications for biomedical research, as well as the question of whether the use of non-human primates should be banned altogether in the EU (SCHEER 2016). In Europe, researchers say, the climate is growing colder for such research (Cyranoski 2016).

While the decreasing number of non-human primates used in the EU may be welcomed and regarded as a beneficial impact of Directive 2010/63/EU, there is rising concern that this decrease has coincided with an increase in the use of non-human primates elsewhere in the world. There is also a concern from some in the scientific community that the opportunity to gain valuable insights into some human diseases will be lost.

Hau (2014) describes how, due to political pressure and the introduction of the new EU Directive, biomedical research with non-human primates is increasingly difficult to carry out in Europe. Consequently, European scientists are seeking collaboration with non-human primate centres outside of Europe (Hau *et al.* 2014).

While the decreasing number of non-human primates used in the EU may be welcomed, there is rising concern that this decrease has coincided with an increase in the use of non-human primates elsewhere in the world.

This has also been noted by Cyranoski (2016) who explains that non-human-primate research is increasingly faced with, "a tangle of regulatory hurdles, financial constraints and bioethical opposition" (p.300). As a result, some researchers have stopped trying to do such work in the West, and he quotes one neuroscientist as saying that, 'red tape drove her to China' (Cyranoski 2016).

Historically, there has been a long tradition of collaboration between European academic institutions and those in the US and Canada but the network of collaborating institutions is becoming increasingly globalised (Macy 2011). This is highly positive in many respects but if animals are to be used in collaborative research, the attention to ethical concerns, animal welfare and the quality of the research must be equivalent among research partners around the globe[41] (Bayne *et al.* 2015). However, regulations, norms, practices and standards in animal research are not currently harmonized as is clearly illustrated by the following case.

Specific Case and Analysis

In 2013 a report published in the British press alleged that an academic from Newcastle University was bypassing British law in his research with wild-caught baboons in Nairobi (Macrae 2013). A professor of Movement Neuroscience, who is part of a team investigating methods to treat conditions affecting the brain such as stroke, spinal cord injury and motor neurone disease, was accused of exploiting a cheap and plentiful source of animals in Nairobi.

The accusation followed an undercover investigation by the British Union for the Abolition of Vivisection (BUAV) who had covertly obtained photos and video footage of the baboons in

[41] It is already a requirement of Horizon 2020 funding that collaborating countries comply with EU laws.

the Institute of Primate Research in Nairobi. BUAV contended that the images revealed disturbing welfare standards and that UK researchers should not accept lower standards when carrying out research in non-UK facilities.

The Newcastle Professor is quoted as saying that while animal welfare standards weren't as high (as in the UK) in Nairobi, they had improved greatly during his time there and that the Institute of Primate Research was committed to making further improvements. In addition, he accepted that the experiments would not be permitted in the UK, but argued that it was better to capture wild baboons, who had lived for four or five years in the wild, rather than breed them in captivity. Experiments on wild-caught animals are not normally permitted in the UK, but he claimed that the reasons behind the ban on using wild-caught primates in the UK did not apply to his experiments in Africa.

"Outcry as UK scientist flies to Africa for experiments on monkeys that are banned here".

In a subsequent article in the Kenyan press, the Institute of Primate Research in Nairobi denied reports that the facility was being used to conduct harmful research on baboons, claiming that the studies were aimed at advancing medical research for the benefit of Kenya and the world.

It added that out of Kenya's 13 non-human primate species, only the two most abundant species (baboons and African Green Monkeys (another Old World primate)) were being used for biomedical research and that, far from being endangered, baboons are considered as pests in the wild and that those being used in the experiments would otherwise have been killed (Kariuki 2014).

This story received significant coverage in the British media with various celebrities adding their voices to the protests (Nelson 2013). A petition was launched by the University Student Union to pressurise the university into ending such experiments and, following public pressure, Newcastle University decided to halt the baboon experiments in 2014.

There are two immediate concerns that arise from this case. First, that the standards of animal welfare in Kenya may have been inferior to the standards required in the EU and secondly, that the baboons had been taken from the wild.

It is not possible to make judgements about the equivalence of standards of animal care without the full facts of the case. However, it is perfectly clear that these experiments would not have been permitted on wild-caught animals in the UK. Of the 2,466 non-human primates used in experiments in the UK in 2014, none had been taken from the wild (Home Office 2015).

For many researchers it would appear that concerns about equivalence of standards in animal research are fundamental. As Niemi (2011) points out, with an unprecedented level of

scrutiny of research possible via the internet, the negative consequences of mere allegations of animal mistreatment are greater than any theoretical advantage to be gained by conducting animal research in a less rigorous environment. This sentiment is echoed by Ogden (2011), who maintains that pharmaceutical companies and biotech companies would not want to be perceived as using outsourcing so that they could bypass humane care and use standards. Generally, it is acknowledged that the pharmaceutical industry has a vested interest in the promotion of high-quality animal care and facilities and high quality research outputs (Medina *et al.* 2015).

However, even for those with the best of intentions, there are challenges for collaborative animal research that stem from a lack of consensus on what should be considered as best practice across various cultures. In addition, regulations on animal research and welfare differ between countries and these regulations are subject to change (Landi 2011).

Even for those with the best of intentions, there are challenges for collaborative animal research that stem from a lack of consensus on what should be considered as best practice across various cultures.

In China, for example, there does not appear to be the same degree of public opposition to the use of non-human primates in research and many new non-human primate research centres are being established. Some of these centres advertise themselves as 'primate-research hubs', encouraging researchers to fly in and out and make use of their extensive facilities (Cyranoski 2016).

In Africa, non-human primates are used in research in a number of countries including Kenya, South Africa and Ethiopia. Some Old World primate species and baboons are considered agricultural pests in many parts of Africa and legislation governing their use in research is generally lacking (Hau *et al.* 2014).

Most African countries are lagging behind high income countries in regard to the existence or adequacy of national and/or institutional policies and guidelines on the use of animals in research. While some African countries have been developing ethical or legal frameworks aimed at safeguarding the welfare of animals used for research, in most African countries there is a serious lack of information in the public domain. Consequently, some researchers from high income countries may be tempted to export their research activities to collaborating African institutions where ethical and legal frameworks on the use of animals may be less stringent (Nyika 2009).

In 2011, Kimwele *et al*. published results from their survey of thirty-nine highly ranked academic and research institutions in Kenya aiming to identify those that used animals, their sources of animals, and the application of the Three Rs. At that time, twenty-eight (71.8%) institutions had no designated committee to review or monitor protocols using animals. Only two of the institutions with an established Animal Care and Use Committee referred to documented guidelines, and neither documented the composition of their committees (Kimwele *et al.* 2011).

Across Africa as a whole, the absence of legal and ethical frameworks and committees to

review protocols that involve animals in research means that animal protection could be severely compromised as well as the validity of the scientific outcome data. In addition, the lack of institutional animal ethics committees promotes the outsourcing of animal research to these unregulated institutions (Nyika 2009).

This situation is compounded by the challenge that most Western academic institutions do not have much experience with local animal care and use regulations in other countries (Macy 2011). Hence, a double ethics review, where the Western committee also provides an ethics opinion is not a solution either.

Recommendations and Conclusion

The following gives our recommendations and a short conclusion.

— The overarching requirement for avoidance of exploitation in animal research is a global code of conduct for research involving animals. There are moves towards this outcome but it is currently far from resolved. In recent years there have been attempts from different organisations to develop global frameworks. In 2012, the International Council for Laboratory Animal Science (ICLAS) and the Council for International Organizations of Medical Sciences (CIOMS) updated their 'International Guiding Principles for Biomedical Research Involving Animals' (CIOMS & ICLAS 2012). These principles also incorporate the Three Rs and are intended to serve as a framework of responsibility for all countries, including those with emerging research programmes.

— In the absence of a global code of conduct, there will inevitably be variations in standards, regulations, legislation, scientific integrity, data validity, and humane practices. In light of this concern, for collaborative research, researchers from high income countries have an obligation to ensure application of the same standards that are upheld in their home nations and home institutions.

— For residents of the EU this entails full compliance with Directive 2010/63/EU in a manner that is both transparent and auditable. Hence, partner institutions must also be transparent and auditable in the application of the principles that are equivalent to those specified in Directive 2010/63/EU. This must be the requirement even when local legislation and regulation are less strict or different.

— In practice this may entail much closer, on the ground, collaboration with partners, working together with local representatives to ensure equivalence in all activities such as animal housing and care as well as experimental procedures.

— European funders of research involving animal experimentation have a particular responsibility to ensure that full compliance with the Directive 2010/63/EU is a necessary condition for their support.

Although non-human primates constitute a small percentage of the number of animals used in research worldwide, their use raises particular ethical concerns. In the absence of a global

code of conduct for animal research, animals in countries where regulations and legislations are less well formulated are at risk of exploitation in research. For collaborative ventures, it is vital that institutions from high income countries apply precisely the same standards that are required in their home countries and institutions. This may entail close working relationships with local partners to ensure equivalence in standards and some investment to achieve that goal.

For non-human primates, the application of equivalent standards may result in a reduction of numbers used in collaborative biomedical research and will result in more rigorous science and improved welfare standards and a better application of the Three Rs.

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3. ICT and Mobile Data for Health Research

David Coles, Jane Wathuta, Pamela Andanda

Abstract

Cell and mobile phone subscriptions had reached 87% of the world's population by 2011 (ITU World Telecommunication 2011). Notably, Africa has 'the fastest mobile phone growth rate in the world and… a proliferation of social media users' (Mutula 2013:31). Mobile phones that can run software applications (apps) have fostered use, inter alia, in health settings to improve diagnosis and personalize health care (Mosa et al. 2012). This fast-paced development saw the number of 'mHealth' apps reach 97,000 as of March 2013 (He et al. 2014).

The application of mobile technologies (mobile phones or other remote monitoring devices) for health-related purposes is termed 'mHealth' or mobile health; in other words, a mobile tool for expanding access to health information and services around the world (K4Health). According to the World Health Organization (WHO, 2011:6), mHealth is the "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices". mHealth has also come to signify any use of mobile technology used to address healthcare challenges such as access, quality, affordability, matching of resources, and behavioural norms (Qiang et al. 2011). Most mHealth interventions nonetheless use mobile phone technology, rather than other mobile handheld devices, due to its versatility as an ICT tool (Leon and Schneider 2012:7).

Africa has 'the fastest mobile phone growth rate in the world and… a proliferation of social media users.

With the pervasive growth in technology infrastructure, mHealth can reach communities in ways that health services and other communication tools cannot. Mobile phones are described as potentially the most widespread embedded surveillance tools, especially due to the use of location sensors and the subsequent possibility of documenting and quantifying habits, routines, and personal associations (Shilton 2009). This case study focuses on the potential ethical issues associated with the use of mHealth apps in medical research and healthcare. mHealth offers "…attractive low-cost, real-time ways to assess disease, movement, images, behaviour, social interactions, environmental toxins, metabolites…" (Collins 2012:1). They have the power to bring the research lab to the patient and obtain real-time, continuous biological, behavioural and environmental data (Collins 2012).

Mobile phones can and do collect a wide range and quantity of personal information from their user, with or without their knowledge, which raises novel and complex ethical and practical challenges. Research teams (and clinicians) need to understand these challenges so that without rejecting mHealth and related mobile technological advancements, any unintended harms are minimized (Carter et al. 2015). Wicklund (2015) observes that clinical studies that utilize mHealth devices and platforms are venturing into more uncharted ethical territory.

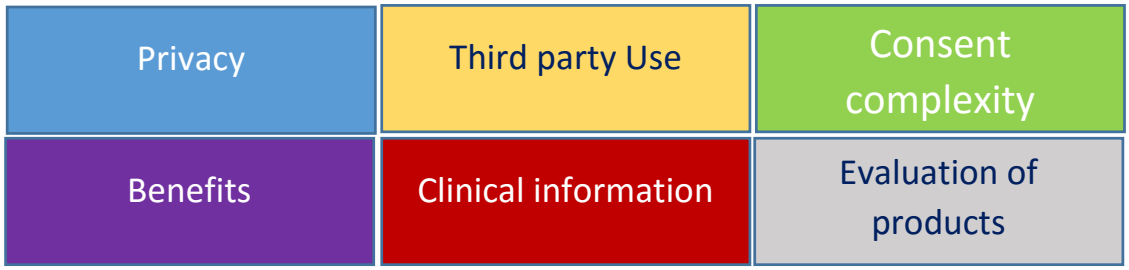
Area of Risk of Exploitation

mHealth software apps can be used, *inter alia*, for large scale collection of health-related data for biomedical research; the so-called 'Big Data' (Park et al.2014; Hsieh et al. 2013). mHealth in general however raises concerns regarding data security issues – from transmission of data to its local storage, and 'ownership' of what is otherwise considered confidential patient data. This data is easy to obtain, but difficult or impossible to retract once shared. In addition to safety and security risks, the use of mobile sensing also causes disruption of social boundaries and challenges gradations between public and private (Shilton 2009). One of the key challenges of using mHealth in Low and Middle Income countries (LMICs) is how to ensure workable approaches to privacy and security (Leon and Schneider 2012:19).

Carter et al (2015) have identified a range of ethical issues raised by the use of mobile phones for research and clinical purposes. These are:

- Protection of privacy,
- Minimizing third-party uses of data,
- Informing patients of complex risks when obtaining consent,
- Maximizing benefits while minimizing the potential for disclosure to third parties,
- Careful communication of clinically relevant information, and
- Rigorous evaluation and regulation of mHealth products before widespread use.

Diagram 2 – Ethical Issues in Mobile Phone Data Use for Research



In practical terms, the issues that are discussed below must be considered carefully:

a) Context-based and fully informed consent should be obtained

Researchers should seek and obtain informed consent before using mHealth technologies in research. Accordingly, participants must be informed and understand the risks and benefits of using mHealth technologies, and subsequently make a free and voluntary decision about their participation. Risks associated with mHealth are complex and these need to be communicated and negotiated. If the study involves collection of data from interaction with identifiable third parties it may be necessary to also obtain their informed consent. This would in turn mean that the mHealth participant will have to disclose their condition and/or mHealth participation (Carter et al. 2015).

b) Only necessary data should be collected

Compared with other health information systems, mHealth collects a much larger amount and broader range of data through patient lifestyles and activities, over an extended period

(He et al. 2014). A potential threat to bear in mind in this regard is the collection of excess raw data to maximize the information that a research team can extract (Carter et al. 2015).

c) Any tracking should be proportionate and the correct person should be tracked

Continuous or intermittent recording and transmission of detailed information about where a person is, and to some extent what they are doing, may pose risks to privacy and confidentiality. There are risks of inadvertent insight into a participant's behaviour revealing information beyond the profiles that are scientifically justified and being sought through data collection. In addition, this poses problems related to informed consent, as privacy may be violated in ways unforeseen by either the investigators or the participants. Text messages (SMS) can be read by persons other than the intended recipient of the information; messages can be forwarded and can remain on unsecured devices for the lifetime of the technology. They could also lead to unintended disclosure of the presence of a medical condition (Labrique et al 2013).

d) Research participants should know exactly which data is collected and who will or could have access to it

This is a great challenge especially in a global research environment, which increasingly requires the sharing of data in publicly available repositories. The case of an alleged breach of smartphone users' privacy by manufacturers of popular smartphone apps for Apple and Android devices is illustrative of this risk. The manufacturers are alleged to have gathered information from Kenyan users' personal address books on the phones, stored it on their own computers, and transmitted it without the knowledge of its owners, all of which testifies to the lack of guarantee of privacy in the use of smartphones (Mutula 2013; Daily Nation 2012).

Security of data collected via mobile phones cannot be guaranteed either, in part because no strict privacy regulations exist.[42] Many mHealth apps do not use encryption when transferring data and even when they do, hackers and governments can still gain access. Potential violations of privacy include hacking of personal data with the known likelihood of identity theft and financial losses, computer malware and virus programs, or malevolent app developers who steal data for commercial or criminal purposes (He et al. 2014).

e) Incentives to take part in research should be proportionate and not result in exploitation

Undertaking research involving mHealth apps often requires having a smartphone. If researchers specifically target those who do not have access to newer devices and other modes of mobile technology they may thereby unduly influence them to take part (Labrique et al. 2013:3). A patient should, however, not be excluded from mHealth monitoring benefits due to their inability to afford a phone capable of supporting the app or to connect with the

[42] Companies like Apple and Google have to comply with the privacy regulations in each of the countries where they collect the data. Where little or no privacy regulations exist this gives the companies great scope in what data they collect and what they use it for. Interestingly Apple have announced that for their new iPhone operating system (IOS10) they will be introducing "Differential Privacy" which they claim will enable them to collect much more user personal data while preserving their privacy. This concept involves introducing numerical "noise" into the data collected to de-identify it (see http://www.theverge.com/2016/6/17/11957782/apple-differential-privacy-ios-10-wwdc-2016). However it is questionable whether this will provide suitable data for research purposes (see Friedman & Schuster 2010).

mobile or internet networks required to transmit potentially large volumes of data. Hence, this requirement needs considerable judgement.

Specific Case and Analysis

The details of the case of tele HIV/AIDS counselling in South Africa were obtained from an interview with Cell-Life's General Manager, Peter Benjamin. The interview was conducted and published by Cathy Boyle (2011). Additional information is available from a report that was prepared on the use of mobile technologies for the monitoring and evaluation of public sector community based health services (Leon and Schneider 2012).[43]

Cell-Life, a non-profit organization, entered into a contract with the South African National Department of Health (NDOH) for a big mHealth project. "Cell-Life started in 2001 as a research collaboration between staff of the engineering faculty of the University of Cape Town (UCT) and the Cape Peninsula University of Technology (CPUT)" (Loudon and Rivett 2013). It became a not-for-profit organization in 2006 (Loudon and Rivett 2013). As per the contractual terms, NDOH set up a national mHealth system that uses cell phones for monitoring an HIV Counselling and Testing (HCT) campaign.

The South African National Department of Health set up a national mHealth system that uses cell phones for monitoring an HIV Counselling and Testing (HCT) campaign.

Cell-Life uses a chat system called MXit, which enables users to send an instant message over a cell phone system. To do this, users have to download a small application that connects them to the MXit server, enabling immediate communication with anyone else on MXit. The app sends SMS-type messages through GPRS[44] thus making text messaging effectively free.

Cell-Life created a website within MXit where it provides all the usual HIV content, information and interactive quizzes. An interesting feature that Cell-Life has included is linking MXit to the National AIDS Helpline, so that users can text on MXit and the message goes through to the computer screen of professional HIV counsellors at the National AIDS Helpline. The counsellors subsequently type back and the text goes back to the users' cell phone screen.

Cell-Life was awarded additional contracts by the NDOH for the design and implementation of a Mobile Monitoring and Reporting system for the national HIV Counselling and Testing (HCT) campaign, and the national Anti-retroviral Treatment expansion programme.[45] These systems have been the subject of research into how software applications for monitoring and

[43] See also Mobile M & E for the National HIV Counselling and Testing Campaign, available at http://www.cell-life.org/projects/health-care-and-testing/

[44] General Packet Radio Service (GPRS) is a packet oriented mobile data service on the 2G and 3G cellular communication system's global system for mobile communications (GSM). Wikipedia.

[45] Mobile M & E for the National HIV Counselling and Testing Campaign, available at http://www.cell-life.org/projects/health-care-and-testing/

evaluation of community based care are used in a research and service delivery context (Leon and Schneider 2012).

The information that is processed and transmitted through the software apps relates to patients' personal information, which is subsequently stored and monitored through the system. The use of mobile phones in this process raises practical ethical issues such as concerns about the protection of information/privacy, and consent to the potential use of such information for research purposes (cfr. part 1.2). As Labrique et al (2013) have observed, although mHealth apps ensure the availability of real-time data that brings with it new and beneficial strategies, nevertheless the rapid adoption of these technologies necessitates careful consideration of the ethical issues associated with their use. Accordingly, it is essential that existing standards and practices be supplemented with new guidelines to ensure adequate protection of patients and vulnerable populations. The gap between the development of ethical standards and guidance and technological innovation needs to be reduced, so that researchers and other stakeholders may have a framework of reference to assess and mitigate the risks ensuing from mHealth research and data collection.

Recommendations

The following measures can help to avert the possibility of exploitation in the context of mHealth:

- Developers should determine when, where and how sensitive data are uploaded and stored, to minimize the risk of privacy violations. In addition, they should take steps, by using encryption and anonymization (Carter et al. 2015; He et al. 2014), to ensure the data collected by an mHealth app are not available to other apps or programs contained on the phone or in third party storage without security and privacy guarantees (He et al. 2014).
- Participants should be able to control what they consent to and how their data may be used and stored. The data should be deleted as soon as they are no longer needed (Albrecht and Fangerau 2015).
- Appropriate regulations of mHealth devices or apps should be developed to ensure their safety and effectiveness, including minimal privacy violations and guarantees that they provide clinically accurate information. Albrecht and Fangerau (2015) have, for instance, recommended the transformation of the fundamental principles of medical ethics in order to make them applicable to mHealth.
- Proven new innovations for improvement of data protection and privacy should be implemented by researchers as soon as possible after they become available.

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4. International Genomics Research involving the San People

Roger Chennells, Andries Steenkamp[46]

Abstract

In 2010 an international genomic research project entitled "Complete Khoisan and Bantu genomes from southern Africa" was published in *Nature* amidst wide publicity.[47] The research aimed to examine the genetic structure of "indigenous hunter-gatherer peoples" selected from Namibia, and to compare the results with "Bantu from southern Africa", including the Nobel peace prize winner Archbishop Desmond Tutu. Four San individuals, each the eldest in their respective communities, were chosen for genome sequencing, and the published article analysed many aspects of the correlations, differences and relationships found in the single nucleotide polymorphism (SNPs)[48] within the sequenced genomes. A supplementary document that was published with the paper contained numerous conclusions and details that the San regarded as private, pejorative, discriminatory and inappropriate. The San leadership met with the authors in Namibia soon after publication, asking why the San leadership had not been approached for permission in advance, and enquiring about the informed consent process. The authors refused to provide details about the informed consent process, other than stating that they had received video-recorded consents in each case.[49] Their view in denying the right of the San leadership to further information was based on the fact that the research project had been fully approved by Institutional Review Boards in three countries,[50] and that they had complied with all the relevant requirements. The San leadership wrote to *Nature*, expressing their anger at the inherent insult, and lack of respect displayed by the process (Ngagaeaja 2011).

Traditional San Leader /Una Rooi

This case study details the most serious aspects of the perceived exploitative nature of the research, and the San response.

Area of Risk of Exploitation

The arena within which this case study plays out is the conducting of genomic research on a vulnerable population, with a focus on the enhanced need for respectful and authentic prior

[46] Thanks to Francesca Cavallaro for additional input

[47] Schuster et al. (2010). Complete Khoisan and Bantu genomes from Southern Africa. *Nature*. 2010 Feb 18, vol. 463, 943-7 (online available at http://www.nature.com/nature/journal/v463/n7283/pdf/nature08795.pdf).

[48] Single nucleotide polymorphism is often abbreviated to SNP, and is a variation in a single nucleotide that occurs at a specific position in a genome, where each variation is present to some appreciable degree within a population.

[49] Vanessa Hayes: Personal email communication to B Begbie-Clench, WIMSA, dated 11 May 2011.

[50] Approvals were obtained from the Institutional Review Board of Penn State University, USA, the University of Limpopo Ethics Committee, South Africa, and the Human Research Ethics Committee of the University of New South Wales, Australia.

informed consent. Whilst the genomic research itself is undoubtedly of potential benefit to humankind as well as to the participant population, the particular risk of exploitation lies in the fact that publication of certain types of information gleaned from genomic research is essentially of a sensitive and private nature, which can result in potential embarrassment, discrimination, and collective psychological damage. The informed consent allegedly gained for this complex research project from the illiterate San participants used for the research, was never disclosed to the San leadership, and as is made clear below, the nature and content of the research publication was indeed damaging to the community on a variety of levels.

Specific Case and Analysis

Kalahari, South Africa

The San peoples of southern Africa as a general population are known to contain the oldest human DNA on earth, and are consequently much sought after for population-wide genomic research aimed at understanding various aspects of human evolution. The San peoples, known to be the earliest "hunter-gatherer" populations of southern Africa, number an estimated 100 000 individuals spread across at least five countries, with the largest populations in Namibia, Botswana and South Africa. Since 1986 the seven dominant linguistic groups have formed elected organisations in each country aimed at representing and protecting the rights of their illiterate rural populations. One of the most important roles of the San Councils of Namibia, Botswana and South Africa are to protect their people from unwanted, inappropriate or exploitative research.[51]

The stated purpose of the genomic research project under discussion was to sequence the genomes of four selected San individuals, and to "characterise the extent of whole-genome and exome diversity amongst them" as well as an individual man from Bantu extraction. In addition it was to "compare the described variants to known data-bases" in order to pinpoint genetic variations in genome-wide data, and to "facilitate inclusion of southern Africans in medical research efforts"[52].

In about 2009 researchers associated with the three universities began the process of obtaining informed consent and taking DNA samples from four selected San elders from three linguistic groupings, described as Tuu, !Kung and Ju/'hoansi. How the researchers conveyed and described the methodology, aims and objectives of the complex research project via translators to the four chosen illiterate elders will perhaps never be known, as the San leadership subsequently formally requested, but were refused access to, this information. According to the published research, "all Bushmen consented via video-recorded verbal consent." In February 2010 the research was published with wide publicity in the popular

[51] http://www.sasi.org.za/index.html
[52] Schuster et al. (2010). *Nature*. 2010 Feb 18 vol. 463, p. 943.

media, in an academic paper entitled, "Complete Khoisan and Bantu genomes from southern Africa" and in an associated paper entitled Supplementary Information.[53]

WIMSA (Working Group of Indigenous Minorities in Southern Africa) Acting Regional Coordinator Ben Begbie-Clench, addressed the authors both verbally and in writing, requesting details of the informed consent process, as set out below. Mathambo Ngakaeaja, deputy director of WIMSA, subsequently wrote to *Nature* on 18 February 2011 objecting to the Schuster publication, describing how central the term 'prior informed consent' is for all research affecting indigenous peoples. After commenting critically on the persistent refusal of the researchers to approach or engage meaningfully with the official San leadership structures, Ngakaeaja stated that the purpose of his letter was "to draw attention to the absolute arrogance, ignorance and cultural myopia that is present here."[54] He continued, "these researchers have basked in the glory of their publication whilst claiming smugly that they complied fully with the ethical requirements."

From the perspective of the San leadership, many aspects of this research study were deeply problematic, and would have been objected to if one of their organisations (e.g. Working Group of Indigenous Minorities in Southern Africa, the South African San Council, the South African San Institute) had been presented with an opportunity to consider the research prior to its commencement, and to approve the final form of the document prior to publication.

The San leaders engaged respectfully with the researchers following publication, requesting details of the informed consent process. Despite much correspondence[55], the authors persistently refused to acknowledge the need to consult with San leadership, or to provide details of the informed consent documentation or process.

The authors persistently refused to acknowledge the need to consult with San leadership, or to provide details of the informed consent documentation or process.

Some examples of why the research project was regarded as exploitative by the San leadership follow.

a) Use of Terminology:

The use of words such as 'Khoisan' and 'Bushmen' and 'hunter-gatherers' showed a lack of consultation with San leaders. All of the aforementioned terms were freely used in the publication, but these terms are each considered sensitive and problematic for different reasons. The San object, for example, to being referred to collectively under the term "Khoisan", a descriptive term coined by anthropologist Leonard Shutze in 1928 as a collective term referring to Khoi pastoralist and San hunter-gatherer groups.[56] The word "Bushman",

[53] Schuster et al (2010). Complete Khoisan and Bantu genomes from Southern Africa. *Nature*. 2010 Feb 18 vol. 463, pp. 943-947. Supplementary information (online available at http://www/nature.com/nature/journal/v463/n7283/full/nature 08795.html)

[54] Ngakaeaja Mathambo (2011) letter addressed to editor of *Nature* on 18 February 2011, Deputy Director, Working Group of Indigenous Minorities in Southern Africa (WIMSA) www.wimsa.org

[55] To preserve personal data protection, the emails held by a lawyer (the main author of this case study) are not reproduced here.

[56] Schlebush, C. (2010). *Nature*, vol. 464/ 5 March 2010.

meaning uncivilized people, is widely regarded as pejorative in certain contexts, and the anthropologically loaded term "hunter-gatherer" was frequently used in the paper, as well as in the Supplementary Information, as implying people with a generally acknowledged low social status. Consultation would have resulted in more acceptable uses of these and other terms.

b) Published conclusions far removed from genomic research:

Much of the discussion in the Supplementary Information sheet related to terms and concepts such as "hunter gatherer", the low status of "hunter gatherers", payment of *lobola* or bride-dowry, and marriage practices. An example is contained in the following sentence.

> "[A] feeling of inferiority associated with the Bushmen or San ethnic classification meant that many Bushmen women tried to uplift their status via marriage to Bantu men."[57]

These conclusions could not have been drawn from the results of the genomic research, nor could they have been permitted by an informed consent process to the collection of genomic data. The publication thus draws on and publishes conclusions drawn from other sources and disciplines, which would *not* have been permitted in a normal research consent process. The bad practice and injustice of publishing information that could not have been envisaged by the participants at the time of their consent would have been lessened had the authors made an attempt to return to the communities and explain the far-reaching and sensitive nature of their findings, prior to publication. The San leadership however have no knowledge of any attempt by the researchers to return to the communities, and to explain the complex nature of the published conclusions.

c) Individual vs collective consent:

It is well known that indigenous, rural and illiterate people do not understand individuality and individual rights in the manner of the West; their identity being deeply collective, and associated with their communities. This research project only obtained informed consent from the indigenous individuals who participated, whilst it is known and accepted that genomic research by its very nature speaks to collective issues. A plethora of research ethics guidelines have been published over past decades[58] setting out certain absolute requirements for research on indigenous peoples, one of which is that collective 'permission' should be obtained from the leadership, in addition to normal informed consent obtained from individuals. Not to do so is perceived as conveying a lack of respect for the community. However one of the authors wrote to WIMSA[59] saying, "As we are dealing with individuals in a personal manner (via their DNA) the individual has a right to participate or not as the information contained is of direct impact to that person." This response does not consider that genetic information also has direct impact on family members of that person.

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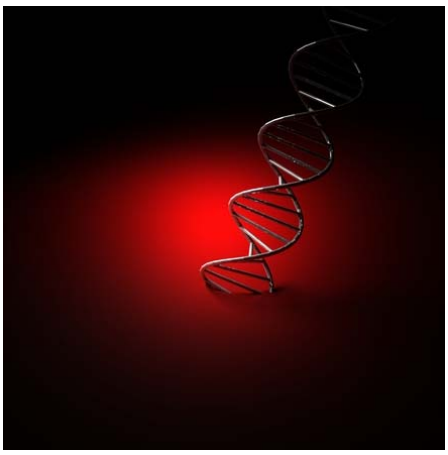
[57] Schuster et al. (2010). *Nature*, vol 463, Supplementary Information, page 3.

[58] Examples are Australia National Health and Medical Research Council, *Guidelines for ethical conduct in Aboriginal and Torres Straits Islander Health Research* http://nhmrc.gov.au/guidelines-publications/e52 and Canadian government, National Health Council, *Research involving First Nations, Inuit and Metis Peoples of Canada* http://www.pre-ethic.gc.ca/eng/policy-politique/initiatives/tcps2

[59] Vanessa Hayes: Personal email communication to B Begbie-Clench, WIMSA, dated 11 May 2011.

d) Lack of respect or reference to indigenous research protocols:

The need for 'respect' to be shown to the particular research community is perhaps the most important underlying theme contained in the various indigenous research ethics guidelines referred to above. The requirement for respect to be shown takes many forms, but can be summarised as authentic communication with the community leadership from the inception to the conclusion of the research project. None of the established suggested methods for showing respect to communities were carried out in this case. The authors subsequently refused to consult with the leadership, relying upon the fact that allegedly none of the elderly and illiterate San participants had demanded to be represented by the San leadership. For that reason, they concluded that the San leadership had no say in the matter.[60] This reliance on individual consent by an illiterate person who could have no idea of how the implications of genomic research related to the collective was and is regarded by the San an abuse of power.



DNA Svilen Milev freeimages.com

e) Failure of Research Ethics Committees (In the US, RECs are termed Institutional Review Boards, or IRBs):

The researchers defended their methodology regarding consent and further aspects of the process by repeating that the project had been approved by no less than four separate Research Ethics Committees. Not one of these RECs referred to the published and readily available research guidelines on indigenous populations, with which they ought to have been familiar, despite the fact that the very purpose of the research was to examine the most famous of indigenous "hunter gatherer" communities. In the words of Prof. Vanessa Hayes, geneticist and co-author of the NATURE paper, these institutional review committees were formally designed to "approve, monitor and review biomedical and behavioural research involving humans with the aim to protect the rights and welfare of the research subjects."[61] In addition she stated that it was their duty to respect the "culture, dignity and wishes of subjects". It is the San view that they had failed dismally in this duty.

f) Findings that contained breaches of privacy:

The academic publication and the associated Supplementary Information contained a number of discussions and conclusions containing intimate, personal, or pejorative information. The following are some examples from the paper which were discussed in the context of "Bushmen-specific phenotypes"[62]; namely how different genetic and environmental influences come together to create an organism's physical appearance and behaviour.

i) "Hunter-gatherer" being associated with low social status:

Commentary in the paper on 'traditional life-style' included phrases such as the following, which contains far-reaching and unsupported assumptions.

[60] Vanessa Hayes, ibid.

[61] Vanessa Hayes, ibid.

[62] Schuster et al. (2010). doi 10.1038, Nature 08795 Supplementary Information, page 8.

"[A] feeling of inferiority associated with the "Bushmen" or "San" ethnic classification meant that many Bushmen women tried to uplift their status via marriage to Bantu men." [63]

ii) Lactase persistence: The following conclusion was drawn. "As expected for a foraging society, we found the Bushmen in our study all to be homozygous for the C-allele suggesting an inability to tolerate milk consumption as adults."

iii) Human pigmentation: Conclusions were drawn about levels of San melanin pigmentation, their susceptibility as a group to skin cancer, and their consequent selective advantage for survival in the Kalahari desert.[64]

Kalahari, South Africa

iv) Lipid metabolism and bitter taste alleles: Complex conclusions were drawn relating to Bushmen digestive tracts, and also the ability to sense a bitter taste, a trait which would potentially assist human survival in the wilds. The 'taste receptor gene' was also discussed in the context of human evolution from Neanderthal to present.[65]

v) Genes related to hearing: Drawing on the findings, speculation was indulged that "Bushmen have better hearing than Europeans".

Lessons Learned

The San leadership have taken the Schuster case as an iconic example of not only the harmful and disrespectful research that can take place despite approval by Institutional Review Boards, but in addition, the need for San themselves to create their own protection mechanisms.

In order to do this the San held a consultative workshop in September 2014 comprising San leaders from Botswana, Namibia and South Africa, as well as genomic researchers, ethicists and lawyers. The purpose of the workshop was to discuss the San's perception of the exploitation inherent in the approach followed by the Schuster research, and to propose a San response to ensure that such research can never again take place.

During 2016 the San held two further workshops under the auspices of the TRUST project, designed to further the earlier discussions, and to confirm proposals to ensure that the San are able in future to manage and control research being done on their communities. These proposals are contained below.

[63] Ibid, page 3.
[64] Ibid, page 5.
[65] Ibid, page 7.

Recommendations

The following recommendations emerged from the San workshop aimed at preventing exploitation in research.

1. Collective permission must be obtained for all research to be carried out on San individuals or communities.
2. The San Council is the elected organisation in South Africa mandated to engage in this process with researchers.
3. The San have drafted a research contract, which is to be completed by all aspirant researchers. This contract contains a commitment to a number of requirements relating to the need for research to be both respectful as well as useful for the San peoples, and includes:
    - Early identification of research useful to the San.
    - Joint development, where appropriate, of design, content, methodology of all aspects of the research.
    - Full details to be provided in advance of all aspects of the research, including (potential) benefits of all forms for the San.
    - Commitment to pre-publication consultation, where appropriate, and post-publication feedback to the community.
4. A San Code of Conduct for research is in draft form, supported by the TRUST project. This will be finalised in order to explain to the world what the core San values are, and how the San communities are to be approached.

San Traditional Leader Dawid Kruiper

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5. Social Science Research in a Humanitarian Emergency Context

Gwenaelle Luc and Chiara Altare

Abstract

The following case study about research in an emergency setting depicts how unexpected findings created conflicts of conscience for NGO workers and exposed research participants and their community to retribution and compromised the local social structure.

The community felt betrayed that findings from the research about female genital mutilation were shared publicly and contributed to stigmatizing their culture. In addition, the NGO involved performed a dual role: that of assistance provider as well as researcher, which endangered the neutrality of the data collection, and in the end, the acceptability of the NGO as assistance provider as well.

Area of Risk of Exploitation

This case study covers two potential areas of ethics risks or potential for exploitation.[66]

First, a potential for ethics risks can exist when the ethical standards developed in one context (Western medical research) are applied in another context without due attention to local social norms or communication with local communities. A case can be particularly serious if a local practice violates the laws of the country the research takes places in, as in this case.

Second, a conflict of interest situation can arise when an assistance provider also conducts research. For instance, this could create expectations among participants, and influence their consent to be enrolled in the study.

Background

A major ethical dilemma when conducting research in a volatile emergency setting including culturally heterogeneous groups is the need to balance the risks and benefits for the research participants. An example of such a setting would be a refugee camp. Acquiring a clear understanding of context-related risks is challenging and, if not properly understood or taken into account, unanticipated risks could lead to the exploitation of participants or communities.

Research in emergency settings, such as refugee camps, is associated with a range of ethical challenges.

Research in emergency settings is associated with a range of ethical challenges, as both implementers and participants might be situated in a position of vulnerability and insecurity. In addition, in an

[66] Health and safety risks to researchers are not discussed in this case given that the researchers are operating as part of an NGO that provides emergency relief in the region anyway.

emergency setting there may be a need for a rapid response, and it might be difficult for local communities (or the aid providers) to distinguish relief from research, amongst other things.

In research, the "do no harm" imperative requires that research participants are not put at any additional risk.[67] This is particularly important in cases where vulnerable participants in emergency settings may not get any direct benefits from the research itself, but may contribute to producing evidence that will improve interventions with similar populations or in similar settings in the future.

Here, we describe a case where research activities did put participants at risk, while simultaneously providing no direct (personal) benefits to them, which led to community complaints. The community felt betrayed because the research did not respond to their needs and priorities, and contributed to stigmatizing their culture.

Specific Case and Analysis

A socio-anthropological research study on health-seeking behaviours was undertaken by a humanitarian NGO in a rural area of an African country where prevalence of child global acute malnutrition (GAM) is high. The study focused on health-seeking practices during diarrhoea episodes among children under the age of 5, as diarrhoea is one of the underlying causes of child undernutrition. The research aimed to study access to and utilization of health services. The National Ethics Review Committee approved the research.

Qualitative field work was conducted which aimed to better understand the cultural values and practices related to the therapeutic path of children with diarrhoea. Interviews were conducted with parents and other key informants in the village (for example, community leaders, elders, traditional healers).

Consent forms were signed by the participants, but as the NGO was mostly known in the area as an assistance provider, it was not always clear to the researchers whether participants freely consented to take part in the research or whether they assumed they had to participate in order to receive assistance, or out of gratitude.

Female genital mutilation, the investigator found, was a traditional treatment for diarrhoea among baby girls (from 3 months of age).

During data collection, the investigator found that a traditional treatment for diarrhoea among baby girls (from 3 months of age) was female genital mutilation (FGM). This practice is intended to remove "impurity" that interferes with the well-being of the girl. FGM is practiced in the village by a traditional healer with a razor blade and without hygienic precautions.

[67] According to *Ethical Principles for Medical Research Involving Human Subjects, World Medical Association Declaration of Helsinki*, 2008.

"If the diarrhoea is caused by a worm, we have to remove the impure part of a girl body; it will kill the worm and cure the girl", a traditional FGM practitioner said during an interview.

According to the testimonies gathered during the research, FGM is highly valued in the local culture. In addition to being considered as an effective traditional cure for girls' diarrhoea, FGM is part of the accepted and expected identity of a woman. 'Uncircumcised' girls are marginalised, a source of shame for their family, and have difficulty finding a husband. FGM also has religious and social significance. This act is symbolically seen as a ritual of incorporation of the girl to the rest of the community.

FGM is considered a violation of human rights at the global level, and is prohibited by law in the country where the research took place. "*Female genital mutilation and cutting is a violation of the basic rights of women and girls,*" said Carol Bellamy, executive director of the UN's Children's Agency (UNICEF), on February 7th 2005, during the International Day of Zero Tolerance of FGM. "*It is a dangerous and irreversible procedure that negatively impacts the general health, child bearing capabilities and educational opportunities of girls and women.*"

In the research setting of this case study, most of the participants of the interviews have never been to primary school and are illiterate, and local habits and regulations take precedence over national or international laws and codes of conduct.

FGM is a violation of the basic rights of women and girls, Carol Bellamy

The National Ethical Review Committee[68] and the research team did not anticipate this finding as its members did not have a deep understanding of the local culture and the norms of this specific community and individuals. As this traditional cure for diarrhoea was an unexpected finding, participants were not previously informed by the researchers of what they could be exposed to, while they proudly exhibited their traditional culture.

However, when a researcher from an NGO witnesses a human rights abuse, there is always a risk that when managing the resulting conflicts, the organization is accused of complicity, and/or of violating the interests of both the individuals and international ethical standards. In this case the researcher acted in accordance with his own model of norms and values and that of national/international codes of law and ethics, rather than the way in which the causal model of illness was understood locally, and the implications of this relating to the social construction of female identity. The researcher and the NGO decided to report those practices in a public report in order to protect baby girls from a recognized and illegal human rights abuse.

[68] This Committee did not involve lay members or representatives of the targeted communities.

However, this had severe consequences: it offended participants and the wider community, and led to the social rejection of girls who did not receive FGM (they were bullied and stigmatized by their entire community), as well as intensifying community tensions. It also jeopardized the NGO's capacity to operate in the area.
Communities felt betrayed by the NGO, as they were expecting humanitarian relief from the organization. They felt that the research was not responsive to their needs as they did not feel any benefit. On the contrary, its findings had exposed vulnerable communities and respondents to retributions from a coercive government, and endangered the local social structure.

Lessons Learned

This case study highlights the risks of exploitation of participants when researchers face conflicts of conscience and have to choose between abusing the trust of the community and protecting vulnerable individuals from violations of their fundamental rights in accordance with national/international laws and ethical codes. A lesson learned for the NGO involved what that researchers need to anticipate the identification of potential ethical challenges by assessing the risks and benefits for potential participants with "due diligence" before the project commences. Risk assessments should not be a vertical and unilateral process, but rather a participatory exercise. This can facilitate the understanding of the context, as interpretations of benefits, risks and harm are specific to each setting.

In this context, it is important to engage in mediation with all stakeholders, which may result in an agreement where each actor would not need to disown his/her values. The research could be ethically acceptable to all if the process and consequences were favorable (or at least neutral) for everyone. To emphasize, when opposing values are involved, it is crucial to engage in a discussion before taking action in order to reach an agreement. If no agreement can be reached in advance of undertaking research, then it is simply not possible to undertake the research involving the community, as some value gaps cannot be overcome.

The NGO also learned that when an organization is conducting research and delivering aid in the same area, biases can affect the voluntary informed consent of vulnerable participants as well as the research design, data collection and interpretation, or the reporting of results. While power differences may be difficult or impossible to eliminate completely, steps can be taken to identify and minimize the most serious potential sources of bias, as thorough, transparent and culturally appropriate information should have been given to participants.

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it is important to engage in mediation with all stakeholders.

Recommendations

Recommendation 1: Carry out a thorough risk and benefit assessment involving community and participant representatives. Ethical approval should also be sought from the community,

and community representatives should participate in the formal Ethical Review Committee process.

Recommendation 2: Beyond simply asking for informed consent, communities should be trained and involved in the ethical approval process. Participants should be made aware of the boundaries of confidentiality and any duties the researchers have to report certain findings. Ensure effective on-going communication (including with representatives of vulnerable sub-groups). Such communication mechanisms should not be interrupted after the departure of the research team from the data collection site but maintained by local partners of the international researchers.

Recommendation 3: Monitor and evaluate the process through which consent is negotiated with the community and obtained from participants.

Recommendation 4: Participation in research should not be linked to receiving assistance and researchers should make this very clear to participants to avoid any misunderstandings. In other words, if an assistance NGO operates in an area, it should be made clear that the benefits of assistance will be open to all, independent of working with the NGO on research.

Recommendation 6: Further work is needed on how to approach unexpected findings that lead to fundamental conflicts of conscience for researchers. Data collection itself should be neutral. There should be a protocol in place regarding the consideration of and response to any unexpected findings.

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6. Healthy Volunteers in Clinical Studies

Klaus Leisinger, Francois Bompart, Karin Schmitt

A highly controversial study involving healthy volunteers in India is described in case 13. This chapter illustrates a major problem involving healthy volunteers from LMICs rather than outlining a specific case.

Abstract

Patients participate in clinical trials for a variety of reasons, first of which is often an expectation of direct health benefits for themselves. By definition, healthy volunteers cannot expect such benefits. In resource-limited settings, healthy volunteers are most often poor people with low literacy levels who may not understand the risks they may take and are in no position to refuse financial incentives. For many of them, participation in clinical trials is a critical source of income.

An added complication to the concerns over truly informed consent is participants who have developed tactics to conceal their involvement in several studies to increase their income. As a result of concealments, these volunteers expose themselves to medical risks (e.g. drug-drug interactions), and also risk biasing study data.

It is recommended to establish compulsory national databases for healthy volunteers funded by those who perform trials and benefit from their outcome.

Medicine
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Area of Risk of Exploitation

In high-income countries, healthy volunteers are sometimes university students with a good literacy level and reasonable living standards. In resource-limited settings also within high-income countries, however, healthy volunteers are most often poor people with low literacy levels who may not understand the risks they may take and are in no position to refuse financial incentives. For many of them, participation in clinical trials is a critical source of income. As a result, they may sign informed consent documentation and yet are a highly vulnerable group that deserves the "specifically considered protection" requested by the World Medical Association´s Declaration of Helsinki Art.19, which says:

Participation in clinical trials is a critical source of income.

> 'Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm… All vulnerable groups and individuals should receive specifically considered protection'.[69]

The Problem

Experience gained through informal discussions as well as a literature review shows that there is not much professional interest in or attention to, ethical considerations regarding healthy volunteers from low-income settings. Consequently there is also very little data available regarding the number of clinical studies using healthy volunteers from low-income settings, making it difficult to grasp the scope of the issue. While most first-in-human (Phase I) clinical trials seem to be performed in high income countries to ensure the quality of these critical studies, a very large number of studies in healthy volunteers are performed in low and middle income countries (LMICs) (Ravinetto 2015:3), particularly bioavailability / bioequivalence studies needed to compare originator and generic medicines.

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Phase II and III clinical studies are performed by international as well as local companies, often through Contract Research Organization (CROs). One of the few available papers on healthy volunteers in LMICs shows how in India, CROs resort to "middlemen" to recruit poor participants, who have no understanding of what the studies are about and who sometimes participate in studies without informing their families. These basically "chose to participate in the trials due to insufficient income and unstable jobs" (Krishna and Prasad 2011).

Resource-poor settings are not limited to the LMICs. A few papers describe the situation of healthy volunteers in the US who have become "professional volunteers" and for whom study participation is a way to earn a living (Edelblute and Fisher 2015; Eliott and Abadie 2008). One should assume that many of the ethical issues related to US "professional volunteers" are highly relevant for their counterparts in LMICs. Many have developed tactics to conceal their involvement in several studies at the same time and have become experts at passing screening tests to enrol in clinical trials, for instance by concealing concomitant studies they are taking part in, medical conditions, concomitant medications or substance abuse (Edelblute and Fisher 2015; Devine et alia 2013). As a result of these concealments, these volunteers expose themselves to medical risks (e.g. drug-drug interactions) and also risk biasing study data, for instance in terms of safety or pharmacokinetic profiles of the tested drugs (Eliott and Abadie 2008).

Many have developed tactics to conceal their involvement in several studies at the same time and have become experts at passing screening tests to enrol in clinical trials.

The Way Forward

One option to avoid some of the risks detailed above is to establish compulsory national databases for healthy volunteers (Devine et. al. 2013; Resnik and McCann 2015). Some countries (e.g. France and Morocco) have set up or are in the process of setting up national healthy volunteers' databases to ensure that a given individual's involvement in clinical trials

[69] http://www.wma.net/en/30publications/10policies/b3/.

is recorded, that sufficient "wash-out periods" between trials are respected and that payments made to volunteers are tracked so as not to exceed certain levels.

Pharmaceutical companies must become involved – financially and conceptually – in the establishment of national data bases and registers that use state-of-the-art information and communication technology to make sure that "per push of a button" all needed information about health volunteers, but also parents of children offered to participate in paediatric trials can be found to avoid participation in more than one trial at a time.

Given the burden of adding new costs to overstretched existing health budgets, the recommendation would be that the costs for such a national register ought to be paid by those who perform trials and benefit from their outcome. The EU-based Pharma industry should take pride in taking initiatives to ensure that this neglected, highly vulnerable, population benefits from the best possible safeguards.

The EU-based Pharma industry should take pride in taking initiatives to ensure that this neglected, highly vulnerable, population benefits from the best possible safeguards.

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7. Human Food Trial of a Transgenic Fruit

Jaci van Niekerk and Rachel Wynberg

Abstract

The research and development of any 'new' agricultural crop created using genetic modification technologies, even if undertaken with the best of intentions, is accompanied by novel human health, environmental, social, economic, and other risks. To date, much of the research that has accompanied the release of genetically modified (GM) crops has focused on the environmental and health impacts. Evidence has been inconclusive, however, with debates remaining highly divided and contested, and each 'camp' presenting evidence to support their respective positions.

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The case presented here does not attempt to elucidate the various positions in the debate but rather concerns the research process of developing a GM 'vitamin-enriched' food for cultivation in a low or middle income country (LMIC). It raises questions not only about the ethical complexities of participant involvement in such trials, but also about the ethics of how research priorities get determined by Northern researchers and philanthropic organisations, without the necessary involvement of the affected LMICs. The case concerns a proposed food trial involving students at a North American university and a banana enriched with the Vitamin A precursor, beta-carotene, through genetic modification. The ultimate goal of the study was to roll out the transgenic banana to Uganda, a country where Vitamin A deficiency was perceived by the researchers and funders involved to be a major nutritional challenge.

The case raises questions not only about the ethical complexities of participant involvement in GM trials, but also about the ethics of how research priorities get determined by Northern organisations, without the necessary involvement of the affected LMICs.

This case solicits questions about exploitation risks relating to human participants, but it also fuels debates about potential impacts on hunger and nutrition in the intended country of release. By highlighting differences between the concepts of food security and food sovereignty (see table below for definitions), the case shines a light on two very different approaches to addressing poverty-induced hunger and malnutrition. The first, supported by institutions such as the World Bank, the G8-led New Alliance for Food Security and Nutrition and large consumer companies, is described by critics as 'nutritionism', and is 'understood as a set of ideas and practices that seek to end hunger not by directly addressing poverty, but by prioritising the delivery of individual molecular components of food to those lacking them' (Patel et al 2015:22). In contrast, food sovereignty aims to reduce malnutrition through an emphasis on diversification and the importance of peoples and countries defining their own food and agricultural priorities, taking into consideration local social, economic, ecological and cultural aspects. Food sovereignty is supported by a growing movement supportive of farmers' rights, women's empowerment and agroecological approaches to farming.

Food Security	Food Sovereignty
According to the United Nations' Food and Agriculture Organization (FAO 2001), achieving food security requires: i) an **abundance** of food; ii) **access** to that food by everyone; iii) nutritional **adequacy**; and iv) food **safety**.	Food sovereignty is defined as **'the right of peoples to healthy and culturally appropriate food produced through ecologically sound and sustainable methods, and their right to define their own food and agriculture systems**' (Declaration of Nyéléni 2007).

Areas of Risk of Exploitation

This case raises two sets of issues relating to risk of exploitation.

Risks of participating in the food trial

The first set of risks pertains largely to the trial participants in the high-income country where the trials were planned. It raises a number of questions relating to:

- how and whether informed consent was obtained from female students invited to participate in the study,
- the potential vulnerability of the student participants, as they may have been unduly incentivised to take part in the study by the US$900 fee, and
- potential human health risks, especially given that this represented one of the first human food trials of a transgenic plant product.

Risks of undermining local food systems

The second set of risks pertains to the potential release of the transgenic fruit in Uganda, in the context of pursuing 'nutritionism' as a research priority. These include:

- risks of undermining local food and cultural systems and imposing inappropriate solutions.
- risks of reducing banana agrobiodiversity.

A Proposed Human Food Trial

In early 2014, Iowa State University (ISU) sent an email to all female students, wanting to recruit 12 volunteers for a transgenic food trial. According to Leys (2014), participants were requested to eat a diet, including genetically modified bananas, provided by the researchers for four days during each of three study periods. They would have their blood drawn to test whether the fruits' enhanced beta-carotene content translated into higher Vitamin A levels in their bodies (AGRA Watch 2016; Gimenez et al 2016). In return for their participation, the students were offered US$900. According to a local paper - the *Des Moines Register* - more than 500 applications were received, from which 12 volunteers were selected (Leys 2015).

Funded by the Bill and Melinda Gates Foundation, the main aim of the study was to assess the efficacy of the banana for eventual roll out in Uganda, an East African country where bananas are a staple food. According to the lead scientist at ISU, the transgenic banana included a gene taken from another banana species, a sweet variety which naturally produces

large amounts of beta-carotene. Residents of Uganda utilise the less sweet cooking type of banana as a staple, hence the selection of this type to be genetically modified by the researchers.

Members of NGOs heard about the proposed study, and along with journalists at the *Des Moines Register*, demanded to know more about it. Initially the lead researcher declined to share information about the study design, claiming that disclosure would be detrimental for her chances at publication (Leys 2014). She relented later, however, relaying through a university spokesperson that she had led a similar study five years previously, with six women eating porridge made from corn similarly modified to produce high levels of beta-carotene (see Li et al 2010).

Petitioning students questioned the transparency, risks, and generalisability of the trial, and maintained that prior informed consent had not been obtained from the participants.

Risks of undermining local food systems

The proposed food trial, and particularly the initial lack of transparency surrounding it, garnered a lot of attention on the ISU campus, prompting a coalition of concerned students to protest. In collaboration with a number of NGOs, the students delivered a 57,000 signature petition to ISU's College of Agriculture and Life Sciences as well as the Gates Foundation's headquarters in February 2016. The students questioned the transparency, risks, and generalisability of the trial, and maintained that prior informed consent had not been obtained from the participants (AGRA Watch 2016). Another exploitation risk hinged on the US$900 fee, a relatively large sum of money, which could have unduly incentivised students to take part in the study, as they may not have been financially secure.

Risks related to unknown human health impacts

As this was the first human feeding trial of this GM product, which had also not been tested on animals previously, the students were being asked to consume a product of unknown safety (Kruzic et al 2016). Concerns were also expressed about the potential health risks for women of childbearing age. A molecular biologist based at the Salk Institute for Biological Studies commented:

> Beta-carotene is chemically related to compounds that are known to cause birth defects and other problems in humans at extremely low levels, and these toxic chemicals are possible - if not likely - by-products of plants engineered to make large amounts of beta-carotene. Since there is no required safety testing of the banana or any other genetically modified organism, doing a feeding trial in people, especially women, should not be allowed (AGRA Watch 2016).

Impacts on local food and cultural systems

Concerns were also raised about the social, economic and environmental impacts of the proposed study. According to Eric Gimenez, Executive Director of the Institute for Food and Development Policy, such questions:

> … recognise that hunger and malnutrition are not just biological or technical challenges, they are social problems rooted in poverty, inequality and a skewed

distribution of resources. Ending hunger can't be reduced to simple gene transfers, and the socioeconomic and agroecological impacts of GM go far beyond the single crops in which they are genetically expressed (Gimenez et al 2016).

Such concerns linked to wider issues about the nutritionism approach adopted through biofortification[70]. Proponents of biofortification recommend its use, especially in staple crops, to complement conventional fortification[71] activities, particularly in targeting the undernourished in remote rural populations (Bouis et al 2011; WHO 2016).

Hunger and malnutrition are not just technical challenges, they are social problems rooted in poverty, inequality and a skewed distribution of resources. Ending hunger can't be reduced to simple gene transfers.

Critics of this approach maintain that malnutrition is best countered with a diet based on a diverse variety of foods, and label biofortification as 'a strategy that aims to concentrate more nutrients in few staple foods……[and] may contribute to further simplifying diets already overly dependent on a few carbohydrate staples' (Johns and Eyzaguirre 2007:3).

Such views have been supported by the much studied Golden Rice example from the Philippines and elsewhere, also fortified with beta-carotene. Stone and Glover (2016), for example, observe that the developers of Golden Rice have yet to produce GM varieties that yield as well as existing varieties, and maintain that the storage qualities of the biofortified rice remains unknown, as does the probability of the beta-carotene being converted to Vitamin A in the bodies of severely undernourished children.

Threats to banana agrobiodiversity

Aside from questions about the efficacy of the eventual banana product, concerns were also expressed about the risks of undermining local food systems and reducing banana agrobiodiversity. This is especially pertinent considering that East Africa is viewed as a secondary centre of banana diversity (after India), with Uganda being the largest producer and consumer in the region (Gold et al 2002). If the GM banana variety were to be adopted in Uganda, it would most likely be grown as a monoculture, impacting food security through erosion of genetic diversity. A significant body of research reveals how diverse plant communities preserve genetic potential for the selection of desirable traits, and withstand plant pathogens better than monocrops (see for example, Zhang et al 2007; Cardinale et al 2012). As described, Uganda is home to banana varieties already higher in beta-carotene than those in the proposed GM variety and with the country being situated in a fertile, tropical zone, the cultivation of foods naturally rich in beta-carotene such as sweet potato, leafy

[70] Biofortification is the process by which the nutritional quality of food crops is improved through agronomic practices, conventional plant breeding, or modern biotechnology [genetic modification]. Biofortification differs from conventional fortification in that biofortification aims to increase nutrient levels in crops during plant growth rather than through manual means during processing of the crops (WHO 2016).

[71] Fortification is the practice of deliberately increasing the content of an essential micronutrient, i.e. vitamins and minerals (including trace elements) in a food, so as to improve the nutritional quality of the food supply and provide a public health benefit with minimal risk to health (WHO 2016).

vegetables and certain fruit, points to affordable, healthy, culturally acceptable and locally produced ways of avoiding nutrient deficiency.

A diversity of bananas for sale in an African market (Source: http://www.crop-mapper.org/)

Lessons Learned

This case yields a number of valuable lessons across high, middle and low income country scenarios for:

- those involved in plant breeding and
- development-related programmes that have LMICs as their focus, as well as for
- funders and
- those serving on ethics committees.

With regard to the trials conducted in a high-income country, the case reveals the importance of ensuring that trial participants make decisions based on a full set of information, and also of examining the rationale behind such trials and fully exploring potential risks to participants. It also suggests that debates about healthy volunteers extend into the domain of agricultural research, a field which is surprisingly undeveloped in the realm of ethics.

Debates about healthy volunteers extend into the domain of agricultural research, a field which is surprisingly undeveloped in the realm of research ethics.

With regard to the impacts of such research in LMICs, the case shows that research driven from high income countries and by philanthropic donors should be sensitive to local peoples' rights to self-determination of their food systems, and to alternative approaches to address nutrient deficiencies. In the words of a concerned Ugandan, 'Just because the GM banana has been developed in Australia and is being tested in the U.S. does not make it super! Ugandans know what is super because we have been eating home-grown GM-free bananas for centuries. This GM banana is an insult to our food, to our culture, to us a nation, and we strongly condemn it.' (Leys 2015)

Recommendations

Human food trials of GM products should be approached with caution. In the absence of precedents, such trials need to be conducted transparently, with participation based on informed decision-making without being unduly influenced by financial incentives.

The determination of R&D priorities should be carefully evaluated in terms of local needs, taking into account social, economic, political and environmental implications. Research involving staple crops should not have outcomes that violate a LMIC's right to self-determination or food sovereignty. Impacts on existing farming systems and on agrobiodiversity need to be carefully considered. Technical solutions such as biofortification should not be introduced at the expense of existing, diverse sources naturally rich in the nutritional substance perceived to be lacking.

Further research is needed to deepen understanding about ethics in agricultural research. This should take cognisance of the need for extensive and inclusive participation in determining research priorities, and should involve regular review to assess the suitability and acceptability of different applications in view of fast-changing technologies.

Recommendations

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8. Hepatitis B Study with Gender Inequities

Olga Kubar

Abstract

This case study is about a study entitled "Comparable randomized double-blind investigation of safety and immunogenicity of vaccine against Hepatitis B in healthy adult subjects" undertaken in Russia with an international sponsor. There were indications of elements of exploitation, which consisted of inadequacies in the study's design compared with its announced purpose, and the indirect inclusion of women research subjects in the clinical trial without their informed consent. On the basis of noncompliance with the applicable regulatory and ethical requirements the study was not approved by the Local Ethics Committee.

Area of Risk of Exploitation

Healthy volunteers in clinical trials contribute to medical progress without any benefits to themselves. In addition, this case is of interest with regard to gender inequities in research.

Case Description

This case study is based on an evaluation undertaken by the LEC of the Research Institute in Russia, at the end of 2014. All documentation required for complete ethical review of the proposed study was submitted in accordance with the national law (National standard "Good Clinical Practice GOST 52379-2005"), the LEC's Standard Operating Procedure (SOP) and international GCP's rules. The proposed clinical trial was entitled: "Comparable randomized double-blind investigation of safety and immunogenicity of vaccine against Hepatitis B in healthy adult subjects".

The main purpose of the proposed clinical trial was to study the safety and immunogenicity of a vaccine against Hepatitis B for its future registration in the country in comparison with a vaccine already marketed in Russia.

The study design intended 2 groups of participants, made up of both men and women. The first group would be vaccinated by an investigational product (vaccine proposed by external sponsor); the second (control) group would be given a well-known vaccine registered in the country. According to the protocol, the female sexual partners of male participants would be indirectly involved. For this group, the study assigned special requirements.

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The requirements for these women (who were not legally and directly involved in the clinical trial) included prohibition and prevention of pregnancy by using contraception during the entire 8 months the study lasted and for 1 month afterwards (even if the actual participant – their sexual partner – withdrew from the study).

Detailed information would be collected about any pregnancy and its outcome, and any Adverse Events (or Serious Adverse Events) would be included in the database as part of the monitoring process.

The investigational product (vaccine) was well-investigated in a series of previous clinical trials (as is clear from the protocol, Investigation Brochure and references), and is already approved in the country of the sponsor and many other high income countries. It is available on the open market for adults and children above 10 years. For this reason, the adequate design of the proposed clinical trial in Russia would be for a Phase III study. However, the protocol was equivalent to the design of a Phase I/II study.

Seventeen visits of the volunteer participants to the Investigator Centre (IC) were planned during the 8 months of the clinical trial and for 1 month after its completion. Visit procedures involved detailed physical examination and collection of blood and urine samples for a wide spectrum of examinations. The participants would come to the IC in the morning and spend a few hours for observation in the Centre. In addition, they would have to buy and use the requested products for contraception.

As a rule, healthy volunteers participating in clinical trials cannot expect any benefits. In this case, it was declared by an external (foreign to Russia) sponsor that benefits were planned, because the participants (volunteers) would be vaccinated against Hepatitis B, and would therefore be protected from this infection in the future.

Analysis

The case study is ethically inadequate at several levels.

The suggestion that the study would be beneficial to participants is controversial. Vaccination against Hepatitis B is included in the National Immunization Calendar of the Russian Federation. Domestically and internationally produced vaccines that are registered and have obtained permission for use by approved order (Order HCM №125n, 21.03.2014) are used. Vaccination against Hepatitis B is freely available to everybody, and obligatory for high-risk groups (new-borns whose mothers are HbsAg carriers, or Hepatitis B patients at the third trimester of pregnancy). Therefore, there were no benefits for participants taking part in the clinical trial.

The autonomy of the women who were indirectly involved in the study was not respected. There was no information/confirmation in any part of the protocol that these women (indirect participants) should be appropriately informed about the procedures, or that their informed consent should be obtained.

The autonomy of the women who were indirectly involved in the study was not respected.

In addition, their indirect involvement in the clinical trial was not covered by insurance, even in the case of pregnancy with a Serious Adverse Event (congenital anomaly/birth defect), because they were not included in the frame of financial

contracts and insurance coverage for study participants. No other guarantee (medical, financial etc.) for these women was described in the protocol or any other study documents. This violates GCP regulations that are compulsory in Russia. According to the National standard "Good clinical practice GOST 52379-2005":

> 'In research which does not connect with treatment (without any benefits for potential participants from a medical point of view) only subjects who personally give, write and date the informed consent can be involved' (it. 4.8.13).

The situation for women indirectly involved in the clinical trial without consent would also contradict the universal ethical principles of the Declaration of Helsinki, October, 2013 regarding vulnerable groups and populations:

- Art 22. "The protocol should include information…., regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study";
- Art 25. "Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary…..no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees";
- Art 26. "The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal".[72]

The requirement to carry out a pregnancy test and prevent pregnancy throughout the study would also violate the women's reproductive rights and represents a direct intervention in the family's planning.

The study documentation required considerable attention to be devoted to the registering and following up information concerning cases of pregnancy/outcomes in these women (without their informed consent). This means that their personal information could be used without their agreement. This also contradicts the general norms guaranteeing the protection of personal data which are fixed by the Federal Law of the Russian Federation, "On information, information technologies and protection of information" of 27 July 2006.[73]

The requirement to carry out a pregnancy test and prevent pregnancy … would also violate the women's reproductive rights.

In addition the Federal Law of the Russian Federation, "On personal data" of 27 July 2006[74] (updated 2015-2016), defines maintaining the confidentiality of information as an obligatory duty, and requires this information not be transferred to third parties without the direct consent of its owner. According to Article 13 of the Federal Law, "Fundamental Principles of

[72] http://www.wma.net/en/30publications/10policies/b3/.
[73] http://www.wipo.int/wipolex/en/text.jsp?file_id=371388.
[74] https://iapp.org/media/pdf/knowledge_center/Russian_Federal_Law_on_Personal_Data.pdf.

Legislation of the Russian Federation on Healthcare“ (2016), “information about the condition of health and diagnosis is determined as a medical secret”.

The situation is also in conflict with the rules of the Declaration of Helsinki, October, 2013, “Privacy and Confidentiality“: “Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information” (Art. 24)[75].

Other areas of exploitation in this proposed clinical trial were identified as unreasonable exploitation of private time, and financial exploitation of participants/volunteers. The study, as noted above, was very time-consuming for participants and there was no compensation for the expenses of transportation, contraceptive products or the time of losing/breaking normal daily work and activities. As a result, Art. 15 of the most recent version of the Declaration of Helsinki, October, 2013 is violated: “Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured”. [76]

This case also points towards a gender injustice. One could argue that one can see “shady discrimination” against vulnerable populations indirectly involved in the study. A fundamental understanding of the gender aspects of research should be guided by the spirit and text of the Universal Declaration of Human Rights (UDHR), 1948, which states that; “…the peoples of the United Nations have in the Charter reaffirmed their faith in fundamental human rights, in the dignity and worth of the human person and in the equal rights of men and women…”.[77]

The ethical conflicts raised by this case study, suggest some general arguments that women can be discriminated against by their limited access to participate in clinical trials, and violation of their reproductive rights. Risk of exploitation is especially present when the golden rules of the protection of autonomy, confidentiality and human vulnerability are ignored. The moral force for the execution of ethical concepts in medical research by the correct process of freely given/obtained informed consent is presented in the UNESCO Universal Declaration on Bioethics and Human Rights[78], 2005, and in many other national and international documents, including the Convention on the Elimination of All Forms of Discrimination against Women adopted by United Nations, 1979.[79]

Diagram 3 – Ethical Issues in Hepatitis Study

[75] http://www.wma.net/en/30publications/10policies/b3/.
[76] http://www.wma.net/en/30publications/10policies/b3/.
[77] http://www.un.org/en/universal-declaration-human-rights/.
[78] http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights.
[79] http://www.un.org/womenwatch/daw/cedaw/.

Outcome of the Application for Ethics Approval

All properly submitted application documents were reviewed according to the established review procedure (LEC's Standard Operating Procedure (SOP). On the basis of detailed review, discussion took place at an LEC's meeting with a quorum of its members present. An independent consultant (specialist in bioethics) was invited to join the meeting after signing an agreement for confidentiality and conflict of interest. Decision-making took place after sufficient time was allowed for discussion, and was reached by consensus according to the LEC's SOP. On the basis of unapproved/unfavourable opinions from all members of the LEC the negative decision was made, with detailed and clearly stated reasons provided to the applicant. The clinical trial was not approved.

Lessons learned and recommendations

1. The system of ethical review worked well in this case, as an unethical study was not approved.
2. The possibility of masking/silencing and blindly exploiting women/pregnant women indirectly in a study requires attention.
3. Gender variety and an assessment of its influence on risk/benefit ratios should be an integral part of clinical trial planning.
4. Clinical trials should exclude any opportunity for non-informed/non-agreed interventions that will impact on the privacy of participants' lives, especially in the context of women's reproductive rights.
5. Unreasonable risks and burdens, including inadequate compensation and overly high time burden must be avoided. .

9. A Controversial International Cooperative Genetic Research Project conducted by American and Chinese Research Institutes in Anhui Province, China

Yandong Zhao and Wenxia Zhang

Abstract

Since 1995, a research team from the School of Public Health of Harvard University (HSPH) had been collecting blood samples from villagers living in Anhui province, China, with the cooperation of local research institutes and the Chinese government. In 2000, the Harvard team was accused of violating research ethics principles by not adequately informing the participants about the research and by not sharing benefits fairly. Subsequent investigations by American and Chinese media and authorities showed that the US research institute, its research personnel and a pharmaceutical company involved are benefiting substantially from the project, whilst the Chinese research participants and the government are not. Three levels of exploitation can be distinguished in this case:

1. The exploitation of local individual citizens as human research participants,
2. The exploitation of the local scientific community in China, and
3. The exploitation of the country's national interest.

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In order to avoid such exploitation, both high income and low and middle income countries should strengthen their institutional arrangements and improve their cooperation mechanisms, in order to ensure that both sides benefit equally from international science and technology (S&T) cooperation.

Area of Risk of Exploitation

Genetic studies in urban and rural areas in Anhui province are the topic of this case study. One of the reasons why the case shows a risk of exploitation is that Anhui is an area not as economically advanced as its neighbouring provinces. For example, in 2015, the GDP per capita in Anhui is 35997 CNY[80] (€4,878), far lower than the more developed neighbouring provinces such as Jiangsu (GDP per capita 87995)[81] €11,925), Zhejiang (GDP per capita 77644)[82] €10,523), and Hubei (GDP per capita 50520)[83] €6,847).

[80] Anhui statistical bureau, 2016, http://www.ahtjj.gov.cn/tjj/web/info_view.jsp?strId=1461911669310505&_indextow=8
[81] Jiangsu government, 2016, http://www.js.gov.cn/jszfxxgk/tjxx/201602/t20160229492951.html
[82] Zhejiangsu government, 2016, http://www.zj.gov.cn/art/2016/3/24/art_5497_2075286.html
[83] Hubei statistical bureau, 2016, http://www.stats-hb.gov.cn/tjgb/ndtjgb/hbs/112361.htm

Background

Since the launch of reform and opening up in the 1970s, international science and technology (S&T) cooperation has been an important means for lifting China's capability and level of S&T innovation. It has also been an indispensable part of China's S&T development. To promote international S&T cooperation, the Chinese government has formulated a series of documents[84], including the *National Outline of International Scientific and Technological Cooperation in the Tenth Five-year Period*; the *Outline for the Implementation of International Scientific and Technological Cooperation Program in the Eleventh Five-year Period;* and the *Special Program on International Scientific and Technological Cooperation in the Twelfth Five-year Period.* The national special program on international S&T cooperation was also added to the system of national S&T programs in 2001.

In pursuing international S&T cooperation, China has upheld the principles of equality, mutual benefit and common development. From cooperation based on joint research projects in the earlier period to the all-round cooperation covering skilled professionals, scientific bases and projects today, China's international S&T cooperation is growing in both breadth and depth. Through years of development, China has emerged as one of the most important partners for joint scientific research in the world, and has established cooperative relations on S&T with more than 100 countries and regions. Joint research efforts involving Chinese and international scientific research professionals are growing wider and deeper.

> "China's share of global science and engineering publications has pulled within a percentage point of those from the United States, according to the latest research statistics published by the US National Science Foundation (NSF)".[85]

In the 82 pieces of *Top Ten News of Basic Research in China* (later known as the *Top Ten Scientific Advances in China*) between 2005 and 2012, 43 are about international cooperation projects (52% of the total), while papers based on international cooperation account for 54% of the 100 key academic papers in the relevant fields (Cheng Yijie et. al. 2015).

Mr Jin Xiaoming, former Director-General of the Department of International Cooperation of the Ministry of Science and Technology of China, has pointed out that in a world where globalization is the trend of S&T progress, an internationalization strategy is the only way to build China into an innovative country. Without internationalization or international cooperation, China will suffer immensely in the pursuit of advanced S&T (Jin Xiaoming, 2012).

For years, international S&T cooperation has played an important role in facilitating China's S&T progress, lifting the scientific research performance and international influence of Chinese scientists, and producing many successful examples of mutually beneficial cooperation. However, it is undeniable

It is undeniable that problems of inequality and unfairness also exist in joint research projects, some of which have undermined the interests of the Chinese public, the interests of the scientific community and even China's national interests.

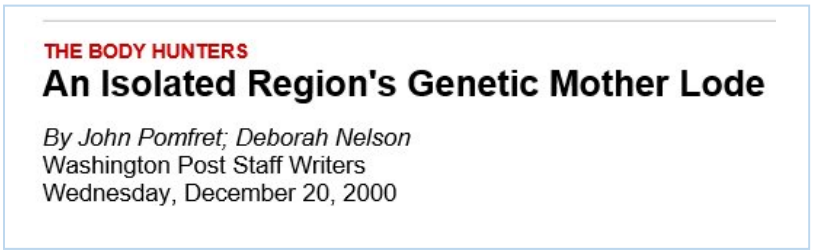
[84] Chinese documents that are not available in English have not been referenced, other than with their title.
[85] http://www.nature.com/news/research-gets-increasingly-international-1.19198.

that problems of inequality and unfairness also exist in joint research projects, some of which have undermined the interests of the Chinese public, the interests of the scientific community and even China's national interests.

A strong case in point is that scientific research institutions and personnel from some high income countries have built on their advantages of capital and project experience to take advantage of the eagerness of Chinese scientists to make their presence known in the international academic community, and have exploited the flaws and loopholes in China's existing laws and administration, to engage in unethical R&D activities in violation of international norms, scientific ethics and even Chinese laws. This has included:

- conducting clinical experiments on human research participants in China which are banned in high income countries;
- collecting samples in China for commercial purposes;
- harvesting China's biological resources and undercutting the intellectual property rights of Chinese scientific research personnel;
- conducting human experiments and/or collecting blood samples without providing sufficient information to the participants;
- exploiting information asymmetries to conceal information about the experiments, and
- ignoring and violating the participants' rights to know.

These problems are particularly serious in fields that undertake research on medical treatment, pharmacy, genetics, environmental and air pollution as well as research projects with potential commercial interests. The "genetic harvest" project conducted by Harvard University in collaboration with Chinese medical research institutions on the farmers in Anhui province in the 1990s is a typical case in point.


THE BODY HUNTERS

An Isolated Region's Genetic Mother Lode

By John Pomfret; Deborah Nelson
Washington Post Staff Writers
Wednesday, December 20, 2000

Specific Case and Analysis

On 20 December 2000, a *Washington Post* article titled "An Isolated Region's Genetic Mother Lode" (John Pomfret & Deborah Nelson, 2000) disclosed that a Chinese American researcher of the School of Public Health of Harvard University (HSPH) had been collecting blood samples from villagers living in the Dabie Mountain region of China's Anhui province since 1995 with the financial support of the National Institute of Health (NIH) and bio-pharmacy companies. The blood samples were transferred to the Harvard genetic bank for research into asthma, diabetes, hypertension and other diseases. Because of the value of these carefully selected blood samples to the research and development of new drugs, the Harvard team received a large amount of research funding from international organizations. The report exposed the loss of China's genetic resources and triggered a stir both in China and worldwide.

Harvard's genetic harvest project was conducted in Anqing city of China's Anhui province between 1994 and 1998, involving tens of thousands of farmers in eight counties. The project,

which was led by an Associate Professor of HSPH as the 'chief scientist', conducted genetic studies on multiple diseases, including asthma, high blood pressure, obesity, diabetes and osteoporosis, while the experiments on asthma and hypertension were funded by the NIH (John Pomfret and Deborah Nelson, 2000, Xiong Lei and Wang Yan, 2001,2002).

The Principal Investigator from HSPH also collaborated with Millennium, a US pharmaceutical company, and received its financial support. The project had three Chinese partners, Beijing Medical University, Anhui Medical University (AMU), and Anqing Municipal Bureau of Public Health. The US-based Principal Investigator started working with the AMU School of Public Health in 1993, and set up the Anhui Meizhong Bio-medicine and Environmental Health Institute in Anqing. The institute chose the Anqing Bureau of Public Health as its local partner, and selected the population groups suitable for taking samples based on grass-root investigation. It collected blood samples through physical examination and acquired DNA samples of the target group for research purposes. The joint research project, which was conducted under the guise of free physical examination for the farmers, mobilized the local population with the help of the local government. Blood samples were collected from farmers in the eight counties (Zongyang, Huaining, Qianshan, Tongcheng, Taihu, Wangjiang, Susong and Yuexi) of Anqing city.

Media reports and the complaints of research personnel from HSPH later exposed details of certain parts of the project that were suspected of compromising research ethics. One can take the asthma project as an example: the approved number of participants was 2,000 persons, but 16,686 persons were recruited. The research personnel also changed the amount of financial subsidies for each recruit for food, travel and job leave allowances; this was designed to be US$10 per day, but participants were paid an actual amount of only 10-20 Yuan per day (US$1.50 to US$3). In addition, the approved volume of each blood sample was much higher than approved. And the bronchodilators used were also different from what was approved (Xiong Lei and Wang Yan, 2002).

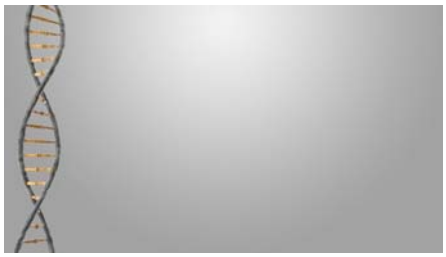
According to the investigation of Chinese journalists, the genetic sample collection was not sanctioned by the relevant ethics committee in China (Xiong Lei and Wang Yan, 2002). There were also serious breaches of the requirements to keep the participants informed. Many farmers who participated in the physical examination were not aware they were taking part in research. They were never shown or briefed about the "letter of informed consent", and did not sign or provide fingerprints on a document of this kind. They did not even know which institution they gave their blood samples to, and nobody told them about the real purpose and results of their 'physical examination' or the rights and benefits they were entitled to as part of their contribution to research. The asthma project is only one of the dozen human genetic research projects conducted by Harvard in China. Other projects also involved genetic screening of blood samples collected from Chinese farmers for the purpose of establishing the genetic links behind diseases like hypertension, diabetes, obesity and osteoporosis. Many of these projects were

There were serious breaches of the requirements to keep the participants informed.

first supported by Millennium before NIH funds flowed in (Xiong Lei, Wang Yan, Wang Chihua, 2003).

In March 1999, Harvard University sent a team to China to ensure the Anhui research was ethically and scientifically sound. Five months later, regulators from the US Department of Health and Human Services launched an investigation into Harvard's genetic research in China. In March 2002, the Department of Health and Human Services found that Harvard's genetic project in China seriously violated the regulations in multiple aspects, including medical ethics, participant safety and supervision and management.[86] On 2 May 2003, HSPH published the investigation results of the US government, which stated that HSPH made some procedural errors in supervision and record-keeping, yet no participant was found to be harmed in any way, so the school would not be penalized (HSPH, 2003). Some bio-medical experts and ethicists in China expressed regret about these results. They insisted that the studies apparently violated basic research ethics, and called for a joint US-Chinese review of the Harvard experiments (John Pomfret and Deborah Nelson, 2000).

In this international research cooperation of "genetic harvest", the actors/participants included international research institutes and research personnel, international companies, Chinese research institutes and research personnel, local government and the local residents who participated in the study.



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During this cooperation, Harvard University and its research personnel, wearing the "crown" of the world-famous, authoritative international scientific research institute with first-class research personnel and commanding advanced technologies, attracted the participation of Chinese partners and sold the idea of building partnerships and the opportunity of co-authorship to the latter in return for the provision of genetic resources used for research purposes. As a result, they obtained access to a valuable pool of research data resources.

In 2003, the Chinese Ministry of Health (MOH) and the Chinese Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) jointly issued regulations on limiting the export of special medical articles involving human genetic resources. However, most of the DNA samples Harvard collected in Anhui had already been shipped to the US. The Principal Investigator himself admitted that for the asthma research alone, 16,400 DNA samples had been transferred to the US (ZHAO Xi-Feng, 2013). In 2002 and 2003, he set up a bio-pharmaceutical company and a bio-pharmaceutical research institute in China. Several Chinese research personnel who had participated in the Harvard genetic project in Anhui became his partners.

[86] Yangcheng Evening News, U.S. Government：There are serious moral problems in human studies of Harvard, http://news.sohu.com/13/95/news148409513.shtml on April 5, 2002

Millennium became the ultimate beneficiary after supplying research funds. As part of the agreement signed with Harvard University, Millennium obtained the genetic information of Anhui farmers and claimed that they owned the relevant patents. In July 1995, Millennium announced that it was in possession of a large collection of asthma genetic samples from China. Soon afterwards, Astra AB, a large Swedish pharmaceutical company, invested US$53 million in Millennium for the research of respiratory disease. Millennium's control of obesity and diabetes genes from China attracted another US$70 million commitment from pharmaceutical giant Hoffmann-LaRoche. The stock price of Millennium soared from US$ 4 per share when it was listed in May 1995 to more than US$ 100 per share in June 2000. Several Millennium senior executives earned a net profit of over US$10 million per person through trade in stocks (Xiong Lei, Wang Yan, Wang Chihua, 2003).

In striking contrast to the above benefits, the research participants from China are not benefiting sufficiently from the project. Chinese research institutes and research personnel might have gained some benefits, such as the opportunity of working with renowned international research institutes, access to research funds and the co-authorship rights to the scientific papers published in international academic journals; all aspects that are appealing to most Chinese scientists. However, the local residents who participated in the studies received nothing but a free meal and an insignificant amount of travel and job leave allowances. In the words of a Chinese journalist, it is China's national interests and the unprotected Chinese farmers that were most harmed by the project, and it is the big US companies, research institutes and research personnel that received the real benefits (Xiong Lei, Wang Yan, Wang Chihua,2003).

It is China's national interests and the unprotected Chinese farmers that were most harmed by the project, and it is the big US companies, research institutes and research personnel that received the real benefits.

Lessons Learned

The above case reveals the dilemma faced by China and other low and middle income countries in conducting international S&T cooperation. On the one hand, opening up and cooperation are an important means for low and middle income countries to build their research capability and achieve faster development. On the other hand, given their disadvantages in their capacity for S&T innovation, including the ability to acquire information, the inadequacy of ethical review and relevant governance systems, it is extremely difficult for them to develop equal partnerships with high income countries in S&T cooperation.

Although the academic community of high income countries has established a relatively mature system of ethical standards for scientific research, the research personnel, once working outside their home countries and in a relatively loose regulatory environment, might exploit the systemic loopholes and regulatory 'vacuum' of the host country, either intentionally or otherwise, and seek improper benefits through potentially illegal acts. In particular, in those research projects driven by commercial interests, when capital uses its economic and technological advantages to exploit resources and benefits from low and

middle income countries in the guise of scientific research, low and middle income countries find it difficult to resist. Different levels of exploitation might be found in this process, including the exploitation of local individual citizens as human research participants, the exploitation of the local scientific community, and the exploitation of local countries' national interests.

What has happened in China is something many low and middle income countries have probably experienced. Most of the cases of international institutions, companies and research personnel exploiting China's biological resources happened in the 1980s, the 1990s and at the beginning of the 21st century. This had a lot to do with China's inadequate management and regulatory system, the lack of substantive ethical review and the weak awareness of protecting rights and interests during that period. In recent years, the Chinese government and the scientific community have gained a deeper understanding of this problem and have taken a series of positive measures.

In November 1998, the Chinese Ministry of Health established the Committee of Ethical Review on Bio-medical Research Involving the Human Body. To regulate international cooperation in genetics, China promulgated the *Provisional Methods for the Management of Human Genetic Resources* in 1998, which clearly stipulated that international cooperation on China's genetic resources must be conducted on the basis of equality and mutual benefit, with a formal agreement or contract, the approval of the Chinese government and informed consent in the sample collection.

In 2003, MOH and AQSIQ jointly issued a notice which prescribed that special medical articles involving human genetic resources shall not be taken abroad without authorization. The *Methods for the Ethical Review of Human-involved Bio-medical Research (Provisional)* was promulgated in 2007.

We find that with the gradual improvement of relevant management rules and regulatory systems in China, the number of cases involving the exploitation of China's resources for biological research purposes is reducing. China has strengthened the rules and regulations concerning IPR protection, generic resources protection and ethical review in international cooperation, enhanced the relevant management and supervision, and closed the loopholes in the administration of research.

At the same time, as China opens wider to the world, its S&T cooperation with international partners is also widening and deepening, and more and more overseas Chinese students are returning to China. All these factors have greatly mitigated the problem of knowledge and information asymmetry, and have enhanced public awareness of protecting rights and interests. As a result, there are fewer cases of high income countries using their R&D advantage to exploit China's resources through international cooperation.

In conducting international cooperation, low and middle income countries can only reduce and prevent the occurrence of exploitation when they are clear about their own resource advantages, build stronger awareness of protecting rights and interests and improve the relevant management systems.

In conducting international cooperation, low and middle income countries can only reduce and prevent the occurrence of such cases when they are clear about their own resource advantages, build stronger awareness of protecting rights and interests and improve the relevant management systems. In particular, in terms of the protection and utilization of traditional local knowledge and the protection of the rights and interests related to biological resources, and genetic resources in particular, low and middle income countries need clear awareness of these issues, whilst the international community should also give them more protection in this regard.

Recommendations

To reduce exploitation in international S&T cooperation and conduct international cooperation truly on the basis of equality and mutual benefit, we must strengthen our efforts in the following aspects:

Equitable research partnership, Shutterstock

1. We need to foster a stronger awareness of mutually beneficial cooperation in the international community. Countries, big or small, rich or poor, developed or developing, must all uphold the established principles of equality, mutual benefit and sharing in international S&T cooperation, and incorporate these principles into the framework of research ethics and responsible research and innovation.

2. The research institutes and research personnel of high income countries must strictly abide by the relevant international norms and ethical standards, especially the international standards concerning the protection of human rights, and the participants' right to be informed, their right to privacy and IPR rights. In this context, the regulatory agencies of high income countries should not only strengthen the management and supervision of the irregularities happening in their own countries but also the institutional design in order to ensure effective supervision of improper acts committed by their research institutes and research personnel in research cooperation with other countries.

3. Low and middle income countries should strengthen the building of ethical standards, promote knowledge of modern bio-technologies, and enhance public awareness of the importance of protecting genetic resources, germplasm resources and patents in order to avoid falling into the trap of technological exploitation, manipulation and deprivation. In particular, they should be alert to the so-called joint R&D activities of certain agencies and the personnel of high income countries who might exploit the disadvantages of low and middle income countries and regions, such as poverty, hunger and information asymmetry, in order to use these as the experimental subjects for research and the utilization of technologies without proper compensation.

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10. Sex Workers Involved in HIV/AIDS Research

Anthony Tukai

***Doris Schroeder**: This case study shows that equitable relationships between researchers and research participants are about* a lot more *than informed consent. For instance, the higher level of research literacy among the sex workers that was achieved in the Majengo clinic is a model for others to follow.*

Pamela Andanda, Fatima Alvarez Castillo and Doris at the Majengo Clinic, 2007

Abstract

The format of this case study is different from the others. It is written as a personal story by an outsider starting to work with sex workers, a vulnerable and stigmatized population in a Nairobi slum. We hope the shared experiences will give a better insight into the difficulties faced by members of this key population as they eke out a living in this context. It is also a positive case study, not one of exploitation despite sex work being an illegal activity in Kenya

My Experience Visiting Majengo

I took an assignment with the Sex Workers Outreach Program (SWOP), a leading sex workers health organization in Kenya promoting the health, safety, and wellbeing of sex workers as well as affirming their rights as workers and as people. The program is funded by CDC-PEPFAR through the University of Manitoba, Canada. I began my assignment by visiting the Majengo slum where SWOP runs a health clinic targeting sex workers living and working from these informal settlements.

I am Kenyan with a background in social work and public health. My public health interest is in HIV prevention, while my social work interest is in interventions. My hope is to build a strong foundation to improve the health and well-being of vulnerable and stigmatized communities such as Lesbian Gay Bisexual Transgender's (LGBTs) and sex workers.

I have lived in Nairobi for a greater part of my life, but like most Kenyans I had never visited a slum in Kenya. I was prepared for the unexpected, but it was like going to a different world. What struck me first were the overcrowding and the variety of activities that the residents were engaged in for survival. The area is densely populated; it felt like being in a city within a city. The road we tried to drive along to access the slum was full of people selling second hand shoes, clothes, and household items. We had to stop and wait for close to ten minutes for the

hawkers to clear a path like parting the red sea during biblical times so that we could get into the clinic compound. With the assistance of a health worker from the Majengo sex workers clinic, I took a walk to meet some of the sex workers who live and work in the area. As I walked, I came across dirty alleys, open sewers, and lots of trash. There were women doing laundry on the sidewalks, and other women sitting beside their doorsteps. Some men were going in and out of the houses while others were just walking around. Many looked as if they had been drinking heavily. I hardly saw any children; the ones I came across were playing outside unsupervised. I believe many of the fortunate children were attending school in other parts of the city while others tried to earn money from the dumpsites where they collected stuff for recycling companies. The houses were small and squeezed together, poorly built with rusted metal roofs.


As I walked, I came across dirty alleys, open sewers, and lots of trash.

The sex workers, to whom I was introduced on the tiny pathways and by the doorsteps, were friendly, saying “Hello” and “Karibu” (welcome). One of them ushered us inside to her tiny room. She looked to be in her mid-50s and had been doing sex work since she was a teenager. She was skinny; I think she weighed no more than 40kgs. Her single room was tiny and extremely crowded, with no space for a kitchen area or a living room. But two beds were squeezed in. One of the beds she said was her “Office… where I service my clients, and the other one is where I sleep when not working.” Hanging on top of her bed were different shapes and colours of underwear; she smiled and said, “Some of my clients prefer me to wear different colours and shapes of underwear, so I keep this for them.”

Seeing the Majengo slums and experiencing a bit of the life there was an eye-opening experience for me that I will not forget for the rest of my life.

About Majengo

About three kilometres away from the Central Business District of Nairobi are the Majengo slums. One of the oldest slums in the country, it is located between Gikomba market (the biggest mitumba, or second-hand clothes market, in East Africa), and Eastleigh a commercial hub that is now known as Little Mogadishu due to the huge number of Somali immigrants inhabiting the area. Majengo slums can be traced back to colonial times in the 1920s, when it was inhabited by East African railway builders and those serving them.

In her book *The Comforts of Home: Prostitution in Colonial Nairobi*, Luise White (1990) describes how cattle epidemics, locusts, famine, and drought swept through Kenya in the nineteenth century. A lack of food and the spread of disease, including smallpox, in central Kenya caused the death of an estimated 70 percent of the population.

After the famine, the Nairobi economy began to boom in the mid-1920s with men and women from neighbouring districts arriving to sell agricultural products. Many ended up staying in

Majengo. Working prostitutes became Kenyan's "urban pioneers," and were among the first residents to live year-round in Nairobi. "These women frequently came not from weak families, but from strong families." (White, p.9). Many of them were able to send money home to bolster rural family fortunes, which were wracked by upheavals. Prostitution emerged as an identifiable form of women's work, taking three forms:

- Watembezi prostitutes (from the Swahili word kutembea, "to walk") offered brief sexual services along the streets;
- malaya (the term means prostitutes) offered more prolonged indoor domestic and sexual services;
- while wazi wazi (open) prostitutes sat in front of their houses raucously and aggressively calling out their prices.

For some women, sex work was casual and intermittent; "He was hungry for sex, I was hungry for money." For others, it involved the only form of survival; "We were hungry, we had to go with men to get money, or have no money" (White, p.85).

Majengo was also known as Sofia Town, an entertainment spot for British soldiers who frequented the village to watch cultural performances by mostly female groups. During the colonial era, Majengo grew into quite a popular area but without the provision of adequate shelter. Its population today is estimated to be over 150,000 people of all ages and different ethnicities. It is divided into four smaller settlements of Sofia, Mashimoni, Kitanga and Digo. The women continue to sell sex, filling the gap of absent wives for men whose wives, girlfriends and families remain back home, in rural Kenya. In addition, men from other counties, continue to visit Majengo for sex.

The Majengo Clinic

The Majengo clinic is a medical facility serving low-income and medically underserved communities. Within the larger compound, it is a special clinic that offered/continues to offer a safe space to the sex workers from the mid-1980s and is also known as the Special Treatment Centre (STC). For a long time it was the only public health centre in Kamukunji, Nairobi providing treatment for sexually transmitted infections (STIs) to the sex workers and their clients. Through funding from the Canadian government, and with the assistance of the public health authority of Nairobi City Council, researchers from the Universities of Oxford, Nairobi, and Manitoba worked to improve existing resources and to provide basic outpatient medical services to the Majengo female sex workers community. In the mid-1980s, the World Health Organization (WHO) designated their operations as a WHO Collaborating Centre for STDs. Some of the common ailments treated were assorted classical STDs, malaria, typhoid etc. Currently, the clinic offers comprehensive HIV prevention and treatment services, birth control methods, gynaecological examinations, TB tests and treatment in addition to

supporting the management of assorted HIV/AIDS-related opportunistic infections. The clinic also serves as a research facility for the collaborating researchers who run two HIV-integrated activities: HIV research and HIV care and treatment. The clinic has over 5,000 sex workers receiving care and 3,200 of them are enrolled in clinical research studies.

Majengo Research

The Majengo Observational Cohort Study (MOCS) started in the late 1980s, and is a long-term cohort study of disadvantaged female sex workers in Nairobi. The study - as expected - did contribute to the development of several candidate vaccines against HIV.

HIV Research studies started when a Canadian scientist, Dr. Frank Plummer, the principal investigator who was undertaking research on STIs in Majengo, discovered that about two-thirds of women visiting the clinic tested positive for the virus in 1985. This changed the focus of his research from general STIs to include the epidemiology of HIV in Africa

Plummer and his team later discovered that a small number of the women had apparently developed immunity to the HIV virus despite long-term exposure through sex with infected clients. This led to other studies to understand the epidemiology and immunobiology of HIV and the risk factors associated with its spread. Blood, cervical, vaginal and saliva samples were drawn from women in this cohort with the consent of those involved. One of the key findings was that when some of the HIV "resistant" women took breaks from sex work, for example, to visit family or pursue alternative employment, temporarily stopping their exposure to HIV, they rapidly lost their immunity and became significantly at high risk of HIV-infection if they resumed sex work.

Majengo Research Participants

Prostitutes they called them in the past. Then they were known as commercial sex workers, and now the term is sex workers. "I don't know what they will call them next," said one of the Majengo clinic workers during my visit. "Sex worker" is the term used by researchers and policy makers and includes female, male and transgender adults aged over 18 years, who sell consensual sexual services in return for cash or payment in kind, and who may sell sex formally or informally, regularly or occasionally. It's a word used by people who think the word "prostitute" is impolite or offensive.

According to the policy on sex work in Kenya, sex work is classified under the Penal Code, Sections 147 to 154. It is illegal and entails a stiff penalty. It is seen as an "immoral activity" rather than a form of labour, and many believe that sex workers deserve to be punished.

In the beginning, sex workers were nervous to register with the SWOP clinic, because they feared that their personal information was being shared with the Kenyan law enforcement agencies. Once they were assured that the information gathered through unique identifiers and biometric tools was for research purposes and would not be shared with any third party, they registered in droves. They also signed informed consent documents for the different

research studies undertaken. In return the SWOP team provided and continues to offer free health care including HIV management. One of the reasons why the clinic has a good record on research ethics is the engagement work with the research community.

Research Literacy among the sex workers

The research has built long-term relationships between the researchers and the women sex workers by establishing peer leaders/educators, who engage in dialogue and negotiations with scientific investigators about the terms and conditions for participation in the research. Over time, these activities have helped to develop and formalize a "community" among the sex workers that had not previously existed. The partnership has enabled a wide range of benefits in the research cohort and wider community such as health education, free distribution of condoms, and the provision of free treatment for a range of sexually transmitted infections. In addition, it has led to effective referral for other healthcare problems, such as non-communicable diseases, cancers and surgical conditions e.g. hysterectomy. Such services are unlikely to have been available otherwise to these women.

The above mentioned peer educators are themselves sex workers. They educate women about their rights, promote behavioural change, distribute condoms and provide referrals to health clinics. Peer educators also address workers' concerns, whether about personal issues, services offered, or the research they are a part of. They are the gate keepers of the sex workers community.

Education about condom use has given sex workers the confidence to negotiate condom use with their clients. Over time, 100% condom use with casual clients has been achieved but condom use with regular clients still remains a challenge. Peer educators have also been active in the provision of general information on the consenting process. Capacity building on the consenting procedures undertaken over the years by the SWOP team seems to have borne fruits. Sex workers currently involved in the PrEP studies stated that they are not subject to any pressure in deciding whether to participate in any of the research projects. "We are free to refuse to consent to any research be it from SWOP or any other stated one of the participants. Consent is voluntary and has always been voluntary at the Majengo clinic," said a sex worker/peer educator.

"We are free to refuse to consent to any research be it from SWOP or any other stated one of the participants. Consent is voluntary and has always been voluntary at the Majengo clinic," said a sex worker/peer educator.

Ethical Concerns and Benefits

The sex workers have long been collaborating with researchers from Kenya, South Africa, Europe and Canada. The Majengo clinic has also been providing better health care than what is offered at other public health facilities. There are obvious issues around informed consent and the possible exploitation of the sex workers in the studies, which have to be dealt with on a continuous basis. For example do the sex workers really understand what they are consenting for or do they trade participation for access to better and free health care? The peer educators - from my assessment - are influential. Do they therefore play a big role in the willingness to participate in the studies? Does the collective

opinion of the sex worker community on particular studies have a larger influence on the individual willingness to participate diluting autonomy and self-determination?

These issues have been raised before and beg answers, for example, in an article in *The Globe and Mail*, a Canadian newspaper; "Sex Slaves for Science" January 7th 2006, and in *Benefit Sharing, From Biodiversity to Human Genetics* (Schroeder and Lucas, 2013). In addition, Andanda and Cook Lucas (2007) in their report "Majengo HIV/AIDS Research Case." have stated that:

> "In the Majengo case, the original, routine issues of negotiation and decision-making related to the conduct of the research studies only involved researchers, ethics review committees and administrations from relevant institutions…there was no formal inclusion of representatives from sex workers in any of this negotiations."

When I asked one of the peer educators about their inclusion in decision making in the past, whilst writing this case study, she confirmed that inclusion and genuine partnership was not emphasized in the past. However, she stated that "Now we are enlightened, this would not happen at the moment without our consent. We must be part of the decision making". The long-term engagement of the clinic with research participants in the spirit of ethical research has over time therefore led to improvements in the positioning and negotiation skills among the peer leaders/ educators. This is easily noticeable on the ground. Other factors noted include:

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- The women's health has been improved because of the access to education and access to high quality care that has reduced HIV incidence, disease burden and mortality.
- Important findings about HIV infections are shared with the sex workers' community as they emerge. This has a great impact on the health of sex workers generally since both partners now practice evidence based interventions and programming. This will be especially true as a greater understanding of novel prevention strategies emerge and are adopted overtime.
- Sex workers in the studies have increased their self-worth and agency by becoming valued partners in the research and by developing a sense of community among themselves. It is important not to romanticize this, because the women's lives are fraught with difficulty, but it is important to note that sex workers have been able to counter assaults on their self-worth due to the illegality of sex work in Kenya by developing a new emphasis on their rights. In their article "The origins of a research community in the Majengo Observational Cohort Study, (MOCS) Nairobi, Kenya." Brandewar et al argue that participation in the MOCS has improved and enriched sex workers' lives, because community engagement activities have helped to create a community that did not exist independently. Majengo sex workers - as part of the growing sex workers movement in Kenya - have formed a local association called Kenya Sex Workers Alliance (KESWA). This

is a local chapter of the global sex worker alliance whose mandate is to train sex workers about their human rights. Sex work being work is a normal slogan among the Nairobi sex workers.

Poor enrolment into the ongoing Pre-Exposure Prophylaxis (PrEP) demonstration project - despite a huge number of potential at risk HIV negative participants from the cohort - presents some real food for thought. From our discussions with the sex workers' representatives, they pointed out that community education, demand creation and advocacy for PrEP among the sex workers was done poorly. The researchers and policy makers have not fully engaged the community in promoting the intervention. Therefore, uptake of the novel intervention despite its potential will remain poor so long as the sex workers' community is not educated and involved in the grassroots advocacy processes. From them, inclusion and the community buy-in and support are key to going forward. This finding also confirms that the Majengo sex workers do indeed practice self-determination in the consenting process

Conclusion and Looking Forward

To be considered vulnerable in a research context does not mean to be weak or to need others always to speak for them.

In a recent TRUST-sponsored high level meeting in Nairobi, the peer educators' demands on inclusion went a notch higher. They demanded to be part of the ethics board that approves any research study involving sex workers. They also requested being included as part of the technical working group to advice on issues concerning sex workers.

While the ethics concerns for a group of sex workers from the Nairobi slums are obvious, I would like to end on two observations. First, to be considered vulnerable in a research context does not mean to be weak or to need others always to speak for them. Many of the sex workers I have met are very clear in expressing their concerns and suggesting ways forward. Second and importantly, sex workers have increased their self-worth by participating in the past and ongoing studies. They are now more empowered to make their own choices be it in the way they receive their health services from SWOP or in making decisions about participating in research projects.

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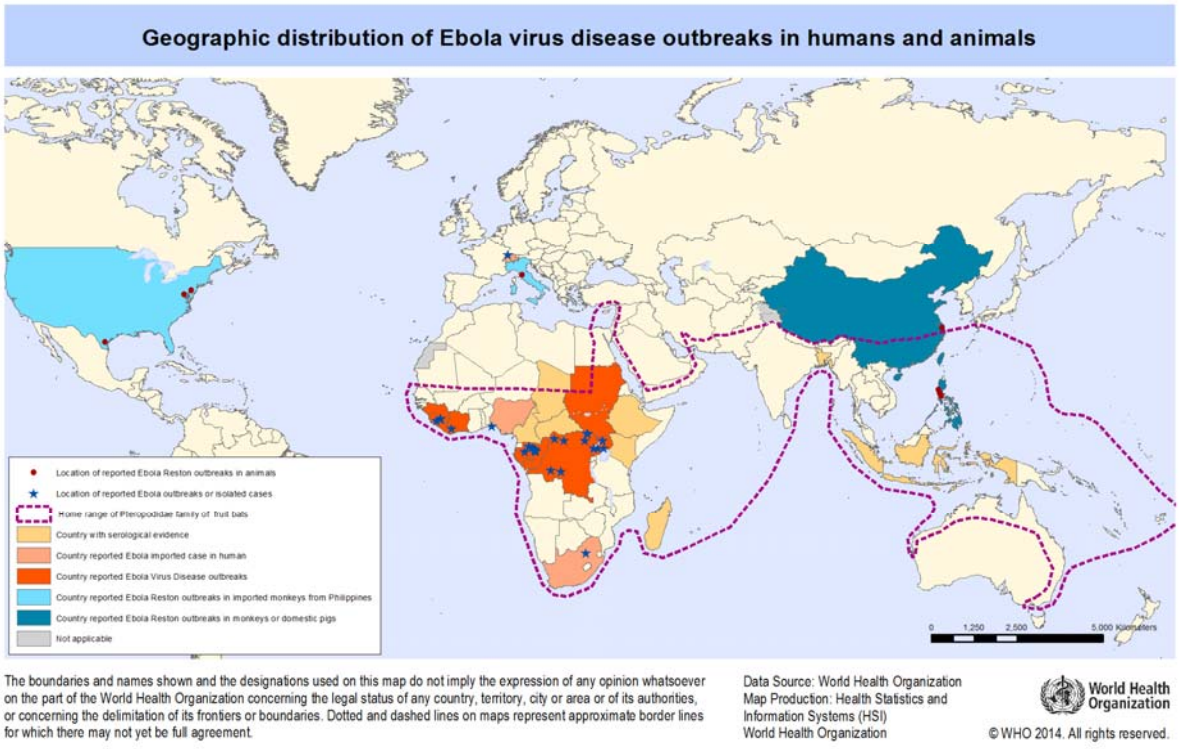
11. Ebola Vaccine Trials

Godfrey B. Tangwa

Abstract

This case study is about a phase I / II clinical trial (testing for safety and immunogenicity) of a candidate Ebola virus vaccine in a sub-Saharan African country in 2015. This occurred shortly after the Ebola epidemic which had broken out in West Africa towards the end of 2013 and which had been brought under reasonable control by 2015. The epidemic had severely affected three countries. However, the country of the candidate vaccine trial had not registered any cases of the Ebola virus disease (EVD).

Diagram 4: Ebola Virus Disease Outbreaks – Global Map



http://www.who.int/csr/disease/ebola/global_ebolaoutbreakrisk_20140818-1.png?ua=1

The study was designed as a randomized double blinded trial in which half of the research participants would receive the candidate vaccine and the other half a placebo. The study is sponsored and funded by one of the biggest Northern multinational pharmaceutical companies, globally well-known and highly respected.

The Protocol had received ethics clearance from the relevant national ethics committee of about 20 members, belonging to various specializations (excepting ethics), representing various governmental and non-governmental structures or associations. Few of the members of this ethics committee have had any formal contact with, or training in, research ethics.

The study was co-ordinated and managed at two laboratories - the local branch of a big Northern diagnostic laboratory and a laboratory of a local regional hospital, with the Minister of Public Health acting as a de facto sponsor for the trial. The overall study was designed as a multi-country, multi-site, trial aimed at recruiting a total of 3,000 research participants across 4-5 sub-Saharan African countries. For this particular country, the chosen recruitment sites were two big cities, each to recruit 200 research participants. The first site was to recruit adults while the second site was to recruit children.

A few weeks after commencement of the study at the first site, the sample size was almost achieved but, before it was completed and before the study could properly commence at the second site, some members of the public raised an alarm. They argued that the study had no justification for the country and that the government, by allowing its conduct, was carelessly risking the health, safety and lives of citizens in the cause of an unproven vaccine that could signal a public health disaster for the country. As a result, the trial was immediately suspended by the highest relevant authority in the country.

> A commentary on this case, and the importance of trust, is provided by Katharine Browne and Doris Schroeder at the end of this chapter, high-lighting differences to a Phase I Ebola vaccine trial in Canada in 2014.

Area of Risk of Exploitation

Phase I clinical trials are trials where the safety of a new treatment is tested in a small group of individuals (often healthy volunteers) to evaluate safety and side effects and to determine dosage. The chances of therapeutic outcomes for the research participants are almost always zero. In this context, the risk of exploitation of low and middle income country participants is particularly high, as – due to low education levels - they are more likely to assume that they would benefit personally. For this reason, phase I clinical studies have previously been carried out only in high income countries but are now increasingly also carried out in low and middle income (LMICs) countries, especially in conjunction with community engagement procedures and where the expected outcomes of the study would be mostly or exclusively of benefit to LMICs. The same applies - with limitations - to Phase II clinical trials whose main purpose is to assess efficacy. In Phase I/II clinical trials in low and middle income countries, it is therefore particularly important to protect research participants.

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Specific Case

This case study is about a phase I/II clinical trial (testing for safety and immunogenicity) of a candidate Ebola virus vaccine in a sub-Saharan African country in 2015.

In early 2015, a team of experts from the Ministry of Public Health evaluated the availability of facilities for Ebola vaccine trials in some medical centres and laboratories. The team included members of the National Ethics Committee (NEC). Equipment inventoried during this visit - in at least one of the centres - is marked as a previous donation from the owner of the

candidate vaccine to be tested. After these visits, two urban medical centres are retained for the Ebola vaccine study.

The visits occurred after the Ebola epidemic which had broken out in West Africa towards the end of 2013 and which had been brought under reasonable control by 2015. The epidemic had severely affected three countries. However, the country of the candidate vaccine trial had not registered *any* cases of the Ebola virus disease (EVD).

The study was designed as a randomized double blinded trial in which half of the research participants would receive the candidate vaccine and the other half a placebo. The study is sponsored and funded by one of the biggest Northern multinational pharmaceutical companies, globally well-known and highly respected. The first medical centre was to recruit 200 adult research participants and the second 200 children. The Protocol of the study, at least for the first recruitment site, received ethics approbation from the NEC. Recruitment was nearing completion at the first site when, following complaints from some members and the public, the study was suspended.

The suspension order was apparently made by word of mouth or by telephone call. The Minister of Public Health who had initially announced the commencement of the study over the radio did not announce its suspension through any public media of communication. However, he did write to the Principal Investigator (PI) at the local branch of the northern diagnostic laboratory to explain that the study was suspended due to public protests and that the trial involving children would now be withdrawn too. The general public, the research participants and their families and communities, knew little about the study, let alone why it was suspended and therefore permitted themselves the most fanciful speculations about it[87].

Case Analysis

This case bristles with ethical problems and issues that go beyond any simple identification of instances of North-South "ethics dumping". It involves subterfuges for standard regulatory procedures and discretion bordering on secrecy that are inconceivable in high income countries, or anywhere else where there is sufficient awareness of the stakes of biomedical research and the ethics particularly of human subjects clinical research.

The risk of exploitation in this case is not limited to a single rubric such as 'no benefit sharing' or 'inadequate informed consent process', but relates rather to the exploitation of the general weaknesses and inadequacies of an entire system, particularly its lack of a credible and adequate research governance and regulatory framework, in a manner suggestive of double standards that again would be inconceivable in a high income country.

This case bristles with ethical problems and issues that go beyond any simple identification of instances of North-South "ethics dumping".

[87] For popular concerns raised in such contexts, see: Geissler P.W. and Pool R. (2006), "Popular concerns about medical research projects in sub-Saharan Africa - a critical voice in debates about medical research ethics". Tropical Medicine and International Health (Editorial), Vol. II, No. 7, pp.975-982.

International regulatory texts are simple and clear on the procedural rules for ethically acceptable conduct of medical research, particularly clinical trials, with human beings as research participants. Part of Article 23 of the *Declaration of Helsinki*, for instance, states:

> "The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified".[88]

And Article 34 on 'Post-Trial Provisions' states:

> "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process".[89]

These minimal conditions were evidently not fulfilled for this case study. The members of the ethics committee that approved the study are all appointees by decree of the Minister of Public Health and function within a civil service system where obedience to hierarchical superiors is regarded as a duty. It is the view of this author that by assuming sponsorship of the clinical trial in this case, the Minister virtually made it the duty of all within the Ministry of Public Health to help facilitate its accomplishment. This would explain why some members of the ethics committee were involved in prior site preparations for the trial, which is inappropriate for an ethics committee, thereby compromising ethical oversight of the study, and putting the independence and transparency of the ethics committee under serious doubt.

There is no doubt that all the members of the approving ethics committee (which in fact acts as the national ethics committee (NEC)), are highly qualified experts but this does not automatically translate into expertise for ethics review. The expertise represented in the committee is roughly as follows: one haematologist, one parasitologist/epidemiologist, one pneumological epidemiologist, one sociologist, one demographer, one x-ray oncologist, one pathologist, one jurist, one parasitologist, one surgeon, one microbiologist/pharmacist, one dental surgeon, one science of education expert, one paediatrician, two community members, one civil society member, one traditional practitioner, and one expert on Islamic religion. This is a highly impressive committee for science review perhaps, but not necessarily for ethics review, if no research ethics training has been provided. And even if ethics training, usually by way of workshops or symposia, has been provided, every research ethics committee still needs an ethics expert by way of someone whose main business and concern - as a member of the committee - are ethics aspects of and ethics issues in the protocol.

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The study was suspended before the recruitment of children had begun at the second site. The inclusion of children in a

[88] http://www.wma.net/en/30publications/10policies/b3/, emphasis added.
[89] Ibid, emphasis added.

clinical study designed for testing safety and immunogenicity is a big ethical issue for which, at best, no justification is available for this study. All over Africa, women and children, because of their vulnerability, high rate of morbidity, easy availability, naivety and trustfulness, bear a heavy burden of clinical research. A competent ethics committee would have checked the burden of research participation against the benefits for research participants and their immediate communities, especially where involving children.

The whole study involves structures and procedures that, on the surface, appear to conform to ethics demands but that in reality violate the principles of research participant protection that are paramount in research ethics. The following section analysis this case further with specific reference to the informed consent documentation.

The Informed Consent Process

The potential research participant information for this study contains inadequacies and issues that any qualified ethics committee should have noticed and raised with the investigators for redress or amelioration before subject recruitment commenced.

Regarding the informed consent process, Article 26 of the *Declaration of Helsinki* states:

> "…each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study".[90]

An analysis of the information sheets given to the potential participants of this clinical trial, shows serious omissions and inappropriate or misleading language for the context (for further information, see also below). Participants were not taken through any informed consent process other than being approached individually by the study physicians or their agents at the chosen site of the study, given the information sheets to take home and asked to come back the next day to sign the informed consent form, followed by procedural instructions, and payment to them of a sum of approximately USD 20. Furthermore, there was no process of community engagement beyond the Minister of Public Health's use of the media to announce the study, emphasizing that it had been approved by the World Health Organization (WHO), and was simultaneously taking place in many other countries. In retrospect, the Minister's announcement could be judged as an inducement which minimized the potential stakes and risks of the study by alluding to the approval of the WHO and the fact that other countries had accepted the trial.

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Some of the issues and questions addressed in the 5-page prospective participants' information sheet (in italics below) are the following, which I have attempted to review and comment the way a competent and vigilant ethics committee might have done:

[90]Ibid, emphasis added.

"Why is this clinical study being done?

This study is done to test a vaccine against Ebola to make sure that it is safe and that it brings about a protective response. You can get Ebola by being in direct contact with the blood or other body fluids of a person who is already sick with Ebola. People infected with Ebola can have many different symptoms, like fever, severe headache, muscle pain, weakness, feeling tired, diarrhoea, vomiting, stomach pain and unexplained bleeding or bruising. Ebola disease can be very severe and is a life-threatening disease".

Only the first sentence of the above response addresses the question asked. But it is misleading and confusing to state that the study is being done to test a vaccine against Ebola whereas in answer to another question below it is stated that "there are no vaccines or treatment against the Ebola virus". The candidate vaccine ought to be called and described accurately for what it is. The rest of the response is not relevant to the question and ought perhaps to be given to another question not asked: What is Ebola and how does one get it?

"Who can take part in this study?

You can take part in this study if you are at least 18 years old, healthy, not taking part in another study, have not been in a country affected by the Ebola epidemic (Sierra Leone, Liberia and Guinea) and have not been in contact with someone who has Ebola in the last 3 weeks".

In the country of this study, the age of majority and consent is 21. Since studies need to conform to local laws and regulations, the age of participation here should not be 18 but 21; or else it should be explained that those below 21 would require the proxy consent of their parent or legal guardian in addition to their own assent.

In the country of this study, the age of majority and consent is 21. Recruiting 18-year olds would have required parental consent and participant assent.

Considering the issue of fairness in the recruitment of study participants, it may be questionable to make the mere fact of having been to an Ebola country and even of having been in contact with an Ebola patient, without however contracting the disease, an exclusion criterion for the study.

"Which vaccine will you get?

You will get the Ebola vaccine, either at the start of the study, or after 6 months into the study. At the start of the study, half of the people in the study (about 1,500 people) will get the Ebola vaccine and the rest of the people will get a placebo (dummy vaccine that looks like a real vaccine but does not have active components in it). Neither you nor the study doctor can choose or will know which vaccine you receive. This will be randomly decided by a computer (like the flip of a coin). We will only tell you and the study doctor which vaccine you received after 6 months into the study, or if there is an emergency".

In this response, apart from repeatedly talking about an Ebola vaccine which does not yet exist, there is the need to explain in simple ordinary language such terms as

'placebo', 'dummy vaccine', 'active components' and to illustrate what may count as an 'emergency'. Informed consent processes must avoid jargon, especially in LMIC settings.

"What does this study involve?

The first study visit, called a Screening visit, is to check if you can take part in the study. The study doctor will ask you some questions, do a physical examination and take some blood to test blood factors. If you are a woman who can get pregnant, the study doctor will also ask a pregnancy test. If the Screening shows that you can take part in the study, you will be in the study for about 1 year. Half of the people to join the study will have extra study procedures done. …if you are part of the group of people that does NOT need extra procedures you will: visit the vaccination centre 4 times after the Screening on Day 0, month 1, month 3 (phone call/home visits), month 6, month 9 (phone call/home visit) and month 12. At Day 0 visit, you will be vaccinated. This is an injection in the muscle of your upper arm. After vaccination, you need to stay at the vaccination centre for at least 30 minutes for observation. If you receive the dummy vaccine at the first visit, you will be vaccinated with the Ebola vaccine 6 months later. …During the entire study, we will check if you have any serious medical conditions. You will not have blood taken during the rest of the study".

The informed consent information includes a range of technical terms, which will be unclear to non-literate research participants.

First and again, the use of technical medical terms is problematic ('screening visit', 'blood factors', 'extra study procedures', 'muscle of you upper arm', 'serious medical conditions'). Second, this may make a good entry in the notebook of the investigator but may not necessarily be meaningful to a prospective subject without prior verbal explanation. What, for instance, is a barely literate person to make of 'Day 0, month 1, month 3 (phone call/home visits)? Would s/he not be wondering how a day could be zero and if s/he would be required to telephone someone or visit them at home?

"What about pregnancy?

We do not know yet if the Ebola vaccine may have an effect on an unborn baby. That is why you should not take part in this study if you are pregnant or trying to get pregnant. …You will need to use birth control during the first 7 months you take part in this study. Tell the study doctor if you are pregnant during the first 7 months of the study. The doctor will follow you up until the delivery of the baby".

This explanation about pregnancy is not free from ambiguity. It is quite clear that I should not take part in the study if I am pregnant or want to get pregnant. It is also clear that, if I want to have sex during the seven months of the study, I should use contraception. But that I should tell the study doctor if I get pregnant during the first 7 months of the study so that s/he can follow me up until the delivery of my baby is rather confusing. A study participant might say: "Getting pregnant and being followed up until delivery is what I want most. So why does the informed consent documentation say that I should not take part in the study if I am pregnant or want to

get pregnant?" This paragraph lacks the crucial explanation to the effect that contraception can sometimes fail because no method of contraception or birth control, excepting abstinence, is 100% effective.

"What benefits can you expect?
You may not benefit from the Ebola vaccine because we do not know yet if the vaccine will be able to protect people against Ebola virus"!

This is at best an incomplete response to the question. Of course, you do not know yet if the vaccine will be able to protect people against the Ebola virus; that is the whole purpose of the trial test. But what, if/when it proves to be able to protect people against Ebola virus disease? How is Article 34 on 'Post-Trial Provisions' of the *Declaration of Helsinki* going to be respected?

"What side effects or risks can you expect?
There is a very small risk that you could have an allergic reaction after vaccination. … That is why it is important that you stay at the vaccination centre for at least 30 minutes after vaccination, where all medical tools are available to treat an allergic reaction".

To avoid misunderstanding amongst research participants with low literacy and education levels, it is better to rephrase this response, not in terms of how small the risk is but in terms of the possibility. "It is possible that you could have an allergic reaction..." followed by an explanation of what an allergic reaction is.

"Are there other vaccines or treatments?
So far, there are no vaccines or treatment against the Ebola virus".

For clarity, the question should be "Are there other vaccines or treatments against Ebola? Also note the confusion if one compares this statement with earlier mentions of a vaccine, for instance in "You will get the Ebola vaccine…." (see above).

"What happens if you leave the study?
If you leave the study we will keep and use the information and samples we collected before you left the study. We will ask you to return to the vaccination centre one more time for a safety follow-up".

The obvious follow-up questions not addressed here are: Why would you keep and use the information and samples you collected even when I have decided to leave the study? And why should I return to the vaccination centre again after I have decided to leave? What safety follow-up are you talking about?

"Who will be looking at the information from this study?
Your information will be protected in accordance with the most stringent applicable law.
When you sign/thumb print this consent form you agree that your information can be viewed and used by site staff, [the pharmaceutical company], agencies and independent ethics committee. … [the pharmaceutical company] may publish the results but your name will not

appear in any publication. If you withdraw consent to use your personal information you will no longer be able to continue in the study".

> The questions that need addressing here are: What is 'the most stringent applicable law' that will be protecting my information and why should my name not appear in any publication of the results in spite of my contribution to it? [See also, the pride by which Canadian research participants in a Stage I Ebola vaccine trial went public with their names, in the supplement after this case study].

"What happens if you get injured while taking part in this study?
If you are harmed by the vaccination in the study or by any of the study procedures, you will be compensated. Your study doctor can give you information about how to obtain compensation in case of injury. You will not be paid for taking part in this study but you will be paid reasonable travel fees to attend to study visits at the vaccination centre".

> This question needs a fuller and clearer answer. Compensation for study-related injury should not vaguely be referred to the 'study doctor'; it should be explained clearly. 'You will not be paid...but you will be paid...' is not good phrasing in informed consent information and needs to be rephrased less ambiguously/misleadingly.

The informed consent form (certificate) states:
"The study has been explained to me. I have read the information or have had the information read to me. I have been given enough time to make a decision. I have had the chance to ask questions and I am happy with the answers that I have been given. I have been told that I can change my mind at any time and stop taking part in the study without giving any reason. By signing/thumb printing this form I agree:

1. *To take part in the study*
2. *That my information is used as described in this form*
3. *That my blood samples are used as described in this form*

Tick as appropriate (this decision will not affect your ability to take part in the study):

YES. My samples may also be used for future research (at the time of the study or after the study is finished) not described in this form with prior approval of the Ethics Committee

NO. Do not use my samples for future research (at the time of the study or after the study is finished) not described in this form."

The tick-able options above are about something as important as the use of samples for unknown future research. This ought to be discussed and justified in the prospective participant information. As formulated above, the section in parentheses is not clear and is liable to be quite confusing. "...at the time of the study or after the study is finished..." should perhaps be changed simply to "...after this study is finished...".

Talking to two of the potential research participants in this study seemed to show that the motivations for participation were mainly the incentives – the healthcare benefits and the money paid. Of course, there are limits to the conclusions one can draw from talking to only

two people. On the other hand, the literature shows that financial incentives and access to health care are a major driver for enrolment in studies in low and middle income countries.[91],[92] As such, this case raises concerns about undue inducements.

This case raises concerns about undue inducements.

Conclusion

The regulation of human subject research and particularly of clinical research is quite advanced around the globe, to the extent that we can talk about a regulatory infrastructure, whose presence or absence in any given context should indicate a priori whether or not research involving human subjects can ethically be conducted within such a context. Such regulatory infrastructure would include, within a non-authoritarian and genuinely democratic context, a legal framework that respects fundamental human rights, especially freedom of inquiry, expression, overseen by well-constituted, qualified and genuinely independent ethics review committees. The absence of such infrastructure or doubt about its genuineness, in spite of appearances, delimits a no-go area for ethical research. The verifiable existence of such an infrastructure should be a pre-condition for human subject research, especially in resource-destitute settings and particularly in the first two phases of investigation. Transparency needs to be part and parcel of any procedures where publicly available regulations need to be followed. Systemic faults tend to render compliance with good procedural rules and practices not only difficult but impossible. It is not just difficult, but impossible to carry water in a straw basket for any distance.

The verifiable existence of an infrastructure that respects fundamental human rights should be a pre-condition for human subject research, especially in resource-destitute settings and particularly in the first two phases of investigation.

[91]Mfutso-Bengo, J., et al. (2008). "Why do individualsagree to enrol in clinical trials? A qualitative study of healthresearch participation in Blantyre, Malawi."; Malawi Med J 20(2): 37-41.

[92]Mduluza, T., et al. (2013). "Study participants incentives, compensation and reimbursement in resource-constrained settings."; BMC MedicalEthics 14(1): 1-11.

Supplement to the Ebola Vaccine Trial Case – The Importance of TRUST

Katharine Browne and Doris Schroeder

The following is an excerpt from a Canadian news article[93]:

Dr. Scott Halperin, seen at the IWK Health Centre in Halifax, will be conducting the first trials of Canada's Ebola vaccine. (PAUL DARROW/The GLOBE AND MAIL), http://tinyurl.com/ngru9aj

"Hundreds of Nova Scotians are volunteering to be injected with an experimental vaccine that might cause aches and fever – but could protect against the Ebola virus.

Within minutes of the Nov. 14 announcement that Halifax's IWK Health Centre was chosen to hold the clinical trial to test Canada's Ebola vaccine, the phones started ringing and e-mails began arriving from people who wanted to participate. A week later, the trial team has heard from about 300 people – it only needs 40 healthy individuals, between 18 and 65, for this first-phase trial."

The Phase I trial for the Canadian-developed Ebola Vaccine (VSVΔG-ZEBOV) was conducted at the IWK Health Centre in Halifax, Nova Scotia. The trial involved 11 clinic visits over 6 months, and each visit required a blood draw. Participants received $1,125 Canadian dollars for their participation in the entire trial.

One of us [Browne] is involved in a study that examines the factors that motivate healthy volunteers to participate in Phase I vaccine trials. The study involves a survey of the motivations of healthy volunteers for the above-mentioned Phase I Ebola vaccine trial, as well as a Phase I trial for a PAL adjuvant[94]. The central hypotheses of the study are that: (

1. financial incentive will be the dominant motivation that participants identify;
2. other motivations will include a desire to contribute to the development of a vaccine, and a desire to help others; and
3. the high-profile nature of the Ebola vaccine trial will play a factor in participant motivations.

Surprisingly, and contrary to the first hypothesis, preliminary findings from the study reveal that financial incentives are neither the sole nor the main determinants in motivating individuals to participate in vaccine trials. The findings do, however, confirm the second hypothesis that participant motivations include desires to help develop a new vaccine and to help others. One research participant later explained to the media that participating in the trial was a life-changing experience for her (see news excerpt below). When asked about the financial incentive provided for participation, she said that she would put it towards her

[93] http://www.theglobeandmail.com/life/health-and-fitness/health/hundreds-of-nova-scotians-volunteer-for-ebola-vaccine-trial/article21712654/

[94] An adjuvant is an immune booster, which may be added to a vaccine; PAL is the name of a particular adjuvant.

university studies. She also noted that another research participant donated the money he received for participating to a children's charity. Concerning the third hypothesis, the findings are unable to confirm or deny that the high profile nature of the Ebola vaccine trial contributed to trial participation.

The study findings, along with the anecdotes from trial participants, support a general trend away from the selfish actor model that underlies classical economic theory and that informs policies and practice, including payment for research participants.

Canadian who received Ebola vaccine says experience has changed her

Ebola vaccine test volunteer …. (right) talks about how she's feeling after receiving a dose of experimental Ebola vaccine. http://www.ctvnews.ca/canadian-who-received-ebola-vaccine-says-experience-has-changed-her-1.2164898

The Canadian experience of the Phase I Ebola vaccine trial provides a remarkable contrast to the almost identical study at the African site. One candidate explanation for the over-recruitment at the Canadian site, on the one hand, and the public outcry at the African site, on the other hand, could be a difference in the levels of trust between research participants and researchers across the two trials. The suggestion here is that there is a lack of trust in North-South collaborations and that this dramatically affects recruitment of research participants. Further research is required to confirm or deny this hypothesis. To enhance trust in such collaborations, we re-emphasize Tangwa's two main conjectures:

- The verifiable existence of an infrastructure that respects fundamental human rights should be a pre-condition for medical research involving human participants, especially in LMICs and particularly in the first two phases of investigation.

- Transparency is essential when conducting trials in LMICs.

In addition, Tangwa's analysis of the informed consent documentation showed a notable lack of awareness of local requirements (e.g. researchers did not seem to be aware of the local age of consent). This is likely to contribute to distrust in North South collaborations.

One could venture that the non-existence of a reliable governance structure and non-transparency combined with insensitivity to local requirements have a major impact on trust.

12. Virus Sharing

Doris Schroeder and Julie Cook Lucas

The case was modified and updated from: Benefit Sharing - From Biodiversity to Human Genetics, Editors: Schroeder, Doris, Cook Lucas, Julie, 2013, http://www.springer.com/us/book/9789400762046 The original chapter was written by Schroeder, Cook Lucas and Krishnamurthy. Thanks to Johannes Rath for suggesting this is an important case for TRUST.

Abstract

In 2011, the World Health Organization ratified the Pandemic Influenza Preparedness Framework (also called PIP Framework). One of the reasons for its establishment was Indonesia' refusal to share avian flu samples unless a framework was established, which ended the exploitation of low and middle income country resources. Today, in 2016, the PIP framework is seen as:

> "an innovative way to make global solidarity a reality and to protect the world against devastating pandemics. In 2014–2015, 119 countries were threatened by 272 epidemic events. So, while the PIP framework exemplifies what the international community can do when committed to preparing to face pandemic disease threats, it is only a start" (Briand, 2016: 180).

This chapter describes the lead up to the PIP Framework's adoption focusing on Indonesia's protests about lack of benefit sharing in virus research.

Area of Risk of Exploitation

Laboratories from high income countries obtain samples for medical research from LMICs, potentially leading to new vaccines and medications, which are then not available to local populations in the countries of origins of the samples.

Viruses Free images
Andrzej Pobiedzinski

Case Analysis

Avian flu (H5N1 influenza type A) is a contagious viral disease, most likely to affect birds. The most dangerous form of avian flu spreads very rapidly and can cause almost 100% mortality among birds within 48 hours.

The WHO collects virus samples for distribution to affiliated laboratories in an effort to monitor and assess the risk posed by avian flu and other similar infectious diseases, to detect mutations and to develop vaccines targeted to specific strains.

Indonesia reported its first human case of avian flu in July 2005, and continued to report an average of five new cases per month from September 2005 to May 2007 (Sedyaningsih et al. 2008: 483). From 2005 to 2006, Indonesia shared by far the largest number of virus specimens with WHO laboratories, including the U.S. Centres for Disease Control and Prevention in Atlanta, Georgia, and Hong Kong University. This was in accordance with the WHO regulations

on public health emergencies of international concern (WHO 2005b). However, towards the end of 2006, Indonesia lost trust in the WHO system and decided to withhold its samples (Sedyaningsih et al. 2008).

According to Indonesian officials, various factors led to the breakdown of trust: individuals who were outside of the WHO system were given access to samples that Indonesia sent to the WHO; laboratory results involving the Indonesian samples were presented at international meetings with little or no notification to the Indonesian government; and papers based on the use of the samples were written without genuine opportunities to include local collaborators as co-authors (Sedyaningsih et al. 2008: 485).

This was in contravention of the WHO's own policy, published in March 2005, regarding the sharing of influenza viruses or specimens with the potential to cause human influenza pandemics, which stated that 'the designated WHO Reference Laboratories will seek permission from the originating country/laboratory to co-author and/or publish results obtained from the analyses of relevant viruses/samples', and that there 'will be no further distribution of viruses/specimens outside the network of WHO Reference Laboratories without permission from the originating country/laboratory' (WHO 2005a).

Viruses Free images
Denis Spelt

Subsequent reports confirmed that members of the WHO Global Influenza Surveillance Network (GISN) routinely shared information derived from virus specimens with firms that were outside of the network, and that some GISN member institutions and private firms filed patent applications using that information (Hammond 2009; WIPO 2007; Sedyaningsih et al. 2008: 486). Indonesian officials argued that allowing pharmaceutical companies (who were not members of the WHO) to have access to the Indonesian samples was not only (again) in contradiction of the WHO's policy regarding virus sharing, but also an indication of the grave unfairness of the system. As Endang R. Sedyaningsih et. al. (2008: 486) put it:

> "Disease affected countries, which are usually developing countries, provide information and share biological specimens/virus with the WHO system; then pharmaceutical industries of developed countries obtain free access to this information and specimens, produce and patent the products (diagnostics, vaccines, therapeutics or other technologies), and sell them back to the developing countries at unaffordable prices. Although it is general knowledge that this practice has been going on for a long time for other major communicable diseases – not just for avian influenza – the fear of potential pandemic influenza has magnified this gap."

Following Indonesia's decision to stop sending samples, the policy that permission should be sought prior to distributing any samples to entities outside of the WHO was overridden by the WHO's Executive Board meeting in January 2007. The new WHO recommendation stressed countries' responsibilities to share their specimens or viruses without imposing 'agreements or administrative procedures that may inhibit the proper functioning of the WHO GISN,

including in particular the timely sharing of material and information and the achievement of the Network's objectives' (Sedyaningsih et al. 2008: 486; WHO 2007b).

Appealing to all members of the WHO in 2007, the organization's director-general, Margaret Chan, said that cooperation was crucial to combating a pandemic: 'International public health security is both a collective aspiration and a mutual responsibility' (WHO 2007c:3). Referring to its specific situation, the Indonesian government noted that the CBD gave sovereignty over biological resources to national governments, a principle which they upheld on behalf of their populations, and that national law required a standard material transfer agreement (SMTA) for shipment of materials outside the country (Sedyaningsih et al. 2008: 487).

Aware of the problem since 2006, the WHO issued a report on 'Best practice for sharing influenza viruses and sequence data' in January 2007 (WHO 2007a). The report emphasized that the 'timely sharing of influenza viruses and the associated genetic and antigenic information is essential for developing the diagnostic tests, vaccines, and strategies necessary to protect populations' (WHO 2007a:1). However, it also recognized that LMICs carried a disproportionate disease burden without the appropriate means to protect their populations' health, a clear sign of vulnerability. For this reason, it noted, it was important that the 'benefits derived from this global system [of virus sharing], including better access to influenza vaccines, must be shared (WHO 2007a:2).

Following a two-day meeting organized by the WHO in Jakarta in March 2007, the Indonesian government resumed sending occasional virus samples to the WHO (Revill 2008). This decision followed agreement among members of the WHO 'on a timetable to make the changes necessary to accomplish … [the] objective of achieving equitable and affordable access to vaccines for developing countries around the world' (Wulandari and Pathoni 2007).

Low and middle income countries carried a disproportionate disease burden without the appropriate means to protect their populations.

WHO 2007

In April 2011, after four years of negotiations, the WHO's Open-Ended Working Group of Member States on Pandemic Influenza Preparedness reached agreement on an alternative framework for influenza virus sharing. The Pandemic Influenza Preparedness Framework (also called PIP Framework), ratified by the WHO at the May 2011 World Health Assembly (WHA), is meant to be responsive to the concerns raised by the Indonesian government (WHO 2011a). Importantly, it recognizes the 'sovereign right of States over their biological resources' (WHO 2011a: PP11). To protect this right, the framework includes the requirement for two binding SMTAs (WHO 2011a: paragraph 5.4).

1. The first SMTA applies to institutions within the GISN and contains terms and conditions which prohibit laboratories from making intellectual property claims in relation to the samples shared with them. In this regard, the first SMTA does not impose any requirements for benefit sharing but rather ensures that no relevant patents are being applied for.

2. The second SMTA applies to those outside the GISN system and imposes two benefit-sharing conditions, selected from a list of options which include: giving LMICs 10% of the resulting vaccines and/or anti-virals; selling 10% of these at an affordable price; or granting manufacturing companies within LMICs licences to produce vaccines or antivirals at affordable royalties, or royalty-free (TWN 2011b; WHO 2011a).

On the whole, the framework is 'an important step forward towards a system for the sharing of influenza viruses and resulting benefits'. In particular, it is 'a milestone as it obliges pharmaceutical industry and other entities (that benefit from the WHO virus sharing scheme) to engage in sharing of benefits (TWN 2011a). In particular, the binding language and the compulsory nature of SMTA 2 is to be welcomed (Wilke 2011).

Lessons Learned

The issue Indonesia has raised through its actions is that when LMICs share virus samples that are critical to the development and production of vaccines and/or antivirals, these donor countries are mostly excluded from the resulting benefits. As noted earlier by Sedyaningsih et al. (2008), any resulting vaccines are sold at a high price and so are largely unavailable to those living in LMICs such as Indonesia. Furthermore, in contrast to many LMICs, high income countries have the funds necessary to obtain supplies of limited vaccines through pre-purchase agreements with manufacturers. As Caplan and Curry (2007) have noted:

> "Indonesia is basically correct: pandemic vaccines that are in development and early testing … are largely already obligated by contract to a limited group of national governments. That list does not include Indonesia or developing nations in general."

These sorts of benefit-sharing issues are highly relevant to global public health. In practice, the timely delivery of samples to the WHO, which is necessary to protect global public health, cannot be separated from the development of meaningful benefit-sharing measures, particularly when vulnerable populations are involved. As the Indonesian case illustrates, as long as sample donors continue to lack access to the benefits that result from their participation in research, their continued participation in such research is precarious. The governments of LMICs may withhold samples when the research process is regarded as exploitive or unfair to their citizens. At the same time, it would have been difficult, without the Indonesian virus samples, to monitor avian flu properly and to develop an effective vaccine. Global public health would have been at significant risk.

Free images Jared Herzog

> Virus sharing is a critical part in the global effort for pandemic preparedness and global health security. Hence, the global community should continue the efforts to create a mechanism for virus access and benefit sharing that is accepted by all nations (Sedyaningsih et al.: 484).

As noted in the abstract, the PIP Framework has been praised as "an innovative way to make global solidarity a reality" (Briand, 2016: 180). No withholding of viruses – similar to the Indonesian case - involving protests over benefit sharing have been revealed in the literature since. However, it has been questioned in a Science article in 2014 (Gostin et. al.: 1295) whether the framework can handle the "growing likelihood that genetic sequence data might be shared instead of physical virus samples". According to the authors, the framework's scope needs to be expanded "to improve its fairness" (ibid.).

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13. Cervical Cancer Screening in India

Sandhya Srinivasan, Veena Johari and Amar Jesani

Abstract

Three clinical trials took place in India between 1998 and 2015 in urban and rural areas of Mumbai, Osmanabad and Dindigul. These trials were funded by the National Institutes of Health, USA and the Bill and Melinda Gates Foundation, in collaboration with the International Agency for Research on Cancer, France. The trials aimed to determine whether trained primary health care workers can conduct cervical cancer screening in a community using cheap methods of testing -- primarily visual inspection with acetic acid -- to reduce the incidence and mortality rate of cervical cancer. These trials did not require regulatory permission as they were non-drug trials, which reveals a weakness in the Indian law and regulations.

This study design placed 141,000 women at a known risk of developing invasive cervical cancer, and dying from it, because it was not detected and treated in time.

The clinical trials were conducted on approximately 374,000 women of whom approximately 141,000 were placed in the control arm (no screening). The standard of care was misconstrued to be no screening, as screening for cervical cancer was not available universally under a government programme in India, although the standard of care for testing of the disease in India has been cytology screening (or Pap smear) since the 1970s. Known and effective methods of screening for cervical cancer were therefore withheld from 141,000 women in areas where it is known to be of high incidence and prevalence. This placed them at a known risk of developing invasive cervical cancer, and dying from it, because it was not detected and treated in time. 254 women in the no screening arm died due to cervical cancer as per the latest published reports on the three trials.[95] This was the case even though a control arm of no screening would not have been allowed in the USA, but was allowed by the US funders for clinical trials in India.

Informed consent in one of the trials was later found by the Office of Human Research Protections, USA, to be inadequate and insufficient. High ethical standards for providing complete information to trial participants would have to be followed in the US for both public and private research, but these were not respected in India in a trial that involved poor and illiterate women.

It is imperative that ethical standards for research be applied equally across nations to prevent “ethics dumping” and protect the rights of human research participants in research no matter where they are located on the globe.

[95] The date periods for deaths in the no screening arms are taken from the dates quoted in the last available publication on each trial. They are: 98 in Mumbai 1998-2011 (Shastri et al 2014), 64 in Osmanabad 2000-2007 (Sankaranarayanan et al 2009), 92 in Dindigul 2000-2006 (Sankaranarayanan et al 2007). The Mumbai trial reported findings up to 2011 though the trial would not have ended before 2015.

Area of Risk of Exploitation

Whilst the trials described in this case study showed a number of ethical shortcomings, the main area of risk of exploitation was a placebo arm [no screening for cervical cancer despite high incidence and prevalence] instead of an accepted standard of care.

Free images Woman from India, Marga de Bruyne

Context

Medical and public health research had crossed national boundaries during colonial times; however, controversies on ethical violations in research conducted by high income countries in low and middle income countries became a real focus once higher ethical standards were established in the former, although the latter continued to seriously lag behind in bringing such standards into their legal and ethical systems.

This unevenness in ethical and legal standards has been used by high income countries to carry out research at reduced financial costs in low and middle income countries. Many participants in such research have suffered avoidable injuries and deaths. The international debate has chastised researchers from high income countries for practicing "double standards" (Macklin, 2004), taking advantage of vulnerable people in vulnerable nations and thus "exploiting" them for their own scientific goals and profit motives. Inequities among researchers, and inequities in ethics standards, have since become major issues of concern in international collaborative research.

The globalisation of neoliberal economic policies has pressured low and middle income countries to open their markets and deregulate their economies. The establishment of the World Trade Organisation in 1995 created an international trade regime favourable to high income countries. One major issue in international trade is the "dumping" of cheap and/or substandard commodities by powerful nations into the economies of less powerful nations, with devastating negative impact on their economies (Howell and Ballantine, 1998). Indeed, "dumping" succeeds 'best' when the commodity being dumped has utility value for the country where it is being dumped.

"Ethics dumping" follows the same pattern as dumping in trade, but in slightly different ways. Ethics dumping takes place because doing such research is either not possible at all in the high income country, or entails high costs due to the value attached to the ethical standards it is required to follow. This is matched in the low or middle income country by either the lack of adequate ethical standards in its guidelines, or the failure to convert and enforce such guidelines into law and mandatory requirements. At the same time, such research is relevant for the low or middle income country, due to the suffering of many people from a range of communicable and non-communicable diseases. It is also possible to tempt local scientists to undertake such research with inadequate ethical standards, in order to find a solution for the problem.

While such research may or may not provide an early solution to the medical problem suffered by people, it invariably tends to provide a justification for using a lower ethical standard, giving less importance to respect for participants, or to avoidable injuries and deaths of vulnerable subjects. Overall, it causes irreparable harm to the nation's desire to bring ethical standards up to an international level.

We provide an example of ethics dumping in three trials conducted from 1998 to 2015 in urban and rural India on testing for cervical cancer. These were funded by the National Institutes of Health (NIH), USA, and the Bill and Melinda Gates Foundation (BMGF), USA, a private foundation that supports public-private partnerships in the development of technological solutions and their inclusion in government programmes, in collaboration with the International Agency for Research on Cancer (IARC), France, a specialised cancer agency of the World Health Organization (WHO).

These trials have been condemned as unethical by public health experts and ethicists as the participants were not offered the same level of protection and consideration as participants in high income countries would have been. Women in the no screening arm of the three trials were merely observed to determine how many would get cervical cancer, and how many would die, if they were never screened. Issues relating to informed consent, the use of placebo / control (that is, in this case, no screening) despite the knowledge and availability of well-known effective methods of testing for cervical cancer, the lack of proper supervision in the intervention arm of the trial, and irreversible harm to the women participants have marred these trials and led to human rights violations.

These trials have been condemned as unethical by public health experts and ethicists as the participants were not offered the same level of protection and consideration as participants in high income countries would have been.

Background on Cervical Cancer Screening in India

Cervical cancer is the fourth most common cancer in women worldwide, with 85% of the global burden of disease in low or middle income countries (Globocan, 2012). It is the leading cause of cancer mortality in Indian women over the age of 15, and too often, women die because they do not get prompt diagnosis and treatment. Researchers note:

> "Nearly 70% of cervix cancer patients in India present at stages III and IV. Around 20% of women who develop cervix cancer die within the first year of diagnosis and the 5-year survival rate is 50%" (Mittra et al, 2010).

This cancer affects poor women the most, especially those living in rural areas, because they are less likely to get screened and treated, and therefore more likely to develop invasive cancer and die from it (Krishnan et al 2013).

In high income countries, regular screening programmes for early detection of precancerous lesions, and their prompt treatment before they progress to invasive cancer, have led to a reduction in incidence of and deaths from cervical cancer (Sankaranarayanan et al 2001). The international standard of screening is cytology, or the Pap smear, an examination of cells on

the surface of the cervix for pre-cancerous lesions. Another test is for DNA of human papillomavirus (HPV), a viral infection closely associated with the development of cervical cancer. The HPV test, which is manufactured by different companies, is being advocated for routine use in high income countries where it costs substantially more than cytology.

Cytology screening has been used in Indian public health services since the 1970s and is available in all major hospitals in the country. Since at least 2001 it has been advocated for inclusion in the government's cancer control programme services (Sankaranarayanan et al 2001). In 2006, guidelines developed by the Indian government and WHO advocated use of the Pap smear at the district level, along with a cheaper, simpler screening method at the primary health centre level (GoI/WHO, 2006). The HPV test is available in the private sector in India, but it is very expensive. Though cytology is available all over India, researchers have held that it is not feasible for population screening in a country like India. Krishnan and others write:

> "Cervical cancer prevention researchers and advocates have argued that the standard approach in high-income countries, namely cytology-based screening, is difficult to establish in LMICs [low and middle income countries] where laboratory infrastructure; trained personnel, such as cyto-technicians and pathologists; and continuous quality assurance processes are largely unavailable… Consequently, research has focused on evaluating screening approaches requiring less training and fewer clinic visits and using existing (or minimal additional) human resources."(Krishnan et al 2013)

An inexpensive cervical screening method is visual inspection of the cervix to detect precancerous lesions. Since at least the 1990s, studies have been conducted of various visual inspection methods, with or without magnification, and after application of contrast chemicals such as acetic acid or iodine to highlight precancerous lesions. These methods do not need to be conducted by a medical professional. By 1999, visual inspection of the cervix after application with acetic acid (VIA) was considered a "promising approach in the detection of cervical neoplasia" (Sankaranarayanan et al 2003) for cancer prevention programmes. VIA was being advocated for inclusion in the cancer screening programme as early as 2001, but it was felt that definitive information on the value of VIA was still lacking.

Study Design

The value of a screening intervention as a public health measure is judged by various criteria: sensitivity, specificity and positive predictive value of the test; the feasibility of implementing it in a health programme; its cost effectiveness, and its impact on incidence and mortality. Such information is gathered through various types of research, including cross-sectional studies, mathematical modelling, implementation projects, and cluster randomized controlled trials.

Within the scientific community, the cluster randomised controlled trial (CRCT) is a classical trial design to evaluate an intervention in the community. The CRCT provides the gold standard of evidence necessary for making public policy decisions. CRCTs test an intervention (preventive or therapeutic) for a disease or condition by giving it to a "cluster" of people, and comparing the results to a control group of clusters, who are given another intervention. The clusters can be slums within a municipal ward, or villages covered by a single primary health centre. The group or sample is chosen from a larger community using a system of randomisation that is meant to eliminate all differences between the two groups (e.g. age, parity) other than the intervention being studied.

When there is no existing effective intervention for the disease being studied, then a trial may compare the intervention to a placebo (e.g. a "dummy pill"). When a non-drug trial tests a preventive intervention, such as screening, then the 'placebo' arm is a 'no screening' arm. However, ethical guidelines governing the use of placebo in research severely restrict the use of placebo or "no intervention" if an effective treatment/test already exists for the disease being studied. This is to ensure that research participants in the control arm do not receive a lower standard of care than is already known to be effective, and are not therefore disadvantaged by their participation. This has been asserted in a number of national and international documents published prior to and during the three trials undertaken in this case study (DoH 2008, ICMR 2000 and 2006, CIOMS 2002). The World Medical Association's *Declaration of Helsinki* first introduced strict guidelines on the use of a placebo control in 2000 (DoH 2000).

Three cluster randomised controlled trials of VIA with "no screening" controls in India

In a review of cervical cancer screening in low and middle income countries, R Sankaranarayanan et al described research on cervical cancer screening in India, which included studies of the impact of awareness and health education, and cross-sectional studies of various visual inspection-based approaches as well as HPV testing. They concluded with the mention of three studies:

> "There are three large, ongoing cluster-randomized intervention trials in India – in Dindigul district (Tamil Nadu), in Mumbai, and in Osmanabad district (Maharashtra) – to evaluate the effectiveness of VIA in reducing cervical cancer incidence and mortality. The intervention programme in Osmanabad district aims to address the comparative efficacy and cost-effectiveness of three different primary screening approaches in reducing the incidence and mortality: VIA, conventional cervical cytology, and HPV testing. The results of these studies are likely to provide valuable leads to the development of public health policies to control cervical cancer in developing countries." (Sankaranarayanan et al 2001)

The trials were conducted on a total of 374,000 women. The 141,000 women in the control arms in these trials received no screening for cervical cancer, but were provided with the so-called "usual care" or "standard care" consisting of health education on cervical cancer,

symptoms, screening and treatment, and the availability of these facilities in their localities. According to the last published report on each trial (Sankaranarayanan et al 2007, Sankaranarayanan et al 2009, Shastri et al 2014), a total of 548 women were recorded to have died in the trials; 254 of them in the control arms of no screening.[96]

The use of 'no screening' control arms went against all established ethical principles, as articulated in national and international guidelines: new interventions must be tested against a proven effective method. In the case of the VIA trials, cytology screening was a proven effective method, and it was available in health services all over the country, including in the institutions which conducted these trials.

When a controversy about these trials using a "no screening" control broke out, one of the investigators stated: "whenever a new intervention is evaluated, it is compared with the standard of care existing in the country". In India, he wrote, there "is no organised or large-scale opportunistic cervical cancer screening programme" anywhere in the country. As a result, "The standard of care for cervical cancer control in India is clinical diagnosis and treatment of invasive cancer only when symptomatic women seek medical attention" (Sankaranarayanan et al 2011). Another researcher stated: "Pap smear cannot be considered the standard of care in India, not only because of the lack of infrastructure and trained manpower, but also because it is not cost-effective" (Pramesh et al 2013).

All the women recruited in these trials were poor, socially disadvantaged, and thus highly vulnerable. The Mumbai study was conducted on women in slum clusters living in tenements, shanties on open ground, or in makeshift huts on the pavements and along the railway lines. Osmanabad, Maharashtra, is "a predominantly rural and socio-economically backward district with a high incidence of cervical cancer". Between 25 and 30% women lived in thatched roof houses. Dindigul, Tamil Nadu, is a "backward rural district" whose high incidence of cervical cancer was a reason to choose it as the site of this VIA trial. Some 65-75% of the women in Osmanabad and Dindigul and 40% in Mumbai had no formal education. The average age of the women in these trials was 40-45 years (range 30-59). They would have had poor access to healthcare, whether because of cost or the inconvenience of long waiting lines and ill-equipped public services, or the low priority given to self-care. Though it is known that the vast majority of women, particularly after they have given birth, suffer from various gynaecological symptoms, 90% of women in the Mumbai trial had never visited a gynaecologist with their complaints.

All the women recruited in these trials were poor, socially disadvantaged, and thus highly vulnerable.

The Mumbai trial

The first study to start was in Mumbai, at the Tata Memorial Hospital and Centre (TMC), a national centre of excellence for cancer research and policy. The study, entitled "Early detection of common cancers in Women in India", was funded by the US National Institutes

[96] The figures are based on the start and cut-off dates given in the study reports: Dindigul (2000-2006): Osmanabad (2000-2007) Mumbai (1998-2011). The Mumbai trial concluded in 2015, but reported results as of 2011.

of Health. The study initially sought to find out if repeated rounds of screening using inexpensive techniques would reduce mortality from cervical cancer.

Women community health workers educated up to the 10th grade were trained to conduct screening with VIA and also to do clinical breast examination for detection of breast cancer. They were required to be supervised and about 10% of women screened were also to be tested by the researchers for cross- checking of the results. Women in both arms were given health education on the causes of cancer. They were also told about the need for screening, and that the screening and treatment were available. Then the women in intervention/experimental arms were provided screenings for cervical cancer, while women in the control arms were provided no screening at all.

The trial started in 1998 and concluded in December 2015. A total of 75,000 women in the intervention arm and 76,000 women in the no screening arm were recruited into this trial. Each woman was in the trial for 17 years. *Women in the intervention arm* were given health education and screening four times, i.e. once every two years. Those who tested positive were directed to the Tata Memorial Hospital where they were given confirmatory tests and treatment if needed. After the four rounds of screening were over, the women were then contacted four times, once every two years, for follow-up. *Women in the control arm,* on the other hand, received health education only once, were not offered any preventive screening for carcinoma cervix, and were observed through surveillance for 17 years. Every two years, through active surveillance, data of women in the control arm were collected to find out the number that developed cervical cancer or died as a result of it. In 17 years, seven rounds of active surveillance were carried out in both arms to document the development of cervical cancer and deaths due to it.

Free images – Maurizio Sartore

Changes were made to the study protocol over a period of time. The intervention was initially "direct visual inspection" without any magnification or contrast (DVI), a technique that had been judged obsolete before this trial began, and was later changed to VIA. The sample size increased from about 35,000 in each arm initially to about 75,000 in each arm. The objectives were later amended to include reduction in incidence from cancers. These details do not appear in the published reports of the study. Cross checking of test results by the researchers was also performed for less than 10% women in the intervention arm.

In 2011, an American physician filed a complaint with the US government's Office of Human Research Protections (OHRP), relating to the Mumbai and Osmanabad trials. An application for documents was also filed by a journalist under the US Freedom of Information Act. The OHRP stated that its jurisdiction was limited to trials funded by the US government and did not apply to research funded by BMGF, a private party (Suba 2014).

The OHRP's investigation found irregularities in TMC's Institutional Review Board (IRB) functioning: Standard operating procedures had not been followed, meeting minutes were not documented, and decisions were taken without quorum. The OHRP also found discrepancies in the informed consent document between the English and the local language translation (Marathi). While the English form gave information on cervical cancer, the tests required for its detection, and where testing was available, the Marathi form did not contain these details.

The OHRP did not find the no-screening arm of the trial to be unethical. By 2011, 98 women who had entered the control arm of the Mumbai trial and received no screening but only health education, had died of cervical cancer. The results of the Mumbai trial were announced at the 2013 meeting of the American Society for Clinical Oncology. The researchers announced that a test for cervical cancer, using just vinegar, and conducted by trained health workers, could bring down mortality from cervical cancer by 31% (ASCO 2013). The findings were reported extensively in the press.

Osmanabad trial

In October 1999, Tata Memorial Hospital with its Rural Extension Project and the Nargis Dutt Memorial Cancer Hospital started a second trial, in the Osmanabad district in rural Maharashtra. They were funded in this trial by the Bill and Melinda Gates Foundation (BMGF).

This trial compared the impact of a single screening of VIA, HPV test or cytology to a 'no screening' control arm in a CRCT. The primary outcomes were the incidence of cervical cancer and the associated rates of death. The researchers stated in their interim report:

> "Whether a screening program using VIA or HPV testing will be followed by a reduction in disease burden and the cost–effectiveness of these alternate approaches based on real program-based information remain to be established. These approaches need to be evaluated in comparison with the established standard cytological screening, with respect to their comparative efficacy and cost–effectiveness, before recommendations can be made concerning their introduction in a public health context" (Sankaranarayanan et al 2005).

Women in the intervention arm were identified through household surveys, and those who consented to be in the trial were given information on cervical cancer and its prevention, and invited to screening camps in each village where trained midwives conducted the screening. Depending on which intervention arm the village belonged in, the women received VIA, Pap smear, or the DNA test for HPV. Women with positive VIA tests were given immediate follow-up tests and on the spot treatment if appropriate; or they were referred to the Nargis Dutt Hospital for further treatment. Samples from the cervix were taken from women in the cytology and HPV arms, and the results sent to them in two weeks. Those with positive tests were given appointments at the hospital for follow-up. Women in the control arm were given education on cancer and its prevention and information about the services available at the Nargis Dutt Hospital. "Since there is little screening for cervical cancer in India, women who did not undergo screening (control group) were considered to receive the standard of care" (Sankaranarayanan et al 2009).

All the women were contacted just once, at the time of the intervention, after which they were surveyed and tracked through the cancer registries and death registries, until the end of the eight years' follow-up period. The trial was conducted in partnership with the IARC and the Association for Cervical Cancer Prevention (ACCP). The ACCP is a member of the IARC and both receive some funding from the BMGF. Screening was started in January 2000 and completed by April 2003 (Sankaranarayanan et al 2005). The findings of the interim report of the Osmanabad trial ran contrary to standard wisdom:

> "Our results show that a high level of participation and good-quality cytology can be achieved in low-resource settings. VIA is a useful alternative but requires careful monitoring. Detection rates obtained by HPV testing were similar to cytology, despite higher investments." (Sankaranarayanan et al 2005)

However, when the final findings were reported in 2009, the researchers concluded that while a single round of screening for HPV reduced both incidence and mortality from cervical cancer, cytology and VIA were no better than no screening at all. The researchers observed that while the test used in the trial, by Digene Corporation, was effective, a cheaper HPV test had been developed, manufactured by Qiagen, a Chinese company.

> "Our results, combined with those of the Chinese study of the new HPV test, indicate that HPV testing is appropriate as a primary screening approach in low-resource settings for women who are at least 30 years of age" (Sankaranarayanan et al 2009).

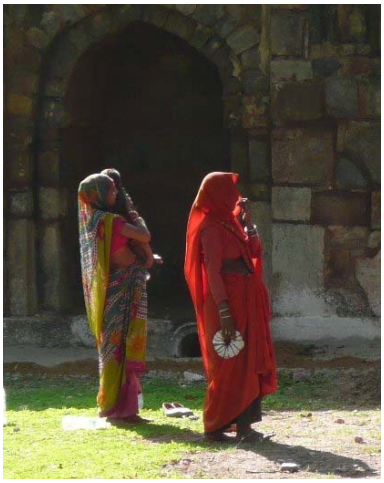
These comments gain significance when one learns that in 2004, Digene had entered into a partnership with the Program for Appropriate Technologies in Health (PATH), an implementing agency for BMGF, to promote the use of HPV testing in low and middle income countries. In 2007, Qiagen Corporation bought Digene Corporation.

Dindigul trial

The third trial started a few months after the Osmanabad trial. In May 2000, the BMGF with IARC initiated another trial of VIA, this one with the Christian Fellowship Community Health Centre hospital in Ambilikkai, Dindigul, and Tamil Nadu. The objective was to evaluate the efficacy of a single round of VIA provided by nurses, with appropriate treatment approaches, in reducing the incidence of and mortality from cervical cancer.

The women in the intervention arm were screened with VIA by trained nurses. Those found positive were offered cryotherapy on the spot, and those with larger lesions were referred for treatment. Screening was completed by April 2003. The control group received "existing care". "No active intervention was provided for the control group" (Sankaranarayanan 2004). The researchers explained: "We used an unscreened control group because there are no organized screening programmes in India" (Sankaranarayanan 2007).

Information on incidence and mortality was collected from cancer and mortality registries as well as through active follow up. Follow up started in September 2003 and was to continue until 2012. However, by December 2006 the researchers concluded that a single round of VIA followed by appropriate treatment reduced incidence and mortality significantly. "Timely implementation of an affordable and effective screening strategy in developing countries is thus crucial, while waiting for further improvements in HPV testing, vaccine technology, costs, and its widespread use" (Sankaranarayanan 2007).



Analysis

While ethics and human rights often offer universal frameworks for research, their actual implementation differs from country to country. Basic ethical principles of research such as that of informed consent, cautions on research on vulnerable populations and the need for monitoring mechanisms to protect participants are laid out in international guidelines. The three trials described in this case study are evidence that principles of research ethics are not always converted into practice.

The VIA trials demonstrate ethics dumping, and the harm that it causes to participants in low and middle income host countries. These trials would never have been granted ethical approval in the USA or France, the countries of the sponsors and collaborator. They exploited regulatory weaknesses and economic and social inequities. They were pushed, approved and accepted by the sponsors (NIH and BMGF, USA) and collaborator (IARC, France) to be conducted in India on poor and vulnerable women.

In these three trials, the universal and fundamental right to life and the right to access to the highest available standard care of the women participants in the control arm of no screening were violated. It was known that as poor women, they were already at increased risk of developing cervical cancer; the denial of known effective and potentially lifesaving screening put them at a predictable risk of developing invasive cervical cancer and dying from it. The denial of screening delayed not only the detection of the disease, but also access to appropriate and timely treatment that could have saved their lives. The standard of care was wrongly construed by the researchers as meaning the universal availability of tests under a programme of the government in India, rather than the universal standard of care used for testing of the disease, which was available in India.

The standard of care was wrongly construed by the researchers as meaning the universal availability of tests under a programme of the government in India, rather than the universal standard of care used for testing of the disease, which was available in India.

For the purpose of public health policy, there was no need for a natural history control arm of no screening. The researchers should have provided an active control arm

using one of the known methods of testing for cervical cancer, as they would have had to if the trials had been conducted in the USA or France.

In addition, the trials ignored the importance of informed consent. Women in the trials were not given adequate information. This violated their right to life, vitiated their consent, and rendered the trial illegal. A trial without the participants' voluntary and informed consent would not have been permitted in a high income country.

What made these unethical trials possible? What were the conditions that enabled ethics dumping in the VIA trials? One needs to understand why host countries seek international support for research, why sponsors fund this research, and whether these reasons are justifiable. These reasons may include: a shortage of locally available funds for research; the interest of organisations in high income countries to conduct research in low and middle income countries as part of their international health agendas; and the relationships between local institutions and international organisations, as well as between researchers' own links with these organisations as part of their own scientific careers. All these create a web of relations that lies at the heart of the resulting double standard.

Research ethics must also contend with the view (Prasad et al 2016) that locally relevant research justifies lower ethical standards. The researchers in these studies have argued that these studies are important because cervical cancer affects and kills poor women more than it does women in high income countries, and this calls for a test that is inexpensive, implementable and effective. They have also asserted that double standards do not cause active harm, as there is no functional screening system in the host country.

Finally, the women participants in both experimental and control arms of these trials are poor, voiceless and invisible. They may view participation in such trials as access to some care. When faced with a powerful medical establishment they will be reluctant to make their grievances public. For instance, the hospital conducting the Osmanabad trial is the only such service in the area. In such a situation, violations of research ethics are less likely to come into the public eye.

Ethical implications of research in communities without universal access to healthcare

Researchers in the VIA trials did not provide the standard of care to participants in the control arm arguing that India did not have an effective universal screening programme and its standard of care for cervical cancer prevention was therefore 'no care'.

Most low and also middle income countries, barring a few honourable exceptions, do not have *universal* access to healthcare. Even when the government is supposed to provide free access to healthcare, individuals are forced to seek care in the private sector and pay for it. The care that people receive is therefore determined not by a universal standard but by what they can afford, or what the government provides, and many people do not get any care whatsoever. This situation has permitted researchers to interpret the standard of care, and their own responsibilities as physician-researchers, in a way that is not in the best interests of research participants.

The standard of care *cannot* depend on, or be defined according to, whether or not it is universally accessible. In the VIA trials, the Pap smear is the universal standard of care because it is universally considered to be an effective screening test for cervical cancer. Any woman who goes to a private or public hospital should expect to be offered it. It is part of the Indian government's cancer prevention programme.

Whether or not the community involved in research has universal access to the standard of care, through the government or private or social insurance, researchers and sponsors must be held responsible for providing this standard preventive, diagnostic and curative care free of cost to participants in the control arm. There is therefore a need to have an explicit provision in ethics guidelines and in the law emphasising researchers' ethical obligation to provide standard care to participants in the control arm as they are under their direct care during the course of research.

Regulatory weaknesses

Guidance for ethics review of non-drug trials is included in the Indian Council of Medical Research's ethical guidelines for biomedical research on human participants (ICMR 2006). The ICMR guidelines acknowledge that denial of available treatment to a control group is unethical. They also state that "proper justification should be provided for using the placebo," and that "In keeping with the Declaration of Helsinki *as far as possible standard therapy should be used in the control arm*."

However, since the trials were non-drug related, prior permission from the Drugs Controller General of India was not required. Thus the VIA trials did not have any legal oversight. The regulatory roles were played by institutional committees – the Institutional Ethics Committees, Scientific Review Committees and the Data Safety Monitoring Committees– and in this case, their authority was limited to within the institution and they were not accountable to a regulatory authority.

US regulatory bodies claimed inability to investigate and act on complaints of unethical research in the Osmanabad and Dindigul trials as these were funded by a private foundation. Hence, these trials were not accountable to the Indian regulator nor the US regulator as they were not government funded. Private foundations in high income countries fund a substantial amount of collaborative research in low income countries, and their lack of accountability to any authority is a matter of concern.

Private foundations in high income countries fund a substantial amount of collaborative research in low income countries, and their lack of accountability to any authority is a matter of concern.

In the case of the Mumbai trial, the US regulatory body applied double standards. The use of a retrospective waiver of written informed consent, or permission to obtain consent after the intervention, goes against the very principle of prior informed consent in research, and would not have been allowed in the US. Likewise, the US Office of Human Research Protections concluded that the no screening arm in the Mumbai trial was not unethical, which would not

have been possible in the US. The trial even continued when the relevant local hospital ethics committee in Mumbai stated that the use of a no screening arm was unethical.

Information about the actual trials, apart from the published papers, was not available easily. This prolonged the harm done to the participants, as the response to claims about the unethical and illegal nature of the trials was delayed.

Recommendations

The following steps are necessary to prevent ethics dumping between high income and low or middle income countries.

Ensure regulation of collaborative research. Studies involving international collaboration should only be allowed in low and middle income countries if mechanisms are in place which ensure that the rights of participants will be respected at all times, and that sponsors, researchers, ethics committees or institutions, whether governmental or private, operating both inside and from outside the host country, are held accountable for their activities in India.

Ensure a framework for transparency. Mechanisms must be put in place to ensure that trials are conducted in an open and transparent manner, and information about ongoing trials must be available and open to expert scrutiny, so as to prevent harm at any stage of the trial. The anonymised data, findings and conclusions of the researchers should be open to scrutiny in open access, in order to evaluate the findings and whether they should be used in public health policy.

Provide compensation for research-related injury. Mariner (1997) writes:

> "Since most legitimate research is intended to benefit society as a whole, the subject assumes risk for society's sake (some would say making a gift to society). Therefore, society has a moral obligation to make the injured subject whole by compensating those who took the risks and suffered thereby. In addition, it may be argued that where society conducts, supports, or sponsors research, it voluntarily assumes an obligation to compensate those who are injured in its enterprise."

Sponsors and researchers must compensate participants who suffer from trial-related injuries, by offering diagnostics and treatment freely and by providing monetary compensation for the loss, injury, harm, mental and physical suffering and expenses incurred as a result of participating in the trial. The mechanism should be simple, so that it causes minimal problems to the participants. In the above trials, proper follow-up of the women in the control arms, testing them with the best known methods, and providing treatment and compensation, would be a step in the right direction. Families of women who died due to the standard of care being withheld, thereby preventing them from accessing timely treatment, must be compensated as well.

***Doris Schroeder**: It is noteworthy that the authors of the only two cases from the bottom-up call competition included in this report (Ebola vaccine trial and cervical cancer screening trial) provided two almost identical first recommendations:*

1. *Studies involving international collaboration should only be allowed in low and middle income countries if a local infrastructure exists, which can ensure the protection of research participants.*
2. *A framework for transparency of ongoing trials must be put in place.*

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Short Notes on Remaining Areas in Horizon 2020 Ethics Review

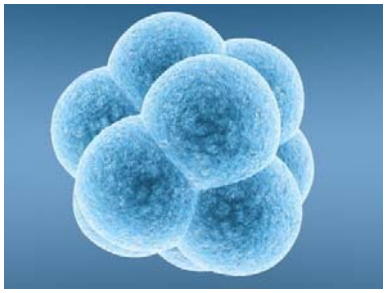
Doris Schroeder and David Coles

Human embryos and foetuses

In December 2013, a Declaration of the Commission (2013/C 373/02) was published about human embryonic stem cell research in Horizon 2020. It includes the following statement[97]:

1. The decision on the Horizon 2020 Framework Programme explicitly excludes three fields of research from Community funding:

— research activities aiming at human cloning for reproductive purposes;
— research activities intended to modify the genetic heritage of human beings which could make such changes heritable;
— research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.



Blastocyst

Our literature review, including grey literature (e.g. electronic news) did not identify a specific case of "ethics dumping" in human embryonic stem cell research. However, in providing an account of "Progress in Human Embryonic Stem Cell Research in the United States between 2001 and 2010", Keyvan Vakili et al.[98] noted the following:

> "On August 9th, 2001, the federal government of the United States announced a policy restricting federal funds available for research on human embryonic stem cell (hESCs) out of concern for the "vast ethical minefields" associated with the creation of embryos for research purposes…. [The policy] stimulated increased collaborative research between US-based scientists and those in countries with flexible policies toward hESC research (including Canada, the U.K., Israel, China, Spain, and South Korea)… [and] encouraged independent hESC research in countries without restrictions.

This suggests that researchers working in countries with restrictions on human embryonic stem cell research will try to collaborate with countries without restrictions. We will – throughout the duration of TRUST – bear this in mind and add an "ethics dumping" case to the website, should one become available.

[97] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:373:0012:0015:EN:PDF, p.1.
[98] Vakili K, McGahan AM, Rezaie R, Mitchell W, Daar AS (2015) Progress in Human Embryonic Stem Cell Research in the United States between 2001 and 2010. PLoS ONE 10(3): e0120052. doi:10.1371/journal.pone.0120052, p.1.

Health and Safety

The Horizon 2020 Ethics Review Process contains one new area, which was not covered in Framework 7: Environment and Health and Safety. We have provided a case for environment above. However, for "health and safety", we would like to add our thoughts rather than a specific case. Whilst we have seen a considerable number of cases, they cannot be used for this report, as we saw them as expert reviewers. Hence, they are confidential. In the literature, there are no "ethics dumping" cases available and for a good reason. It is not a case of "ethics dumping". Why is that so?

By health and safety concerns in relation to North–South collaboration we mean the following (and so does the Ethics Review Process, we believe):

istock

Health and safety precautions/regulations/efforts in North-South collaborations deal with the safety, health and welfare of people engaged in work or employment in international collaborations between high-, middle- and low-income countries.

By ethics dumping we mean purposeful exploitation of low and middle income research participants/resources as well as exploitation based on insufficient ethics awareness.

The main health and safety concerns that are covered by the *ethics* review of Horizon 2020 in the context of North-South collaboration are Northern researchers traveling to Southern countries. This is so because health and safety deals with work-related issues. For instance, if Chinese workers were put at risk through inappropriate interviewing by a Northern researcher, this would not strictly be a health and safety issue (even though the lines are not drawn very clearly). It would be a risk issue associated with the research.

The mobility of high income settings researchers has increased dramatically over the last decade. Whilst it was mostly anthropologists who travelled into low and middle income countries (LMICs) in the past, to undertake research, almost all disciplines do so today: from social scientists, to art and film historians, political scientists and various theorists (e.g. war theory).

Job mobility and experience abroad is a key criterion on the CVs of high income researchers. As a result, more and more research is undertaken outside one's own area of experience. For instance, a war theorist might include in his/her application for research funding practical fieldwork in Syria, Iran or Iraq. An art theorist might include fieldwork to LMICs on all continents to cover street art as a form of resistance against the corrupt or violent political establishments. A sociologist working on fair trade might add fieldwork interviewing workers in high-risk Chinese manufacturing. This can pose risks for researchers and research participants if no local partnerships have been established or no prior experience of working in LMICs is available.

The following problems need to be resolved in this context.

- The health and safety of the Northern researcher needs to be ensured.
- In medical research, no research should be undertaken on vulnerable populations in LMICs unless it is informed by local needs. This is clearly stated in many international guidelines, see for instance, Art. 20 of the Declaration of Helsinki.[99] Such assessments are not required for non-medical research presenting the risk of helicopter social science research with all benefits going to the researcher.
- Researchers who are inexperienced in working in LMICs can put research participants at risk (as noted above, for instance, when interviewing Chinese workers without sufficient knowledge of the context).
- When scientific reviewers approve a proposal which then moves forward to the ethics committee, which deletes significant parts of the proposal as too dangerous, the funder is put in a very difficult position. The changed proposal might no longer pass the scientific review if the original proposal puts the researchers and possibly also research participants at risk.

One suggestion for resolving some of the above is as follows:

- Equitable research partnerships are not possible without local collaborators, which could be made compulsory for research involving human participants or local resources in LMICs, unless a good argument can be provided why this is not possible or desirable.

Equitable research partnerships

[99] http://www.wma.net/en/30publications/10policies/b3/

Appendix

Case Study Resources

The following provides other open access case books that may be useful.

- COHRED, 2016. Public Health Ethics: Cases Spanning the Globe. http://www.springer.com/us/book/9783319238463.

- UNESCO, 2011. Casebook on Human Dignity and Human Rights, Bioethics Core Curriculum. Casebook Series, No. 1. http://unesdoc.unesco.org/images/0019/001923/192371e.pdf.

- UNESCO, 2011. Casebook on Benefit and Harm, Bioethics Core Curriculum Casebook Series, No. 2. http://unesdoc.unesco.org/images/0019/001923/192370e.pdf.

- WHO, 2009. Casebook on Ethical Issues in International Research. http://www.who.int/rpc/publications/ethics_casebook/en.

The following high-calibre PhD thesis contains a range of excellent case studies.

- Ravinetto R., (2016). *Methodological and Ethical challenges in Non-Commercial North-South Collaborative Clinical Trials*, Leuven: Leuven University Press.

Contributors

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Dr Francesca Irene Cavallaro holds a PhD in Cognitive Sciences and a degree in Philosophy. She currently works as individual specialist in UNESCO's Bioethics and Ethics of Science and Technology Section, and as part time senior communication and engagement manager for the South African San Institute, SASI. From 2008 to 2013 she served as senior researcher and clinical research coordinator at Tecnalia Research and Innovation (Spain), where she developed a thorough knowledge of both the industry and policy perspectives on R&D projects related to health, ageing and ICT. From 2014 to (January) 2016 she was Research Fellow at the Centre for Professional Ethics,

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Dr Kate Chatfield is a social science researcher and ethicist. She holds positions as a senior lecturer in the School of Community Health and Midwifery at UCLan and as a senior researcher at UCLan Cyprus. Her teaching responsibilities include research methodology and research ethics; her research interests include sustainability, equity and equality in healthcare; responsible research and innovation; ethical challenges in health care and research; as well as animal welfare and animal rights.

Dr Roger Chennells works as legal advisor for SASI and is senior partner of the human rights law practice Chennells Albertyn (Stellenbosch, South Africa) since 1980. Specialized in labour, land, environmental and human rights law, he has over the years developed an interest in indigenous peoples as well as intellectual property aspects of heritage, working with the San peoples for many years as legal advisor. He has worked for the aborigines in Australia, and has assisted the San people in land claims as well as benefit sharing. Roger's PhD was funded by the Wellcome Trust, and his thesis title is Equitable Access to Human Genetic Resources: Balancing Benefit Sharing and Undue Inducement (Springer, 2016).

Dr David Coles is Senior Research Fellow at the University of Central Lancashire's Centre for Professional Ethics and a Research Associate at the University of Newcastle's School of Agriculture, Food and Rural Development. He is also Director of Enhance International Limited, a consultancy company, reviewing and providing advice on ethical and policy aspects of scientific research. Previous experience includes Joint Programme Manager for the European and Developing Countries Clinical Trials Partnership, with responsibility for coordinating EU Member States' funding of poverty-related diseases; as well as developing and implementing the EU system of ethics review for the European Commission for research proposals to the EU Framework Programme.

Dr Francois Hirsch is the Head of the Inserm Office for Ethics and the Assistant Director for Ethics and Regulation of the Institute for Health Technologies. He has a background in immunology, quality in research and ethics in medical sciences. After having participated in various committees for the French medical agency, Francois is currently a member of one of the French registered ethics committees for clinical research (*Comité de Protection des Personnes Ile-de-France VII*). Francois has organised or taught in several training programmes on ethics and good clinical practice in Africa and mentored a number of doctoral students on ethical issues linked to the limited access to health care systems.

Solveig Fenet first studied political science and international relations at the University of Montreal and obtained her Master degree in European Studies at the University Paris-Sorbonne. Before joining Inserm as researcher, Solveig was an economic analyst at the French Development Agency (AFD) assessing the management performance of water

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Dr. Amar Jesani is an independent consultant – researcher and teacher - in bioethics and public health. He is co-founder of the Forum for Medical Ethics and its journal, the Indian Journal of Medical Ethics (www.ijme.in), published since 1993, and presently its editor. He is Visiting Professor at the Centre for Ethics, Yenepoya University, Mangalore, India and Associate Faculty at the Centre for Biomedical Ethics and Culture, Karachi, Pakistan. He is a Member of the Institutional Review Board, Tata Institute of Social Sciences, Mumbai; the International Research Ethics Committee of *Médecins Sans Frontières* and the Central Ethics Committee of the Indian Council of Medical Research, Delhi, India.

Veena Johari is a Mumbai-based lawyer working on human rights and public health. She was with the Lawyers Collective HIV/AIDS Unit for 10 years before setting up her own firm, Courtyard Attorneys, which focuses on access to medicines and patent opposition on pharmaceutical drugs. She works on legal and ethical issues relating to clinical trials in India and is the legal expert in the research ethics committee of the KEM Hospital, Mumbai. She is on the editorial board of the Indian Journal of Medical Ethics.

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Prof. David Morton is Professor Emeritus of Biomedical Science and Ethics at the University of Birmingham, UK. He is a veterinary surgeon whose research interests concern the recognition, assessment and alleviation of pain and distress in animals. He was (retired July 2012) a member of the EU's (EFSA (FDA equivalent)) scientific panel on animal health and animal welfare. He was also a government adviser for the UK's legislation controlling the use of animals in research (Animals (Scientific Procedures) Act 1986). He has sat on working groups at the Nuffield Institute in the UK, and at the Hastings Centre and the Kennedy Institute in the USA, reporting on animal experimentation. He was the prime author of the OECD's Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation. He chaired the UK's Joint Working Group on Refinement, and received the Commander of the Most Excellent Order of the British Empire (CBE) on Animal Welfare.

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Jaci van Niekerk is a researcher based in the Department of Environmental and Geographic Science at the University of Cape Town. She completed a Master's dissertation in 2009 which examined the early implementation of access and benefit-sharing legislation in South Africa, in the context of a medicinal plant endemic to the region, *Pelargonium sidoides*. Her research revolves around issues of social and environmental justice, with a particular focus on the impacts of policies and technologies on agricultural biodiversity and the livelihoods, wellbeing and food sovereignty of small-scale farmers.

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TRUST Case Studies Workshop in Mumbai, March 2016, under the leadership of FERCI