BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Brandon Brown	Assistant Professor Director of Global Health Projects UCI Program in Public Health
eRA COMMONS USER NAME (credential, e.g., agency login) bbrown53	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of California, Los Angeles	Postdoc	2011	Global Health
Johns Hopkins School of Public Health	PhD	2010	International Health
University of California, Los Angeles	MPH	2006	Epidemiology
University of California, Irvine	BS	2004	Applied Mathematics

A. Personal Statement

Dr. Brandon Brown is an epidemiologist with over 10 years of research experience on sexually transmitted infections, and with ongoing studies of HIV, cancer screening, human papillomavirus, and vulnerable populations including MSM and FSWs. He is currently the Research Director at an NGO in Peru, and collaborates on HIV related research projects with other Peru based organizations. Brandon is a consultant ethicist at UC Irvine, and teaches graduate and undergraduate ethics courses, and is leading the UCI IRB Ambassador program to develop the next generation of public health ethicists. Brandon is the Director of the UCI global health, research, education, and translation (GHREAT) program, and his current research focuses on HIV, HPV, and research ethics with marginalized populations.

B. Positions and Honors

Positions

04/12-Present Director of Global Health Projects, UCI Program in Public Health, Irvine, CA
09/11-06/14 Lecturer and Undergraduate Director-UCI Program in Public Health, Irvine, CA
01/11-09/11 Postdoctoral Fellow-UCLA, Los Angeles, CA
04/11-07/11 Visiting Scholar-UCSD, San Diego, CA
06/07-08/07 Research Contractor on HIV Projects-UCLA School of Medicine, Los Angeles, CA
03/06-05/06 HIV Data Collector-Health Research Association, Los Angeles, CA
08/05-06/06 Staff Research Associate-UCLA, Los Angeles, CA
06/05-08/05 Program Director-CAMP Summer Science Academy, Irvine, CA
09/04-06/05 Graduate Student Researcher-Department of Epidemiology, Los Angeles, CA
06/04-09/04 Summer Intern-National Cancer Institute, Bethesda, MD
06/03-09/03 Summer Intern-Human Sciences Research Council, Cape Town, South Africa

Honors (past 10 years)

2014 Diversity Development Program Member, UCI
2013 National Society of Collegiate Scholars Distinguished Member, UCI
2013 UCI Council on Research Computing and Libraries Grant, UCI
2013 UROP Faculty Mentor of the Month, UCI
2012 UCI Council on Research, Computing and Libraries Grant, UCI
2011 AIDS Institute International Travel Grant, UCLA
2011 **NIH** International Papilloma Virus Travel Award, UCLA
2011 New Investigator in Global Health Fellow, UCLA

2010	Mary and Carl Taylor Scholarship in International Health, JHSPH
2009-2011	**NIH** NRSA Dissertation Fellowship, JHSPH
2009	Dan David Prize in Global Public Health, JHSPH
2008-2009	**NIH** International Maternal and Child Health Training Grant, JHSPH
2008	Carol Eliasberg Martin Scholarship in Cancer Prevention, JHSPH
2006-2008	Minority Health Predoctoral Fellowship, JHSPH
2005	International AIDS Research Training Award, UCLA
2005-2006	California Endowment Fellowship-Work in Underserved Communities, UCLA
2004	**NIH** Predoctoral Research Training Award in Viral Epidemiology
2004	McNair Researcher of the Year Award, UCI
2004	Minority Biomedical Research Scientist (MBRS) Training Grant Recipient

C. Research

Ongoing Research:

NIH Fogarty Global Health Fellowship
The impact of community led total sanitation on health in Kenya — June 2013-May 2014
Role: Faculty Mentor

NIH R01 PAR-11-145 International Research in Infectious Diseases — July 2012-June 2017
Syphilis and HIV: Translating technology to understand a neglected epidemic
Role: Co-I

NIH Loan Repayment Program — July 2012-May 2015
The role of Genital Warts in HIV acquisition among MSM in Peru
Role: PI

NIH R25 DA031608 Fordham Research Ethics Training Institute — July 2012-June 2014
Experiences and Impressions in a Clinical Trial of HPV Vaccine with FSWs
Role: PI (Director-Celia B. Fisher)

Merck IISP 39619 — Oct 2011-Dec 2014
The role of Genital Warts in HIV acquisition among MSM in Peru
Role: PI

Completed Projects:

University of California Global Health Institute (UCGHI) — Feb 2013-March 2014
Reducing HIV/AIDS-related Stigma through PhotoVoice
Role: Faculty Mentor

UC Mexus — Dec 2011-Dec 2012
Cervical cancer prevention among female sex workers in Tijuana, Mexico
Role: PI

USAID/Peru Development Assistance Fund Program — October 2011-July 2012
Sexual health, community education, and STI outreach activities for MSM
Role: Co-PI

Merck IISP 37983 — May 2010-April 2012
HPV prevalence in multiple anatomical sites among MSM in Peru
Role: Co-PI

Merck IISP 35706 — May 2008-April 2012
Acceptability of HPV vaccine in brothel based FSWs in Peru
Role: Co-PI

D. Publications

Published Papers:

1. Petros G, Airhihenbuwa CO, Simbayi L, Ramlagan S, Brown B. HIV/AIDS and OTHERING in South Africa: The Blame Goes On. Culture, Health and Sexuality 2006; 8(1): 67-77.
2. Brown BE and Brown BJ, M, Welch R, Cranston B, Hanchard B, Hisada M. Haplotypes of IL6 and IL10 and Susceptibility to Human T Lymphotropic Virus Type I Infection among Children. The Journal of Infectious

Diseases 2006; 194: 1565-9
3. Brown BJ, Huang M-H, Karlamangla AR, Kado DM, and Seeman TE. APOE- ε4 and vitamins B6, B12, folate, or homocysteine interacting to predict cognitive function and longitudinal decline: MacArthur Studies of Successful Aging. Journal of Nutrition, Health, and Aging 2010.
4. Brown B, Carcamo C, Blas M, Valderrama M, and Halsey N. Peruvian FSWs: understanding HPV and barriers to vaccination. Vaccine 28 (2010) 7743-7747.
5. Brown B, Blas M, Cabral A, Carcamo C, Gravitt P, Halsey N. Oral sex practices, oral HPV, and correlations between oral and cervical HPV prevalence among female sex workers in Lima, Peru. International Journal of STDs and AIDS 2011; 22: 655-658.
6. Brown B, Blas M, Cabral A, Byraiah G, Guerra-Giraldez C, Sarabia-Vega V, Carcamo C, Gravitt PE, Halsey NA. HPV Prevalence, Cervical Abnormalities, and Risk Factors among Female Sex Workers in Lima, Peru. International Journal of STDs and AIDS 2011; 23: 242-247
7. Brown B, Blas M, Cabral A, Carcamo C, Gravitt P, Halsey N. Randomized trial of HPV4 vaccine assessing the response to vaccine in two schedules among Peruvian FSWs. Vaccine 2012; 30: 2309-14.
8. Brown B and Klausner JD. High-level evidence demonstrates male circumcision reduces Human Papilloma Virus infections. HPV Today n26.
9. Munoz K, Sharoff N, Brown B. Reducing HPV Transmission in the Developing World through Education and Targeted Vaccination. Journal of Global Health Perspectives (November 18, 2012).
10. Brown B, Davtyan M, Galea J, Chow E, Leon S, Klausner J. The role of human papillomavirus in human immunodeficiency virus acquisition in men who have sex with men: a review of the literature. Viruses-Special Issue on HPV 2012; 4(12):3851-8.
11. Davtyan M, Munoz K, Urada L, Brown B. Transactional Sex-A Clients Perspective from Peru. Journal of Human Sexuality (Volume 16-March 12, 2013).
12. Brown B and Merritt M. Incentive Parameters for International Human Subjects Research in Low-Resource Settings. IRB: Ethics and Human Research 2013; 35(2): 14-17
13. Nurena C, Brown B, Galea J, Sanchez H, Blas M. HPV and genital warts among Peruvian men who have sex with men: Knowledge, attitudes and treatment experiences. PLoS One 2013; 8(3):e58684.
14. Nasiruddin M, Halabi M, Chen K, Dao A, Brown B. Zombies—A Pop Culture Resource for Public Health Awareness. Emerging Infectious Diseases 2013; 19(5): 809-813.
15. Brown B, Blas M, Heidari O, Carcamo C, Halsey N. HPV4 completion and reported change in sexual behaviors following HPV vaccination among FSWs in Peru. IJSA 2013; 24: 531-535.
16. Shroff N, Brown B, Kinsler J, Cabral B, Blas M, Carcamo C, Halsey N. Barriers and Facilitators in the Recruitment and Retention of Peruvian Female Sex Workers in an HPV Vaccine Trial. Vaccines and Vaccination 4: 198.
17. Deiss RG, Leon SL, Konda KA, Brown B, Segura ER, Galea JT, Caceres CF, Klausner JD. Characterizing the syphilis epidemic among men who have sex with men in Lima, Peru, to improve understanding of disease transmission and treatment. BMC Infectious Diseases 2013;13 (426): 1-7.
18. Soohoo M, Blas M, Carcamo C, Byraiah G, Brown B. Cervical HPV Infection in Female Sex Workers: A Global Perspective. Open AIDS 2013; 7: 58-66.
19. Moss T, Nguyen M, Martin C, Klausner J, Brown B. Integration of HIV, syphilis, and hepatitis testing at a Community Based STD Testing Facility in Miami, Florida. LGBT Health 2014; 1: 1-4.
20. Munoz K, Davtyan M, Brown B. Revisiting the Condom Riddle: Solutions and Implications. Electronic Journal of Human Sexuality (Volume 17-January 29, 2014).
21. Folayan MO, Haire B, Harrison A, Brown B, Odetoyingbo M. Ethical Issues in Adolescents Sexual and Reproductive Health Research in Nigeria. Developing World Bioethics (Published before print June 9, 2014).
22. Dutcuic T, Gorman N, Tanjisiri S, Brown B. A Preliminary Health Needs Assessment of the Romanian-American Population in the Southern California Region. California Journal of Health Promotion 2014; 12 (1): 53-61.
23. Brown B, Kinsler J, Ukpong M, Allen K. Post-Approval Monitoring and Oversight of U.S.-Initiated Human Subjects Research in Resource-Constrained Countries. Journal of Bioethical Inquiry 2014; 11 (2): 119-123.
24. Folayan MO, Peterson K, Haire B, Brown B, Audu K, Makanjuola O, Pelemo B, Marsh V. Debating ethics in HIV research: gaps between policy and practice in Nigeria. Developing World Bioethics 2014; 11:119–123.
25. Kinsler J, Blas M, Cabral A, Carcamo C, Halsey N, Brown B. Understanding STI/HIV risk and condom use patterns by partner type among female sex workers in Peru. Open AIDS 2014; 8: 17-20.

26. Brown B, Klausner K, Galea J, Leon S, Sanchez H, Calvo G. Risk factors for ano-genital warts in a community-based sample of HIV-uninfected MSM in Lima, Peru. Sexually Transmitted Diseases 2014; 41: Suppl.1.
27. M Folayan, Gottemoeller M, Brown B, Mburu R. Getting to Zero the Biomedical Way in Africa: Outcomes of deliberation at the 2013 Biomedical HIV Prevention Forum in Abuja, Nigeria. BMC Public Health (Accepted June 2014).
28. Brown B, Folayan M, Imosili A, Durueke F. HIV self-testing in Nigeria: Public opinions and perspectives. Global Public Health (Accepted July 2014).
29. Brown B, Davtyan M, Fisher C. Peruvian FSW ethical perspectives on their participation in an HPV vaccine clinical trial. Ethics and Behavior (Accepted July 2014).
30. Folayan M, Odetoyinbo M, Harrison A, Brown B. Rape in Nigeria: a silent epidemic among adolescents with implications for HIV infection. Global Health Action (Accepted July 2014).

Published Conference Abstracts:

1. Risk Factors for Ano-Genital Warts in a Community-Based Sample of HIV-Uninfected Men Who Have Sex with Men in Lima, Peru. CDC STD Prevention Conference, Atlanta GA 2014.
2. Integration of Syphilis, Hepatitis C, and Other STD Screening with HIV Testing in a Community Based HIV Prevention Program in Miami, Florida. CDC STD Prevention Conference, Atlanta GA 2014.
3. Assessment of Participant Characteristics at a Gay Men's Community Health Center in Lima, Peru. CDC STD Prevention Conference, Atlanta GA 2014.
4. Recent syphilis infection among high-risk men who have sex with men (MSM) in Lima, Peru. CDC STD Prevention Conference, Atlanta GA 2014.
5. High Prevalence of CT/NG Infection in Extragenital Sites Among MSM in Lima, Peru. CDC STD Prevention Conference, Atlanta GA 2014.
6. Cervical HPV Infection in Female Sex Workers: A Global Perspective. UC Global Health Conference, Davis, CA 2014.
7. Using financial incentives for HIV prevention studies in diverse global contexts - A review of the literature. UC Global Health Conference, Davis, CA 2014.
8. Risk factors for HIV infection at a gay men's community health center in Lima, Peru. UC Global Health Conference, Davis, CA 2014.
9. Rape in Nigeria: the Silent Epidemic Among Adolescents Living with HIV/AIDS. Symposium on Gender Equity and Global Reproductive Health, UCSD 2014.
10. Addressing HIV/AIDS-Stigma through PhotoVoice: A Qualitative Approach. The 4th International Conference on HIV Stigma, Washington, DC 2013.
11. Creative Learning by Teaching Using Media-Undergraduate Public Health Students in Action. APHA, Boston, MA 2013.
12. Research in Sexual and Reproductive Health in Adolescents in Nigeria. Global Health and the Law Conference, Sydney, Australia 2013.
13. Transactional Sex-A Client's Perspective from Peru. UC Global Health Conference, Riverside, CA 2013.
14. Issues affecting uptake of HPV vaccine among Peruvian MSM. UC Global Health Conference, Riverside, CA 2013.
15. On the job' student training in human subject's research. Advancing Ethical Research, San Diego CA 2012.
16. Stigma in the Context of HIV/AIDS: A Community Perspective. The 3rd International Conference on HIV Stigma, Washington, DC 2012.
17. HPV and genital warts among Peruvian men who have sex with men: Knowledge, attitudes and treatment experiences. International Papillomavirus Conference, San Juan, Puerto Rico 2012.
18. Barriers and Facilitators in the recruitment and Retention of Female Sex Workers in an HPV Vaccine Trial. International Papillomavirus Conference, San Juan, Puerto Rico 2012.
19. Change in sexual behavior and HPV knowledge in Peruvian female sex workers following participation in an HPV vaccine clinical trial. University of California Global Health Conference, Berkeley CA 2012.
20. Incentive Parameters for International Human Subjects Research. Advancing Ethical Research, Washington DC 2011.
21. HPV prevalence, HPV4 completion, and immune response among Peruvian female sex workers. International Papillomavirus Conference, Berlin, Germany 2011.

22. HPV Prevalence and Risk Behaviors among FSWs in Peru-Data from an HPV Vaccine Study. Global Health Council, Washington DC 2011
23. HPV Prevalence and Risk Behaviors among Female Sex Workers in Peru-Data from an HPV Vaccine Study. IDSA, Vancouver 2010
24. Bringing health facilities to the people: HIV voluntary counseling and testing (VCT) in a public place. AIDS 2010 Vienna, Austria 2010.

Invited Talks

1. *AIDS Grand Rounds* (July 11, 2014-Orange, CA) titled 'Global HIV Epidemiology'
2. *HIV/AIDS on the Front Line Conference* (April 16, 2014-Irvine, CA) titled 'HIV Global Epidemiology'
3. UCI *Diversity in Medicine* (March 12, 2014-Irvine, CA) titled 'HIV stigma in developing countries'.
4. Southern California Sexual Health Summit (Feb 13, 2014-Los Angeles, CA) titled 'HIV Stigma: from Global to Local'
5. Biomedical HIV Prevention Forum (Nov 18, 2013-Abuja, Nigeria) titled 'Ethical considerations in handling HIV prevention research protocols'

E. Professional Development

Computer Skills: STATA, EpiInfo, SAS, ATLAS.ti, Entryware, Endnote, Microsoft Office Package
Certificates: Behavioral Theory in HIV/STD Prevention (2005 LADHS), Vaccine Science and Policy (2008 JHSPH), Human subjects research (2011 renewal CITI)
Memberships: Infectious Disease Society of America (2010-Present), International Society of Vaccines (2010-Present), Global Health Council (2008-Present), APHA (2006-2008)
International Travel: Peru, South Africa, Mexico, Singapore, China, Nigeria, Vietnam, Thailand, Germany
Reviewer: Grants and fellowships-NIH Early Career Reviewer (ECR) program at the Center for Scientific Review, ASPPH/CDC Public Health Fellowship Program. Journals-Vaccine, American Journal of Public Health, LGBT Health, Journal of Health, Nutrition, and Aging; Clinical Interventions in Aging, International Journal of STD and AIDS, Journal of Health Care for the Poor and Underserved.
Leadership: Director-GHREAT, Director-Undergraduate Program, Chair-Curriculum Committee, Director-IRB Ambassador Program, Director-Honors Research Program, Director of Research-Epicentro, Peru, Faculty Advisor-Global Health Journal Club, Faculty Mentor-CAMP

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ETHICAL ISSUES IN ADOLESCENTS' SEXUAL AND REPRODUCTIVE HEALTH RESEARCH IN NIGERIA

MORENIKE OLUWATOYIN FOLAYAN, BRIDGET HAIRE, ABIGAIL HARRISON, MOROLAKE ODETOYINGBO, OLAWUNMI FATUSI AND BRANDON BROWN

Keywords
Africa,
research ethics,
informed consent,
adolescent,
Nigeria,
Sexual and Reproductive Health

ABSTRACT

There is increasing interest in the need to address the ethical dilemmas related to the engagement of adolescents in sexual and reproductive health (SRH) research. Research projects, including those that address issues related to STIs and HIV, adverse pregnancy outcomes, violence, and mental health, must be designed and implemented to address the needs of adolescents.

Decisions on when an individual has adequate capacity to give consent for research most commonly use age as a surrogate rather than directly assessing capacity to understand the issues and make an informed decision on whether to participate in research or not. There is a perception that adolescents participating in research are more likely to be coerced and may therefore not fully comprehend the risk they may be taking when engaging in research.

This paper examines the various ethical issues that may impact stakeholders' decision making when considering engaging adolescents in SRH research in Nigeria. It makes a case for lowering the age of consent for adolescents. While some experts believe it is possible to extrapolate relevant information from adult research, studies on ethical aspects of adolescents' participation in research are still needed, especially in the field of sexual and reproductive health where there are often differences in knowledge, attitudes and practices compared to adults. The particular challenges of applying the fundamental principles of research ethics to adolescent research, especially research about sex and sexuality, will only become clear if more studies are conducted.

INTRODUCTION

Adolescents are individuals between childhood and adulthood who are in the process of reaching physical, psychological and sexual maturity. The Nigerian adolescent health policy recognises the adolescent age range as the second decade of life, 10 to 19 years[1] in line with the definition by the World Health Organization.[2] Adolescents represent one fifth of the world's population but constitutes a larger proportion of the population of low and middle income countries (LMIC) compared to developed countries due to the demographic transition.[3] Individuals aged 10 to 19 years constitute 11% of the population in high income countries, 18.1% of middle income countries, and 23% of low income countries.

[1] Federal Ministry of Health, Nigeria. National Adolescent Health Policy. 1996.

[2] WHO. 10 facts on adolescent health. 2008. Available at: http://www.who.int/features/factfiles/adolescent_health/en/index.html. [Accessed 20 March 2014].

[3] UNICEF. Progress for Children: A report card on adolescents, Number 10, April 2012. Available at: http://www.unicef.org/media/files/PFC2012_A_report_card_on_adolescents.pdf [Accessed 20 March 2014].

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Conflict of interest statement: No conflicts declared

The Nigerian population is young with well over 55% of the population below 29yrs.[4] There is therefore the need to pay particular attention to the health needs of this population. The data on age of sexual initiation and rates of sexual violence make it clear that more adolescent-specific research needs to be conducted to construct an evidence base for the planning and implementing adolescent-specific sexual and reproductive health programmes in Nigeria. Data cannot be extrapolated from older populations because adolescent experiences are specific to their societal context, shaped by factors including gender expectations and the socialisation processes at family levels.[5] Development of guidelines that would support and promote the conduct of ethically valid research among adolescents in Nigeria is therefore essential.

It is worth noting that adolescence is a combination of physical, psychological and social changes that manifest differently in different cultural settings. Therefore, it is crucial to consider each adolescent as a reference unit when developing, planning and implementing programmes related to their needs.

There are several justifications for conducting research on adolescents' SRH. These include the need to understand the determinants of specific patterns of sexual behavior and practices, predictors and age of onset of sexual activity, the life-long impact of sexual behavior on adolescents' physical and psychological health, and the health and psycho-social needs that results from these issues.

One rationale for conducting biomedical or socio-behavioural research is that it may lead to discovery of information that could guide the delivery of appropriate preventive and therapeutic services. Therefore, research on adolescents' reproductive health can lead to development of interventions that may maximize adolescents' health. The omission of adolescent focused research perpetuates inadequate understanding of their particular reproductive health needs.

The Nigerian constitution considers a person under 18 years a minor with limited legal capacity. This minor in most situations requires a legally authorized surrogate decision maker (parent, guardian or family member) to act on their behalf.[6] However, The Child Rights Act[7] provides that a child who has attained the age of 16 years has the right to give consent for scientific investigation without parental consent. In practice, adolescents aged 15 years and older are regularly engaged in national surveys on HIV prevalence.[8]

In this paper, we will consider whether the need for more information about adolescent SRH justifies the lowering of the legal age of consent in Nigeria. In making this assessment, we will consider the level of demonstrated need for evidence-based SRH programs for younger adolescents. We discuss issues of capacity, coercion, and risk assessment in and by younger adolescents and whether extrapolation of findings from other populations is adequate.

SEXUAL AND REPRODUCTIVE HEALTH NEEDS OF ADOLESCENTS IN NIGERIA

A large number of adolescents initiate sex early. The median age of sexual debut being 16 years for girls and 17 years for boys.[9] Studies have shown only 10.5% of adolescents in Nigeria use contraceptives, including condoms, perhaps, partly due to lack of detailed knowledge about the use of different contraceptive methods and their safety profiles.[10,11] Emerging evidence shows that the use of hormonal contraceptives may increase the risk for HIV transmission as well as increase the risk of acquisition of new HIV infection.[12] This evidence might complicate contraceptive decision-making. Accordingly, it is important to understand how and when adolescents make contraceptive decisions, what the points of access to these contraceptive tools are, and how appropriate information on contraceptive choices related to their SRH may be made easily accessible.

There is currently little known about factors that drive choice of sexual practices and sexual behaviours in adolescents in Nigeria. Evidence shows that early sex initiation increases the prospect for multiple sex partnering. Data from Nigeria show a large proportion of adolescents age 15 to 19 years engage in high sexual risk

[4] National Population Commission [Nigeria]. National Demographic Health Survey 2003, 2008.

[5] A.O. Fatusi & M.J. Hindin. Adolescents and youth in developing countries: Health and development issues in context. *Journal of Adolescence* 2010; 33: 499–508.

[6] Federal Government of Nigeria. Constitution of the Federal Republic of Nigeria. 1999.

[7] Federal Ministry of Women Affair, Nigeria. Convention on the right of the child. Second country report. 2004.

[8] Federal Ministry of Health, Nigeria. HIV/STI Integrated Biological and Behavioural Surveillance Survey 2007, 2010; Federal Ministry of Health, Nigeria. Behavioural Surveillance Survey 2003; Federal Ministry of Health, Nigeria. National HIV/AIDS Reproductive Health Survey 2003, 2005, 2007; National Population Commission [Nigeria]. *op cit* note 4.

[9] Federal Ministry of Health, Nigeria. National HIV/AIDS Reproductive Health Survey 2007.

[10] National Population Commission [Nigeria]. Nigeria Demographic and Health Survey 2008. Calverton, Maryland: National Population Commission and ORC Macro. 2009.

[11] H. Birungi, J.F. Mugisha, J. Nyombi, F. Obare, H. Evelia & H. Nyinkavu. Sexual and reproductive health needs of adolescents perinatally infected with HIV in Uganda. July, 2008.

[12] R. Heffron, D. Donnell, H. Rees, C. Celum, N. Mugo, E. Were, G. de Bruyn, E. Nakku-Joloba, K. Ngure, J. Kiarie, R.W. Coombs & J.M. Baeten; for the Partners in Prevention HSV/HIV Transmission Study Team. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012; 12(1): 19–26.

behaviour. In one study, 64.7% of sexually active boys and 71.4% of sexually active girls had unprotected sex with a partner who was neither spouse nor co-habiting partner in the last 12 months.[13] This high risk behaviour was comparatively higher in other age groups.

Adolescents also face sexual violence and coercion in their daily lives; a growing SRH issue. The prevalence of sexual violence ranges between 15 to 40% in sub-saharan Africa[14] with studies showing rates of sexual coercion and abuse among adolescents in Nigeria ranging from 11 to 55%.[15] The report of rape ranges between 4% and 6%, with a recent study of adolescents showing 12 (0.05%) male and 69 (31.4%) female adolescents reported forced sex.[16]

ADOLESCENCE AND RESEARCH

Adolescents face unique intrinsic and extrinsic challenges when considering participation in research. Intrinsic ones include developmental considerations in physiology, pharmacology, and behaviour. Extrinsic considerations are those in the community, ethical, legal, and regulatory arenas and those in the design of clinical trials for adolescents to feasibly participate.[17] Adolescence is divided into three broad developmental periods: early adolescence (11 to14 years) which is cognitively dominated by concrete thought processes, with limited ability to comprehend potential consequences of risk behaviors; middle adolescence (15 to17 years) which is characterized by the emergence of abstract cognitive processes, which revert to concrete thinking during stress; and late adolescence (18 to19 years). Each of these periods is defined by unique cognitive and physical developmental attributes that are on a continuum.[18] By mid adolescence (normally around the ages of 14 to 16), the cognitive abilities of adolescents are roughly the same as biologically mature adults. Adolescents' behavioural code is frequently defined by their peer group with major conflict developing between the adolescent and parent as they strive for greater autonomy.[19] Late adolescence is defined by well-developed abstract cognitive processing with the peer group being replaced by more adult type close personal relationships.[20] It is important to understand this dynamic developmental trajectory to contextualize the variety of adherence behaviors adolescents display when it comes to their health care.

Intellectually, by mid adolescence, individuals are generally able to understand long-term risks and the benefits of research. Adolescents of the same age bracket are also frequently inclined toward risk taking, and are acutely sensitive to peer influence. These factors can affect their understanding of risks and their capacity to make consistently sound judgments about long-term benefits. This is important as research participants who consent to participate must be able to understand the long term implications of information provided about the study.

Ethical guidelines have traditionally treated adolescents as 'vulnerable,' meaning their capacity to give consent without duress may be easily compromised. This challenge requires a balance between recognizing the emerging autonomy of adolescents, their differential rates of development, and their potentially immature response to personal risk. Potential risk needs to be weighed against the potential benefits to be derived from their participation in research. Research involving adolescents needs to be designed to ensure that it takes into account these characteristics, including adolescents' tendency toward altruism,[21] and rebellion, influence of peer pressure, as well as their increased sensitivities around body image,[22] privacy, and confidentiality.[23]

The Need for Distinct Data on Adolescent Populations

Adolescents represent a critically important user group for SRH products as they bear a disproportionate share

[13] National Population Commission *op cit* note 12.

[14] A.O. Fatusi & R.B. Blum. Adolescent Health in an International Context: The Challenge of Sexual & Reproductive Health in Sub-Saharan Africa. *Adolescent Medicine: State of the Art Reviews* 2009; 20(3): 874–886.

[15] A.J. Ajuwon, A. Olaleye, B. Faromoju & O. Ladipo. Sexual behavior and experience of sexual coercion among secondary school students in three states in North Eastern Nigeria. *BMC Public Health* 2006(23); 6: 310; A.J. Ajuwon, B.O. Olley, I. Akin-Jimoh & O. Akintola. Experience of sexual coercion among adolescents in Ibadan, Nigeria. *Afr J Reproductive Health* 2001; 5(3): 120–131.

[16] Ibid; A.J. Ajuwon, W. McFarland, S. Hudes, S. Adedapo, T. Okikiolu & P. Lurie. Risk-related behavior, sexual coercion and implications for prevention strategies among female apprentices tailors in Ibadan, Nigeria. *AIDS & Behav* 2002; 6(3): 233–241; O.I. Fawole, A.J. Ajuwon, K.O. Osungbade & O.C. Faweya. Prevalence of violence against young female hawkers in three cities in south-western Nigeria. *Health Education* 2002; 102(5): 230–238; Federal Ministry of Health, Nigeria. Integrated Behavioural and Biological Sentinel Survey, 2007.

[17] B.G. Kapogiannis, E. Handelsman, M.S. Ruiz & S. Lee. Introduction: Paving the way for biomedical HIV prevention interventions in youth. *J Acquir Immune Defic Syndr* 2010; 54: S1–S4.

[18] B.J. Rudy, B.G. Kapogiannis, M.A. Lally, G.E. Gray, L.G. Bekker, P. Krogstad & I. McGowan. Youth-specific considerations in the development of preexposure prophylaxis, microbicide, and vaccine research trials. *J Acquir Immune Defic Syndr* 2010; 54 Suppl 1: S31–S42.

[19] Ibid.

[20] Ibid.

[21] P.D. Stanford, D.A. Monte, F.M. Briggs et al. Recruitment and retention of adolescent participants in HIV research: findings from the REACH (Reaching for Excellence in Adolescent Care and Health) Project. *J Adolesc Health* 2003; 32: 192–203.

[22] M.S. Birkeland, O. Melkevik, I. Holsen & B. Wold. Trajectories of global self-esteem development during adolescence. *J Adolesc* 2012; 35(1): 43–54.

[23] P.D. Stanford et al. *op cit*. note 21.

of STIs and HIV, in addition to risks of unplanned pregnancy. The claim that it is reasonable and sufficient to extrapolate safety and effectiveness data derived from those over 18 years to younger adolescents is flawed on two levels – the physical and the social. A Global Campaign for Microbicide report notes the biologic and behavioral differences between young adolescent girls and older women justify separate safety and effectiveness data on sexual and reproductive health products.[24] The cervixes of younger female adolescents are not fully mature, making them biologically more susceptible to STIs. Adolescents' menstrual patterns also differ from adult women, as some 80% of adolescents will have cycles without ovulation within four years after menarche. Without ovulation, adolescents lack progesterone, which may influence the vagina's local immune responses.[25] At the social level, younger adolescents differ from adults in significant ways that could affect how they use SRH products.

In Nigeria, despite the stipulated legal age of consent of 18years, a large proportion of adolescents are sexually active. The 2008 national demographic health survey (NDHS) shows that 23% of women aged 15–19 years had begun childbearing, 18% have had a child and 5% are pregnant with their first child. Also, 12.4% of male and female respondents were married by 15 years, 15.3% of women and 6.2% of men had their first sex experience by 15 years, and 29.7% of female and 6.8% of male 15–19 year old respondents had had sex within the last 4 weeks of the survey.[26] These data emphasize the need for early engagement of adolescents in sexual and reproductive health research that can help in the design of programmes that address their SRH needs.

Adolescent health data is important to develop evidence-based policies and programmes that support adolescent health; to increase access to and use of health services for adolescents; and to strengthen contributions from the education, media and other sectors to improve adolescent health. There are a number of reproductive health problems that are restricted to, or occur also in, adolescents which cannot be solved with existing knowledge. As a result, there is an ethical duty of beneficence and justice to conduct appropriate research to address these problems.

One of the key ways that adolescents below the age of legal consent have gained access to SRH services is through assessment of competence–specifically, whether the young person can demonstrate an understanding of the nature and implications of the proposed treatment, including the risks and alternative courses of actions.[27] Applying a similar test in the research context would remove a major objection to enabling greater participation of minors in research – the objection that minors might not understand their range of choice and thus be more vulnerable to coercion. Applying specific and individual tests of competency, and documenting it, has a clear advantage over age–in that it recognises the developmental and cognitive differences that exist within groups of young people who mature at different rates.

INFORMED CONSENT

Informed consent is a fundamental requirement in research participation. It is obtained through a dialogue that respects the individuality of each prospective participant and allows ample opportunity for the prospective participant to ask questions. Every research protocol must clearly explain how the study team members intend to ensure understanding and comprehension of all study information.

Informed consent must be voluntarily obtained and devoid of undue inducement and coercion. It is also described as the principle of 'respect for persons'[28] which acknowledges that individuals with capacity have the right to make autonomous decisions. While the capacity for autonomous decision-making varies considerably across cultures and stages of adolescence, it is important to consider that the involvement of parents (and guardians) in an informed consent process may jeopardize the autonomous decision-making of the adolescent, in addition to possibly compromising confidential information about the adolescent.

Paediatric Regulations and Legislation

As noted in the introduction, the Nigerian Constitution[29] and the section 277 of the 2003 Child Rights Act[30] define a minor as a person under the age of 18. This implies that people under the age of 18 years have limited legal capacity and are vulnerable to decision making that is not fully competent. They therefore need a legally authorized surrogate decision maker-usually a family member to act on their behalf. Section 64(2) of the Child Rights Act

[24] Z. Essack, C. Slack & A. Strode. Overcoming key obstacles to adolescent involvement in HIV vaccine and microbicide trials: A roadmap for stakeholders. Global Campaign for Microbicides: 2008.

[25] L.L. Heise & S.Y. Wood. Rethinking the ethical roadmap for clinical testing of microbicides. 2005. Available at: http://www.global-campaign.org/researchethics.htm. [Accessed 20 March 2014]; A. Strode, C. Slack & Z. Essack. Child consent in South African law: Implications for researchers, service providers and policy-makers. *S Afr Med J* 2010: 100: 247–249.

[26] National Population Commission *op cit* note 10.

[27] R. Wheeler. Gillick or Fraser? A plea for consistency over competence in children. *BMJ* 2006; 332(7545): 807. doi: 10.1136/bmj.332.7545.807.

[28] Belmont Report, 1979.

[29] Federal Government of Nigeria. *op cit* note 6.

[30] Federal Ministry of Women Affairs. *op cit* note 7.

however provides that an adolescent who has attained the age of 16 years has the right to give consent for scientific investigation without parental consent. The 2011 (version 7.0) National Health Research Ethics Code for Nigeria also contains provision for soliciting consent from parents or legal guardians and for obtaining assent from minors participating in research. It explicitly states in section F(c) that minors should not be excluded from research without explicit reasons for doing so.[31] Unfortunately, the code is not explicit about age for consent and assent. However, the working principle upheld by the National Health Research Ethics Committee is that assent needs to be given by adolescents between the ages of 12 and 17 years while their parents give consent for those who are not considered mature minors.[32] This is partially in in line with the requirement of the Section 29(4b) of the constitution of the Federal Republic of Nigeria which states that '*any woman who is married shall be deemed of full age*'. Children below 12 years in Nigeria are not however, required to give assent (personal communication, Prof Clement Adebomowo, National Health Research Ethics Committee Chairperson). The above shows clearly that for Nigeria, the age for consent for participation in research is still very unclear. it also highlights the need for the development of regulation and legislation governing adolescent engagement in research in Nigeria.[33]

Parental Consent

Parental consent alongside that of the adolescent is a major concern. Within the Nigerian legal context, parental consent and assent for adolescents below the age of 16 years is needed before participation in any form of research – except for mature minors.[34] This clause raises multiple ethical dilemmas. First of all, there is the legal dilemma of who provides parental consent. Singh et al.[35] noted that some minors live with surrogate caregivers who are not formally appointed or legally recognised as the adolescents' guardian. In these instances, it is practically impossible to seek parental consent or to determine who, if anyone, is the legal guardian to authorise an adolescent's participation in a study. In Nigeria, this legal dilemma poses challenges for the conduct of research in the field. The 2008 National Demographic Health Survey showed that 9% of those under the age of 15 years were living without their biological parents.[36] A recent analysis of a data collected on adolescent studies showed that 18.9% of adolescents aged 10–19 years reside with guardians.[37] Research practice however limits parental consent to recognized legal guardians. The law has implications for the exclusion of adolescents participants resident with surrogate caregivers from research which could otherwise have been of benefit both to adolescent participants and the broader population. Similarly, the law does not legally identify an unmarried adolescent heading a household (a situation very well recognized and documented following the HIV epidemic in many countries in Africa) as a matured minor. This action negates the principle of justice which promotes fair selection of study participants, as participants' exclusion should be on the basis of their ineligibility due to scientific parameters and social protection.

Secondly, is the potential to compromise an adolescent's privacy where parental consent is sought for SRH research. For many communities in Nigeria, parents prefer to talk with their families or respected people in their community before reaching a decision about providing consent for an adolescent to participate in a sexual and reproductive health research. This is especially true when research involves more invasive procedures such as blood draws and vaginal examinations. This consultation is also likely to occur if there are no clear therapeutic benefits accruable from participation in such studies, as it is the case for most HIV prevention research. It is however plausible for ethics review committees to waive a requirement for parental permission for adolescent participation when there are compelling reasons warranting this action. Such justification for a waiver must establish a case for ethical duty of beneficence and justice for the conduct of the research on this group with evidence to show the research is appropriate for the group. In Nigeria, ethics committees may have to act based on their informed discretion as the Section F(f13) of the National code provides limited guidance on this subject matter.

[31] National Health Research Ethics Committee of Nigeria, Federal Ministry of Health, Department of Health Planning and Research. National Code for Health Research Ethics version 7.0. 2007. Available at: http://www.nhrec.net/nhrec/NCHRE_10.pdf [Accessed 20 March 2014].

[32] Matured minors refers to a young person who has not reached adulthood as defined by the laws but whose maturity is such that (s)he can interact on an adult level for certain purposes such as consenting to medical care and in this case, research. Such an individual is assumed to have the capacity to understand the nature and consequences of the proposed treatment and is adjudged to have the competency to understand what it takes to participate in research.

[33] Federal Ministry of Health, Nigeria, *op cit* note 8.

[34] Matured minors are defined as individuals who has not reached adulthood as defined by state law but who may be treated as an adult for certain purposes. Based on the Nigeria constitution, matured minors are married adolescents.

[35] J.A. Singh, S.S. Karim, Q.A. Karim, K. Mlisana, C. Williamson, C. Gray, M. Govender & A. Gray. Enrolling adolescents in research on HIV and other sensitive issues: lessons from South Africa. *PLoS Med* 2006; 3(7): e180. Epub 2006 Apr 18.

[36] National Population Commission *op cit* note 10.

[37] A recent national survey that evaluated the sexual and reproductive health need of adolescents living HIV in Nigeria was conducted by Positive Action for Treatment Access with funding support by Ford Foundation West Africa Office. Dissemination on study result was conducted on 14 May 2013 at Sheraton Hotel and Towers, Abuja, Nigeria.

The code states that: *'Consent in other situations, including research involving children, persons with diminished autonomy, vulnerable populations and other extraordinary situations, including waiver of consent, are described in other guidance documents issued by NHREC'*.[38]

Implications of Parental Consent for All Adolescent Research

Privacy and confidentiality are considered critical for adolescent enrollment in research.[39] Researchers struggle to strike a balance between parental involvement and the need to protect the adolescent's privacy and confidentiality especially with regards to sex and sexuality. This becomes complex when enrolling teenagers who are below the legal age for sexual consent. The principles of ethics require that researcher's respect study participant's autonomy and right to confidentiality. The assurance of data security is likely to promote adolescents' engagement in sexual and reproductive health research. Requiring adolescents to seek parental consent for their participation in the study may nullify this obligation to assure confidentiality[40] and may compromise the quality of generated data. In extraordinary circumstances, however, there may be a need to disclose information divulged by a minor during research to the 'legal' caregiver. For example, a 12 year old who tests HIV positive and needs to be enrolled for ARVs may need to have information disclosed to the parent in order to provide access to treatment.

Guideline 14 of the Council for the International Organisation of Medical Sciences Guidelines tries to address the potential challenges that may arise with parental consent when adolescents are enrolled in research. It states that: '*Some studies involve investigation of adolescents' beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. For studies on these topics, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the adolescents at some risk of questioning or even intimidation by their parents*' (CIOMS, 2002).[41]

Zuch et al. argued that strict adherence to the implementation that require active parental consent will deter from the conduct of school based adolescent sexual and reproductive health studies for a number of reasons including introduction of significant sample bias into the data.[42]

The complexity of obtaining parental consent hinges on balancing the requirement of the law and compliance with ethical principles because it is required that the norms and standards (both legal and ethical) that govern adolescent research in any country must be complied with. Unfortunately, there is little clarity on how to manage confidentiality in research involving adolescents. In research where parents give consent, complex privacy issues arise. As noted, a parent may give consent for enrolment, but adolescents may expect confidentiality for some components (such as their risk behaviour). There is also tension around how to manage confidentiality when the setting has laws about disclosures that must be reported to authorities. In Nigeria, the National Health Research Ethics Code provides limited guidance on this. While it recognises the need to protect research participants' privacy it does not explicitly address the implication of this with respect to adolescents engaged in research. The onus therefore currently rests with the researcher and the ethics committees to ensure that the study design ensures the privacy of any adolescent engaged in research within the ambit of existing legal frameworks while ensuring the scientific validity and the ethical integrity of the study conduct.

PARENTAL CONSENT: REALITY IN THE FIELD

Independent of the laws and guidelines, there are cultural and social issues that may promote and support the need for parental consent prior to adolescents' engagement with research. These cultural and social issues may become the main consideration in the question on the morality of not obtaining parental permission prior to adolescent engagement in research. For example, enrolling adolescents without parental permission could alienate communities at the cost of losing support for the study.

In Nigeria, open discussions about adolescents and issues that relate to them are limited and conservative. The perceptions and opinions of many policy makers, public opinion leaders and gatekeepers are sometime not supportive of discussion of sexual issues among adolescents. It is assumed that adolescents will be more promiscuous if they learn about sexuality and prevention of

[38] National Health Research Ethics Committee of Nigeria *op cit.* note 31.

[39] P.D. Stanford et al. *op cit* note 21.

[40] K. Ringheim. Ethical and human rights perspectives on providers' obligation to ensure adolescents' rights to privacy. *Stud Fam Plann* 2007; 38(4): 245–252.

[41] Council for International Organizations of Medical Sciences (CIOMS). ISBN 92 9036 075 5. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS, in collaboration with WHO, 2002; guideline point 14. Available at: http://www.cioms.ch/frame_guidelines_nov_2002.htm. [Accessed 20 March 2014].

[42] M. Zuch, A.J. Mason-Jones, C. Mathews & L. Henley. Changes to the law on consent in South Africa: implications for school-based adolescent sexual and reproductive health research. *BMC Int Health Hum Rights* 2012; 12: 3. doi: 10.1186/1472-698X-12-3.

HIV/AIDS. Furthermore, to date, scientific justification for adolescent enrolment in any research has not been articulated in a way that key stakeholders, like community representatives, can continuously appreciate.

Therefore, to successfully enroll and retain adolescents in research, it may be worthwhile to first of all, consult and engage the community prior to research protocol submission to the ethics committee as this creates the opportunity to discuss the rationale underpinning the inclusion of adolescents in the research, as well as the reasons for not making parental consent for an adolescent's participation in a study a requirement where such is the case. Secondly, it gives the opportunity to extensively engage adolescents, youth and parents in research design and implementation. Thirdly, it gives the opportunity to inform the adolescents about the benefits and risks of research. Fourthly, the potential challenges associated with such research design must be carefully examined and discussed in such a way that makes them understandable, and can facilitate community investment in actions to address them. The inclusion of adolescent perspectives at every stage of the research development process, especially in clinical trials, is essential. Scientific experts also need to clarify the differences in adolescent and adult SRH issues thereby justifying adolescents' engagement in SRH research.

CONSIDERATIONS FOR INFORMED CONSENT BY ADOLESCENTS IN NIGERIA

In summary, the informed consent process should take into consideration the capacity of the adolescent to consent; the role of surrogate decision-makers who should be able to consent when adolescents do not have capacity; and possible restrictions on the autonomy of adolescents or their proxies to consent. Unfortunately, while the National Child Rights Act specifically specified the age limits for consenting in research, evolving evidence points to a need to lower the current age for consenting to enable younger adolescents engage in research that can inform programme development and programming apt to address their needs.

One major concern about adolescents is their ability to comprehend. As medical evidence shows, cognitive development of the adolescents is near that of the adult by 14 years such that '*decision making and reasoning ability is as good as that seen in adulthood and involves the flaws*'.[43] It may therefore be important to advocate for changes in the law so it can permit adolescents 14 years and above with proven evidence of sufficient maturity, and with the mental capacity to understand the benefits, risks, and social and other implications of the outcome, to participate in research in general and sexual and reproductive health research specifically, without parental consent. It is now for the ethics committees to be able, each within its peculiar cultural context, to calculate the risk and-benefit for the research and adjudge that the implementation of such research would not expose the adolescent to undue risk taking cognisance of age and cultural peculiarities. In addition, sexual and reproductive health research protocols that would engage adolescents who are 14 years old should critically appraise the informed consenting processing and evaluate for perceived threats to consent such as inadequate education and developmental characteristics of adolescents engaging in decision-making. It may be inappropriate to assume that all 14 year olds in Nigeria should be excluded from parental consent prior to engagement in sexual and reproductive health research. Rather, researchers may need to always develop tools and processes to impart information, assess understanding, and enhance the voluntariness of decisions to participate in SRH research conducted in adolescents particularly those that require therapeutic interventions. Researchers should ensure the adolescent demonstrates capacity for comprehension and required actions.

When ethics committees do not feel confident that the risk associated with research are acceptably low, parental consent for research participation may be required. Thus, consent norms for adolescent research participation needs to reflect the reality that research is of varying complexity and risk. For simple and low-risk research, exceptions to the norm of parental consent may be appropriate, provided that other protections are in place, including competent ethical reviews. In addition, community endorsement of research plans should be a major factor in research ethics committee consideration on whether to allow adolescents to provide autonomous consent for participation in a study. The World Health Organisation provides comprehensive guidelines on engagement of adolescent in research which could serve as a useful guide for research protocol review.[44]

While the ethical-legal framework for consent is specified in Nigeria, its understanding and application by ethics reviewers needs to be addressed through trainings. This is underpinned by the work of the New HIV Vaccine and Microbicide Advocacy Society (NHVMAS) which has been engaged for over 5 years in building the capacity

[43] A.C. Peterson & N. Leffert. Developmental issues influencing guidelines for adolescent health. *Journal of Adolescent Health* 1995; 17: 298–305; C. Lewis. How adolescents approach decisions: changes over grades seven to twelve and policy implications. *Child Development* 1991; 52: 538–544.

[44] World Health Organisation. Position paper of the scientific and ethical review group on reproductive health involving adolescents. Available at: http://www.who.int/reproductivehealth/topics/ethics/adolescents_guide_serg/en/index.html. [Accessed 20 March 2014].

of ethics reviewers in the country on the ethics of biomedical HIV prevention research. These trainings are conducted in such a way that ensures knowledge and skills acquired are applicable to other research fields.[45]

The most notable study about ethical involvement of adolescents in research is the HPV vaccine study which resulted in the licensing of HPV to prevent cervical and anal cancers in adolescents. This is one successful story in the conduct of ethical trials that engages adolescents on health issues of particular concern to them.[46]

Within the African continent, there are recognizable efforts in South Africa focused at addressing adolescent engagement in sexual and reproductive health research. The engagement of 16 year old adolescents in the Carraguard study is a step in this direction.[47] The proposed engagement of adolescents in post CAPRISA 004 studies is also one effort in this direction.[48] More recently, the engagement of 12–17 year old in the SASHA project which was preparing adolescents for HIV Vaccine research in South Africa is another good example.[49]

Locally, adolescents have long being engaged in multiple social science and epidemiological researches. The Integrated Behavioural and Biological Sentinel Surveys, the National HIV/AIDS Reproductive Health Surveys and the NDHS engaged participants aged15 years.[50] The studies capture issues relevant to sexual and reproductive health.

The authors feel that in view of the cultural sensitivity to open discussion about sex, the ethics of engagement of adolescents in sexual and reproductive health research may be an issue of debate for a while to come. A starting point may be the conduct of a workshop to resolve various dilemmas about the ethics of engaging adolescents in sexual and reproductive health studies, some of which have been highlighted in this paper. This workshop may provide the ground for starting to think through the ethics of engagement of youths in SRH research in the Nigerian environment more specifically taking cognizance of Nigeria's peculiar, diverse and sometimes contradictory traditional, religious, legal and social systems.

CONCLUSION

The ethical dilemma of engaging adolescents in SRH research is intertwined with legal and regulatory issues. For example, the appropriateness of including adolescents in research when the risks are more than 'low' or 'minor increase over minimal' is a difficult and thorny ethical issue. Consideration should be given to adolescents to consent unassisted to participate in research as long as the parents or legal guardians or the community is unlikely to object to the adolescent's participation and the study protocol justifies why adolescents should be included as participants.[51]

Ethical guidelines in Nigeria should consider the feasibility of engaging adolescents aged 14 years and above (rather than the current consideration of 16 years and above) in research without the need for parental consent. The peculiar challenges of applying fundamental ethical principles for adolescents engaged in research especially in cultures sensitive to open and public discussions about sex and sexuality, and how to resolve them can only be learnt from practical field experiences. Ethics is an ever evolving field and ethical consideration of adolescents' engagement in sexual and reproductive health research shall continue to constitute central themes in many ethical discourses for a while to come.

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[45] M.O. Folayan, A. Adaranijo, F. Durueke, A.J. Ajuwon, A.A. Adejumo, O. Ezechi, K. Oyedeji & O. Akanni. Impact of three years training on capacity of ethics committees in Nigeria. *Developing World Bioethics* 2012: Sep 24. doi: 10.1111/j.1471-8847.2012.00340.x.

[46] J. Paavonen, P. Naud & J. Salmerón et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; 374(9686): 301–314.

[47] ClinicalTrials.gov. Efficacy study of the vaginal gel Carraguard to prevent HIV transmission. Available at: http://clinicaltrials.gov/show/NCT00213083. [Accessed 20 March 2014].

[48] FACTS 002 is a planned Phase II safety study to test tenofovir gel use in sexually-active young women 16 and 17 years of age. Available at: http://www.facts-consortium.co.za/ [Accessed 20 March 2014].

[49] Press release: SASHA project preparing for adolescent HIV vaccine trials in South Africa completed. Available at: http://www.edctp.org/Press_release.401+M5a547e2d46d.0.html. [Accessed 20 March 2014].

[50] Federal Ministry of Health, Nigeria, *op cit* note 8.

[51] Ethics in Health Research: Principles, Structures and Processes. Pretoria: Department of Health; 2004.

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DEBATING ETHICS IN HIV RESEARCH: GAPS BETWEEN POLICY AND PRACTICE IN NIGERIA

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ABSTRACT
HIV prevention is a critical health issue in Nigeria; a country that has one of the worst HIV epidemic profiles in the world. With 270,000 new infections in 2012, Nigeria is a prime site for HIV prevention research. One effect of the HIV epidemic has been to revolutionalise ethical norms for the conduct of research: it is now considered unethical to design and implement HIV related studies without community engagement. Unfortunately, there is very little commensurate effort in building the capacity of local persons to engage actively with researchers, and there is no existing platform to facilitate dialogue between researchers and communities engaged in research in Nigeria. In an effort to address this gap, we undertook a series of three community dialogues (Phase One) and two community-researcher interface meetings (Phase Two) in Nigeria. This paper aims to give an empirical account of the dialogue from these community engagement processes and provide a resulting critique of the implementation of research ethics practices in Nigeria. It is anticipated that the outputs will: (i) support researchers in designing community-based research protocols; (ii) inform ethics committees of key considerations during research protocol reviews from a community perspective; and (iii) inform policy makers and research sponsors about issues of primary concern to communities with respect to HIV research.

INTRODUCTION

HIV prevention is a critical health issue in Nigeria. The country is one of the most HIV-affected nations in the world with a burden second only to South Africa.[1] Sexual transmission of HIV accounts for about 80% of HIV infections in Nigeria,[2] and condoms remain the only established, readily available measure for prevention of new infections. Condom use with casual partners is estimated at 98% among female sex workers (FSW), 62% among injection drug users (IDU) and 52% among men who have sex with men (MSM).[3] In the general Nigerian population, condoms are used by less than 40% of sexually active men and women.[4]

With 270,000 new infections in 2012,[5] Nigeria is a prime site for HIV prevention research. Understanding

[1] Joint United Nations Programme on HIV/AIDS (UNAIDS). UNIADS Report on Global AIDS Epidemic. 2012.
[2] National Agency for the Control of AIDS (NACA), Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Bank. Modes of HIV transmission in Nigeria: analysis of the distribution of new infections in Nigeria and recommendations for prevention. 2009, 2010.
[3] Federal Ministry of Health, Nigeria. Integrated Behavioural and Biological Sentinel Survey. 2010.
[4] Federal Ministry of Health, Nigeria. 2012 National HIV and AIDS and Reproductive Health Survey (NARHS Plus). 2013.
[5] Federal Ministry of Health, National Agency for the Control of AIDS, Joint United Nations Programme on HIV. 2012 Nigeria HIV Estimates, Spectrum. 2013.

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sexual practices as linked to national epidemiological profiles is vital to the national HIV prevention response. One important response to the epidemic is to concentrate resources in identifiable populations who carry the heaviest burden of HIV infections. For Nigeria, these populations include MSM, FSWs, and IDUs. Together, these high-risk groups constitute 3.4% of the general Nigerian population, but account for 40% of the HIV burden.[6] At the same time, 80% of new infections occur through heterosexual transmission.[7]

The HIV epidemic has generated a revolution in the field of health research ethics.[8] Specifically it is now considered unethical to design and implement HIV related studies in host communities without in-depth consultation with critical stakeholders such as local authorities, NGOs, advocacy groups, and research participants a process described as community engagement.[9] The UNAIDS and The Global Advocacy for HIV Prevention (AVAC) developed the Good Participatory Practice guidelines document (GPP) that details expected engagement processes with communities as well as mechanisms that give communities opportunities for input throughout the lifecycle of clinical research.[10] The Nigerian National HIV Research Policy also promotes active engagement with targeted communities in the design, implementation and monitoring of HIV research. Specifically, section 6.2 of the policy notes, as part of its ethical framework for HIV research implementation, that researchers should 'ensure that HIV and AIDS research protocols have well defined formal mechanisms such as a Community Advisory Board (CAB), which engages and consults the community in study design, implementation, monitoring, information and result sharing'.[11]

However, it is likely that only about 10% of the research conducted in Nigeria receives ethics approval. Community members are increasingly interested in being consulted in the design, implementation and monitoring of the growing number of research projects.[12] As of October 15, 2012, there were 45 clinical trials registered in Nigeria on the Clinical Trials.gov website;[13] and it is likely that only about 10% of the research conducted in the country receives ethics approval. In terms of HIV/AIDS research, the country has hosted multiple studies involving populations most at risk for HIV infection (MSM, IDU, FSW) since 2000. These include one phase 1 cellulose sulphate microbicide study, one phase IIb cellulose sulphate microbicide study and one phase IIB SAVVY microbicide study; a phase IIb HIV tenofovir pre-exposure prophylaxis study,[14] two Integrated Biological and Behavioural Sentinel Survey studies,[15] mapping and size estimation of MSM, IDU, FSW and

[6] NACA/UNAIDS/World Bank. *Op. cit.* note 2.

[7] Ibid.

[8] Major changes in HIV and AIDS health research ethics began in June 1994, when a World Health Organization meeting convened to create a research agenda for perinatal HIV transmission. Scientists concluded that placebo controlled trials offer the best option for treatment assessment. This decision sparked an ethical debate over the use of placebo and established standards of care in international clinical trials. Subsequent trial designs were based on new placebo standards. Lurie and Wolfe (1997) claimed that 15 out of 16 of the new trials were unethical. They argue that decisions on the standard of care were not based on available alternative treatments or previous clinical data, but rather on the policy of governments whose economy makes it difficult for them to afford the prices of drugs (Lurie and Wolfe 1997, 855). Since this claim, a number of researchers have debated ethical standards in clinical research (Angell 1997, 2000; Bayer 1998; Benatar 2001; Botbol-Baum 2000; de Zulueta 2001; Lurie and Wolfe 1999; Shapiro and Meslin 2001; Schuklenk and Ashcroft 2000; Temple 2002; Varmus and Satcher 1997). The Helsinki Declaration updated in 2000 took a stance and set a standard for care equivalent to that of the country conducting the research rather than the host country. Just four years later, Kent et. al. (2004) found that out of all the HIV, tuberculosis and malaria-related clinical trials conducted between January 1998 and November 2003 in Sub-Saharan Africa, only 16% provided care that met recommended ethical guidelines. In October 2013, the Helsinki Declaration was revised again to increase the protections of clinical trial participants. Specifically, research sponsors, research scientists, and host governments share increased responsibility toward research participants' safety and protection.

[9] Community engagement became a critical factor in HIV clinical research after the failure the early tenofovir pre-exposure prophylaxis trials that sparked intense and prolongued community debates and captured widespread attention in the international media and medical literature. See: L. Miller, M.O. Folayan, D. Allman, B. Nkala, L.M. Kasirye, L.R. Mingote, G. Calazans, R. Mburu, F. Ntombela & M. Ditmore. How Ethical is Your Clinical Trial. *International Journal of Clinical Practice* 2010; 64(9): 1179–1182; M.O. Folayan, L. Mutengu-Kasirye & G. Calazans. Participating in Biomedical Research. *JAMA* 2009; 302: 2201–2202; AVAC Community Consultations on Good Participatory Practice Guidelines. Partner Report-Back Meeting 30 April–2 May, 2009, Johannesburg. South Africa. New York: AVAC; 2009; Creating Effective Partnership for HIV Prevention trials: report of a UNAIDS Consultation, Geneva 20–21 June, 2005. AIDS 2006; 20: W1–W11.

[10] Joint United Nations Programme on HIV/AIDS (UNAIDS), AVAC. UNAIDS/07.30E/JC1364E. Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials. Second edition. Geneva: UNAIDS, 2011. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110629_JC1853_GPP_Guidelines_2011.pdf. [Accessed 5 May 2014].

[11] National Agency for the Control of AIDs, Nigeria. National HIV/AIDS Research Policy. 2010.

[12] Creating Effective Partnership for HIV Prevention trials: report of a UNAIDS Consultation, Geneva 20–21 June, 2005. (2006). AIDS 20: W1–W11.

[13] ClinicalTrials.gov. Clinical Trial Database. Website. Accessed October 15, 2012.

[14] Nigeria HIV Vaccine and Microbicide Advocacy Group. The challenges of developing new HIV technologies for HIV prevention: a situation report on research and development of new HIV prevention technologies in Nigeria. November 2004.

[15] Federal Ministry of Health, Nigeria *Op cit*. note 3; Federal Ministry of Health, Nigeria. Integrated Behavioural and Biological Sentinel Survey. 2007.

male sex workers population surveys[16] among others. Yet, despite the growing interest in conducting large HIV prevention research in the country, there is very little effort expended on building the capacity of local persons to engage actively in the field, and no existing platform to facilitate dialogue between researchers and communities conducting research in Nigeria.

Up until now, the focus on community engagement in research has been on reviewing research protocols in an effort to address community concerns. Such reviews enable ethics committee members or community advisory boards to identify and ultimately minimize culturally specific risks.[17] The place of dialogue has been conscribed to the negotiation of packages for study participants including standard of care for HIV prevention research.[18] However, dialogue that facilitates community engagement in health research however has other utility – it allows researchers and community representatives to gain shared understanding of project-related priority areas for intervention, enables communities to clarify the scope of the research project and project related procedures and terminologies and enables researchers to develop a relationship of mutual trust and understanding with the community in recognition of inequalities and power differences between international researchers and community members.[19] Community dialogue is one aspect of the community engagement process and a process widely used on health programming but less so in health research and clinical trials.[20]

In an effort to address this gap between existing extensive clinical research and a lack of mechanisms that facilitate trial dialogues, we developed and implemented a novel approach to community engagement in order to better understand ethical issues in HIV/AIDS. This included Community Dialogue events in three major cities in Nigeria (Phase One), leading to two community-researcher interface meetings (Phase Two) styled as 'Round Table' discussions. This paper aims to describe these processes and give an account of the main outcomes so as to provide a linked critique of research ethics practice in general and HIV prevention research ethics practice specifically in Nigeria. It is anticipated that the issues raised in this paper will provide support to research stakeholders in Nigeria and other similar setting in three main ways: (i) it will support researchers in the design of community-based research protocols; (ii) it will inform ethics committees of key considerations to be taken into account during research protocols review from a community perspective; and (iii) it will inform policy makers and research sponsors about issues of primary concern to communities with respect to HIV research.

THE COMMUNITY DIALOGUE AND ROUNDTABLE EVENTS

Background to the Community Engagement Activities

The design of the community engagement activities described in this paper was developed at a one-day stakeholder meeting. Attendees included representatives from several organized communities, including men who have sex with men, female sex workers, people living with HIV/AIDS and injecting drug user. The group identified key gatekeepers and stakeholders working with the community to be engaged in the programme, based on their own and other colleagues' experiences.[21] Key gatekeepers were defined as community members who were often approached for community member recruitment during research or HIV programme activities to facilitate the participation of other community members. The one-day meeting focused on three prominent areas of concern in research ethics: informed consent, community engagement in research, and standard of care in HIV research. The meeting began with a Community Dialogue whose aim was to discuss and develop consensus on key issues within these areas of focus. Following the Community Dialogue was a Round Table meeting. In attendance were HIV/AIDS research stakeholders as well as representatives from the Community Dialogue events. The aim of this second meeting was to discuss the concerns and findings of the Community Dialogue and to incorporate them into ethical research practice. The Round Table events included stakeholders with experience of direct and indirect involvement with the conduct of HIV research among most-at-risk populations in Nigeria. These included policy makers, programmers, programme sponsors, researchers and ethics committee members. An

[16] Population Council, Nigeria. Estimating the population of male sex Workers (MSW) in Nigeria using capture – recapture method. Available at: http://www.popcouncil.org/pdfs/2012HIV_Evidence-for-Action01.pdf [Accessed 5 May 2014]; Population Council, Nigeria. Formative Assessment and Geo-Mapping of Female Drug Users in Kano, Kaduna, Abeokuta, and Lagos, Nigeria. Available at: http://www.popcouncil.org/pdfs/2012HIV_Evidence-for-Action01.pdf [Accessed 5 May 2014].

[17] J.H. Moore. Native Americans, scientists and the HGDP. *Cult Survival* 1996; 20: 60–62.

[18] Joint United Nations Programme on HIV/AIDS (UNAIDS), AVAC. UNAIDS/07.30E/JC1364E. *Op. cit.* note 9.

[19] A. Vallely, C. Shagi, S. Kasindi, N. Desmond, S. Lees, B. Chiduo, R. Hayes, C. Allen, D. Ross. Microbicides Development Programme. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* 2007; 7: 133.

[20] Ibid.

[21] The Initiative for Equal Rights (TIER) and International Rectal Microbicide Advocacy (IRMA) works extensively with the LGBTI community; Safehaven and Lifelink works with FSWs; Positive Action for Treatment Access (PATA) works with PLHIV; and Christ Against Drug Abuse Ministry (CADAM) works with IDUs.

Table 1. Summary of participants at the Community Dialogue meetings

Place & Date	*Participants*
Lagos 28th June 2012	15 total: One community representative from Ibarapa (Oyo State) and Ifon (Ogun State) respectively[22] who are community leaders[23]; 11 representatives of FSW, MSW, MSM, PLHIV, IDU communities; one journalist and one layperson from an ethics committee that handles protocols of multiple national studies involving MARPs.
Osogbo 22nd August 2012	43 total: representatives of non-governmental organisations, programmers and policy makers engaged with HIV programming for MARPs and PLHIV in Osun State.
Abuja 11th September 2012	13 total: Four community representatives from the community hosting the NICCAV[24] project in Nigeria, eight representatives of MSM, FSW and IDU populations; one journalist; and one layperson from an ethics review committee that handles multiple HIV research related protocols that involve MARPs

important underlying aim of these community engagement activities was to develop a research advocacy agenda for partnering organisations in Nigeria, including wide dissemination of the outcomes of the Round Table events in the coming years.

Phase One: Community Dialogue

Table 1 provides a summary of the participants at the one-day Community Dialogue events held in the cities of Lagos, Osogbo and Abuja. These events lasted between 8 and 10 hours, often with evening meetings. Activities included information sharing, group discussions and plenary discussions. The first Community Dialogue meetings were held in Lagos and Abuja, and the findings from these events fed into discussions at the Osogbo meeting.

In all Community Dialogue meetings, the first two hours were used to share general information with participants on basic aspects of clinical research and key information on HIV prevention and treatment research, using a specially developed research literacy training guide. This guide covered the following topics: (i) what is research; (ii) why is research important; (iii) why should we care about research; (iv) payment for participation in research; (v) informed consent; (vi) confidentiality; (vii) HIV prevention: existing tools; (viii) HIV prevention: new tools; and (ix) community involvement in research.

The remainder, and main part, of the one-day dialogue focused on sharing background information and discussing participants' experiences as research participants or recruiters of research participants, and their perceptions on three key areas – informed consent, standard of care for HIV research, and community engagement in research – as three separate sessions. Each session was introduced through a short plenary talk, followed by group discussions in which participants were asked to share their experiences as research participants or recruiters of research participants, identify priority issues and put forward their recommendations. All groups presented the highlights of their discussions in a plenary discussion. Throughout the day, discussions were managed by a facilitator, who was a member of the New HIV Vaccine and Microbicide Advocacy Society (NHVMAS),[25] and issues discussed were recorded by a note taker. At the end of the community dialogue, the note taker and representatives of the group developed a summary of the consensus reached during the discussions, which was presented to and agreed upon by participants at an evening meeting. The consensus statement was presented at a subsequent Round Table meeting.

Phase Two: Round Table Meetings

Two round table meetings were held immediately after the community dialogue events in Lagos and Abuja. Present at the meetings were all the community representatives who participated in the preceding Community Dialogue and invited researchers, ethicists, academicians, programmers, representatives of government research regulatory agencies, and policy makers and other stakeholders who were directly linked to HIV prevention and treatment research.

At the meeting, community representatives shared the consensus statements reached during the prior day's

[22] Ibarapa is the research community for medical and dental health projects for the School of Medicine and Dentistry, University of Ibadan and Ifon is the research community for the dental school of the University of Lagos.

[23] Gatekeepers in this context mean local community leaders. These include chiefs and community heads with whom researchers will often meet to take permission to work with the local geographical communities. All communities in Nigeria have such communities. The gatekeepers for the four research communities are to be engaged in this project.

[24] The Nigeria Canadian government funded HIV Vaccine demonstration project titled' Creating a common platform for HIV vaccine research and HIV care and treatment program'. This is popularly called the NICCAV project.

[25] The New HIV Vaccine and Microbicide Advcacy Society (NHVMAS) was established in 2003 by Nigerian scientists and activists to ensure proactive and early involvement of the Nigerian Government and its citizens in the research and development of new HIV prevention technologies. It operates as a non-governmental organisation with a mission to contribute to the prevention of HIV infection by promoting a supportive environment for the conduct of research and development of new HIV prevention technologies.

discussions. All participants extensively discussed the issues raised. Finally, consensus was reached on how best to address the gaps identified with the informed consent process and community engagement in research. The groups also identified key issues to take forward for wider dissemination to national audiences like research institutions, HIV implementing partners, regulatory agencies, academic institutions, teaching hospitals, medical centres, ethics committees, policy makers, CSOs, research funding agencies, and other identified relevant agencies.

OUTCOMES OF THE COMMUNITY DIALOGUE AND ROUND TABLE MEETING

In this section, we describe the most important agreed-upon issues at Community Dialogue events that were then taken up at the Round Table discussions. The three target topics were informed consent, community engagement, and standard of care (Lagos only). We also present the main emerging recommendations from Round Table events in these three topics.

1. Informed Consent

During community dialogue events in all sites, many concerns were raised about the informed consent processes. Across all sites, many community representatives perceived that the current standards of consenting for research participation were low and, in many cases, reported that informed consent might not occur at all, increasing the risks of different forms of research misconduct. Round Table participants felt that research misconduct often disproportionately affected the most vulnerable participants, particularly those who did not understand their rights as participants. For example, it was noted that participants are sometimes asked to pay for research-related investigations. Research participants often agree to making payments because they are unaware they are participating in research; they assume the investigations are part of their health care package, and are not aware of their rights as research participants. Meeting members agreed that such misconduct would be less likely if research participants were made aware of their rights during consenting for research participation. Discussants at the Round Table event in Abuja noted that the tendency for such misconduct could be higher when research is funded by the principal investigator in comparison to research that receives external funding.

In all sites, many of the main issues raised during Community Dialogues were related to situations where recognised national and international policies and guidelines for ethical conduct in research were not fully implemented *in practice*. The main areas taken forward from the Community Dialogues to the Round Table meetings provide illustrations of this perceived shortfall between policy and practice, summarised below:

Lagos:

- Researchers sometimes fail to implement consent processes, even when approved as part of the study protocol.
- Researchers overemphasize benefits and avoid talking about risks when providing information on studies during consent processes.
- Insufficient information is given about the purpose of research during consent.
- Highly technical language is used in consent forms which is difficult for many people to understand.

Osogbo:

- Researchers sometimes fail to implement consent processes.
- Participants are not given enough information about their right to not participate and their right to withdraw from research if they choose to do so.

Abuja:

- Negotiation of compensation often takes place during recruitment of participants rather than prior to protocol approval.

As a result, in all sites a key recommendation from the Round Table events was that Ethics Review Committees should strengthen their capacity to monitor research they approve – including monitoring of informed consent – to reduce the risks of research misconduct, in line with the National Health Research Ethics Code.[26] As noted by a member of staff of a research regulatory agency in Nigeria:

> *The process of informed consent is still challenging in Nigeria. Sometimes during clinical trial monitoring visits, we find irregularities concerning the process of informed consent. Although researchers are required to have the informed consent in the local language, this is not often the case. The adequacy of informed consent is supposed to be addressed by the ethics committee while the National Agency for Food and Drug Administration and Control [NAFDAC] looks at the scientific aspect of the research. We see informed consent forms approved*

[26] Federal Ministry of Health, Nigeria. The National Code for Health Research Ethics. Version 7.0. Available at: www.nhrec.net [Accessed 5 May 2014].

Table 2. Site specific recommendations for informed consent processes from Round Table Events

Site	*Recommendations*
Lagos	• Informed consent forms should more clearly contain information on the goal of the research, procedures and schedules, study duration, compensation, confidentiality/anonymity, the risks and benefits associated with study participation, the study product if any, and the voluntary nature of the project. • There should be increased efforts to train researchers on the importance of the informed consent, and how to conduct the informed consent process. Particular issues were the rights of participants to withdraw without fear of penalty or discrimination; and ensuring the benefits and risks/burdens of research were accurately described. • Training plans for research field workers should be assessed by ethics committee to ascertain their competency to be able to administer consent. • Informed consent forms should be available in local languages for ease of understanding; verbal translation of English to local language is not acceptable • Communities should have access through simple communication systems to voice their concerns, including requests to withdraw from research. • When participants withdraw from studies, there must be assurance that all the data related to the individual is withdrawn.
Abuja	• There is a need to create a regular platform for communities and researcher dialogue. This will also help ethics committee identify community concerns and how to address this when reviewing research protocols. • Ethics committees have the responsibility to educate their communities about their role and responsibility in research. • Research protocols should include timelines for planned project implementations so as to enable ethics committee assess the adequacy of time allocated for study implementation. This will reduce the tendency to compromise on proper study implementation processes when they are faced with pressure of time for project completion

by ethics committees and wonder if the protocol was critically appraised.

From the subsequent Round Table discussions on informed consent, the main recommendations highlighted the importance of:

i) Strengthening training on informed consent processes for researchers and field workers, including highlighting the importance of voluntariness;
ii) Ensuring that information given during consent is sufficiently comprehensive to support informed choice for research participation, in terms of content and language;
iii) Setting up easily accessible communication mechanisms within study communities through which research participants and other community members could ask questions, discuss issues, and get concerns efficiently communicated to research teams;
iv) More detailed project implementation timelines need to be included in study protocols. Ethics review committees need to check if sufficient time and resources have been invested for study implementation so as to prevent compromising the informed consent process during study participant recruitment.

See Table 2 for a summary on the discussion on informed consent.

2. Community Engagement

Across Community Dialogues and Round Table events, there was much discussion around community engagement[27] in research. During Community Dialogue events at all sites, it was agreed that:

i) There is inadequate community engagement pertaining to the design, implementation, monitoring and evaluation of research that involves them.
ii) One form of inadequate community engagement is based on a common misconception amongst researchers that Civil Society Organisations (CSO) are broadly representative of 'communities' and provide a reasonable means of recruiting and communicating with community members, a practice that should be discouraged.
iii) Research updates and outcomes are poorly disseminated to communities and individuals involved in research.
iv) There is very little effort made to strengthen general research literacy amongst communities who participate in research, so that community members are only able to respond to the information specific researchers share with them.
v) Community engagement is often too heavily focused on gaining access to community members for purposes of recruitment into studies.

[27] In these discussions, the word 'community' referred to the specific 'sub-group' (e.g., men who have sex with men [MSM] or sex workers) and/or geographic community from which trial participants will be drawn (K West Slevin, M Ukpong & L Heise. Community Engagement in HIV Prevention Trials: Evolution of the Field and Opportunities for Growth. Aids2031 Science and Technology Working Group, No 11, November 2008:3). Community engagement means involving these communities hosting research trials in the research decision-making process.

A key underlying theme across these issues related to the extent to which community members' and communities' interests are adequately considered by researchers given 'low levels' of engagement. Speaking to the low investment in promoting general research literacy within communities, a community representative noted:

> *Researchers must create a level ground to enable them to relate and communicate with the community. They should change the mindset that the community does not know or cannot understand the science of research [and] hence they do not need to be engaged in the research processes.*

Similarly, it was seen that community engagement should aim to ensure that research projects address local needs. In the words of community representatives during Community Dialogue:

> *'Researchers have to advise funders of research projects on issues that are of importance to the Nigerian community and not just implement what is of importance to foreign donors in Nigeria'*

> *'Most of the operational/implementation research in our community is initiated by foreign partners and does not allow for local context. What are we doing about this?'*

Specific concerns from each of the Community Dialogue sites that were also discussed at the Round Tables are summarized below:

Lagos:

- Research protocols often show no evidence of community involvement yet ethics committees approve them nonetheless.
- Ethics committees do not monitor research studies they approve to ensure that community engagement happens in the field.

Osogbo:

- Researchers make poor efforts at identifying communities representatives to work with during research programmes.

Abuja:

- Minimum community engagement occurs at the design stage of the research, but extensive engagement during the implementation.
- Police officers should be considered as members of Community Advisory Boards constituted for research involving vulnerable communities.
- Where CSO are formally engaged on projects, Terms of References are not drawn up to guide their work.

The main recommendations made by participants at the Round Table discussions were that:

i) Community engagement should happen throughout the lifecycle of research – from the design to the dissemination stage in line with the requirements of national health research ethics codes and national HIV research policies, and should involve a wide range of community stakeholders.
ii) Both formal and informal ways of engaging with community members are important. An example of a formal approach is for researchers to develop a Memorandum of Understanding (MOU) with representative community members that can be submitted to ethics review committees as part of study protocols.
iii) Study protocols should always include information on how research updates and findings will be communicated to participants and participant communities.
iv) Recruitment of research participants should be done by trained research team members, although other community based groups can be involved in providing information to the community about the research.
v) Although CSO should not be primarily involved in recruitment of participants in studies, these organisations can play a key role in promoting research literacy.
vi) Research regulatory agencies should interact with research communities during their monitoring visits to evaluate level and efficacy of community engagement in the research projects.

3. Standard of Care

The issue of standard of care was only central to discussions by community representatives in Lagos State. In this section, we describe the two main issues emerging from Community Dialogue and Round Table discussions in Lagos.

i) *Differences between national and international standards of care*: Community Dialogue participants raised concerns about differences between national and international standards of care for HIV prevention and treatment research. Standard of care in HIV prevention and treatment research in Nigeria are only required to conform to national research ethics guidelines, which describe standards that are often lower than those in other countries and those obtainable in Nigeria. At the Round Table discussion, it was agreed that national and global standards should both be considered in developing the care package for research participants in Nigeria. A particular importance for this policy was seen in the

ability to 'rachet up' standards of care for HIV/AIDS more generally in the country over time, as research feeds into policy.

ii) *Researchers' responsibilities for participants' health care*: Community Dialogue participants raised concerns that study participants are sometimes asked to bear the costs of managing illnesses that develop during the course of studies with a long duration. They also felt that participants engaged in HIV treatment (antiretroviral therapy) research should have continued access to drug therapy after completing or voluntarily withdrawing from studies. Participants in the Round Table events agreed on the importance of researchers planning in advance to manage all forms of foreseeable research related injuries, including those described in the study protocol and the consent form; researchers should adequately discuss this issue with study participants. Further, Round Table participants considered it morally important that researchers support participants in treating other chronic illnesses occurring during clinical trial participation as much as possible. One reason discussed was the difficulty community members have in distinguishing between 'research-related' and 'non-researcher-related' illnesses, leading to loss of trust and difficulty in conducting studies. This has led to researchers being viewed by participants as unreasonably ignoring their responsibilities.

DISCUSSION

In this paper, we set out to describe a relatively novel process of community engagement undertaken in three major cities in Nigeria that included a range of important research stakeholders for HIV/AIDS research. In doing this, we aimed to highlight the main issues perceived by community groups in the areas of informed consent, community engagement and standard of care; and to describe the outcomes of discussions between community groups, researchers and other HIV/AIDS research stakeholders on these issues. In this discussion, we focus on four related areas emerging from the process overall. Firstly, we underline the importance of perceptions of a gap between policy and practice in relation to 'implementation' of research ethics policies on the ground, and its relationship to risks of different forms of research misconduct. Secondly, we recognise the potential for greater engagement of communities to contribute to closing this gap between policy and practice, as seen by participants in these discussions, while noting some challenges for these ideas from the literature. Thirdly, we discuss some implications of the views raised on standard of care for research on HIV/AIDS. Finally, we comment on our experiences of using the community engagement approach described in this paper, although a formal evaluation of the process was not planned as part of the activity.

Gaps between Policy and Practice

Perceptions of gaps between policy and practice in ensuring ethical conduct of research in Nigeria were described in two ways; through poor adherence of researchers and other research staff to guidelines on the ethical conduct of research, and through inadequate oversight of studies by national regulatory bodies with responsibility for the ethical conduct of research. In fact, issues in adherence to research guidelines is directly suggested by the fact that many of the ethical issues raised during Community Dialogues are already covered by many existing ethical guidelines, including those developed in Nigeria. At the same time, the National Health Research Ethics Code[28] that governs the activities of ethics committees in Nigeria clearly stipulates a role for ethics committees in providing regulatory oversight for researchers and for ensuring community engagement in research.

Gaps between policy and practice were seen as particularly important in HIV prevention and treatment research, with high risks of research misconduct linked to the fact that participants are often stigmatised, vulnerable and/or disempowered. While past HIV prevention trials conducted in Nigeria have recruited FSW,[29] the Nigerian legal system is unsupportive of the rights of MSM, IDU and FSW,[30] limiting their ability to seek redress for injustices related to these forms of high risk behavior. Worldwide, HIV prevention trials have included IDUs, MSMs and other high risk groups who often face similar forms of discrimination and stigmatization;[31] as would also be

[28] Federal Ministry of Health, Nigeria *Op. cit.* note 14.

[29] V. Halpern, F. Ogunsola, O. Obunge, C.H. Wang, N. Onyejepu, O. Oduyebo et al. Effectiveness of cellulose sulfate vaginal gel for the prevention of HIV infection: the prevention of HIV infection: results of a Phase III trial in Nigeria. *PLoS One*. 2008; 3(11): e3784. doi: 10.1371/journal.pone.0003784; P.J. Feldblum, A. Adeiga, R. Bakare, S. Wevill, A. Lendvay, F. Obadaki, M.O. Olayemi, L. Wang, K. Nanda & W. Rountree. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized trial in Nigeria *PLoS One* 2008; 23; 3(1): e1474. doi: 10.1371/journal.pone.0001474.

[30] The section 214 and 215 of the Nigerian Criminal Code criminalises homosexuality and commercial sex work. This contravenes the section 35(1) of the 1999 constitution which provides that 'Every person shall be entitled to his personal liberty and no person should be deprived of such liberty . . .'

[31] K. Choopanya, M. Martin, P. Suntharasamai, U. Sangkum, P.A. Mock, M. Leethochawalut et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; 381(9883): 2083–90. doi: 10.1016/S0140-6736(13)61127-7. Epub 2013 Jun 13; R.M. Grant, J.R. Lama, P.L. Anderson, V. McMahan, A.Y. Liu, L. Vargas, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010 Dec 30; 363(27): 2587–2599. doi: 10.1056/NEJMoa1011205. Epub 2010 Nov 23.

likely for research involving these key populations in Nigeria. Despite extensive and active ongoing efforts in the country to build the capacity of ethics committees, their ability to ensure that research approved by the committees are monitored has been recognized as a continuing challenge.[32] Given the importance of HIV and AIDS research and the particular legal and social vulnerabilities of populations likely to be involved in these studies, it is important to give particular attention to building the capacity of ethics committees to review and monitor research in this area, including the plans for community engagement and on-going evidence of its implementation.

Communities' Contributions to Closing This Gap between Policy and Practice

Participants in these discussions emphasized that community engagement should support stakeholders in identifying unethical practices as well as adequately resolving them. These views are particularly important given challenges for ethics committees in providing sufficient research oversight functions, as described above. One important form of community engagement recognized in these discussions was an effort to promote research literacy within populations likely to be involved in research, to counter low understanding of clinical research. An interesting element of these recommendations was the potential role of CSO's in Nigeria as *sustainable* and *independent* bodies in promoting research literacy. CSO are not-for-profit, non-governmental organisations operating in the public interest, seen as a 'third sector' of governance[33] and strongly developed in many Western European countries. Knabe and McCathy[34] and Koen et al.[35] identified the significant roles CSO can play in the politics of public health research. The same role of CSO in HIV treatment and prevention research is well recognised.[36] Knabe and McCathy[37] described CSO's roles within the public health sector as mobilizing researchers and communities, supporting research themes, and lobbying to use public health evidence in policy and decision-making. While recognizing that 'third sector organizations' have also been critiqued, including for their potential to serve special rather than general or public interests,[38] it seems likely that CSO in Nigeria can play important roles in promoting community research literacy roles if they receive the needed education and support.

A further form of community engagement seen as essential in these discussions was consultation with the community. As also discussed in the literature,[39] participants advised that consultation should happen early in the research process; should occur during the design, development, implementation, and dissemination of research results; and the consultative process should occur in a sustained manner. The GPP,[40] the National Health Research Ethics Code,[41] the HIV Research Policy[42] and several other key documents[43] all address and promote the same practice.[44] At the same time, it is well recognized that community consultation is not a straight forward process either in theory or practice; these issues could not be explored in these discussions, given limitations of time and scope. Further discussion would

[32] A.J. Ajuwon & N. Kass. Outcome of a research ethics training workshop among clinicians and scientists in a Nigerian university. *BMC Med Ethics* 2008; 24(9): 1. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2246144/?tool=pubmed [Accessed 5 May 2014].

[33] A Ghaus-Pasha. Role of civil society organizations in governance. Sixth Global Forum on Reinventing Government Towards Participatory and Transparent Governance. 24–27 May 2005, Seoul, Republic of Korea. Available at: http://unpan1.un.org/intradoc/groups/public/documents/un/unpan019594.pdf [Accessed 5 May 2014].

[34] A. Knabe & M. McCarthy. Civil society organisations and public health research – evidence from eight European union new member states. *Cent Eur J Public Health* 2012; 20(4): 287–293.

[35] J. Koen, Z. Essack, C. Slack, G. Lindegger & P.A. Newman. 'It Looks Like You Just Want Them When Things Get Rough': Civil Society Perspectives on Negative Trial Results and Stakeholder Engagement in HIV Prevention Trials. *Dev World Bioeth* 2012 Sep 24. doi: 10.1111/j.1471-8847.2012.00338.x. [Epub ahead of print].

[36] K. West Slevin, M. Ukpong & L. Heise. Community Engagement in HIV Prevention Trials: Evolution of the Field and Opportunities for Growth. *Aids2031 Science and Technology Working Group*, No 11, November 2008.

[37] A. Knabe & M. McCarthy. *Op. cit.* note 27.

[38] M. Taylor & D. Warburton. Legitimacy and the role of UK third sector organizations in the policy process. *Voluntas: Independent Journal of Voluntary and Nonprofit Organizations* 2003; 14(3): 321–338.

[39] L. Miller et al. *Op. cit.* note 8.

[40] UNAIDS/AVAC. *Op cit.* note 9.

[41] The page 27 of the 2006 edition of the National Code of Health Research Ethics notes that Ethics Committees should protect communities participating in research from exploitation. It then further went on to state specific requirements of actions.

[42] National Agency for the Control of AIDs, Nigeria. National HIV/AIDS Research Policy. 2010.

[43] The page 109 of the National HIV/AIDS response review 2005 to 2009 published by the Federal Government in December 2009, identified community engagement in HIV/AIDS research throughout the entire phase of the research process as an emerging issue. It notes that policies that promote community engagement in all phases of research processes is welcomed; Page 55 of the October 2009 National HIV/AIDS policy review report notes that the current Food and Drug Regulatory Agency (NAFDAC) guidelines not facilitating community engagement efforts is a challenge and something that needs to be addressed. An actionable policy recommendation made was that '*host communities should be involved at every level of community based research*.'

[44] Of note, the 2002 CIOMS International Ethical Guidelines for Biomedical Research guidelines do not describe the principles of community engagement. As these guidelines are currently under review, we would strongly advocate that a full articulation of expected standards of community engagement should be included in the forthcoming version.

have been valuable in relation to challenges in the literature, including: identifying the 'community' itself; understanding who should represent a community in a process of consultation; ensuring that consultation is a genuine attempt to include the views of community representatives in fundamental decisions about research; and being clear about ways in which informed and balanced views from community representatives can be sought, given the technical and often complex nature of many studies and research ethics itself.[45] In relation to mechanisms, Round Table discussants promoted both informal and formal approaches for community consultation, including seeing formal mechanisms (such as MOUs) as likely to be important where negotiation between different research stakeholders was needed.

Standard of Care for Research on HIV/AIDS and Community Engagement

One area of community consultation recommended by UNAIDS/WHO guidelines is discussion and negotiation with communities about the standard of care provided to participants during studies. In this respect, community members in Abuja seemed more interested in discussing standard of care packages in the context of overall 'compensation' for study participants, while those in Lagos were more fixed on the need for local implementation of international standards of care, for both local and internationally-funded research. Findings in Lagos differ from the position on standard of care packages in resource-limited settings, which argues that use of local standards of care is acceptable in the conduct of international research.[46] In the Lagos discussions, community members argued that applying global standards of care during the conduct of local HIV research has an important long term potential to 'ratchet-up' the standards of care. This was seen as particularly true where community involvement in research is based on concepts of continuous mutual education and respect, partnership, and consensus-building to promote local ownership of research outcomes. This stance aligns with Benatar and Singer's[47] aspirational goal of promoting access for study participants to the highest achievable standards of care in research.

At the same time, there are concerns that the standard of care in HIV prevention and treatment research in Nigeria are only required to conform to national research ethics guidelines, which describe standards that are lower than those in other countries and those obtainable in Nigeria. This disparity at the national level resulted from a delayed revision of the national guidelines despite evolving evidence in the field. A good example is the national STI guidelines.[48] At the time of the meeting, the national guidelines for the management of STIs were last revised in 1996. The management of many STIs have since evolved and the practice in the field differs significantly from that defined by the national guidelines. In other words, practice can outstrip guidance documents in Nigeria, and this is a significant concern if the slow development and review of guidelines hinder access to obtainable (global) best practice.

As for community consultation on standards of care, discussions on the way that study participants should be compensated for their involvement in research are likely to be challenged by differences between researchers and community members' understanding of research aims and procedures. There are also likely to be different levels of awareness regarding research ethics guidelines including the importance of balancing risks of 'exploitation' of study participants against those of 'undue inducement'. Ensuring greater mutual understanding between different research stakeholders on these issues would help to ensure compensations packages are fair and objectively determined as much as possible, and avoid compensation being seen as payment for labour.[49] Where this happens, ethics committees may play a lesser role in determining compensation packages: a departure from a defined traditional role.[50]

Many community members believe that researchers are responsible for ensuring access to care for participants, including for chronic conditions. Such views are linked to standards of care and 'compensation' packages within a wider concept of 'fair benefits'.[51] This concept describes the value of considering study benefits that include those

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given to study participants and study communities both during and after the completion of studies. These include structural benefits such as employment and capacity building. Further, the questions raised about study participants' rights to access forms of care not included in study protocols reflects a prominent debate in the literature on researchers' ancillary care responsibilities.[52] The GPP refers to this as non-HIV related care and encourages researchers to refer study participants for care. While ethical practices in HIV research recognizes the place for morally praiseworthy[53] efforts in research, decisions on the feasibility of including such care packages should take account of community views regarding the importance of these forms of ancillary care, prior to research budgeting. The responsibilities of researchers to provide such care has been seen as dependent on the prevalence and seriousness of the condition needing care, the availability of such care from other sources, the nature of the relationship (duration and intensity of engagement) between researchers and participants in particular studies, and the cost/resource implications, including for the conduct of similar studies in the future, and other research in the same community.[54] At the same time, provision of care for participants in studies can also generate ethical issues. For example, where clinical trials facilitate access to care and support services that might not otherwise have been available, this ease of access to much needed care can serve as a form of *soft coercion*.[55]

Model for Community-Research Dialogue

Finally, the authors determined that the community-research interface can be empowering for both community representatives and researchers when a platform for dialogue is created. Indeed, such opportunities to have such engaging discussions are rare. The informal 2-stage consultation method used in this community engagement activity was very much appreciated by researchers and community participants. The process created an opportunity for communities to become more research literate and for researchers to become more community literate; one of the key operational requirements identified for successful engagement of communities in research.[56] The authors however do not think that this single event is all that is required for empowerment of community members and researchers to enable both parties to address all ethical concerns with research design and implementation. Mechanisms need to be defined to promote and sustain dialogue between the two parties, the ramification of which is beyond the scope of this paper to discuss. Also, more discussion of this nature on both formal and informal methods for consultation are central to taking the issues identified through this consultation forward.

CONCLUSION

Facilitating platforms that promote community dialogue about the conduct of research in communities are important to shape critical discussions about ethical practices in research conduct. One critical outcome of this dialogue is consensus on a view that unethical practices have less to do with the multiplicity of ethical guidelines but rather, the ability of researchers to imbue the practice of ethics. Efforts therefore need to be invested in teaching and training researchers on ethical conduct of research in general and the ethics of HIV prevention and treatment research specifically. Additionally, for countries where human rights abuses are prominent, research community members need to be empowered to ask the right questions about research through support for and promotion of research literacy programmes.

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OPINION

Letters: Education about Ebola an imperative

September 26th, 2014, 5:49 pm · View comments

Published: Sept. 26, 2014 Updated: 5:54 p.m.

Irvine, **Brandon Brown, MPH, Ph.D,director, UC Irvine's Global Health Research, Education and Translation program**: The current outbreak of Ebola is the worst outbreak since 1976, and is present in Guinea, Liberia, Nigeria, Senegal and Sierra Leone. The short duration infection and mortality, and the rapid transmission of infection, leads experts to estimate as many as 1.4 million infections before the epidemic halts. Ebola has taken over 2,200 lives – people with families – so far, and there is little that can be done to treat infections in resource-poor settings.

The unspoken heroes of this epidemic are the health care workers who brave potential infection to save the lives of those infected. We have the same heroes at hospitals in every country, who risk all to prevent death. The fact that those infected by Ebola are several thousands of miles away is no excuse for low knowledge on the topic, or inaction.

Americans have been infected as well. We are all one human family, and regardless of our skills, we must take the opportunity to educate ourselves and do what we can to prevent all deaths. Our local and national leadership and media must make our education of Ebola a priority.

Body cameras protect public and police

Bioethical Inquiry
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CRITICAL PERSPECTIVES

Post-Approval Monitoring and Oversight of U.S.-Initiated Human Subjects Research in Resource-Constrained Countries

Brandon Brown · Janni Kinsler · Morenike O. Folayan · Karen Allen · Carlos F. Cáceres

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Abstract The history of human subjects research and controversial procedures in relation to it has helped form the field of bioethics. Ethically questionable elements may be identified during research design, research implementation, management at the study site, or actions by a study's investigator or other staff. Post-approval monitoring (PAM) may prevent violations from occurring or enable their identification at an early stage. In U.S.-initiated human subjects research taking place in resource-constrained countries with limited development of research regulatory structures, arranging a site visit from a U.S. research ethics committee (REC) becomes difficult, thus creating a potential barrier to regulatory oversight by the parent REC. However, this barrier may be overcome through the use of digital technologies, since much of the world has at least remote access to the Internet. Empirical research is needed to pilot test the use of these technologies for research oversight to ensure the protection of human subjects taking part in research worldwide.

Keywords Ethics · Oversight · Post-approval monitoring · Developing countries · REC

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Ethical Violations in Human Subjects Research

The history of human subjects research is riddled with ethical violations. Some violations in the United States have been well documented such as the Tuskegee syphilis and Willowbrook experiments (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Beecher 1966) and the Havasupai case (*Havasupai Tribe v. Arizona Board of Regents* 220 Ariz. 214, 204 P.3 d 1063 [2008]). The increase in U.S.-funded research involving human subjects internationally, especially in resource-constrained settings (RCS), has resulted in a rise in ethical violations in non-U.S. settings and is not as well documented as in the United States. Studies in RCS where ethical violations have been identified include the Trovan trial in Nigeria (Khan 2008), the Yanomami tribe study in the Amazon (Nugent 2001), and genetic studies in China (Sharav 2000).

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More recently, details of the Guatemala syphilis study emerged, which led to the development of the Presidential Commission for the Study of Bioethical Issues report titled *Ethically Impossible*: *STD Research in Guatemala from 1946 to 1948* (Reverby 2011; Obama 2010). This report presumably scratches the surface of ethical violations likely occurring in RCS where regulatory oversight of research is still evolving. Clearly the magnitude of ethics violations in RCS—many of which are becoming recognized as prime destinations for U.S.-led clinical trials for many reasons—is not fully known. While groups have begun to explore the issues raised when U.S.-funded research is conducted in RCS (Klitzman 2012), more work is needed. Unfortunately, documentation of poor compliance or noncompliance with the research protocol is limited, with little reference to this in the literature. The literature is, however, rife with reports of ethical misconduct. One such documented report is the shutdown of the Tenofovir trial in Nigeria due to poor adherence to required protocol standards (Mills et al. 2005).

Table 1 lists different types of violations that may occur during the conduct of human research in developing countries, broken down into issues with data, human subjects, and study procedures. These violations vary by severity and may take place even when there are clearly written research protocols, the investigators are highly competent, and the study team is well trained. While some of these violations may occur in research studies in general (e.g., failure to protect data, not obtaining informed consent, changing study protocol/methods without approval), others may be unique to research in RCS. For example, there are several ethical issues that might arise when research is being conducted in one country and the research ethics committee (REC) of the principal investigator's (PI) institution is located in another country. In such a case, the local REC should play a bigger role in study oversight. Issues of particular relevance include how data with identifiers will be transported between countries and how local norms (cultural, social, economic, and political) will be addressed regarding informed consent, adherence to study protocol, and subject compensation. Understanding the local standard of care also will be critical to developing appropriate procedures for maintaining drugs/medications. Moreover, the physical distance between institutions often creates challenges with regard to communication between the PI's REC and the local REC. In addition, RECs in some settings are still evolving, with the main challenge for many being the ability to provide regulatory oversight for a growing portfolio of research studies, thus creating additional opportunities for ethical violations to take place. The violations may be an effect of poor planning by the U.S. institution and be no fault of the host institution.

U.S. REC Oversight in Resource-Constrained Settings and Post-Approval Monitoring (PAM)

One of the key functions of RECs in the United States and in many African and Latin American countries is to provide oversight for the research they approve based on regulations set forth in the Common Rule (45 CFR 46 Subpart A, 21 CFR 50 & 56), the Declaration of Helsinki, the International Conference on Harmonisation guidance documents, and United Nations guidelines. RECs are expected to ensure that human research conducted by U.S. investigators in RCS offers the equivalent levels of protection that would be required at the PI's home institution and meets local laws and cultural context. Additionally, it is expected

Table 1 Potential ethics violations in developing countries without PAM

Data issues	Falsification or fabrication
	Failure to protect data—hard copy and electronic
	Loss of data when transferred between sites
	Not retaining data for an appropriate time
Human subject issues	Not obtaining informed consent
	Limited consideration of local norms (cultural, social, economic, political) when obtaining consent, providing compensation, and conducting study procedures
	Subjects coerced/pressured to participate (e.g., small villages or cities)
	Violating subjects' privacy
	Therapeutic misconception
	Withholding test results
	Inadequate or inequitable standards of care
	Inadequate provision of ancillary care
	Lack of plans for post-trial access to a successful product
	Refusing to provide available care or treatment
Study procedures	Over-enrollment
	Changing randomization assignment without REC approval
	Not reporting serious adverse events and unanticipated problems
	Failure to properly maintain drugs/concomitant medications
	Not maintaining REC approvals

that RECs provide ongoing monitoring of the research to ensure continued human subjects protection. Investigators are expected to report protocol violations and unanticipated problems involving risk to subjects or others to the REC. Many RECs in the United States have post-approval monitoring (PAM) programs, which take place after REC approval and help ensure compliance to approved protocols. However, U.S.-initiated studies may not have the resources to conduct PAM in international settings, where local conditions and regulations also must be respected. Countries in RCS may have their own PAM programs, though there is considerable variation internationally.

The goal of PAM is to review active protocols to ensure the research is being conducted in accordance with the approved research protocol and to assure risk to subjects is not greater than originally anticipated. RECs may select studies for PAM or conduct PAM in response to serious adverse events or to a specific request. A PAM program administrator will often visit research study sites in the company of the study PI or his or her designate, observing procedures and noting any inconsistencies with the protocol. The principal investigator often has the opportunity to address any deviations by submitting an amendment to the protocol. The PAM visit is an opportunity for study investigators to request any help they may need. Findings are reported at the next REC meeting. The report of the visit and any follow-up visits are filed in an investigator's REC protocol file. Ideally, the investigator should receive a brief follow-up visit to document completion of any corrective actions related to deficiencies highlighted in the PAM report.

In general, PAM can reduce the likelihood of ethical violations by providing educational training that facilitates best practices and regulatory compliance. The process also can provide significant additional information that enables an institution to be confident that it is meeting both the letter and the spirit of the U.S. federal as well as international regulations developed to ensure the protection of the rights of human participants in research. Moreover, the process could lead to the development of policies and initiatives that provide comprehensive response to misconduct in all countries, including an international framework for PAM (Resnic and Master 2013; Ana et al. 2013).

In the absence of local PAM infrastructure and capability, U.S. PAM activities at research sites in other countries is a major challenge, with distance being the primary obstacle. With limited resources, it may not be practical (staff availability, time, and travel restrictions) or cost-effective (fees for flights, hotel, food) for a U.S. REC to conduct an in-person site visit. Moreover, utilizing local RECs for PAM also has its challenges, as the local REC may lack the capacity to conduct these reviews. Alternative options are needed to address the challenges of conducting research oversight in RCS.

PAM Options and Solutions in Resource-Constrained Settings

PAM in U.S.-initiated studies in RCS should be done jointly with input by the U.S. REC and local REC as a partnership, and always with local regulations prioritized. RECs in some RCS are gradually building their capacity, and with additional training these skills could be utilized for their own conduct of PAM activities. This is ideal, as local researchers, institutions, and communities should be involved in study design and standards. Still, variation in REC experience is vast, which may range from weak to strong RECs, PAM resources built into international networks, and oversight from the federal government. In general, RECs without significant PAM experience should be guided through collaborative training exercises to ensure long-term sustainability to increase research oversight capacity (Cáceres and Mendoza 2009). Regardless of local REC strengths and PAM capability, the REC in U.S.-initiated studies should play a role in PAM of the study as the institution of primary responsibility and should work to support the local REC. In addition, PAM should be of the highest priority when vulnerable populations are involved in the study protocol (Borek, Allison, and Cáceres 2010).

In the global digital age, much of the world (even most impoverished areas) has at least remote access to the Internet. This allows for the possibility of a digital presence for PAM as an alternative to a physical presence. For example, PAM activities such as web-based educational training and secure file-sharing applications (Howes and D. Wolf 2012 could potentially prevent ethical violations from occurring in the first place by observing training sessions via the web and reviewing research-related documents prior to the commencement of the study protocol to help avert potential violations before they occur. Virtual visits and recordings (via Skype, FaceTime, Google Chat, WebEx) can replace in-

person visits by RECs for areas with a reliable Internet connection. Secure file-sharing with Dropbox or cloud computing software can ensure complete transparency. For low-technology areas, a local REC visit or liaison may be appropriate for monitoring. If none of these options is available, and the local REC is less experienced with PAM or institutional and research team capacity is low, a U.S. REC visit may be most appropriate. In practice, U.S. REC-driven or locally driven PAM policies can include oversight taking place quarterly or annually in human subjects research. Violations or protocol deviations may be identified at an early point and rectified according to REC best practices.

Potential benefits of using technology to facilitate PAM of research in RCS are vast, including reduced expenses in a sparse research funding environment and facilitation of communication and ethics education with the local RECs and with investigators, creating more of a collaborative process that may further help reduce ethical violations. Funds can be written into research grants to support the technology needed for PAM as well as to provide human subjects and ethics training to research collaborators in non-U.S. countries. This should be considered a requirement for future federally funded international research.

The use of digital technology for PAM would eliminate costs associated with domestic travel and, if needed, U.S. RECs travelling to distant sites. The technology would, however, still require that REC members invest time for the process and the building of the human capacity of the PAM administrative officer with requisite interpersonal and communication skills to interact constructively with researchers. The use of digital technology in RCS also comes with its own challenges. These include funding the technology, ensuring access to (reliable) Internet connectivity, maintaining records electronically, and managing different time zones for international communication. Also, the use of digital technology for PAM does not address issues of trust and respect for the local REC in performing its own oversight.

Next Steps

Investment in the piloting of the use of digital technology for PAM is important. In 2012, the Harvard School of Public Health reported on the use of web-based conferencing to conduct PAM with investigators in low- and middle-income countries. It examined the advantages associated with PAM, including promptly identifying protocol deviation and record-keeping deficiencies and addressing these issues (Howes and D. Wolf 2012).

International standards for the proper conduct of PAM in RCS are needed. PAM should be prioritized and funds for this monitoring should be made available. Considering the time it took to learn about the Guatemala syphilis experiments, it is imperative to develop methods to prevent potential violations from occurring. Unfortunately, post-approval noncompliance will occur despite even the best-run PAM program with or with our digital technology. The documentation of these violations is important for many reasons, including the provision of helpful information to assist in the design of the best use of digital technology for PAM to address these on-site challenges. Also, there is a need for empirical research to further explore the technologies currently available to enhance the ability of RECs and other research regulatory agencies to protect research subjects.

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