THE REBECCA PROJECT FOR HUMAN RIGHTS

Health Safety and Dignity for Vulnerable Families

UNETHICAL MEDICAL RESEARCH IN AFRICA
Funded or Assisted by
US-Based Institutions and/or US Government

NON-CONSENSUAL RESEARCH IN AFRICA
THE OUTSOURCING OF TUSKEGEE Part II

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Preface

The purpose of this note is to call attention to recent even continuing unethical research directed and supported from the United States (US), and to motivate responses to stop unethical research – through the public awareness and criticism (transparency) as well as through Congress and the courts (enforcing adequate laws and regulations).

This note lists medical research sponsored or assisted by the US government and/or private companies headquartered in the US that, based on available information cited in this note appear to violate ethical standards and/or US regulations. Projects are listed and discussed according to offenses: (1) not asking for informed consent; (2) not warning people about specific identified risks; (3) exposing babies to unnecessary risks; and (4) not reporting or investigating unanticipated problems.

For each project cited for alleged ethical and/or regulatory offences, this note:

(a) describes the alleged offence(s) with references to published evidence;

(b) cites relevant ethical guideline(s) in the World Medical Association's Declaration of Helsinki (DoH), revised to 2008, available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and/or and/or the relevant text in the US Code of Federal Regulations, Title 45 Part 46, Protection of Human Subjects (45 CFR 46; available at: http://ohsr.od.nih.gov/guidelines/45cfr46.html) ;

(c) references previous attention to the alleged offences; and

This is not intended to be an exhaustive list of all medical research activities managed and/or funded by US-based institutions with serious ethical or regulatory offenses.

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1. Ethical issue: Not asking for informed consent

1.1 Ghana, 1993-99: Trial of four methods to deliver family planning services in Navrongo, Kassena-Nankana District

Study identification		
	Study name:	Navrongo Health Research Center Community Health and Family Planning Project
	US research organization:	
	US funders:	Population Council, Rockefeller Foundation, USAID, Gates Foundation, Andrew Mellon Foundation
	Study ID number:	No number
Study synopsis		
	The project tested four modalities to deliver family planning information and services in four parts of Kassena-Nankana District: clinic-based without community meetings; clinic based with community meetings; village service delivery without community meetings; village service delivery with community meetings. To evaluate the impact of the different ways to deliver family planning advice and services, the project selected a panel of approximately 1,900 compounds, which it visited annually during 1993-1999, to survey resident adults about "reproductive behavior and preferences, contraceptive use, and fertility determinants" (p 146, Debpuur 2002). The project reported that various interventions reduce desired family size and fertility.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	Not asking an Institutional Review Board to review and approve its plans for repeat surveys of adults over 6 years, including sensitive questions about reproductive attitudes and sexual behavior.	DoH 15, CFR46.109(a)
	Not getting informed consent from participants repeatedly surveyed on sensitive issues.	DoH 24, CFR46.116
Public criticism, investigation, litigation		
	Rebecca Project raised these issues in Nonconsensual Research in Africa (see reference below).	
References		
	Debpuur C, Phillips J, Jackson EE, et al. The impact of the Navrongo Project on contraceptive knowledge and use, reproductive preferences, and fertility. Studies in Family Planning 2002; 33: 141-164.	
	Phillips JF, Bawah AA, Binka FN. Accelerating reproductive and child health programme impact with community-based services: the Navrongo experiment in Ghana. Bull WHO 2006; 84: 949-955.	
	Rebecca Project for Human Rights. Nonconsensual Research in Africa: the Outsource of Tuskegee. Washington DC: Rebecca Project, 2011. Available at: http://www.rebeccaproject.org/images/stories/files/NonConsensualResearch20111120.pdf (accessed 7 February 2012).	

1.2 Nigeria, 1996: Trial of Trovan to treat meningitis in children

Study identification		
	Study name:	Unknown
	US research organization:	Pfizer
	US funders:	Pfizer
	Study ID number:	No number

Study synopsis		
	Pfizer arranged for doctors in Kano, Nigeria, to test trovafloxacin (Trovan), an experimental drug to treat bacterial meningitis, on children during a meningitis outbreak. 190 children were included in the trial. Children in the control arm received a non-standard low dose of the recommended drug, ceftriaxone. Eleven children died during the trial and others suffered permanent damage to their health.	
Ethical issues		
	Alleged offenses	Relevant DoH and/or CFR clause
	Not getting an Institutional Review Board to review proposed research.	DoH 15
	Not getting informed consent.	DoH 24
Public criticism, investigations, litigation		
	SOMO (2008) and Rebecca Project (2011) have called public attention to ethical misconduct in this study. Cases against Pfizer have been filed in the US (2001) and in Nigeria (2005 and 2007). Pfizer is reportedly settling with families out of court. The suit in the US was brought under the Alien Tort Statute.	
References		
	Center for Research on Multinational Corporations (SOMO). SOMO briefing paper on ethics in clinical: #1: Examples of unethical trials, updated February 2008. Amsterdam: SOMO, 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 7 February 2012).	
	Rebecca Project for Human Rights. Nonconsensual Research in Africa: the Outsource of Tuskegee. Washington DC: Rebecca Project, 2011. Available at: http://www.rebeccaproject.org/images/stories/files/NonConsensualResearch20111120.pdf (accessed 7 February 2012).	
	I. Uwugiaren, "Nigeria: Pfizer Directors Declared Wanted," AllAfrica, 10 Jan 2008, <http://allafrica.com/stories/200801100283.html> (Jan 2008).	
	A. Jack & D. Mahtani, "Pfizer to fight $9bn Nigerian class action on drug trials," Financial Times, 6 Jun 2007.	
	"Nigeria sues drugs giant Pfizer," BBC News, 5 June 2007, <http://news.bbc.co.uk/2/hi/africa/6719141.stm> (Jan 2008).	
	J. Stephens, "Panel Faults Pfizer in '96 Clinical Trial In Nigeria," Washington Post, 7 May 2006, <http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html> (Jan 2008).	
	A. Lin, "Class Action Against Pfizer Is Dismissed," New York Law Journal, 24 Aug 2005, <http://www.law.com/jsp/law/LawArticleFriendly.jsp?id=1124787914475> (Jan 2008).	
	Alliance for Human Research Protection (AHRP) case against Pfizer," 23 Oct 2003, <http://www.ahrp.org/infomail/03/10/14.php> (Jan 2008).	
	Abdullahi v. Pfizer, Inc., 562 F.3d 163 (2d Cir. 2009).	
	McNeil Jr DG. Nigerians receive first payments for children who died in 1996 meningitis drug trial. New York Times, p 4a, 11 August 2011.	

1.3 Uganda, 1997-2001: Trial of Nevirapine to prevent HIV mother-to-child transmission

Study identification		
	Study name:	Effectiveness of AZT and Nevirapine in preventing HIV transmission from Ugandan mothers to their newborns
	US research organization:	Research Triangle Park
	US funders:	NIH, Boehringer Ingelheim
	Study ID number:	NCT00006396
Study synopsis		
	The study recruited 626 pregnant HIV-positive women, then randomized them to two groups to test two treatments to prevent mother-to-child HIV transmission. One group of mothers and their babies received Nevirapine; the other group received a short-course of Zidovudine. The study team reported that a lower percentage of babies in the Nevirapine groups got HIV (8.2% vs 10.4% at birth; and 13.1% vs 25.1% by age 14-16 weeks). From these results, short-course	

	Zidovudine had little or no impact on transmission, while Nevirapine roughly halved mother-to-child HIV transmission through 4 months.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	The study team did not get informed consent from participants about changes in the trial protocol.	DoH 24 CFR 4**6.116**
	The study team did not report serious adverse events	DoH 15 CFR 46.111(a)
Public criticism, investigations, litigation		
	According to SOMO: "In the HIVNET 012 trial, investigators failed to get patients' consent about changes in the experiment and administered wrong doses. There were serious problems in record keeping and delays and underreporting of fatal and life threatening problems. Fourteen deaths were not reported. Researchers acknowledged thousands of side effects and adverse reactions were not disclosed. Procedures for divulging Serious Adverse Events (SAEs) were not followed. Boehringer Ingelheim, the company that markets the drug and audited the trial, asked [NIH] to destroy an early copy of the research report in case the study would be audited by the US Food and Drug Authority (FDA)." Rebecca Project (2011) has also criticized this study.	
References		
	Center for Research on Multinational Corporations (SOMO). SOMO briefing paper on ethics in clinical: #1: Examples of unethical trials, updated February 2008. Amsterdam: SOMO, 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 7 February 2012).	
	ClinicalTrials.gov. Effectiveness of AZT and Nevirapine in preventing HIV transmission from Ugandan mothers to their newborns, last updated 24 September 2008. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00006396 (accessed 8 February 2012).	
	Rebecca Project for Human Rights. Nonconsensual Research in Africa: the Outsource of Tuskegee. Washington DC: Rebecca Project, 2011. Available at: http://www.rebeccaproject.org/images/stories/files/NonConsensualResearch20111120.pdf (accessed 7 February 2012).	
	Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999; 354: 795-802.	
	Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission nof HIV-1 in Kampala, Uganda: an 18-month follow-up of the HIVNET 012 randomised trial. Lancet 2003; 363: 859-868.	
	"Selected documents AP obtained in the investigation of nevirapine's use in Uganda," from AP website, <http://www.honestdoctor.org/documents.html> (Jan 2008).	
	Solomon, "AP Exclusive: Top U.S. officials warned of concerns before AIDS drug sent to Africa," AP, 13 Dec 2004, <http://www.lubbockonline.com/stories/121304/upd_075-4013.shtml> (Jan 2008).	

1.4 Uganda and Zimbabwe, 2004-06: Trial of antiretroviral treatment (ART) structured treatment interruption

Study identification		
	Study name:	Development of Anti-Retroviral Therapy in Africa – a randomized trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa
	US research organization:	[managed from Medical Research Council, United Kingdom]
	US funders:	Rockefeller Foundation; Gilead
	Study ID number:	Trial ID number: ISRCTN13968779

Study synopsis		
	The trial randomized adults to two groups. One group received continuous antiretroviral treatment (ART), while the other received ART with structured treatment interruption: 12 weeks on and 12 weeks off. In some cases, the study reduced time off ART, based on participants' health and CD4 count. The trial began in July 2004. After reviewing data to May 2005, the Data Safety and Monitoring Committee allowed the trial to continue. A second review in March 2006 decided that participants in the treatment interruption group had a greater than 2-fold risk of disease progression (new/recurrent WHO stage 4 or death). This trial paralleled other trials of structured treatment interruption which reached similar conclusions: (a) the SMART trial in the UK, US, and Copenhagen, 2002-06, with clinicaltrials.gov identifier NCT00027352; and (b) the TRIVACAN trial in Cote-d'Ivoire, 2002-07, with clinicaltrials.gov identifier NCT00158405.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	1. Information provided to participants prior to their consenting to join the trial did not adequately detail health risks.	DoH 24 CFR 4**6.116**
	2. Participants randomized to STI were pressured to remain in the trial to access ART.	DoH 9, 22, 24 CFR 46.111(b)
	3. The project did not ensure post-trial access to second- and third-line ART for participants who developed resistance to ART drugs during STI.	DoH 6, 11 CFR 46.111(a)(1)
	4. The trial did not begin with equi-poise; the question was not if STI led to worse health outcomes than continuous ART, but rather how much worse.	DoH 6, 11 CFR 46.111(a)(1)
	5. The trial may have been continued too long after STI was demonstrated to be bad for health.	DoH 6, 11 CFR 46.111(a)(6)
Public criticism, investigations, litigation		
	Trial participants and supporters, including the media in Uganda, and ACT-UP in Paris, raised several ethical issues while the study was on-going. Participants complained that their health was suffering in the STI arm.	
References		
	Centre for Research on Multinational Corporations (SOMO). SOMO briefing papers on ethics in clinical trials: #1: examples of unethical trials, updated February 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 14 December 2011).	
	Danel C, Moh R, Chaix M-L, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. J Infect Dis 2009; 199: 66-76.	
	Danel C, Moh R, Minga A, CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomized trial. Lancet 2006; 367: 1981-1989.	
	DART trial team. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/µl. AIDS 2008; 22: 237-247.	
	Development of Anti-Retroviral Therapy in Africa – a randomized trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa. Available at: http://www.controlled-trials.com/ISRCTN13968779/13968779 (accessed 14 December 2011).	
	Development of Antiretroviral Therapy in Africa. Protocol number 1.2. 24 August 2004. Available at: http://www.actupparis.org/IMG/pdf/DART-PROTOCOL.pdf (accessed 14 December 2011).	
	Kavuma RM. AIDS research kill 50 – angry activists claim. Weekly Observer (Uganda), 8 Jun 2006.	
	The Strategies for Management of Antiretriviral therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. NEJM 2006; 355: 2283-2296.	

1.5 Cameroon, Ghana, and Nigeria, 2004-2006: Trial of pre-exposure prophylaxis (PrEP) to prevent HIV infection among high risk women

Study identification		
	Study name:	Study of Tenofovir disoproxil fumarate (TDF) for prevention of HIV
	US research organization:	Family Health International (FHI)
	US funders:	Gilead, NIH, Bill and Melinda Gates Foundation
	Study ID number:	ClinicalTrials.gov identifier: NCT00122486
Study synopsis		
	This was a phase 2 trial (safety and efficacy) of TDF for HIV prevention among women with multiple sex partners. Recruitment and follow-up went as planned in Ghana; recruitment and follow-up were cut short in Cameroon (by the government) and Nigeria (by FHI) after activists in Cameroon and Paris raised ethical concerns. The study team reported that the intervention (daily oral TDF) reduced HIV incidence by 65%, but because follow-up time was curtailed, the result is not significant (i.e., there is at least a 5% chance it is a statistical error).	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	1. Participant information sheet and informed consent form not available in a relevant language (French)	DoH 24 CFR 4**6.116**
	2. The project did not provide women with female condoms	DoH 6, 11
	3. The project did not ensure post-trial access to the intervention drug.	DoH 14, 33
	4. The project did not arrange antiretroviral treatment for women who contract HIV infections during the trial.	DoH 6, 11
Public criticism, investigations, litigation		
	Non-government organizations (NGOs) in Cameroon (Reseau Ethic Droit et SIDA) and France (ACT-UP) brought four ethical concerns (see table) to FHI, Government of Cameroon, and the media (Yomgne 2009). With the exception of the first issue (documents not in a relevant language), the conditions criticized in the Cameroon portion of the trial have been common in HIV prevention trials in Africa. What was unique in the Cameroon trial was that local and European organizations criticized these conditions.	
References		
	Centre for Research on Multinational Corporations (SOMO). SOMO briefing papers on ethics in clinical trials: #1: examples of unethical trials, updated February 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 14 December 2011).	
	FHI 360. Study of Tenofovir disoproxil fumarate (TDF) for prevention of HIV. Clinicaltrials.gov, 2006. Available at http://clinicaltrials.gov/ct/show/NCT00122486 (accessed 13 December 2011).	
	FHI ends clinical trial of ARV drug Tenofovir. Plus NEWS, 10 Aug 2005.	
	Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, Grant R, et al. Tenofovir disporxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2007: 2: e27. Available at: http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pctr.0020027#s5 (accessed 13 December 2010).	
	The trials of Tenofovir trials. Lancet 2005; 365: 1111. Available at: http://www.thelancet.com/journals/lancet/article/PIIS014067360571850X/fulltext (accessed 13 December 2011).	
	Yomgne CT. The Cameroon experience, pp 19-28 in: Ukpong M, Peterson K. Oral Tenofovir controversy II: voices from the field. Lagos: New HIV Vaccines and Microbicides Society, 2009. Available at: http://www.nhvmas-ng.org/publication/TDF2.pdf (accessed 13 December 2011).	

2. Ethical Issue: Following people at risk without warning them of their risk

Background

In 1988, the US Office for Protection from Research Risks established the policy that "Individuals may not be given the option 'not to know' the result" of their HIV test (US Department of Health and Human Services, Policy on informing those tested about HIV serostatus, available at: http://www.hhs.gov/ohrp/policy/hsdc88jun.html). However, the US government has funded many studies of risks for HIV in Africa, including randomized controlled trials, which did not follow that policy, enrolling participants who did not receive the results of their HIV test. One common defense researchers give for following HIV-positive people who did not know is that they did not want to know. But there is another way to approach the issue: If someone does not want to receive the results of their HIV test, the researcher can refuse to enroll them in the study.

Similarly, US policy is to warn sexual partners of persons known to be HIV-positive that they might be exposed to HIV: "To the extent possible, known partners of a person with HIV infection shall be notified that they may have been exposed to HIV and should be encouraged to be counseled and tested." (See: US Department of Health and Human Services, PHS policy on partner notification, 1990, available at: http://www.hhs.gov/ohrp/policy/hsdc90may.html.) Moreover, US law requires states receiving federal funds for specific health programs to ensure that "a good faith effort be made to notify a spouse of a known HIV-infected patient that such spouse might have been exposed to the human immunodeficiency virus." (See: Department of Health and Human Services, A compilation of the Ryan White CARE Act of 1960, as amended through 1996, available at: http://www.caear.org/downloads/RW_1996_amendments.pdf.)

2.1 Uganda, 1989-ongoing: Study of HIV transmission and HIV-related mortality in a large rural cohort

Study identification		
	Study name:	Rakai Community Cohort Study
	US research organization:	Columbia University, Johns Hopkins University
	US funders:	NIH, Rockefeller Foundation, USAID, John Snow Inc.
	Study ID number:	Current NIH grant number: 5U01AI075115-05
Study synopsis		
	In 1989, the study began to follow an open cohort of more than 1,000 rural adults in Rakai, Uganda. The study expanded to circa 12,000 adults in 50 villages from 1994/95. The study has tested adults (and at times children) for HIV every 10 months to a year. The cohort has been used as the basis for many studies. For adults who wanted to know their HIV status, the project offered HIV tests and counseling; as of 1994, only 10% of participants knew their HIV status; this increased to 80% by 2002 (p 41, Kumwenda, dissertation 2008). In recent years, the study has encouraged people to learn their HIV-status and to share it with their partner (Kairana et al, AIDS Care 2011).	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause

	Not protecting participants (HIV negative partners of HIV-positive men or women): Following HIV discordant couples (only one infected) not aware of their situation to observe spouse-to-spouse HIV transmission. During 1994-98, the project followed 415 discordant couples, recording 90 new infections in formerly HIV-negative spouses (Quinn et al, N Eng J Med 2000). In a large subsample of these couples "56% of HIV-1-positive partners…had requested and received HIV counseling, and 25% stated that they had informed their spouses" (p 1152, Gray et al, Lancet 2001).	DoH 3, 11 CFR 46.111(a)(1)
	Not protecting participants (HIV-negative babies of HIV-positive mothers): Following pregnant and breastfeeding HIV-positive women not aware they are infected and their babies. During 1994-98, the study identified 725 HIV-positive pregnant women. Only 49% of all pregnant women received their test results (Gray et al, Am J Obstet Gynecol 2001). The project followed babies to age 2 years, determining that 16% were infected before or during birth and 16% during a median 20 months of breastfeeding (Brahmbhatt et al, J Acquir Immune Defic Syndr 2006). Prevention of mother-to-child transmission was possible: In 1994, the US Public Health Service recommended Zidovudine to reduce mother-to-child transmission by two-thirds (Lurie and Wolfe, N Eng J Med 1997). Even if this intervention is deemed too difficult for Uganda, the project could have protected infants by warning HIV-positive mothers to avoid breastfeeding after 6 months.	DoH 3, 11 CFR 46.111(a)(1), CFR subpart D: additional protections for children
	Not protecting participants (HIV-positive adults): Following participants who are not aware they are HIV-positive and without offering prophylaxis for opportunistic infections or antiretroviral therapy to record HIV-related sickness and death. During annual home visits, the study team examined and asked participants for symptoms characteristic of opportunistic infections and recorded deaths. During 1994-98, the death rate for HIV-positive adults was 19.8 time greater than for HIV-negative adults. Survival with AIDS was often less than 1 year (Sewankambo et al, AIDS 2000). Not until the President's Emergency Plan for AIDS Relief (PEPFAR) arrived in 2004 did the study arrange antiretroviral treatment (ART) for HIV-positive participants.	DoH 3, CFR 46.111(a)(1)
Public criticism, investigations, litigation		
	In 2000, the editor of the New England Journal of Medicine criticized the study for not warning spouses at risk, noting that "such a study could not have been performed in the United States"(p. 967, Angell, N Eng J Med 2000). Gisselquist criticized the study for following and not warning in a 2008 book and 2009 article (see references, below).	
References		
	Angell M. Investigators' responsibility for human subjects in developing countries. N Eng J Med 2000; 342:967-969.	
	Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquire Immune Defic Syndr 2006; 41: 504-508.	
	Gisselquist D. Points to Consider: responses to HIV/AIDS in Africa, Asia, and the Caribbean. London: Adonis & Abbey, 2008. Also available for free download at: http://sites.google.com/site/davidgisselquist (accessed 7 February 2012).	
	Gisselquist D. Double standards in research ethics, health-care safety, and scientific rigor allowed Africa's HIV/AIDS epidemic disasters. Int J STD AIDS 2009; 20: 839-845.	
	Gray RH, Wabwire-Mangen F, Kigozi G, et al. Randomized trial of presumptive sexually transmitted disease therapy during pregnancy in Rakai, Uganda. Am J Obstet Gynecol 2001; 185: 1209-1217.	
	Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 discordant couples in Rakai, Uganda. Lancet 2001; 357: 1149-1153.	

	Johns Hopkins Bloomberg School of Public Health. Ongoing Current Research Studies. Available at: http://www.jhsph.edu/rakai/research_services/current_research.html#RCCS (accessed 6 February 2012).
	Kairana R, Gray RH, Kiwanuka N et al. Disclosure of HIV results among discordant couples in Rakai, Uganda: a facilitated couple counseling approach. AIDS Care 2011; 22: 1041-1051.
	Kumwenda N. The effect of HIV-1 subtypes on HIV transmission and disease progression in Rakai District, Uganda. PhD dissertation. Case Western Reserve University, 2008. Available at: http://etd.ohiolink.edu/view.cgi/Kiwanuka%20Noah.pdf?case1206989292 (accessed 16 December 2011).
	Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Eng J Med 1997; 337: 853-856.
	Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med 2000; 342: 921-929.
	Sewankambo NK, Gray RH, Ahmad S, et al. Mortality associated with HIV infection in rural Rakai District, Uganda. AIDS 2000, 14: 2391-2400.
	US Department of Health and Human Services. Research Portfolio Online Reporting Tools (RePORT), project information, project number 5U01AI075115-05. Available at: http://projectreporter.nih.gov/project_info_description.cfm?aid=8131726&icde=11293041&ddparam=&ddvalue=&ddsub= (accessed 7 February 2012). See NIH project number: 5U01AI075115-05

2.2 Zimbabwe, 1997-2001: Trial of vitamin A to prevent mother-to-child HIV transmission

Study identification		
	Study name:	Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO)
	US research organization:	Johns Hopkins University
	US funders:	USAID; Bill and Melinda Gates Foundation; Rockefeller Foundation
	Study ID number:	ClinicalTrials.gov identifier: NCT00198718
Study synopsis		
	This randomized controlled trial enrolled 4,495 HIV-positive mothers within 4 days of delivery, and then followed mothers and babies for up to 2 years, observing HIV infections and deaths in the children (Humphrey et al, J Infect Dis 2005). The trial gave mothers and/or babies vitamin A to see if it would reduce mother-to-child HIV transmission. It had no effect. As the study was designed (p 951, Piwocz et al, J Nutr 2005) "Mothers could learn their [HIV test] results at any time during the study..., but they were not required to do so. This feature makes ZVITAMBO unique. All other studies of infant feeding and HIV have been conducted among mothers who knew their HIV status."	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	Not protecting participants (HIV-negative babies of HIV-positive mothers): Mothers were not warned they were HIV-positive and were a threat to infect their children through breastfeeding. Only about 15% of HIV-positive women learned their HIV status during the 2 years of the project. 141 HIV-positive mothers infected their babies, presumably through breastfeeding, between month 6 and month 24 after delivery (Humphrey et al, BMJ 2010). Also: No mothers or babies received antiretrovirals to prevent mother-to-child transmission. Prevention of mother-to-child transmission was possible: In 1994, the US Public Health Service recommended Zidovudine to reduce mother-to-child transmission by two-thirds (Lurie and Wolfe, N Eng J Med 1997).	DoH 3, CFR 46.111(a)(1) CFR subpart D: additional protections for children
Public criticism, investigations, litigation		

	Gisselquist criticized the study for following and not warning in a 2008 book and 2009 article (see references in section 2.1, above).
References	
	Humphrey JH, Iliff PJ, Marinda ET, et al. Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. J Infect Dis 2006; 193: 860-71
	Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. BMJ 2010; 341: c6580.
	Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Eng J Med 1997; 337: 853-856.
	Marinda E, Humphrey JH, Iliff PJ, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. Ped Infect Dis J 2007; 26: 519-26.
	Piwoz EG, Iliff PJ, Tavengwa N, et al. An education and counseling program for preventing breast-feeding-associated HIV transmission in Zimbabwe: design and impact on maternal knowledge and behavior. J Nutr 2005; 135: 950-5.

2.3 Uganda, 2003-07, continuing to 2013: Trials of male circumcision to protect men or women from HIV infection

Study identification		
	Study name:	Two studies are linked: Male Circumcision for HIV Prevention in Rakai, Uganda (NCT00425984); Trial of Male Circumcision: HIV, Sexually Transmitted Disease (STD) and Behavioral Effects in Men, Women and the Community (NCT00124878).
	US research organization:	Johns Hopkins University
	US funders:	NIH (for NCT00425984); Bill and Malinda Gates Foundation (for NCT00124878
	Study ID number:	ClinicalTrials.gov identifiers: NCT00425984, NCT00124878
Study synopsis		
	The study funded by NIH recruited 4,996 HIV-negative men, randomly assigning them to the intervention group (to be circumcised) or to the control group (to remain intact); over two years the study reported men in the circumcised group acquired HIV only 49% as fast as men in the control group. The NIH study refused to recruit men who did not want to hear the results of their HIV test; "willing to hear HIV results" was an inclusion criteria (ClinicalTrials.gov, NCT00425984). The study funded by Gates enrolled men and women, including those who did not want to hear their HIV test results, as follows: (a) 922 HIV-positive men, (b) HIV-negative men who did not want to hear the results of their HIV test; and (c) 3,700 women partners of HIV-positive men in both the NIH and Gates studies. The study randomized HIV-positive men to be circumcised or remain intact, then followed wives to see who got HIV. Wives of circumcised men acquired HIV 49% faster than wives of men who remained intact.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	Not protecting participants (HIV-negative men and women with HIV-positive spouses): Following HIV discordant couples (only one infected) not aware of their situation to observe spouse-to-spouse HIV transmission. In the trial of circumcising men to see if it affected HIV transmission to wives, the study followed 159 HIV-negative wives, of which 25 acquired HIV infection. The trial did not insist that HIV-positive men learn their results and share it with their wives.	DoH 3, CFR 46.111(a)(1)

	In the trial of circumcising men to see if it protected them from HIV infection, the study observed knew the HIV status of several thousand wives, but did not insist that wives accept their test results or share them with their husbands. The study reported 49 HIV infections among men reporting no non-marital relationship, but has not reported the HIV-status of any wives (Gray et al, Lancet 2007).	
Public criticism, investigations, litigation		
	This aspect of the project has not been criticized.	
References		
	Bill and Melinda Gates Foundation. Johns Hopkins University. Available at: http://www.gatesfoundation.org/Grants-2008/Pages/Johns-Hopkins-University-OPP22006_03.aspx (accessed 6 February 2012).	
	Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. Lancet 2007; 369: 657-666.	
	Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomized controlled trial. Lancet 2009; 374: 229-237.	
	Wawer MJ, Tobian AAR, Kigozi G, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomized trial in Rakai, Uganda. Lancet 2011; 377: 209-218.	
	ClinicalTrials.gov. Trial of male circumcision: HIV, sexually transmitted disease (STD) and behavioral effects in men, women and the community, last updated on 9 August 2007. Available at: http://clinicaltrials.gov/show/NCT00124878 (accessed 25 June 2011).	
	ClinicalTrials.gov. Male Circumcision for HIV Prevention in Rakai, Uganda, last updated 23 August 2007. Available at: http://clinicaltrials.gov/ct2/show/NCT00425984?term=NCT00425984&rank=1 (accessed 8 February 2012).	

3. Ethical Issue: Exposing babies to unnecessary risks

3.1 Gambia and Kenya, 2010-2012: Trial of an HIV vaccine in children

Study identification		
	Study name:	The trial can be found under several names: In documents of the European and Developing Countries Clinical Trials Partnership, the trial has a short name, PedVacc, and a long name: Development of an infant vaccine against mother-to-child transmission of HIV-1 through breast milk. In the Pan African Clinical Trials Registry the name for the portion of the trial in Gambia is: Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-uninfected mothers. In the Pan African Clinical Trials Registry the name for the portion of the trial in Kenya is: Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1-infected mothers.
	US research organization:	University of Washington
	US funders:	Bill and Melinda Gates Foundation
	Study ID number:	Kenyan trial: Pan African Clinical Trials Registry, and WHO's Integrated Clinical Trials Registry Platform identifier: PACTR2009010001152787 Gambian trial: Pan African Clinical Trials Registry identifier PACTR2009010001152787
Study synopsis		

	These are Phase 1/2 trials that study vaccine safety and immune response, but are not designed to study its effectiveness in stopping HIV. The stated overall goal of these and proposed future vaccine trials in infants is to develop a vaccine to prevent mother-to-child transmission of HIV through breast milk. The Gambian trial administered vaccine to 24 5-month old healthy infants with HIV-1/2-negative mothers and followed another 24 children in the control group. The trial followed children for 36 weeks, with last follow-up visit scheduled for October 2011 (Afolabi 2011). The Kenyan trial administered vaccine to 5-month old healthy infants with HIV-1-infected mothers and to controls. Each group is projected to include 36 infants (Pan African Clinical Trials Registry. PACTR2009010001152787). Group receiving vaccine and controls were both divided into sub-groups of breastfed and formula-fed children. The trial follows and tests children for a year, and is expected to end in 2012 (Okwemba 2011). The MVA.HIVA vaccine used in these trials is "a component of a more complex future vaccine) in infants" that "has been previously tested in 13 studies in the UK and Africa, involving a total of 375 adult volunteers and is safe and well tolerated" (EDCTP, 2011), but neither this nor any other vaccine has demonstrated effectiveness. As of May 2011, the study in The Gambia is completed while that in Kenya is still in progress (EDCTP 2011). A parallel trial, funded by the Medical Research Council of the UK and European and Developing Countries Clinical Trial Partnership tested the vaccine among children in South Africa.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	Not protecting children: Because a number of studies in Africa have reported that giving mothers ARTs reduces HIV transmission during breastfeeding to approximately 0.2%-0.3% per month, there is little reason to consider that a vaccine would have much impact on children's risk for HIV. None of the vaccines available – based on testing among adults – provide reason to expect that they will protect children from MTCT. HIV vaccine trials have been done on HIV-negative infants in the US, but not in recent years.	DoH 3, CFR 46.111(a)(1) CFR subpart D: additional protections for children
Public criticism, investigations, litigation		
	Rebecca Project (2011) criticized an earlier vaccine trial in Ugandan children.	
References		
	Afolabi M. PedVacc001: Safety and Immunogenicity of a Candidate HIV-1 Vaccine, MVA.HIVA, Administered to Healthy Gambian Infants Born to HIV 1/2 Uninfected Mothers. AIDS Vaccine Conference, Bangkok, 14 September 2011. Available at: http://www.hivvaccineenterprise.org/conference/2011/sites/default/files/OA09.06,%20Afolabi.pdf (accessed 9 February 2012).	
	European and Developing Countries Clinical Trials Partnership (EDCTP). Press release, HIV Vaccine Awareness Day, 18 May 2011: Available at: http://www.edctp.org/Press-release.401+M5e57102d145.0.html (accessed 9 February 2012).	
	European and Developing Countries Clinical Trials Partnership (EDCTP). Project profiles: development of an infant vaccine against mother-to-child transmission of HIV-1 through breastmilk. Available at: http://www.edctp.org/Project-Profiles.245.0.html?&no_cache=1&tx_viprojects_pi1%5baction%5d=show_project&tx_viprojects_pi1%5bid%5d=47 (accessed 9 February 2012).	
	Hanke T. Development of an infant vaccine against mother-to-child transmission of HIV-1 through breastmilk. European and Developing Countries Clinical Trials Partnership, no date. Available at: http://www.edctp.org/uploads/tx_viprojects/Project_Profile_-_CT_HIV_33111_Tomas_Hanke.pdf (accessed 9 February 2012).	
	Okwemba A. Kenya: First Babies Get HIV Vaccination. Daily Nation, 23 April 2011. Available at:	

	http://allafrica.com/stories/201104240003.html (accessed 9 February 2012).
	Pan African Clinical Trials Registry. PACTR200812000090411 6 http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?_nfpb=true&_windowLabel=basicSearch_1_2&basicSearch_1_2_actionOverride=%2Fpageflows%2Ftrial%2FbasicSearch%2FviewTrail&basicSearch_1_2id=90 (accessed 9 February 2012). [This appears to describe the Gambian trial mixed with some information about a South African trial.]
	Pan African Clinical Trials Registry. PACTR2009010001152787. http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?_nfpb=true&_windowLabel=basicSearch_1_2&basicSearch_1_2_actionOverride=%2Fpageflows%2Ftrial%2FbasicSearch%2FviewTrail&basicSearch_1_2id=115 (accessed 9 February 2012). [This appears to describe the Kenyan trial.]
	Plus News, Nairobi. Steady progress in infant AIDS vaccine trials. 27 April 2011. Available at: http://www.plusnews.org/PrintReport.aspx?ReportID=92591 (accessed 9 February 2012).
	WHO, international clinical trials registration platform. Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-uninfected mothers, last refreshed 7 February 2012. Available at: http://apps.who.int/trialsearch/trial.aspx?trialid=PACTR2008120000904116 (accessed 8 February 2012). [This describes a parallel trial funded by UK's MRC and EDCTP, managed UK's MRC, and conducted in South Africa.]
	WHO, international clinical trials registration platform. Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-infected mothers [in Kenya], last updated 7 February 2012. Available at: http://apps.who.int/trialsearch/Trial.aspx?TrialID=PACTR2009010001152787 (accessed 9 February 2012).

4. Ethical Issue: Not reporting and investigating adverse events

Background

To protect research participants anywhere in the world, researchers funded by agencies of the US government that accept the Common Rule (45 CFR 46) as well as their US institutional review boards and US-based managing institutions are legally obligated, to report and investigate "unanticipated problems." An unanticipated problem is a serious adverse that appear to be linked to someone's participation in research. (Office for Human Research Protections, Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events, 15 January 2007, available at: http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm).

4.1 Kenya, 2002-06: Trial of male circumcision to protect men from HIV infection

Study identification		
	Study name:	Male circumcision and HIV rates in Kenya
	US research organization:	University of Illinois, Research Triangle Institute, University of Washington
	US funders:	NIH
	Study ID number:	ClinicalTrials.gov identifier: NCT00059371 International Standard Randomized Controlled Trial Number: ISRCTN47258104
Study synopsis		
	The trial recruited 2,784 men willing to be circumcised, then on a random basis assigned half to an intervention group to be circumcised first, and the other half to a control group to remain intact (uncircumcised) until the end of the study. The study team followed and retested all men – circumcised and intact – at scheduled visits over as long as 2 years. The study reported that men in the intervention (circumcised) group got HIV on 47% as fast as men in the intact (control) group. Overall, 69 men got HIV during the trial.	
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause

	Not protecting participants. The trial reported incident HIV infections in 4 men 1 month after circumcision (tests found no HIV in blood from the baseline survey). Three of the 4 men reported no sexual activity during the month (Bailey et al., 2007). Among circumcised men, HIV incidence at the rate of 3.8% per year during the first month after circumcision (calculated from 4 infections in 1,268 circumcised men) exceeds average annual incidence of less than 1% during the remainder of the trial. Possible paths for HIV transmission during circumcision include contaminated skin-piercing instruments and contaminated multidose vials of local anesthetic.	DoH 3, 11 CFR 46.111(a)(1)
	Not reporting and investigating unanticipated problems: The study's published account of adverse events does not recognize these (reportedly) non-sexual HIV infections shortly after circumcision as adverse events. Based on an exchange of letters between Gisselquist and OHRP in 2009, there is no indication the study team, IRB, research institutions, or OHRP considered these infections to be unanticipated problems to be reported and investigated.	DoH 15 CFR 46.109(e)
Public criticism, investigations, litigation		
	Gisselquist identified HIV infections statistically linked to circumcisions provided by the project as unanticipated problems in a journal article (Gisselquist, Account Research 2009) and in a letter to the Office for Human Research Protections (OHRP). The OHRP responded in a letter denying the infections were unanticipated problems.	
References		
	Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007; 369: 643-656.	
	ClinicalTrials.gov. Male circumcision and HIV rates in Kenya, last updated 28 May 2008. Available at: http://clinicaltrials.gov/ct2/show/NCT00059371?term=NCT00059371&rank=1 (accessed 8 February 2012).	
	Gisselquist D. HIV infections as unanticipated problems during medical research in Africa. Accountability in Research 2009; 16: 199-217.	

4.2 Malawi, 2003-05: Case control study of risks for HIV incidence

Study identification		
	Study name:	Intravaginal treatment of disturbances of vaginal flora among infected and uninfected women in Malawi
	US research organization:	Johns Hopkins University
	US funders:	Bill and Melinda Gates Institute for Population and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, 3m Pharmaceuticals
	Study ID number:	ClinicalTrials.gov identifier: NCT00140764
Study synopsis		
	This case control study of risks for HIV incidence was embedded in a randomized controlled trial of the impact of metrodinazole gel (to treat bacterial vaginosis) on HIV incidence. Use of the gel had no impact on HIV incidence. The study tested women for HIV and collected information on behavioral risks every 3 months. In a review of data from cases (women who acquired HIV infection) and controls (women who remained HIV-negative), the study team noted that use of hormone injections for birth control at the previous quarterly visit was associated with a 10.4 times greater risk to test HIV-positive at the next visit.	
Ethical issues		

	Alleged offenses	Relevant DoH, CFR clause
	Not protecting participants.	DoH 3, CFR 46.111(a)(1)
	No reporting and investigating unanticipated problems, ie, serious adverse events that are statistically linked to participation in the research. The study protocol suggests the project clinic administered some if not all of the hormone injections statistically linked to HIV incidence.	DoH 15 CFR 46.109(e)
Public criticism, investigations, litigation		
	Gisselquist called attention to HIV infections statistically linked to hormone injections as unanticipated problems in a journal article (Gisselquist, Account Research 2009) and in letters to the Office for Human Research Protections (OHRP) and to Johns Hopkins. The OHRP responded in a letter that the project was not under their jurisdiction; Johns Hopkins has not responded.	
References		
	ClinicalTrials.gov. Intravaginal treatment of disturbances of vaginal flora among infected and uninfected women in Malawi, last updated 9 August 2011. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00140764 (accessed 8 February 2012).	
	Gisselquist D. HIV infections as unanticipated problems during medical research in Africa. Accountability in Research 2009; 16: 199-217.	
	Kumwenda NI, Kumwenda J, Kafulafula G, Makanani B, Taulo F, Nkhoma C, Li Q, Taha TE. HIV-1 incidence among women of reproductive age in Malawi. Int J STD AIDS 2008; 339-341.	
	Kumwenda JJ, Makanani B, Taulo F, et al. Natural history and risk factors associated with early and established HIV type 1 infection among reproductive-age women in Malawi. Clin Infect Dis 2008; 46: 1913-1920.	
	Taha TE, Kumwenda NI, Kafulafula G, et al. Intermittent intravaginal antibiotic treatment of bacterial vaginosis in HIV-uninfected and -infected women: a randomized clinical trial. PLoS Clin Trials 2007; 2: e10. Available at: http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pctr.0020010 (accessed 14 December 2010).	

Other References & Articles: HIV/AIDS:

http://aids-freeworld.org/Our-Issues/Womens-Rights/~/media/Files/Womens%20Rights/UN%20gag%20order%20reproductive%20health.pdf

http://www.nytimes.com/2011/10/13/opinion/a-contraceptives-risks.html

http://www.nature.com/nm/journal/v2/n10/abs/nm1096-1084.html

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