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Aun Lor Date

What is Research in Public Health Practice?
Social Construction and Cultural Interpretation of Research and Practice at the Centers for Disease Control and Prevention

By
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Master of Arts, Emory University, 2013

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An abstract of

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

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2014

Abstract

Anthropological theories and methods have been indispensable for understanding how organizational culture influences institutional behavior, policy and decision-making. This dissertation uses anthropological theories and methods to examine how institutional culture and historical events shape the Centers for Disease Control and Prevention (CDC). It focuses on one specific activity within the organization – the process of distinguishing public health *research* from *nonresearch* as the initial critical step in the federally-mandated Human Subjects Protection system. The research/non-research determination process is used as a window into the institutional culture of CDC as it developed in the past two decades. A central question was whether CDC employees share a set of beliefs and behaviors about human subjects protection, research/non-research determination process, and the more complex and time-consuming formal procedures of the Institutional Review Board (IRB). A multi-method data collection strategy included: ethnographic participant-observation, archival study, case studies, interviews, focus group discussions, and an online survey (N=432). The historical development of this cultural pattern is described. The culture of Public Health values the population's interests over individual rights. It therefore tends to define activities as Public Health *practice* rather than *research*. The dissertation describes how this cultural pattern was influenced by sociocultural, political and economic forces through the close examination of Measles and HIV studies, both of which triggered negative public reaction and resulted in the restriction of CDC's project assurance in 1995 and suspension of its international studies in 1997. Findings included: there was no general agreement on how research is distinguished from nonresearch; general familiarity with the regulatory definition of research; agreement among CDC employees that the research determination process and IRB procedures are burdensome; widespread agreement of the difficulty of distinguishing research from practice; and a consensus that, ethical oversight of public health activities should be based on the level of risk to the participants. However, the critical issue is that only a vague definition of "minimal risk" exists as general guidelines for determining risk level. In conclusion, the tensions within the CDC human subjects protection system reflect the same sociocultural, political, and economic forces that define CDC as an institution.

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To
My late mother and my family

Acknowledgements

This journey was longer than I had expected or could have anticipated. I had encountered many obstacles, but there were also many supportive individuals along the way. While they had no obligation to do so, they helped me achieved a personal and professional goal that would not have been possible otherwise. To them I owe more than my gratitude, but I hope that through what I have learned and shared through this experience will partly make up for the times, efforts, and thoughts they have invested in me. I could not have completed this dissertation alone. In no particular order, I want to acknowledge them below.

I knew nothing about anthropology when first learn about the department and the field, but I made instant connection with the people in the department. It was their sense of curiosity and humanity that drew me to the department. Bradd Shore was the first anthropology professor I met during my undergraduate years at Emory. I was sitting on a bench in the Emory Quadrangle and Bradd walked by and sat down on the same bench. For some reason, we started talking, not about any academic topic, but about life in general. I do not recall the exact detail of the conversation, but I did learn that he was a professor in the anthropology department. Meeting Bradd enticed me to take some courses and learn more about anthropology. I became a teaching assistant for several classes, and served as editor of the Emory undergraduate *Anthropology Journal* during my senior year. George Armelagos is a personal hero. George always says, "Let me know how I can help you," and he would follow through should you take him up on his offer. George is the epitome of the generous human spirit. What an amazing human being he is! My dissertation advisor, Peter Brown, is of the same generous spirit, caring and supportive, and would go out of his way to help a student or anyone, and never really questioned why. Peter shared his own personal tragedy, the untimely death of his older brother from HIV/AIDS in the 1990s, as a way to address and fight social stigma, discrimination, and disparity that are still prevalence in the world today. I can personally relate by sharing my own experiences as a survivor of the Cambodian Killing Fields and as a refugee in the early 1980s. Craig Hadley, who served on my committee is nurturing to his students. I felt an instant connection with Craig as I do with Peter, George, and Bradd.

When I was a student at the Rollins School of Public Health, many of my professors were former CDC employees. I was fascinated and inspired by their life work, most of which were accomplished while they were CDC employees. Stan Foster, for example, was a smallpox warrior, who made significant contribution to the global smallpox eradication campaign, as well as in public health in general. He is a personal hero and public health hero to many, not only because of his selfless dedication to public health, but his selfless dedication to his students. I remember when he spent times late one evening listening to me gave a practiced talk on landmine problems in Cambodia. It was the talk that galvanized my landmine advocacy and human rights work as a student and set in motion the health and human rights activities at Emory. It was a small seed that grew and still being nurtured by many people and programs at Emory today. Others such as Bill Foege, Jim Curran, and Phil Brachman, to name a few, had made significant contributions in

public health while working at CDC. My encounters with them have been beneficial to my personal and career endeavors.

I also want to extend my sincere gratitude to many other CDC and Emory colleagues and friends who supported my endeavor. To the late Stephen B. Thacker, who supported my educational and professional development, I hope to continue his commitment to social justice and health disparity through my work in public health. I am saddened that I was not able to complete this dissertation before his untimely passing from Creutzfeldt-Jakob disease. To Robin Ikeda and Carol G. Crawford, it would not have been possible without their support. I wish to express my sincere gratitude to my other CDC and Emory colleagues and friends. They are listed in no particular order: Tanja Popovic, Barbara DeCausey, Natalie Brown, Larry Slutsker, Timothy Holtz, Basia Tomczyk, Bob Spengler, Jordan Tappero, Mark White, Lata Kumar, Alan Hinman, Steve Albert, Goldie MacDonald, Kakoli Roy, Drue Barrett, Kendra Hatfield-Timalchy, Leonard Ortmann, Craig Hales, Glen Abedi, Brian Rha, Mary Wilson, Laura Youngblood, Micah Bass, Wendy Carr, and Marsha Wilson. Due to the nature of the study there are many others whom I did not mention by names, but who made it possible for me to carry out this study. They supported me in various ways, including being tolerance of my presence during meetings and being interviewed and observed. I am in deep gratitude to the United States Public Health Service Long Term Training program.

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Acronyms and Terminologies

45CFR46	Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Service, Part 46, Protection of Human Subjects, also known as the Common Rule.
Accreditation	The recognition of an institution meeting the established or required standards; the process for obtaining such recognition.
ADS	Associate Director for Science – A senior science official responsible for ensuring the scientific and ethical quality of public health activities at any program level.
Assurance of compliance	A written pledge an institution made to OHRP that the institution will comply with federal regulations (45CFR46.103).
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
Commissioned Corps	The Commission Corps (CC) is a uniformed service of the United States Public Health Service. The history of CC dates back over 200 years under the Act for the Relief of Sick and Disabled Seamen under John Adams. (http://www.usphs.gov/aboutus/history.aspx.
CSTE	Council of State and Territorial Epidemiologists
DHHS	U.S. Department of Health and Human Service
DHS	Department of Health Seroprevalence Survey
EIS	Epidemic Intelligence Service
EISC	Excellence in Science Committee
Engagement	An institution is considered engaged in human subjects research when its employees or agents (i) obtain data about living individuals through intervention or interaction for research purposes; or (ii) obtain individually identifiable private information about living individuals for research purposes; or (iii) receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator http://www.hhs.gov/ohrp/policy/engage08.html.
Emergency response	A public health activity undertaken in an urgent or emergency situation, usually because of an identified or suspected imminent health threat to the population, but sometimes because the public or government authorities perceive an imminent threat that demands immediate action. The primary purpose of the activity is to document the existence and magnitude of a public health problem in the community and to implement

	appropriate measures to address the problem (Langmuir, 1980).
Epi-Aid	Request for epidemiologic assistance
Federally-supported	"Pertaining to Federal agencies, provision of funding, identifiable private information, or supplies, products, drug, other tangible support. Does not include mere provision of Federal staff time and assistance absent other forms of financial or material support" (CDC 2010).
FWA	FederalWide Assurance - A mechanism offered by OHRP in accordance with 45 CFR 46.103, whereby institutions promised to comply with the requirements set forth in the Common Rule.
HSA	Human Subjects Activity - what CDC Human Research Protection Office was known before it was changed to HRPO during the 2005 reorganization.
HSC	Human Subjects Contact (aka, Human Subjects Advisor, Human Research Protection Coordinator, Human Subjects Specialist)
HSM	Human Subjects Manager
HSO	Human Subjects Office – A common term used to refer to Human Subjects Activity.
HSR	Human Subjects Review
Human subject	Defined as "A living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information (45CFR46.102f).
IRB	Institutional Review Board
MOH	Ministry of Health
MPA	Multiple Project Assurance – the term and process is now obsolete. It has been replaced by the FederalWide Assurance (FWA).
MWCA	Malaria Control in War Areas – A small unit in the US PHS, which evolved into CDC.
NBAC	National Bioethics Advisory Committee
NCD	Non-communicable disease
NIH	National Institute of Health
NHANES	National Health and Nutrition Survey
NPRM	Notice of Proposed Rule Making
OHRP	Office for Human Research Protection (formerly OPRR)
OPRR	Office for the Protection from Research Risk (now OHRP)
PGO	Procurement and Grant Office
PI	Principle Investigator
PO	Project Officer

PRAMS	Pregnancy Risk Assessment Monitoring System
Program evaluation	A public health monitoring and evaluation activity, often developed as part of an ongoing program, where results will provide feedback to the program for ongoing program improvement.
Surveillance	Ongoing, systematic collection, analysis, and interpretation of outcome-specific data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease or injury (Thacker and Berkelman 1988).
SME	Subject matter expert
Research	Research is defined as "systematic investigation, including development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of 45 CFR parts 46, whether or not they are conducted or supported under a program which is considered research for other purposes."
TSS	The Tuskegee Syphilis Study
UAT	Unlinked anonymous testing
US PHS	United States Public Health Service
WMA	World Medical Association

Preface

"The eight men who are survivors of the syphilis study at Tuskegee are a living link to a time not so very long ago that many Americans would prefer not to remember, but we dare not forget. It was a time when our nation failed to live up to its ideals, when our nation broke the trust with our people that is the very foundation of our democracy. It is not only in remembering that shameful past that we can make amends and repair our nation, but it is in remembering that past that we can build a better present and a better future. And without remembering it, we cannot make amends and we cannot go forward. So today America does remember the hundreds of men used in research without their knowledge and consent. We remember them and their family members. Men who were poor and African American, without resources and with few alternatives, they believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed."

President William J. Clinton (May 16, 1997)

This dissertation was partly inspired by my personal experiences living under the Khmer Rouges Regime in Cambodia from 1975-1979. This period became known as the Cambodian Killing Fields or Genocide (Kiernan 1978), because more than 1.5 million Cambodians were killed, starved, or perished from diseases and malnutrition, including my father, three brothers, and my only sister. Those four torturous years shaped my life and determined my future. They shaped my career, and inevitably, influenced the topic of this dissertation.

I came upon CDC headquarter buildings in 1991 as an undergraduate student at Emory University. My first employment opportunity was taking a work-study job in a basement laboratory in Building 1, a yellowish, five-story brick building, which has since been demolished and replaced with modern, new buildings. Later during my undergraduate years, I conducted malaria parasites research in the old CDC Chamblee laboratory, also demolished. In 1997, I accepted a fellowship position in what was the Epidemiology Program Office (EPO), a program that included the oldest and most prestigious CDC epidemiological training program called the

Epidemic Intelligence Service (EIS). In late 2000, I took a full time position as the first Human Subjects Contact (HSC) in EPO. It was only one year since CDC implemented its 1999 Guidelines for Defining Public Health Research and Public Health Nonresearch. EPO was dissolved during CDC reorganization in 2005 and I have worked in several other programs since.

Many people provided their thoughts and knowledge of the cultural practices at CDC during informal discussions and interviews, but the observations, analyses, interpretations, and conclusions are mine alone. The issues are complex, but I hope that the information presented here will shed some light on a difficult and unexplored topic. I was particularly wary of protecting my informants from any potential consequences that may result from my divulging of the information I gathered from them. My study was not a secret at the agency. Most everyone I encountered on an individual or small group basis knew what I was doing. Many knew each other. They knew what my job was and they understood the importance of the study. Many told me how glad they were that I was conducting this project. Out of personal respect for my colleagues, I felt awkward using pseudonyms. Instead I used a third person format in my narrative.

Chapter 1: Introduction

Research Determination in Public Health: A Problematic Beginning

"Discussions with CDC personnel indicated that the distinction between human subjects research and routine, nonresearch public health practice was poorly understood and inconsistently applied. Overall, it appeared that many CDC personnel lacked a thorough understanding of HHS regulatory requirements for the protection of human subjects."

OPRR Investigation Report (1995: 11)

This dissertation is an ethnography of the human subjects[1] protection policy and cultural practices, including the research determination practice, at the Centers for Disease Control and Prevention (CDC), focusing on the question of "What is research in public health?" Determining what activity constitutes research has been a long standing issue for CDC, ever since it adopted the Department of Health and Human Services (DHHS) Policy for the Protection of Human Subjects (Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Service, Part 46, Protection of Human Subjects, also known as, the Common Rule) in the early 1980s (Santelli 2000). The Common Rule defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (DHHS 2009: §46.102d). This definition is principally based on a socially-constructed definition developed by members of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission), encapsulated in the Belmont Report (Levine 1979). However, the Common Rule provides no guidelines on how this definition should be interpreted, leaving it to the institution, such as

[1] The word "subjects" is generally written in plural term and will be written this way throughout the dissertation including in combination with other terms, such as, "human subjects research."

CDC, to socio-culturally constructed and interpreted the definition on its own. In its effort to interpret the regulatory definition in the late 1990s, CDC had seized on the term "designed," that research must be "designed" to generate generalizable knowledge, and introduced the "primary intent" concept as a cultural model for distinguishing public health research from public health nonresearch (practice). For CDC if the "primary intent" or "purpose" of an activity is to develop or contribute to generalizable knowledge, then the activity is research, but this approach to interpreting the regulatory definition has invited criticisms and controversies, both within and outside of CDC.

In public health, determining whether a project is research, known at the CDC as *research determination*, is a critical step in the human subjects protection process. Once a project is determined to be non-exempt[2] human subjects research it has to be reviewed and approved by an institutional review board (IRB) that provides ongoing ethical oversight of the research (McCarthy 1984). However, how research is defined and the criteria and process for distinguishing research from nonresearch have yet to be explored in-depth in anthropology or in any other field, including public health. A literature search was conducted in JSTOR, Google, Yahoo, Google Scholar, and in publication databases such as PubMed with the following terms, "research determination," "human subjects research determination," "what is research," and "defining research."

[2] Criteria for IRB exemptions are described in Chapter 3.

Literature Review

Many studies (Feldman 2009, Gray 1978, Emanuel 2004, Guillemin 2012, Wichman 2006, Silberman 2011, McCormack 2012) have been published on how an institutional review board (IRB)[3] works, including international ethics review committee (ERC)[4] (Mamotte 2009; Bartlett 2008), but lack in-depth exploration of the history, criteria and processes for distinguishing the differences between research and nonresearch.[5] Research determination presents operational challenges for CDC and its partners. Santelli and colleagues (2000) identify the needs for CDC to better separate the differences between public health research and nonresearch and the need to develop an approach for protecting individual rights in nonresearch activities.

An article by Wedeen, a physician working with the Department of Veteran Affairs at the time, in the *Archives of Environmental Health*, describes the problem of distinguishing research from nonresearch and criticized CDC's approach as one that was developed more for "organizational convenience, rather than to protect human rights" (2000: 231). "The distinction between practice and research is unclear in public health," according to Wedeen, "because investigators do not undertake data collection and evaluation to primarily benefit the individual. Public health activities are intended for the benefit of the populations" (2000: 231). Although Weeden offers no better suggestion on how public health research and nonresearch should be defined, he raises many important points that will be discussed in this

[3] Throughout this dissertation, when I talk about IRB, I am referring to IRB in general and not specifically to CDC IRB.
[4] IRB is internationally known as ethics review committee or ERC in many countries.
[5] The term "nonresearch" is written without the hyphen (-) in CDC policies and guidelines.

dissertation, including how research has been defined and the determination practice at CDC.[6] In 2002 Wedeen published a more scathing commentary in the *American Journal of Public Health* (AJPH) critical of the approach public health has taken in defining research and public health activities. Wedeen points to the fundamental problem of protecting individual's privacy and confidentiality in nonresearch public health activities and argues that because a public health activity is not "designed to develop generalizable knowledge", meaning that they are categorized as nonresearch, "does not abrogate the obligation of the public health community to protect privacy" (2002: 1884). Although this second commentary does not specifically mention CDC, according to some CDC colleagues, this was a direct criticism of the approach the agency had taken to defining research following the restriction of its multiple project assurance (MPA) in 1995 (OPRR 1995).[7] Assurance, in human subjects protection, is essentially a promise an institution makes to the Office for the Protection from Research Risk (OPRR), renamed the Office for Human Research Protection (OHRP), that their investigators abide by a commonly accepted ethical guideline or principle, such as the Common Rule or other internationally accepted ethical principles, e.g., the World Medical Association Declaration of Helsinki (WMA 2013). Wedeen (2002) suggests that an IRB should have oversight of all public health activities whether they are research or nonresearch. Many at CDC and in public health in general have argued that this is

[6] The reason why I used the term "processes" is because CDC comprises of many different centers, and each center has a slightly different research determination process.
[7] CDC uses "primary intent" of an activity as the distinguishing criteria for demarcating research and nonresearch in its 1999 Guidelines for Defining Public Health Research and Public Health Nonresearch.

not only impractical, but unnecessary for most public health activities.

The late Jonathan Mann (1997) had similar concerns and in the early 1990s proposed a human rights framework for public health, but Mann never suggested that ethical oversight of public health activities should fall under the IRB microscope. Mann suggested that "inadvertent discrimination is so prevalent that all public health policies and programs should be considered discriminatory until proven otherwise, placing the burden on public health to affirm and ensure its respect for human rights" (1997: 9). The "burden of proof" is on the public health practitioners to prove[8] that their activities are not harming individual's and community's rights.

No one I encountered at CDC has argued that the answer to protecting individual privacy, confidentiality, and rights in general must always lie with the IRB. The generally accepted belief among researchers at CDC is that administrative delays from IRB and other bureaucratic review processes can result in opportunity costs that could lead to loss of lives, although this assumption has not been investigated. This belief has deep historical roots at CDC, which I discuss in Chapter 2. According to Lisa M. Rasmussen, a professor in the Department of Philosophy at the University of North Carolina, Charlotte:

> The observed faults of IRBs have been well summarized and include inconsistency, delay, grammatical pedantry, excessive conservatism regarding legal risk, ignorance of fields reviewed, and threats to academic freedom. Minimal-risk research is a particular area of controversy because the bureaucratic burden of human subjects research oversight seems severely disproportional to the potential risks of harm to research

[8] Mann never says who public health practitioners should prove to, but I take it that, because a human rights framework should be part of public health program planning, that they must determine for themselves that their activities are not harming individuals' and community's rights.

> participants, as well as to the effort required to conduct the research itself (2009:11).

For public health activities where the level of risk to participants is low, the risk to benefit ratio is often in favor of the participants in public health activities. The risks posed by researchers are usually low or minimal, while the risk of dying from diseases or a health problem is often significantly higher. Wedeen agrees stating:

> It is generally agreed that the public's interest outweighs the individual's rights to privacy in the presence of imminent, life-threatening emergencies. Determination of the magnitude and source of the threat cannot await the niceties of confidentiality or IRB review (2000: 237).

This does not, however, exempt public health nonresearch from ethical requirements or oversight, but ethical oversight does not necessarily need to be or have to be with the IRB. A possible alternative or complementary approach being developed at CDC is the voluntary submission of study protocols through the public health ethics consultation process. This process is coordinated by the CDC Public Health Ethics Committee (PHEC). However, ultimately it is the responsibility of the investigator and program to accept or to decline recommendations from the consultation, and to ensure that risks are minimized and individual and community's rights are protected. Other strategies may include better trainings in ethics and human rights for investigators. Wedeen (2000) argues that whenever new data are collected from human subjects, there must always be consent. Many CDC informants I encountered expressed the same sentiment. Many have argued that whether a project is defined as "research" is irrelevant in human subjects protection. During a discussion about the history of research determination at CDC, a former Human Subjects Manager (HSM) said:

> One of my fundamental opinion there and throughout the whole discussion, which remains unsatisfied by everything I have seen, is a thoughtful treatment of why the distinction matters at all, ethically. Almost every discussion I have seen began with the premise that the distinction matters and given that the distinction matters, how do we articulate it and act on what has been decided from having articulated it. Even the Belmont Report, doesn't go, I meant it's a very brief document, I can't really discredit it, but it doesn't really go into why the distinction is important, just declare the distinction between research and practice in the Belmont Report itself focuses exclusively on biomedical practices, is relevant, and sort of resolve from there as well.

Many argued that the level of oversight should be based on the level of risk, although there are no guidelines on how risk levels should be determined. Only the regulatory definition of minimal risk is currently available in assessing risks. "Minimal risk" is defined as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of health persons" (DHHS, 45CFR46.303d). Consent is always a major consideration if not a requirement whenever human participants are involved, but CDC investigators often see IRB as part of the problem, rather than a solution. IRB members do not always have the ability or expertise to properly evaluate a study, particularly for studies in other countries, and especially for social and behavior research.

A former CDC colleague who gave a seminar at CDC believes that the IRB was constituted to ensure that minimal ethical standards are in place, which in essence is set up to protect the institution from accusation of misconduct. However, the activities and conduct in the field are generally out of sight of the IRB that ultimately limits the protections an IRB can provide to participants. People at CDC often talked about "doing things right" and "doing the right things." Regulatory compliance, no

matter what the intended consequences, is "doing things right," but it may not always means "doing the right thing." In these situations how the ethical activities are carried out by the investigators are paramount.[9]

Problems with IRBs

Scholars and researchers have argued that the IRB has been problematic if not a broken system (Annas, 2006; Fassin, 2006; Glickman et al, 2009; Marshall, 2003). Annas suggests that IRBs are the "product of institutions" and were developed to protect the institutions and researchers rather than human subjects in the research (2006: 542). Beauchamp believes that IRBs have inherent conflict of interest:

> The ethical review of research protocols is generally performed within and by employees of the very institutions in which the research will be carried out. This problem of conflict of interest is a cornerstone of the system of research review, and this system of review clearly does not always function to protect the best interests of research subjects (2011: 383).

Human Subjects Contacts (HSC) at CDC, consisting of approximately 20 individuals at any given point in time, have been delegated the authority to make research determination. They also have conflicting feelings about where their responsibilities lie, whether to protect the investigators and institution or to protect participants in public health activities?[10] Investigators often contribute to this dilemma by their

[9] IRB approval for nonexempt research is for one year and exemption approval granted by CDC Human Research Protection office is for three years. Site visits and follow ups, other than annual continuation for nonexempt research, are not routinely conducted unless major problem arises.

[10] Centers' Human Subjects Contacts (HSC) and Associate Directors for Science (ADS) are the two main groups of individuals having been authorized by CDC to make research determination and provide ethical oversight of public health activities for their centers. Their duties also include

preferences for obtaining a nonresearch determination and avoiding the CDC IRB, because of their perceptions of the burden they might face and their perceived harm to the study population caused by the delay in implementation.

Social scientists in general often encountered problems when submitting research for IRB review, because IRBs were developed within the biomedical context, where research interventions pose physical risks to human subjects. Annas even suggests that, because IRB is dysfunctional as an oversight system, particularly for socio-behavioral research, that anthropologists should find "another way out" (2006: 542). The general debate among scholars, ethicists, and public health practitioners has essentially led to the same conclusion, that the procedural burdens placed by the IRB on relatively low risk research detract attention from the greater socio-structural problems that placed individuals at higher risk of ill-health and death (Petryna 2005, Lederman 2007).

Controversy over CDC's Interpretation

In 2004, Wedeen wrote yet another commentary in response to an article written by two former CDC employees (MacQueen and Buehler 2004) that discusses the CDC's approach in defining public health research that is based on the "primary intent" of the activity. Again, Wedeen reiterates his earlier assertion that such an approach to defining research is more "to defend traditional public health practices and for organizational convenience, rather than to protect human rights" (2004:

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providing guidelines to investigators about how best to navigate the human subjects protection system.

1841). Wedeen's suspicion is understandable, because it is difficult to assess investigator's intent (Casarett 2000). Wedeen sees this approach as arbitrary arguing that "attempts to evade the protection of federal regulations in the belief that the ends justify the means are worrisome" (2004:1841). Ivor Pritchard, who works at OHRP in the Department of Health and Human Services (DHHS), supports CDC's interpretation, but finds flaws in the rationale:

> The problem with this position is that it separates the intention[11] to develop generalizable knowledge, and arbitrarily assigns priority to the former. This separation flies in the face of the reality that a considerable number of research activities derive their focus from the researcher's interest in solving some practical problem. Indeed, the argument has been made that the most successful research activities have been driven by a combination of scientific and public benefit interests" (2001:12).

For Wedeen even "intent to publish" is a sufficient criterion for putting a public health activity under the IRB microscope (2004: 1841). However, if intention to publish alone defines an activity as research, then CDC would certainly be considered a "research" agency as opposed to a "practice" agency. CDC encourages its investigators to publish important lessons-learned from all of its activities, whether research or nonresearch. External criticisms and commentaries such as those by Wedeen and ongoing discussion with OHRP contributed to debates within the agency and caused CDC to revisit its own 1999 Guidelines for Defining Public Health Research and Public Health Nonresearch (1999 Guidelines), not necessarily because CDC saw anything wrong with the guidelines, but to see how it can be improved and as a way to respond to external concerns.

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[11] Pritchard may be interpreting CDC's concept of "primary intent" as investigator's intent. Although that may be true, because investigator develop the project objectives, it is generally broader. Intent is generally driven by the nature of the public health activity at hand.

In 2001, the Council of State and Territorial Epidemiologists (CSTE) recognized this inherent difficulty when it commissioned a report for making distinctions between public health research and practice (Hodge and Gostin 2004).[12] The report does not provide ethnographic details about the practice at CDC, but it does, however, describe some of the principles behind CDC's rationales, which Wedeen has criticized. The report also offers a framework for states and other public health organizations in making distinctions between research and practice. Hodge and Gostin (2004: 15) proposes the following definition of public health research, "The collection and analysis of identifiable health data by a public health authority for the purpose of generating knowledge that will primarily benefit those beyond the participating community who bear the risks of participation."

A framework like CDC's own 1999 guidelines, which were later revised and became an official CDC policy in 2010, does not guarantee that a "correct" determination will be made by following such guidelines, nor does it translate into consistency in practice. As I discuss in subsequent chapters, there are many grey areas, starting with the regulatory definition.

CDC Culture and Practices

In collecting data for this dissertation I did not set out to evaluate a CDC public health program in a particular country in order to determine why the program may have failed to achieve its public health objectives. I did not set out to identify what role(s) local or CDC culture may have played in a program failure. In

[12] I was interviewed by Hodge in 2002 and later provided critical review of the report.

my case it was not about blaming culture or people's understanding of culture. Instead it was a way to explore for the issue of why CDC had not been able to develop a policy and interpretation of the regulatory definition of research that is less confusing for its scientists and partners. The goal of this study was not to identify and place blame on individuals, groups, or programs, or even the cultural practices as the possible reasons for CDC's own failure to develop a policy that everyone can understand or agree on, but to examine the practices in of themselves as a part of the larger CDC culture that evolved as a result of its particular history. The study is more about describing the CDC research determination practice as part of the larger CDC culture. The goals of this dissertation are:

- To understanding how this research determination practice came to be;
- To describe the roles of CDC investigators and programs and how individuals were constrained by regulatory and policy requirements;
- To under how individuals navigated and negotiated the research determination process, and lastly,
- Why individuals resisted against the higher authority within the approval chain.

CDC investigators and staff have always complained about the lack of clarity in the regulatory definition of research and in CDC policy since it was implemented in 1999, but the complaints appeared to have more to do with the procedural burdens and delays created by the confusion. Although both the Common Rule and CDC policy were meant to provide some flexibility, flexibility came at the price of reduced clarity.

The confusion can be found even among HSCs. During one of my first interviews for this study, I asked a center HSC, "How do you define research?" Her response was:

> Well, I don't know if the line is crystal clear there, because as we were sending stuff over to CDC OD, CDC OD says that we are not engaged in research. I guess the definition that we see all the time was "systematic methods and generalizable use" and over time the focus is generalizable. A lot of time it's what people say makes it not research, saying it's not generalizable.

It appears that for this HSC, generalizability is the key term in defining, but as we will discuss, the issue is much more complex. CDC staff has a need for clarity because they see it as a way to reduce the delays to implementing their projects.

Summary of the Research Determination Practice at CDC

According to Batteau, "Positions and relationships of command are culturally structured, and the lines of authority on an organizational chart are simply the truce demarcation from an earlier round of culture wars" (2001: 726). The research determination practice was defined after the culture clash CDC had with OPRR in the 1990s. The culture clash resulted in the development of the 1999 Guidelines, which evolved into the 2010 Policy on Distinguishing Public Health Research and Public Health Nonresearch (2010 Policy). Both of these documents state, "All CDC activities must be reviewed to determine whether they are research involving human participants" (CDC 1999: 3; CDC 2010: 2). The current determination processes at most CDC centers are typically bureaucratic, beginning with the submission of a project description or protocol by the CDC Principal Investigator (PI)[13] to his or her immediate supervisor for review and approval. After approval,

[13] The CDC PI is not always the study's main PI. Often CDC investigators are invited to join a study initiated by external partners. The designation of a CDC PI is used mostly for the purposes of the

the supervisor submits the project to the branch chief. If it is a project being developed by a CDC PI at a CDC country office, he or she submits it to the country director or designee for review and approval. The branch chief or country director submits the request to the Division Associate Director for Science (ADS) for Division approval. The division ADS or designee provides subject matters expert (SME) review for the project then submits it for final research determination[14] to the Center's Human Subjects Office (HSO) within the Center's Office of the Associate Director for Science (OADS) (Figure 1). There are of course, variations and exceptions to this usual process, e.g., some divisions send protocols to a standing committee set up for SME review.

In summary the research determination process follows this linear pathway: Investigator → Supervisor → Branch Chief/Country Director →Division ADS → Center Human Subjects Office.

Different Centers may have different categories and/or sub-categories that a project can be designated. Typically the main categories a project may be determined are the following:

I. Not human subjects research;
II. Research, but not human subjects;
III. Human subjects research, but CDC not engaged;
IV. Human subjects research, CDC engaged.

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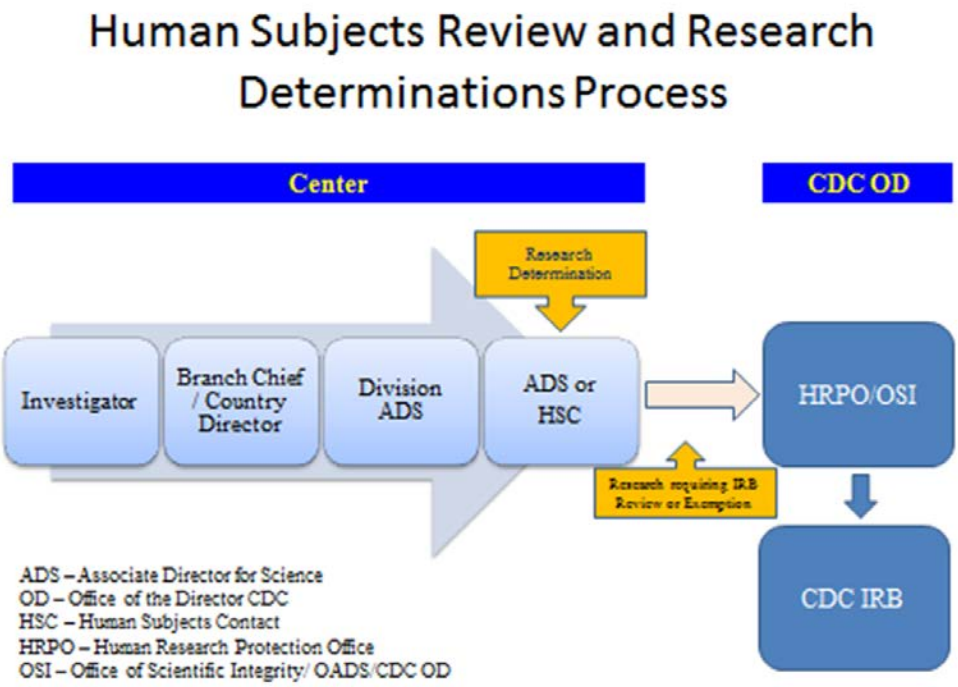
bureaucratic process for communication and protocol tracking. Other CDC investigators are typically listed on the study protocol if the study is not an existing study.

[14] Final research determination is typically made at the center level, although CDC policy does not discuss whether it can be delegated further down the bureaucratic chain.

Figure 1: Human Subjects Review and Research Determination Process



Under each category, Centers usually have sub-categories. For examples, under category I above, the subcategories usually are: outbreak investigation, routine surveillance, program evaluation, laboratory proficiency evaluation, and public health program activity. Category II encompasses subcategories such as animal research, research using de-identified, existing data or specimens, research about deceased persons, and research involving data about health facilities or other units and not about persons. Category III encompasses research where CDC investigators do not interact with study participants, have access to identifiable or linked data/specimens, or in case where a nondisclosure agreement is signed prohibiting the release of identifying code to CDC. Category IV is when CDC is

engaged in non-exempt human subjects research that must be sent to CDC IRB for approval.

Requests are usually submitted via emails, although some Centers, Divisions, and Branches have their own submission and tracking systems. Currently, there is no CDC-wide system for research determination, although efforts are underway to develop such a system.[15] Having multiple processes for research determination certainly contribute to inconsistency in practice.

Theoretical Orientation and Position

This dissertation examines CDC human subjects protection and research determination practice through a cultural lens. Why cultural? Other discipline including public health typically uses quantitative method usually employing one-time survey or interview to evaluate a program. Although this approach can provide a snapshot of the current practice, it does not provide an understanding of how "things got to where they are" and it does not provide an understanding of how individuals and groups act and how they contribute to the evolving practice. A cultural approach permits us to evaluate the underlying factors surrounding a particular action, e.g. individual drives, motivations, reasoning, that govern actions (Hamada 1989). As Batteau put it, culture is not simply "the way we do things around here" (2001: 726). Culture has been defined in many different ways. Geertz views culture as Max Weber had that "man is an animal suspended in webs of significance he himself has spun," and culture composed of those "webs" (1973: 5).

[15] CDC is currently developing a CDC-wide electronic submission system through a process called the Science, Service, and Support (S3P) project. S3P is briefly described in Chapter 6.

Further, Geertz believes that the study of culture cannot be an "experimental science in search of law but an interpretive one in search of meaning" (Ibid). Tyler describes culture as "that complex whole which includes knowledge, belief, art, morals, law, custom, and any other capabilities and habits acquired by man as a member of society" (1873: 29). For the purpose of this dissertation, my sense of culture is as Batteau described, ". . . culture is that which is cultivated, the stories, myths, symbols, rituals, and stylized actions and interpretations the group uses to make sense of what they are doing, what they have done, and what they should do" (2001: 727).

My views, like those of Singer (1994) and Batteau (2001), are drawn on many years of experiences working for the organizations we studied. Singer in his study of the Hispanic Health Council's organizational culture worked with the organization for eight years and Batteau had seven years of experiences working in the corporate world as engineer, salesman, and software developer. Like those of Singer and Batteau, my own views may be [tainted] by my position and interests at CDC. I consider myself to be a dedicated CDC employee, as Singer was an employee of the Hispanic Health Council. I felt obligated to generate results that would be useful for CDC. In this sense, my initial instinct was to take an applied anthropological approach as promoted by contemporary medical anthropologists (Sargent and Johnson 1996, Brown 1998, and Hahn 1999).

The debate over whether applied research can be effective has been ongoing in social science. Shipman raised many relevant questions in a 1968 article asking readers:

> Can research efforts be effective unless they are independent undertakings; independent, that is, of influences manifest or latent likely to contaminate the rigor and objectivity of the research? Can any research be accepted as valid unless the researchers are free to pursue their inquiries as fully independent, professionally responsible, intellectual entrepreneurs? Can a service program committed to action objectives be intimately linked with a research program dealing with the same general set of problems without producing incompatibilities likely to eliminate the reality of the research component? (1968: 556)

Evans-Pritchard did not see any problem with applying knowledge obtained to help resolve administrative problems. In fact he believes that applied and pure research to be complementary (Evans-Pritchard 1946). Medical anthropologists in general feel that their studies should benefit the people and community they work in and that findings should be useful to stakeholders involved whether in shaping health policy, developing intervention, or improving practices (Sargent and Johnson, 1996). My observations and analyses may tend to focus more on the critical side, but my intention was to be constructive and to provide useful information and insights into improving the system.

The research determination culture that was created in the midst of a crisis at CDC was already being implemented (described in Chapter 2). As Batteau explains, the "Positions and relationships of command are culturally structured, and the lines of authority on an organizational chart are simply the truce demarcation from an earlier round of culture wars" (2001: 726). The cultural boundaries have already been determined, and I joined as a new actor at the latter stage of scene one. The main functions of a HSC are to guide CDC scientists in protocol development, research ethics, and to make research determination. From 2000 to 2007 I collected considerable amount of data, reviewed thousands of protocols, provided

consultations and guidelines to hundreds of investigators, and observed and encountered many people from investigators, supervisors, ADS, and other CDC employees as they negotiated, adapted, conformed, commanded, and resisted the regulatory requirements, policies, and cultures.

The notion that science and research can be objective, value-free endeavors has been an ongoing debate by both anthropologists and non-anthropologists (Shipman 1968, Proctor 1991). In ethnography it is the researcher that attempts to walk in the shoes of the subjects in order to understand firsthand what is going on in the lives and minds of the people being studied, but each pair of shoes are also worn by individuals with different perspectives and experiences, which may or may not accurately reflect the organizational culture. In my opinion there is no single scientific endeavor where the researcher does not bring their bias. We already show our own bias by the fact that we select a particular topic and population we want to study. I know also that long after I leave my professional career at CDC, some aspects of the cultural practices will remain the same as I practice them. My contribution as an actor on the CDC stage will in some little way contribute to the current or future culture, but this is part of the natural order of cultural evolution.

In examining the contexts in which CDC human subjects protection and research determination processes were developed, it is important to consider its historical roots that were linked to its political economic environment (See Chapter 2). The decision by the US Public Health Service (PHS) to locate CDC in the south was influenced by the politics in Washington, wartime policy, malaria, and office space shortages among other factors. The political economic limitations that the

agency faced also contributed to shaping the current policies and cultural practices. The history, politics, regulations, policies, and institutional cultures were, as Farmer (1997) put it, part of the structural forces that inevitably had impact on CDC. Wedel, in discussing the anthropology of public policy, states:

> Its focus instead is simultaneously wider and narrower: wider insofar as its aim is to explore how the state (or to be more exact, those policy makers and professionals who are authorized to act in the state's name) relates to local populations; and narrower to the extent that its ethnographic focus tends to privilege the goal of understanding how state policies and government processes are experienced and interpreted by people at the local level, keeping in mind that anthropologists are recasting the "local" or the "community" to capture changing realities. . . An anthropology of policy, however, is equally interested in understanding the cultures and worldviews of those policy professionals and decision makers who seek to implement and maintain their particular vision of the world through their policies and decisions. From an anthropological perspective, what happens in the executive boardroom, the cabinet meeting, or the shareholders' annual general meeting is no less important than that which occurs at the level of the factory floor or locality. Thus, an anthropological approach to the study of policy incorporates the full realm of processes and relations involved in the production of policy: from the policy makers and their strategic initiatives to the locals who invariably shape and mediate policy while translating and implementing it into action (2005: 34).

The anthropology of public policy can be said to go back even further to the founding days of colonial anthropology, but it is not simply concerned with describing local cultures to the people in power. It is not simply about the western hegemonic influences on indigenous groups or developing countries. This dissertation examines the political and historical roots (see Chapter 2) that shaped human subjects protection policy at the national level (Chapter 3) to its implementation and interpretation at a local institutional level (Chapter 4 and 5).

Design and Methods

This dissertation uses a holistic lens to provide an epistemological and heuristic understanding of the history, sociopolitical, and economics factors that influenced CDC cultural practices related to research determination. The study focuses on the issues surrounding the historical events leading to the development of CDC human subjects protection practices, the interpretation of regulatory definition of research, and the research determination processes.

Design

A multi-methods approach using both qualitative and quantitative methods was used to collect data. Results from the quantitative data are dispersed throughout the dissertation, as supporting data, in chapters 3, 4, and 5.[16] The study was conducted in two phases. Phase I was mostly qualitative, with activities using informal interview and discussions, focus groups, observation of meetings, participant-observation, and archival study conducted to understand the cultural, historical, and political contexts that shaped CDC policies, human subjects protection and ethical practices. Phase I informed the semi-formal interviews and survey questionnaires in Phase II. Data collection occurred over a 20 month period from January 2012 to August 2013, however, my personal experiences on the issue expand over a period of more than a decade. An agency-wide survey consisted of 41 questions was implemented at CDC in July 2012 via Survey Monkey. The case

[16] For the dissertation I focus on the qualitative part of the study. I will write another report for CDC from a public health perspective focusing more on the quantitative data, and incorporating public health ethics in the report.

studies in Chapter 5 were collected and followed up and informal discussions occurred throughout the study period. Cases in Chapter 5 were selected based on the most common public health activities at CDC – outbreak investigation, program evaluation, and public health surveillance. For the most part, these activities have been traditionally viewed as nonresearch at CDC. Other historical cases, such as HIV seroprevalence study, EZ measles, and AZT study, are described in chapters 2 and 3.

Setting and Study populations

Although CDC employees are stationed throughout the United States (US) and the world, most of the nearly 15,000 personnel work at several locations in Atlanta, Georgia. The main facilities are at the Clifton Road campus (aka Roybal Campus) next to Emory University and the Chamblee campus located on Buford Highway in Chamblee, Georgia. At the time CDC was found in 1946 (see Chapter 2) malaria was still a problem in the South, which defined its early mission and determined the types of people who would join the organization.

In her book about the history of CDC, Etheridge describes CDC original buildings as "unprepossessing," quite different from the mini-metropolis that it is today (1992: xv). There was no fence surrounding the Clifton Road complex, which consisted of several buildings, most of which are no longer standing, and replaced with new buildings that were built after the Terrorist Attacks on September 11, 2001 and anthrax attack of October 2001. Entering the buildings and visiting CDC employees was a relatively simple process and anyone could drive within the building complex without being checked. It was a reflection of an open atmosphere

of CDC at the time. Everything changed after September 11, 2001. In the aftermath of the terrorist attacks, CDC received congressional appropriation to upgrade its facilities and security. New security fences were built around CDC main complexes, security guards were armed, and security cameras installed. A small human made stream runs through the center of the Clifton campus into a small lake where each spring a family of ducks made it their home. The center of the contemporary campus provides a park-like atmosphere, giving CDC employees a place to get away from the more hectic environments inside the gleaming glass buildings where public health decisions are made. Getting inside CDC buildings now requires going through airport level security clearance.

CDC has a diverse workforce with professionals now working in 173 occupational series. CDC workforce composed of 61% woman, 7% disabled, and minorities make up 37% (State of CDC Report 2008). Over 80% of CDC employees have at least a bachelor degree, with more than 50% having advanced degrees. CDC as a whole is the object of this ethnographic inquiry; however, the focus on human subjects protection and research determination means the roughly 20 HSCs, 20 ADSs, and many scientists were my main informants. The focus of these sub-groups is to elucidate their individual and group perceptions of their duties and responsibilities and the structural and power relations in the research determination process. The relationships of these sub-groups to other CDC entities and structures were also examined to understand the social, political, and structural constraints of their personal agency.

Participant-observation

Chilungu (1976) argues that native researchers, if trained in research methods, would be better people to describe their own culture than outside researchers. One of the first things a graduate student does, often as part of their degree requirements, before going out to study a new culture is to learn the language. Language is an introduction to a new culture which allows for uncovering the underlying assumptions about the culture. As a long time CDC employee I am fluent in the CDC language. According to Chilungu (1976) there is no evidence that the biases inherent in a native researcher present anymore obstacle to good research than the biases inherent in a non-native researcher. According to Chilungu, "Choosing to study foreign cultures has meant that one could write about them with very little care as to accuracy of observation and choice of words" (1976: 548). On the other hand native researchers must take care to ensure that their observation is accurately reflected in the culture they are enculturated into.

I may be considered a native researcher, because I have worked at CDC for over 15 years and in different capacities. This study benefits from my own experiences and understanding from the many years working in the field. I understand the people, culture, and practices, because I am one of them, subjected to the same structural, cultural, and political forces. On the other hand, I have always considered myself an observer. My own initiatives and participation in activities at the agency may have influenced some of the policy and decision-making processes either before or during the research process, and hopefully after. That is an inherent part of ethnography -- our very presence can alter the environment that we study.

Many postmodern anthropologists such as Scheper-Hughes (1995) believe that it is an ethical responsibility that our research benefits the subjects of our study.

Participant-observation data were collected during daily work activities during January 2012 to July 2013. Notes were taken in Microsoft Word and electronic documents were saved on a thumb drive. When the opportunity came up for individualized conversation, I engaged people about the study, asking them specific questions related to their perception and understanding of the definition of research and process. Participant-observations took place at various CDC locations throughout the study period. Anonymous notes were taken and documents obtained of important and relevant issues that may be discussed during meetings, conference calls, seminars, informal conversations, consultations, and daily work activities.

Interviews and Survey

In-depth, semi-structured and informal interviews and discussions, some on an ongoing basis, with approximately 100 informants[17] were conducted among HSCs, ADSs, investigators, and other CDC staff. HSCs and ADSs are the two groups of individuals, typically scientists, at CDC who make formal research determination. Questions (Appendix A) about individual's knowledge, beliefs, and practice, were used as a general guide, but most interviews were driven by the job position and roles of the individuals I interviewed. Most of the interviews were unique to the individuals and ended up not following any specific format. Interviews were not standardized across individuals. Interview times may be as short as five minutes to

[17] In reality, I encountered and discussed with many more individuals and I cannot provide a specific number, because any number would not be accurate. They all informed this dissertation write up.

almost two hours in some cases, and on an ongoing base with other individuals. The 41-question survey (Appendix B) were related to issues surrounding the definition of research, interpretation of CDC policies and guidelines, ethical principles, perceptions of human subjects practices, and issues of institutional engagement.

Recruitment

Individuals for interviews were recruited by emails and personal contact through during daily encounters. An announcement of the survey was distributed to approximately 4000-5000[18] CDC employees, including locally employed staff in foreign countries, resulting in approximately 432 responses (~10% response rate). The announcement included a link to the survey on Survey Monkey where participants could complete it anonymously. Announcements for the survey were also sent out to various internal CDC groups via centers' announcement and listserves.

Data Management

Anonymous notes were taken during participant-observation. Group discussions were audio-recorded and notes taken. Seventeen semi-formal interviews were digitally audio-recorded for note taking and accuracy purposes. Notes from semi-formal interviews were entered into MAXQDA10 for subsequent

[18] I was informed by the person who sent the announcement to one particular listserve that the listserve contains over 3000 individuals across CDC. The announcement was also sent to most of CDC Science Workgroups listserves and by some centers to their own listserves. These other listserves are likely to include several thousand individuals.

coding and analysis.[19] Archival records contained names of individuals, but were publicly available, although notes were taken anonymously from the archival records. The transcription of each interview is roughly 10-page, single-spaced, or about 200 pages total. Approximately 150 pages, single-spaced notes were taken from participant-observation. Simple descriptive analysis of survey data were done using the built in statistical analysis functions in Survey Monkey.

Ethical Considerations

Interviews were conducted at the interviewees' places of preference, usually their offices, to ensure participants' privacy and confidentiality. Notes from recorded interviews were typed in Microsoft Word without any identifiable information. At CDC, a protocol and a research determination form were submitted through the CDC research determination review process. The protocol was determined to be nonresearch, program evaluation. Given its relevance to the study as part of the participant-observation, this process is described in Chapter 4. The dissertation proposal was also submitted to Emory University IRB for formal research determination and review. Emory IRB determined that proposal did not meet the regulatory definition of research. The study methods presented no physical risk to the participants. Any potential risk to the study participants was related to the possibility that a "sensitive" response or criticism is linked to a

[19] Most interviews were informal, varied in length, and were not recorded. I transcribed and analyzed the recorded semi-formal interviews using MAXQDA10. These interviews provide various perspectives and insights about CDC human subjects protection and research determination practices. I developed many codes in an effort to identify trends, but each interview were unique, because I permitted my informants to talk freely when I thought they were discussing relevant issues.

person, which could jeopardize their position, standing, and/or reputation. To ensure this did not occur, data that may contain identifiable information (such as audio recording) were destroyed after transcription or relevant notes taken. Interviews and focus group discussions were transcribed or note taken anonymously. Final data were not linked to study participants nor to their particular program or center. Verbal informed consent was obtained from participants involved in interviews and discussion groups. Individuals who were observed in various forums and meetings were likely aware of my study. As consent is an ongoing communication process I made every attempt possible to ensure that people were aware of the study.[20]

Challenges and Limitations

There were challenges in recruitment and willingness of people to be interviewed or to participate in focus group discussions, although this was only about 10 individuals. No one actually refused my request outright. They simply did not respond to my emails or calls. After two attempts at contacting them, I assumed that they did not want to be bothered. I cannot be certain of their reasons, but it could be related to the perceived risks that their responses may come back to haunt them, for example affecting their position. Most people I approached were willing to participate. I also encountered some challenges with recruitment for the survey. During the time of the study CDC changed the way agency-wide announcements

[20] At CDC, when a project is determined as nonresearch, it does not need to follow the Common Rule requirements for informed consent. As a "native researcher" I have apparent conflict of interest, therefore it was particularly important that I kept everyone apprised of my activities.

were sent. In the past, CDC announcements were sent out to employees individually. Agency-wide announcements were consolidated into one announcement. The change meant that only a one or two-sentence summary was permitted to go into the announcement, although a link to a more detailed description was permitted. I decided to not submit my survey announcement through the new consolidated announcement system for fear that it might get lost among the other announcements. I sent my survey announcement with link to the survey in Survey Monkey to different centers and groups, e.g., CDC scientific workgroups, and asked members to share with other CDC employees. Some centers sent my announcement through their center-wide listserves. I also sent the announcement to individuals I know and asked them to spread the word using a snowball technique.

Another recruitment challenge was related to my requests for sample protocols each for ones that have been determined by the Centers to be research or nonresearch. Only two Centers responded giving me a total of four samples. I wanted to analyze and compare to see whether informed consent was included in both research and nonresearch. Due to the unresponsiveness from the Centers I abandoned this effort.

It was also difficult to find documents describing the historical events leading to the restriction of CDC multiple project assurance and suspension of all its international research in 1997, because of poor record-keeping practice at CDC. Finding individuals who were involved in these events was also difficult, because most of them have retired or left CDC, leaving no contact information. One particular set of archival documents I was looking for were the meeting minutes from the CDC

Excellence in Science Committee (EISC) around 1993 to 1995. EISC is the CDC-wide committee composed of all centers' Associate Directors for (ADS), which has the responsibility for developing and approving major CDC scientific policies. OPRR restricted CDC MPA in 1995 and suspended all of CDC international research (96 in 32 countries) in 1997. Afterward, under pressure from OPRR, CDC worked furiously to develop its human subjects protection policy and guidelines for defining public health research and nonresearch. In my quest for the material, current staff in the CDC OADS, Office of the Director (OD) that has administrative responsibilities for the EISC meetings diligently searched for the materials at my request, but they were unable to find them.

I was disappointed, but not deterred from finding materials and people with knowledge of the events. Part of the reason why these materials were lost was likely due to the frequent reorganizations and staff turnovers. The office was supportive of my search for the materials and I promised that I would share what I found, because these were important historical events for CDC, and it would be shameful if they were lost. CDC library did not have documentation about these events, but asked me to share with them what I found. I contacted the CDC Information Technology and Service Office (ITSO) to see if they might have archived backup of old CDC intranet webpages that had in the past posted the EISC minutes. ITSO did not have the backup. I contacted the CDC Management and Analysis Service Office (MASO) requesting that they checked the Federal Record. MASO was able to find some materials sent by OADS for permanent archiving. As it turned out, the archived were hardcopies and there was no way I can query what kinds of documents were stored

in the boxes. There is also a cost to access the archived materials at the Federal Record facility and I must ask OADS to submit a request for these materials, 12 boxes in all. It was possible for me to request the materials through the Freedom of Information Act (FOIA), but I decided not to go that route, because I would only be able to review the materials onsite. Requesting them as a federal official meant I could bring things back to review.

After some efforts OADS submitted a request for me to go to the Federal Records Facility at 4712 Southpark Boulevard, Ellenwood, GA 30294 and I was able to bring materials back. Although I never found the EISC meeting minutes from 1993-1995 that I was looking for, the archives provided important materials and information that either confirmed or disputed information I had gathered from interviews. I found that people's memories can be unreliable, e.g., in regards to what were thought to be the two major events that lead to the suspension of CDC MPA and international research. This shows the value of taking a holistic, multi-method approach to understanding this issue. I would have made some inaccurate statements had I not reviewed the archived materials, which included notes and correspondences between senior officials, investigation report from OPRR, among other documents.

With any qualitative and interpretative study, this dissertation is telling one version of the story. Although I have presented the events as I observed them and my interpretations of them, other individuals at CDC may have different interpretations and stories to tell. The results from the interviews, discussions, and survey are based on questions that I as an individual saw as of interest to the topic.

The study results are limited to the practices I observed as informed by my own experiences at CDC, although understanding this critical junction in the human subjects protection process may be useful for other institutions, including federal, local, and international governmental and nongovernmental agencies.

Chapter Overview

In Chapter 2, I describe the history, people, politics, and cultures at CDC from its early days in 1942 started out as a small unit within the US Public Health Service (PHS) to the late 1990s. This chapter focuses on the historical events that influenced CDC organizational culture and how these events and culture influenced current practices, including the research determination policy and practices.

In Chapter 3, I describe the federal regulations, policies, and guidelines that govern CDC human subjects protection oversight and the research determination practice and examine how they developed differently among different CDC centers. These regulations, policies, and guidelines were often seen as the sources of confusion and variation in practices at CDC ever since they were implemented, starting with the Common Rule in the early 1980s to CDC policy and guidelines in the late 1990s. It could also be argued, however, that CDC policies and guidelines were developed to permit flexibility in decision-making and prompt public health responses. This chapter also describes the institutional structures and power relations among various authorities and actors within the human subjects protection and research determination processes. These relationships affect everyday practices as discussed in chapter 4 where various actors, including

investigators, supervisors, ADSs , continually enforced, interpreted, negotiated, and advanced their particular individual and group's understanding and interests of the regulations, policies, and guidelines.

In Chapter 4, I describe the research determination practice at CDC. I describe the social structure and every day practice since the 1990s after formal research determination process was implemented. I present selected survey results that focus on personal behaviors, beliefs, and practices, as well as providing examples of the early process and requirements. I also describe how research determination practice failed to evolve since it was formally implemented in 1999, the problems related to research determinations, and the beginning of regulatory audit in 2011.

Chapter 5 provides a more detailed description of four case examples to show the complex sociopolitical and cultural nature of the research determination practice. The cases, although based on real life examples, were made generic in an effort to protect the confidentiality of programs and the privacy of individuals who were involved in these cases. Making them generic does not take away the critical issues inherent in them. The cases are related to outbreak investigation, public health surveillance, and program evaluation, which are CDC's most common public health activities.

Chapter 6 presents my conclusion about the social construction of CDC research determination process and how CDC history and culture influenced the research determination culture. Chapter 6 also touches on current efforts at CDC to improve the research determination process and ensure regulatory compliance.

These include the determination audit by HRPO and the Science Services Support project (S3P), an enterprise-wide effort to develop a new online tracking and submission system that will include research determination and protocol submission to CDC IRB. The chapter will also briefly discuss the implications of the upcoming proposed revision to the Common Rule as CDC anticipates its implementation in the foreseeable future. Finally, I describe the public health ethics consultation process initiated at CDC that may help move the debate beyond regulatory compliance to fostering an environment that help ensure ethical, cultural practices, in spite of the confusions over how to define research.

Chapter 2: A Cultural History

The history of CDC and regulatory ethics in the 1940s
Research Determination Problems and Practice at CDC in the 1990s

In the early 1940s, "Dr. Joseph Mountin, a visionary leader in the Public Health Service, believed that the public health needs of the states could best be served by centers of excellence, each concentrating on a special area of expertise. There should be one for environmental issues, one for the emerging problems of Arctic health, and one for man's ancient enemy, communicable diseases. MWCA [Malaria Control in War Areas] had the structure to handle the latter assignment and the transition was relatively easy. The Communicable Disease Center would provide service to the states and give scientific research a practical application."[21]

Elizabeth W. Etheridge (1992: xvi)

To understand CDC's culture one has to go back to the beginning of its history. Brannen (1992) proposes the concept "issue cultures" as an explanatory model for organizational culture that evolved as a result of key historical events. "Issue cultures" as Brannen described, "form around key events in the organization's history, affecting the proportions of cultural attributes which define and redefine the cultural norm of the new organization" (1992: 10). We also need to have an understanding of how an "organization" is defined. Batteau defines "organization" as a "social form defined by goal-oriented instrumental rationality" (2001: 726). Organization is created for a purpose, an instrument for achieving specific mission or goal. The focus of instrumental rationality is to adopt the most economical and effective mean to achieve an end (Stanford Encyclopedia of Philosophy 2013).

Research determination practice evolved around key events. Many of the

[21] Dr. Mountin's vision of a communicable disease center was likely formed in the early 1940's. MWCA was formed in February 1942, two months after Pearl Harbor was attacked. MWCA became the Communicable Disease Center on July 1, 1946.

more recent historical events that lead to the development of CDC policy on distinguishing public health research and public health nonresearch were largely unknown to staff at the agency. No one I spoke to provided the exact details of why in 1995 CDC MPA was restricted and what lead to the suspension of all 96 CDC international research studies in 1997. These historical events and outcomes, critical to the understanding of the research determination practice, must be documented for the sake of the agency's integrity and posterity. The contemporary research determination practice itself is a dynamic "negotiated culture" among the various actors who came from a broad array of disciplines and backgrounds within the context of the overarching CDC culture and history. To understand CDC cultures we need to visit these historical events.

Early History and the Emergent of CDC Cultures[22]

CDC's cultures are mainly the products of its unique history. The factors that influenced the development of its human subjects protection and research determination practice and how CDC came to define what is research and what is not, need to be understood within its political economic history. These roots date back to the Malaria Control in War Areas (MWCA), a small unit within the US Public Health Service (PHS), created two months after Pearl Harbor was attacked on December 7, 1941, to protect US military bases against re-introduction of malaria in the South (CDC 1996, Etheridge 1992). MCWA was the vision of Dr. Joseph W. Mountin, director of PHS State Service division (CDC 1996). Initially, Mountin

[22] Much of the discussion about CDC early history was based on Etheridge's 1992 book, *Sentinel of Health*.

envisioned an organization that would protect military personnel from malaria at the more than 600 military bases, but foresaw a broader role for CDC in combatting communicable diseases in the future (Ibid).

In February 1942, Surgeon General Thomas Parran instructed Dr. Louis L. Williams, the PHS' chief malaria expert, who became the first director of MCWA, to go to Atlanta, Georgia, to develop a headquarter for malaria control (Etheridge 1992). Atlanta was an ideal location because most military bases were in the South and malaria was still a problem in the region. Parran sent a letter to all state health officials announcing the creation of the new organization initially named the National Defense Malaria Control Activities, which was later changed to MCWA. Space shortage ruled out the possibility that this new organization would have its headquarters in Washington. Parran decided on having the MCWA headquarter in Atlanta, although according to Etheridge's account Williams had considered Texas and California. Williams selected Mark Hollis, a PHS engineer, to be his executive officer. Hollis found office spaces in a building on Peachtree Street as the first MWCA headquarter. Staff was recruited from academia, other federal agencies, and from the Commission Corps, although most had little expertise in malaria, and had to be trained, initially at the National Institute of Health (NIH) and later at MCWA.

According to Etheridge, "They learned fast, however, and with no rigid lines of responsibility and no turf to maintain, these outsiders contributed much to MCWA's ability to wage war on malaria" (1992: 4). They worked efficiently as a team. Physicians diagnosed malaria cases, parasitologists worked in the laboratory, and engineers worked on malaria control, surveying land and developing drainage

(Ibid). The Commission Corps officers were major contributors to the reputation and efficiency of MCWA, which became a hallmark of CDC cultural identity. Organizational efficiency became one of the main driving forces when CDC re-organized. Under the most recent organizational improvement initiative that began in 2009, a strategic goal was to "improve efficiency of day-to-day functioning (personnel, procurement) and save money" (Frieden 2009).

Malaria, still a problem in the southern states, was considered a national security threat, because of its impact on training of soldiers at US military bases. According to Etheridge, "The Communicable Disease Center would provide service to the states and give scientific research a practical application" (1992: xvi). CDC was envisioned to be at the forefront in the battle against "man's ancient enemy, communicable diseases" (Ibid). After malaria disappeared, its focus shifted to other communicable diseases. It was not envisioned to be a research-focus agency, but an agency to apply scientific knowledge in the battle against communicable diseases. Urgent infectious disease (outbreak) investigations would become its first culture, which exerted influences on every other subcultures and practices at the agency.

According to Etheridge (1992) most of MCWA's early staffs were engineers and entomologists. Physicians were mainly relegated to diagnosing malaria in the field, and entomologists and parasitologists worked in the laboratory, while malaria control was left up to the engineers. MWCA Staff often worked six days a week and as their tasks grew more staff were recruited and trained. Training of public health professionals became a major activity and became an important component of CDC's mission (Etheridge 1992). Dr. Mountin encouraged MCWA's staff to be innovative,

because funding was scarce due to war needs.

One of the first major challenges for MCWA was the lack of transportation. MCWA had 400 bicycles at the time, but what they needed were trucks for carrying supplies. Seeking authorization to purchase vehicles would have been difficult, but reimbursable interdepartmental transfer was permitted among federal agencies (Ibid). The problem was solved during a trip Mark Hollis took to Washington when, during lunch at a Naval Air base, he found out about 200 surplus trucks that were 60 percent paid for, at Camp Blanding, Florida. Hollis contacted Surgeon General Mountin. Mountin wanted to contact the War Department to seek authorization for the transfer, but Hollis convinced Mountin that going directly to the military base would be better. Hollis went to Florida and met with an engineer at the base. The two shared college stories (the engineer was an alumna of Georgia Tech and Hollis graduated from Georgia State) and came to an arrangement about the trucks. The engineer told Hollis that he can take all the trucks except for the ones he marked with X's. There were 123 unmarked trucks, which Hollis, with the help of state troopers, transferred to MCWA. Obtaining the trucks without formal authorization and accountability was illegal, but it exemplifies CDC unconventional methods for getting around the system and "getting the job done." Without accountability, Hollis could have sold the trucks for personal benefits, but because he did not, it also gave CDC credibility and underscored the character of its people.

Another problem MCWA faced was the shortage of shovels. Hollis found out that the Works Progress Administration (WPA) was unloading its warehouses and other government agencies can request and have items shipped to them. Hollis

thought this process was too slow and suggested that they just claim a whole warehouse, which Mountin agreed. In addition to the shovels, MCWA also obtained other tools that were in the warehouse. According to Etheridge,

> The rather unorthodox way in which MCWA got its trucks and shovels was symbolic of the degree of freedom that existed in the organization. The geographic scope of its operations and the urgency of its mission set MCWA apart from the rest of the PHS (1992: 8).

Three important early historical attributes mentioned above were contributing factors to the development of CDC cultures. First, CDC was envisioned as the center of excellence that would put scientific research and knowledge to practice, particularly against communicable diseases. From the beginning of its history CDC was meant to be an organization that put scientific knowledge to practice. Second, the urgent nature of CDC early missions and resource shortages meant that CDC employees had to work hard and be innovative with what resources they had, as well as in how they obtain additional resources to do their work. As "necessity is the mother of all invention" CDC had to be creative, and had built a reputation for innovation and efficiency. Third, the distance from the politics of Washington gave CDC freedom from the watchful eyes in Washington. This freedom fostered innovation and creativity, but can also mean CDC did not always do things by the book, which was no secret to anyone in Washington. According to Etheridge, "Officials in Washington at the Bureau and Division levels recognized that the Atlanta institution had to have a degree of autonomy and freedom," because of the urgent nature of its mission (1992: 8).

> The immediate result was to eliminate much governmental red tape. This doubtless played a part in the notable esprit that marked the organization

> from the start. All the emphasis was on getting the job done. Mountin was MCWA's 'defense line' in Washington and protected the staff when they did not follow the book. Sib Simmons, who had a long and distinguished career in public health, remembers the freedom of those days during the war, when the 'red tape' people were all in the Army. If Simmons wanted something, he bought it on the market…….MCWA's distance from Washington—both geographic and administrative—born of wartime necessity, was a legacy long cherished by its much larger successor (Etheridge 1992: 8).

CDC leaders also made sure that employees got what they needed without interference. According to Etheridge, **"**They believed passionately that they were doing important work, and Sencer[23] was determined to make it possible for them to work with the least possible interference" from the politics in Washington (1992: 152). An internal article posted the following excerpt from Etheridge's book on CDC intranet, "Sencer believed that good epidemiology and disease investigation were the best guardians of public health. He had little faith in legalism and regulation" (1992: 166).

CDC leaders were optimistic by nature, although Closser (2010), in talking with some CDC staff, describes CDC's optimism as "reality optimism." One of her informants stated that "there is optimism but there's also… a kind of….reality optimism…..realism would be better" and CDC "doesn't like B.S." As an insider, I can relate to the statement, because CDC often explicitly states that it bases its actions first and foremost on science[24], but I believe optimism at CDC goes much deeper. Most of the people I have worked with and talked to feel that they are doing what

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[23] Dr. David Sencer was the longest serving CDC director from 1966 to 1977. CDC expanded dramatically under Sencer adding malaria, smallpox, nutrition, tobacco control, health education, environmental, occupational health and safety, among other programs (CDC Intranet article, June 9, 2011).

[24] CDC mission – www.cdc.gov/about/organization/mission.htm.

they are doing because they believe that they can make a difference in improving people's health and lives. There is a sense of humanitarian urging and higher calling among CDC staff. People often say that the goal of public health "should be to put ourselves out of a job." Even though this may be disingenuous, this sense of selflessness is a principle subscribed to by some at CDC. It is a social and cultural phenomenon that also attracts people with a similar sense of optimism and humanity to CDC. In his message to CDC employees in anticipation of the recent government furlough, CDC Director Tom Frieden expressed his frustration. In the message he said:

> I've always felt that public health is a calling – it gives us the privilege of doing the most good for the most people…. CDC is committed to saving lives and protecting people, and will continue to operate as America's health protection agency. Every one of you is a part of that mission. There is uncertainty at the moment, but no uncertainty about the persistent threat of emerging pandemics, drug-resistant infections, and the leading causes of death, injury and illness (CDC All Hands Meeting: August 12, 2013).

Former CDC director Bill Foege exudes optimism and belief in the work and capability of CDC as a public health force to change the world. When asked whether he had any doubts that the global smallpox eradication would be successful, Foege said:

> It is interesting about thoughts at the time of eradication. Mine seem to have been much different than most. For me, the high point was when I saw in my mind that this could happen. All of our actions were simply carrying out the plan, and so I felt no surprise at the end. It seemed inevitable. I was content to leave (India) before smallpox was gone because I had no doubt that it was on track. Indeed, it always seemed to me that surprise was inappropriate because it indicated a lack of faith in the idea. I don't think that resonates with many, however (CDC Intranet Story 2013).

Another major culture that developed as a result of its history is the culture of constant change and re-organization towards improvement and efficiency. The

word “efficiency” can be heard almost anywhere at CDC, whether in the hallway, elevator, conference room, personal office, or bathroom. One day I heard the word echoed in an elevator by a CDC staff, apparently after he had just met with CDC director. CDC always strives for organizational improvement and efficiency. Changes were inevitable even though changes were often politically, socially, and economically-motivated by the changes in Washington, which usually resulted in a new director being appointed at CDC.

Lastly, there is also a general perception among other professions that public health professionals may to some extent be considered as “self-righteous” individuals. They may be seen as unselfish and are driven by noble causes, but this can also blind them in their pursuit of disease outbreaks and public health achievements, including sometimes overlooking individual rights for the greater good. The CDC, having been fortunate to be blessed with some extraordinary leaders throughout its history, can be vulnerable to being complacent, especially when the organization is highly praised and admired by the public. Great leaders often conveyed a public persona that brought praises to CDC, and in turn CDC employees are perceived to exemplify the same virtues as its leaders. A “self-righteous” image can have a negative impact on CDC and affect individual’s conscious and unconscious thinking. I will not discuss this in any significant detail, but there are implications and challenges when conducting ethical training among self-righteous individuals if training and greater ethical awareness is to be seen as a step forward in moving beyond regulatory compliance. On the other hand, there was also a fear of being moral imperialists. During the time of the OPRR suspension of all of CDC

international research CDC had argued that "U.S. ethical rules ought not to apply in many of the very nations where the agency failed to adhere to the regulations" (Epstein and Sloat 1998: 1). According to response from CDC, "We shouldn't be dictating a code of ethics for other countries. Telling them how things should be done is often viewed as imperialistic" (Ibid).

Historical Development of Regulatory Ethics

CDC human subjects protection and research determination culture was not formed within the confined space of CDC buildings in Atlanta. Before formal ethical guidelines and regulations became the cultural norms in biomedical research, there was self-regulation. Ethics was considered to be embodied in the researchers and they were deemed to be in the best position to impose ethical rules and restrictions on themselves (Fassin 2006). Self-experimentation, such as research conducted by members of the Yellow Fever Commission led by army physician Walter Reed, were accepted practices before World War II (Moreno 2001). At the end of WWII in 1946, the American Military Tribunal in the first of twelve trials prosecuted 20 Nazi doctors and scientists who were accused of the most heinous experiments on concentration camp prisoners (Pellegrino 1997). In their verdicts, the tribunal also presented a set of ten ethical principles, known as the Nuremberg Code, designed to ensure that human participants will be protected in future medical research (Annas 1992; Aagaard-Hansen 2008). Although the Nuremberg Code was not binding, according to the National Institute of Health (NIH) it was the "first international code of research ethics" and the foundation of modern biomedical ethics (aka,

bioethics), which influenced current ethical guidelines and codes, including the Common Rule (DHHS 1979), the Belmont Report (DHHS 1979), the World Medical Assembly Declaration of Helsinki Report (WMA 1964) among other ethical principles (Shuster 1997). The first principle in the Nuremberg Code emphasizes the most fundamental ethical practice in human subjects protection today, stating that "The voluntary consent of the human participant is absolutely essential" (DHHS 2005). The code established the ethical principle that informed consent of the research subject is absolutely necessary for experimentation with human subjects. Other principles also include the avoidance of harm, qualification of researchers, and right to withdraw (DHHS 2005).

WWII atrocities were not the only events leading to the current regulatory and ethical code and oversight of human subjects research in the US. These developments were also NIH's response to a series of research and medical abuses in the US, including the thalidomide case that came to public attention in the late 1950's (Eisenberg 1995). Thalidomide was prescribed as a sleep aid and anti-nausea drug during pregnancy, but soon was found to cause severe birth defects and abnormalities. Although it was approved in some European countries, the US Food and Drug Agency (FDA) had not approved thalidomide for medical use and US patients were often given thalidomide without their knowledge and their informed consent. In 1962 US Congress passed an amendment to the Food, Drug, and Cosmetic Act requiring for the first time that pharmaceutical companies provide proofs to the FDA that their product is safe and effective before marketing them to the public. The thalidomide abuse in addition to other research scandals, including

the Brooklyn Jewish Chronic Disease Hospital case where elderly patients were injected with cancer cells without their consent, and the Willowbrook hepatitis research in Staten Island, New York, where 700 mentally disabled children were deliberately infected with Hepatitis A virus, among other abuses caught the attention of the director of NIH, who appointed a committee to review ethical requirements of NIH-funded research (Moreno 2001). Although the committee basically reaffirmed the status quo, NIH director and the Surgeon General established the National Advisory Health Council that endorsed an establishment of formal institutional oversight. In 1966 the Surgeon General issued a federal policy that required all PHS-funded research institutions to establish research ethics committees (Moreno 2001), which became today's IRBs. NIH established OPRR and issued the Policies for the Protection of Human Subjects in 1966 (Moreno 2001).

The Tuskegee Study of Untreated Syphilis (TSS) first came to public attention in an Associated Press story in July 1972 (CDC 2013). The study initially began in 1932 under PHS among 600 black men of whom 399 had syphilis and 201 did not. During recruitment, the men were told that they would be treated for "bad blood," a local term that refers to a variety of illnesses including syphilis, anemia, and fatigue. The men were promised free medical care, meals, and burial insurance. The men were never told that they were part of a research study and were misled into thinking that they were getting free and complete medical examination and treatment. The purpose, as the title of the study indicates, was to learn about the natural course of untreated syphilis, results that would be generalizable and would add to scientific knowledge. They were tricked into believing that a spinal tap was a

special treatment (Brody 2013). They never consented to be research subjects. When the study began, there was no known effective treatment for syphilis. Even when penicillin was found to be an effective treatment for syphilis, it was not given to the participants. The study, which lasted for 40 years from 1932 to 1972, was transferred to CDC in 1957 when the Venereal Disease Division of US PHS became a part of CDC (CDC 1996). In 1973 a lawsuit was filed on behalf of the participants and a financial and medical settlement was reached in 1974. A government program, currently run by CDC, was established to provide lifetime medical care and burial services to the survivors. The program was extended to their wives and children in 1975. On May 16, 1997 President Clinton apologized to the victims on behalf of the Nation.

TSS led to Congressional passage of the National Research Act in 1974, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter, the Commission). The Commission developed the Belmont Report (DHHS 1979), which outlined the fundamental principles for the ethical conduct of biomedical research and attempted to distinguish the differences between what constitutes research and what constitutes practice. Three basic principles were established under the Belmont Report, and include 1) respect for persons, 2) beneficence, and 3) justice (DHHS 1979). The Commission came together on the backdrop of TSS when the line between research and practice was blurred. A definition of research did not exist and no formal ethical oversight of TSS was in placed. The Commission knew it was important to distinguish what activities need to undergo human subjects review. According to

Beauchamp, "this Commission advanced the view that research protocols involving human subjects should have a high level of peer review, a level not required for patients in medical practice" (2011: 383). In 1974 the Department of Health and Human Services (formerly the Department of Health Education and Welfare) established the Common Rule (DHHS 1974). In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended all federal agencies to adopt the HHS regulations (NIH 2009). The Common Rule has been revised several times (1979, 1991, 2009) since it was drafted. DHHS currently is operating under the 2009 revision, but a new revision is forthcoming, perhaps in 2014.

OPRR Regulatory Investigations in the 1990s (Figure 2)

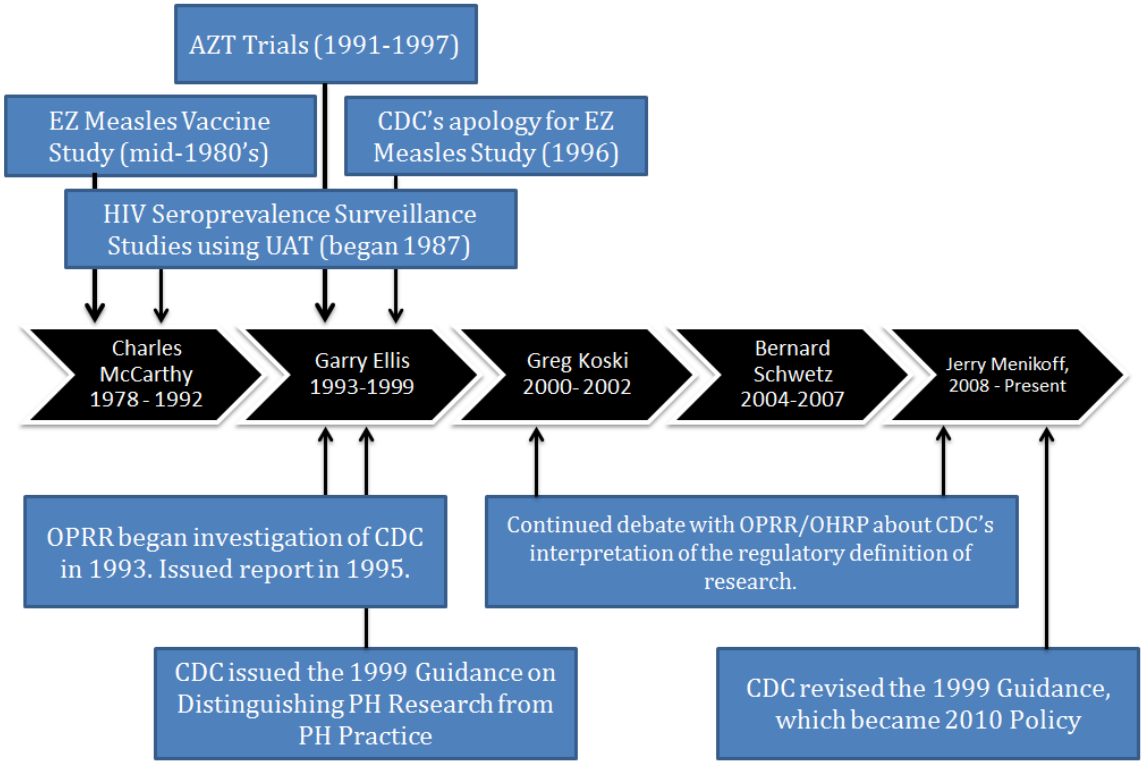
CDC still cherishes the distance and relative freedom from the politics in Washington, although the distance has significantly shortened since the days of MWCA. In the world of human subjects protections, what distance and freedom still remained was challenged in 1993 when OPRR, still a part of NIH at the time, investigated CDC for apparent noncompliance with the Common Rule mandates, resulting in the restriction of CDC MPA and suspension of all its international research (former CDC Colleague, internal CDC memo). The investigation was part of an increasing regulatory oversight in the 1990s after a new director, Gary Ellis, took the helm at OPRR in 1993. According to a CDC colleague, Charles McCarthy, the first director of OPRR from 1978 to 1992 (NIH 2011), took a less regulatory approach and conducted few investigations during his tenure, although perhaps largely due to

the constraint in resources. Gary Ellis who was named director of OPRR in 1993 took a more aggressive approach to regulatory oversight (Hamilton 2005). According to Hamilton, "Gary Ellis brought more suspensions in 20 months than in the 20 years prior to his 1993 appointment. Every sanction involved clinical studies" (2005: 192-193). On August 12, 1993, Ellis sent a letter to all IRBs that "mandate for obtaining legally effective informed consent prospectively from each research subject" (OPRR 1993). The letter notes that:

> Recently, we have become aware of the use of a consent procedure referred to as "deferred consent" or "ratification." Informed consent procedures which provide for other than legally effective and prospectively obtained consent, fail to constitute informed consent under the HHS regulations for the protection of human research subjects. Similarly, the waiving of informed consent, using a method other than that requiring the IRB findings and IRB documentation specified at 45 CFR 46.116(c) or (d), is not in compliance with the regulations (OPRR 1993).

According to a CDC colleague, from 1990-1992, OPRR conducted one to two compliance oversights each year, however, from 1994 to 2000, there were 34 investigations resulting in restrictions and suspension of many institutions' MPAs, including CDC's, Massachusetts Eye and Ear Infirmary, University of California, San Francisco, University of Florida, University of Virginia, Duke's University, University of Illinois, among others (NBAC 2001: 54-56).

Figure 2: Events Leading to OPRR's Investigation of CDC



Timeline is according to OPRR's Directors' tenure.

Politics, rather than actual research abuses, may have played a more important role in the increased number of oversight investigations during the mid to late 1990s. According to Burman, "the number of regulatory actions [investigations] by FDA and OPRR tripled from 1997 to 1999, and regulatory actions against academic medical centers increased even more sharply (1 in 1997 compared with 14 in 1999)" (2001: 153). Burman notices that among the key OPRR findings from the investigations in 1999 of 22 IRBs were procedural issues, related to inadequate documentation, continuing review, inadequate written procedures, deficient consent forms, and inappropriate use of waiver of informed consent and

expedited review. Other findings include inadequate training for investigators, inadequate review of safety reports, and inadequate attention to vulnerable populations. No actual harm was discovered, but there were insufficient safeguards in place to ensure protection of human subjects.

The increased regulatory oversight and restriction and suspension of an unprecedented number of institutional IRBs and research lead to a congressional inquiry in 1998 (CDC Colleague). DHHS Secretary Donna E. Shalala attributed the increase to the increasing number of research studies, "The recent explosion in biomedical research has presented new challenges and created new potential ethical dilemmas" (CDC Colleague). Others viewed it differently. According to another CDC colleague, a former high-level CDC employee described to her what he felt was the reason behind the increased regulatory investigations stating that:

> Ellis was much more concerned about enforcement and in some ways, took the allegations, the complaints, more seriously with investigating them…though when we saw all the shut downs occur, I really think that that was due to a personal agenda that he had… he wanted to get OPRR out of NIH and the shutdowns were a mechanism to do that (CDC Colleague).

These shutdowns put the focus on NIH, because OPRR was an office within the agency. OPRR's mandates have expanded beyond oversight of NIH's research, and therefore, it makes sense that it became independent from NIH. In June 2000, OPRR was renamed the Office of Human Research Protections (OHRP) and was moved outside of NIH and became an office within DHHS. Greg Koski, who was previously the Director of Human Research Affairs, Partners HealthCare System in Massachusetts General Hospital and Harvard Medical School, was named the first director of OHRP (DHHS 2013).

"Quiet" Commotion at CDC in the 1990s

The title of this section conveys my overall impression of what appeared to be the atmosphere and perception among the general CDC staff during the time of OPRR suspension of CDC MPA. Although there was a general frantic feeling at the national scene over OPRR regulatory activities which resulted in the restriction or suspension of MPA's of many institutions (Burman 2001, NBAC 2001), it was relatively quiet at CDC. A colleague also agreed, "The low profile of investigation of CDC stands in stark contrast to the other institutions that had their MPAs restricted or suspended in 1995, e.g., University of Virginia, University of California at Los Angeles." Many people I spoke to, who were around at the time of the suspension, did not seem to remember the events or what lead to the suspension. Very few people even remembered that it happened. The events seemed to be absent from the broader organizational consciousness. One colleague shared with me her knowledge and sent me an unpublished document about some of the historical events.

In reviewing archived documents I found at the Federal Records facility, there were some discussions implying that CDC should deal with these issues quietly. One senior scientist stated, "I suspected that it would be best to avoid airing our dirty laundry regarding our problems with OPRR as this is unlikely to encourage engagement of the public health community and it is likely to worsen our relationship with OPRR"[25]. Almost two decades later, I am still encountering this

[25] Available from CDC OADS Archive, Control # T7909A, Box 25, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294

sentiment coming from CDC staff, that any revelation of CDC "dirty laundry," might damage CDC reputation. I am not sure if I would view past problems with OPRR as "dirty laundry" if we put them into historical context. These were shortcomings, exacerbated by inadequate allocation of resources for monitoring and oversight that had already been reported in the media. CDC had tried to correct some of the inaccuracies and misleading statements made in the media. From a historical, political economic perspective, it had not been very long (12 years) since CDC agreed to abide by the Common Rule requirements to the time of OPRR's investigation of CDC (1981 to 1993). Given CDC cultural history, twelve years was probably too short for CDC culture to adapt to new requirements, develop new practices, allocate adequate resources for oversight and tracking of research studies.

Obviously, any attempt CDC made to correct the inaccuracies reported in the media was probably seen as CDC being defensive, which in some sense it was, but understanding CDC problems from the political economic and historical contexts would certainly help the public understand the difficult situations CDC was in. If CDC had any "dirty laundry" then CDC airing them out, take responsibility, apologize, and make amends, as David Satcher[26] (Fisher 1996) did in the Edmonston Zagreb (EZ) measles vaccine study case (described below), would send a more positive message to the public then giving any appearance that CDC was trying to cover up. Details of these events can be found at the National Records facility.[27]

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[26] Dr. David Satcher, the first African American to head CDC, was director from 1993 to 1998 (MMWR 2007, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5623a3.htm).
[27] CDC Archive, Control # T7909A, Available at the Federal Records Center, 4712 Southpark Blvd.,

At the time of the restriction, CDC had its own MPA, but according to the former colleague who joined CDC Human Subjects Activity (HSA), what HRPO was known at the time, in the CDC OADS, CDC failed to ensure that funded research partners also obtained assurance of compliance with OPRR (OHRP). In its own defense, CDC noted in an internal memo to the National Bioethics Advisory Commission (NBAC) in 1998 that in the mid 1980's "recognizing the difficulties in negotiating assurances, OPRR did not require that CDC obtain assurances."[28]

According to a former colleague, "OPRR closed down all of our international activities (97 studies in 32 countries [two figures that I'll never forget because they haunted me for a year]) because we had failed to get assurances."[29] A CDC colleagues states, "[It] seems one person was running HRPO at that time and as that person explained to me, when there is only one person running an office, some things have to go on the back burner." Another former colleague who was recruited in 1997 by CDC OADS to help address this issue described the surprise and chaos she came upon when joining HSA. "Two figures that I'll never forget because they haunted me for a year, because we had failed to get assurances." She added:

> As you know, according to 45CFR46, we were supposed to have a procedures manual (nope, didn't have one), a health educator (ditto), and adequate staff to oversee the research protocols coming into our office (no to that one, too). I spent a year putting international assurances in place, after which we hired someone to handle assurances only. I then assumed my position as Public Health Educator to design and implement training for investigators and IRB members.

Ellenwood, GA 30294.

[28] Although I found no evidence that OPRR acknowledged this statement, I also found no evidence that they refuted it; therefore my assumption is that it was true. The statement is too sensitive to be made up by anyone at CDC. An article by OPRR's first Director, Charles McCarthy, also appears to support this statement, when he states that OPRR took a pragmatic approach in regulating research.

[29] The 1998 CDC memo to NBAC, however, states that 96 studies (rather than 97) were suspended by OPRR.

The issue of obtaining assurance for multiple-partners research is inherently a complex problem. Each institution that receives federal funding or support must file its own assurance with OPRR. The process requires the head of the institution or another designee to take research ethics training and sign an agreement with OPRR that the institution will abide by the Common Rule requirements. In addition, all research investigators must take scientific ethics training before they can engage in human subjects research. This was probably what led OPRR to exempt CDC from acquiring such assurance for international research in the first place. However, the challenges for CDC human subjects protection program were beyond obtaining project assurance.

A CDC colleague described CDC's approach to human subjects protection as "laissez-faire" and foot-dragging. Her rationale for this conclusion was that CDC viewed the unethical events related to TSS as an anomaly, something that will never be repeated, and because CDC was not known as a research institution, CDC took its time in implementing the Common Rule requirements. Thomas Puglisi, director of Division of Human Subjects Protections at OHRP, said "The identification of numerous international studies where all the required protections for human subjects were not in place was an indication of a need for systemic improvement at the CDC," (Epstein and Sloat 1998)[30]. Gary Ellis, director of OPRR, railed at CDC failure stating:

> The volume of what was out of compliance is startling. It's not that researchers are bad people. But sometimes they get so caught up in their

[30] The article by Epstein and Sloat is found on an internet website. There is no page number for the quote.

> immediate goals and the sense of the goodness of what they're doing that they fail to see the larger ethical implications of their actions (ibid).

CDC reassured the public that it was certain no human subjects was harmed, but the written assurance was missing and certain regulatory requirements were not met in many of the studies. The restriction of CDC MPA and suspension of all its international research were not related to any harm to subjects, but to shortcomings related to regulatory compliance and inadequate monitoring and tracking, which were related to its financial situation.

Another former colleague told me that when he arrived in 1998 within the CDC HSA that there were approximately 1000 IRB protocols, but by the time he left CDC five years later, there were over 2100 protocols. In his first year there was a 40% (between 1998 and 1999) increase in the number of submissions. By this time (1999), CDC centers were beginning to implement formal determination process, which was likely the reason why more projects were determined to be human subjects research requiring CDC IRB approval.

The Straw that Broke the Camel's back

Accounts differ as to the events thought to be the "straw that broke the camel's back," that led to OPRR's investigation of CDC. Some current and former CDC staff, including staff who worked in the CDC HSA during this period thought it might have been the short course AZT trials (NIH 1997) to prevent mother-to-child-transmission of HIV. According to another colleague, "OPRR's interest in CDC began in the late 1980's, when it started to get unwelcome press coverage of its HIV

seroprevalence surveillance activities (De Zulueta 2001)." Another colleague currently working at CDC thought it was the EZ Measles (Fisher 1996) that led to OPRR's investigation. These events are described in more details below. The National Bioethics Advisory Committee (NBAC) 2001 Report Exhibit 3.1, provides details about OPRR's required actions for CDC made reference to the measles case:

> Provision of updated information to measles research participants, development of conflict of interest guidelines for IRB members, review of staff support and resources for IRBs, development of an educational program, a proposal for a mechanism to ensure performance site assurances for international research, and a comprehensive review of IRB policies and procedures were required (2001: 52).

According to one CDC colleague:

> It was actually the Short Course AZT trials in Cote d'voire (to stop mother-child transmission of HIV) that raised the red flag for OPRR. Peter Lurie and his group put us in the lime light because the consents were taken while the women were in labor, a stressful time. That was in May of 1997, the same month that President Clinton apologized to the Tuskegee survivors. Yes, EZ Measles (June 1990-October 1991) played a role but it was the AZT trial that was the straw that broke the camel's back.

The AZT study led to OPRR's discovery that CDC had not obtained assurance from collaborating institutions as required under the federal regulations and to the suspension of all CDC international studies. Finding the "straw" was not the goal of the study, though the search gave some insight about the nature of the OPRR investigation and to the confusion at CDC.

Comparing to investigations conducted among academic institutions, the OPRR investigation of CDC was kept relatively quiet within. It turned out that the EZ measles and HIV seroprevalence studies (described below) were the two cases described in OPRR's 1995 Investigational Report, although it was likely a

combination of factors, including the changing political landscape at OPRR resulting in increasing regulatory oversight in general, press reports of institutional noncompliance and allegations of unethical conducts, and public complaints that led to the investigation of CDC practices.

EZ Measles

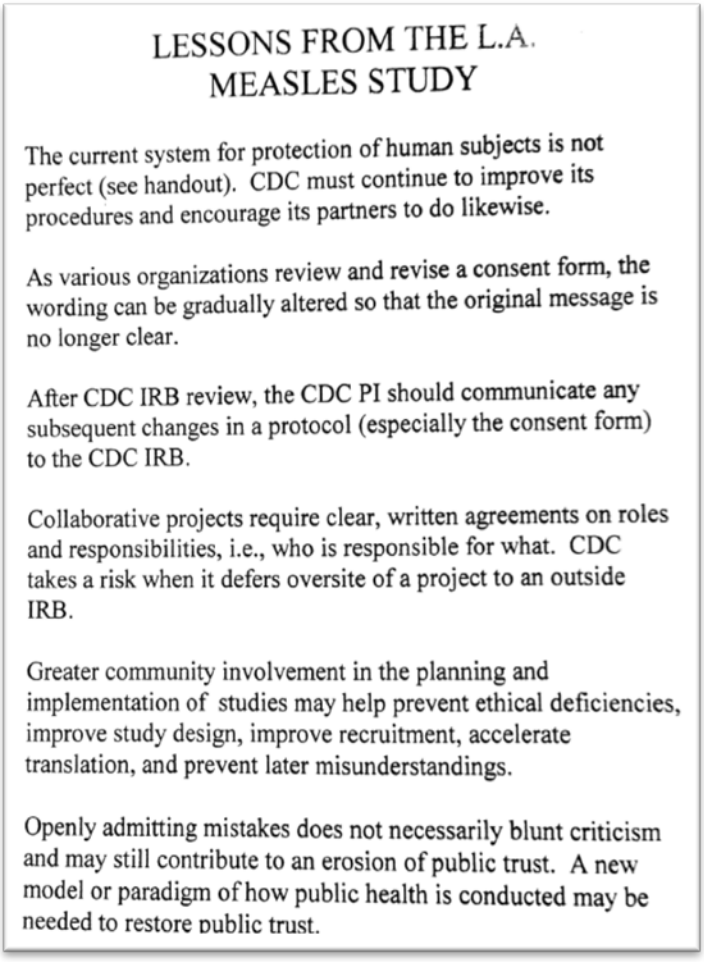
Measles is highly contagious respiratory disease caused by the measles virus. Complications from measles include ear infection, pneumonia, encephalitis, and about one to two in 1000 cases resulted in death (CDC 2013: Measles). In the US, vaccination has led to a 99% reduction in the number of cases since measles vaccine was introduced in the US in 1963. Newborn infants are protected by maternal antibodies during the first few months of life, but maternal antibodies also interfere with live measles virus vaccine, so it was recommended for infants at 9 months, and changed to 12 months in 1965, and to 15 months in 1976 (CDC 2013: Measles).

In the mid-1980's, studies were conducted using high potency EZ measles vaccine for infants aged 4 to 9 months in Haiti, Senegal, Guinea Bissau, and Mexico. Later studies were conducted in Cameroon, Gambia, Bangladesh, Togo, Iran, New Guinea, Peru, Rwanda, Sudan, South Africa, Egypt, Philippines, Uzbekistan, Thailand, and Zaire (Fisher 1996, Special Studies Report 1995, "Edmonston-Zagreb Measles Vaccine Project," Los Angeles County, Department of Health Services, Acute Communicable Disease Control). These studies were promising and showed high seroconversion rates in high maternal antibodies. However, several of the African studies also indicated increase mortality among infants receiving high dose EZ

measles vaccine (Fisher 1996), although an expert panel review concluded that these were likely not related to the vaccine.

In the early 1990s measles outbreaks were occurring among infants under 15 months in Los Angeles, California. CDC, in collaboration with the Los Angeles County Department of Health Services and Southern California Kaiser Permanente conducted an EZ measles vaccine study to compare to the Moraten vaccine. The Los Angeles study was halted in October 1991 following numerous reports of increased mortality from the African studies (Fisher 1996). On June 17, 1996 CDC Director Dr. David Satcher, admitted in the *Los Angeles Times* that the study failed to disclose the experimental nature of the EZ Measles study and failed to obtain informed consent according to the federal regulatory requirements. Kaiser considered this an administrative oversight and both CDC and Kaiser insisted that no baby was harmed by the vaccine (Fisher 1996). In an internal document CDC acknowledges the problems and mistakes made during the review process, including the multiple revisions and breakdown in communication, as well as the need to involve community in the planning and implementation of the study (Figure 3).

Figure 3: Lessons from the L.A. Measles Study



LESSONS FROM THE L.A. MEASLES STUDY

The current system for protection of human subjects is not perfect (see handout). CDC must continue to improve its procedures and encourage its partners to do likewise.

As various organizations review and revise a consent form, the wording can be gradually altered so that the original message is no longer clear.

After CDC IRB review, the CDC PI should communicate any subsequent changes in a protocol (especially the consent form) to the CDC IRB.

Collaborative projects require clear, written agreements on roles and responsibilities, i.e., who is responsible for what. CDC takes a risk when it defers oversite of a project to an outside IRB.

Greater community involvement in the planning and implementation of studies may help prevent ethical deficiencies, improve study design, improve recruitment, accelerate translation, and prevent later misunderstandings.

Openly admitting mistakes does not necessarily blunt criticism and may still contribute to an erosion of public trust. A new model or paradigm of how public health is conducted may be needed to restore public trust.

Source: CDC OADS Archive, Control # T7909A, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294.

HIV Seroprevalence Surveys

Beginning in 1987, CDC conducted a series of studies as part of the Comprehensive Family of Surveys to help state and local health departments conduct sentinel surveillance assessing the incident and prevalence of HIV infection among "various segments of the population (OPRR 1995: 7). Among the populations were persons with sexually transmitted diseases, intravenous drug (IVD) users, persons with tuberculosis, blood donors, homeless persons, among other

populations (Pappaioanou et al 1990). The studies would use unlinked blood specimens for HIV testing without the informed consent. This was the beginning of the controversial unlinked anonymous testing (UAT), which is no longer used in the United States. UAT refers to the use of anonymous blood specimens for HIV testing, but without obtaining informed consent of individuals. Under UAT it is impossible to link back test results to individuals, which many argued is unethical and represents a missed public health opportunity, because of the potential preventive measures an individual can take upon knowing one's own HIV status. CDC IRB had approved all of these studies, but CDC requested OPRR to review the surveys. OPRR convened a 12-member ad hoc panel and determined that these studies did not meet the regulatory definition of human subjects research for the following reasons:

> A. The activity caused no interaction or intervention with living individuals (i.e., the activity resulted in no collection of information or specimens that would not otherwise be obtained); and
> B. The activity utilized no information or specimens that could be linked, directly or indirectly, to identifiable living individuals (1995: 7).

CDC accepted OPRR's determination and considered the studies as "not constitute human subjects research under HHS regulations," although CDC IRB continued to review the studies annually, because of the sensitivity related to UAT. In today's practice, CDC IRBs no longer review nonresearch studies, although they do review studies that fall under FDA regulations, such as investigational new drug or device study, even if they do not meet the Common Rule's definition of research.

One of the HIV seroprevalence studies was the "HIV Seroprevalence Survey in Childbearing Women: Testing Dried Blood Specimens on Filter Paper for HIV Antibody" (OPRR 1995: 7). OPRR received allegation from Scott Isaacman, of the

John Marshall Law School[31] that the study was in noncompliant of the Common Rule and the HHS policy on notification of HIV test results, because informed consents were not obtained, and women were not given the test results. It was also alleged that CDC IRB was "improperly constituted as to number, diversity, expertise, and possible conflict of interest" (OPRR 1995: 8). In the report, OPRR reaffirmed their decision and concurred with CDC that the studies were not human subjects research and did not required IRB review, that informed consent was not required because the studies used residual (leftover) excess blood specimens from the routine testing that have been de-identified. Therefore, no consent was necessary. However, OPRR also admonished CDC on the makeup of the IRB that it did not:

> . . . appear to satisfy this requirement, especially given the fact that much of the research reviewed by CDC-ATSDR IRBs is national in scope. OPRR strongly recommended that CDC-ATSDR expand the diversity of its IRB membership to address this concern, and CDC-ATSDR has supplemented the membership of its IRBs accordingly (1995: 11).

The Site Visit from OPRR in 1993

The site visit from the Compliance Oversight Branch of OPRRR in 1993 led the investigation of CDC human subjects protection program as a whole. OPRR concluded that:

> Discussions with CDC personnel indicated that the distinction between human subjects research and routine, nonresearch public health practice was poorly understood and inconsistently applied. Overall, it appeared that many CDC personnel lacked a thorough understanding of HHS regulatory requirements for the protection of human subjects" (1995: 11).

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[31] CDC OADS Archive, Control # T7909A, Box 25, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294

The report also identified CDC failure to ensure that institutions that conducted CDC-supported research had appropriate "OPRR-approved assurance of compliance with the HHS human subjects regulations" (OPRR 1995: 12). OPRR issued nine corrective action steps that CDC must take as summarized below:

1. CDC and its research partners (Kaiser and the Los Angeles Health Department) must inform in writing all parents of all subjects who participated in the EZ measles vaccine study about the "(a) the current status of the research; (b) plans for completion of the research and notification of subjects about results; and (c) any reasonably foreseeable future risks of participation in the research, either from the standard Mora ten vaccine or the experimental EZ vaccine.
2. CDC develops a policy on conflict of interest.
3. CDC increases staff support for human subjects protection to "ensures adequate staffing, at both the professional and administrative levels, for the IRB recordkeeping and human subjects education functions of this office. CDC-ATSDR should also ensure that the office is provided with sufficient work space and computer tracking systems to perform its functions effectively."
4. "CDC-ATSDR should develop a systematic program for continuing education of CDC-ATSDR personnel about human subject protection requirements." These includes basic training for junior staff and continuing training of senior staff, training for IRB members, and develop a written manual for IRB procedures and decision making.
5. CDC-ATSDR should develop written guidelines addressing the requirements for OPRR-approved Assurances and IRB review for human subjects research involving foreign performance sites.
6. CDC-ATSDR should carefully monitor its recently revised award management mechanisms to ensure that all entities engaged in human subjects research supported by CDC-ATSDR hold applicable OPRR-approved Assurances and meet IRB review certification requirements. OPRR recommends that CDC-ATSDR explore options for computerized tracking of such information.
7. OPRR will work with CDC-ATSDR to develop Assurance mechanisms and IRB review arrangements that are suited to the particular challenges faced by CDC-ATSDR in meeting unique public health responsibilities. OPRR recognizes that existing mechanisms may not lend themselves readily to the special circumstances faced by CDC-ATSDR. OPRR strongly recommends that CDC act as quickly as possible to develop a preliminary proposal outlining the parameters for this undertaking.
8. OPRR recommends that all CDC-ATSDR components, including the

> National Institute for occupational Safety and Health (NIOSH), be included in a unified CDC-ATSDR MPA document.
> 9. In preparation for the renewal of its MPA, CDC-ATSDR should conduct a comprehensive review of all IRB policies and procedures to ensure that they are consistent with the requirements of HHS regulations at 45 CFR 46.
>
> (OPRR 1995: 14-18)

In summary, OPRR mandated that CDC apologizes for the EZ measles, develop a policy on conflict of interest, increases staff support for human subjects protection, develops training and manual for staff, develops guidelines for distinguishing research from practice, develops an assurance mechanism, and include all components of CDC under a single MPA. OPRR restricted CDC MPA, delayed its renewal during the investigation, and required CDC to provide quarterly reports on the updates of their implementation.

> The requirement to address the corrective actions described above constitutes a restriction to the continued extension of the MPA. This restriction will remain in effect pending successful renegotiation and subsequent renewal of the MPA by OPRR after corrective actions are implemented. During the period of restriction, CDC-ATSDR must submit Quarterly Reports to OPRR summarizing its progress in addressing the corrective actions. (OPRR 1995: 18).

AZT Trials

Although the AZT trials were not mentioned in OPRR's report, it is worth mentioning that the two studies that CDC was engaged in were major sources of headache for CDC during the time when CDC was responding to OPRR. Former CDC staff in the HSA seemed to believe that it was one of the events that led to OPRR investigation of CDC human subjects protection program in the first place, although this assertion is questionable. In a randomized, double-blind, placebo-controlled trial published in the *New England Journal of Medicine (NEJM)*, AZT (zidovudine),

given orally to HIV-positive pregnant women, was found to have a 67.5 percent relative reduction in the rates of HIV transmission compared to the placebo group (Connor et al 1994). The original studies were conducted in the United States and France from 1991 to 1993 as part of the AIDS Clinical Trials Group (ACTG) Study 076. The results were so groundbreaking and positive that the studies were terminated early after the study's Data and Safety Monitoring Board (DSMB) recommended that zidovudine be given to all patients and end enrollment (Connor et al 1994). The US PHS recommended ACTG 076 be used as standard of care for HIV-positive pregnant women who had not been treated with AZT previously (CDC Colleague, Lurie et al 1997).

Despite these groundbreaking results and recommendation, NIH and CDC continued to fund AZT trials using randomized placebo-control design, 15 as of 1997 (Lurie et al 1997) in developing countries. CDC collaborated in two studies in Thailand and Cote d'Ivoire to determine the most effective short-course regimens (NIH 1997; Epstein and Sloat 1998). The rationale for the short -course study in developing countries was a political economic one. According to statements issued by CDC:

> This regimen has become "standard of care" in the United States; and, as a direct result, there has been a dramatic decrease in HIV infections and reported AIDS cases among children in this country. However, the 076 regimen is currently not used, and is probably not affordable, in the developing world where annual national health budgets are often less than $10 per person. The cost of the drugs alone for the 076 regimen are at least eighty times that amount. The "short course" AZT regimen now being investigated involves giving oral AZT only in the last four weeks of pregnancy and during labor. This regimen is estimated to cost roughly $50. If this trial demonstrates effectiveness in reducing perinatal HIV transmission, it is clear that this new regimen would be a far more feasible option for women in developing world. Throughout most of the developing world where millions

> of women are infected with HIV, pediatric AIDS is a very serious and growing problem. Perinatal HIV transmission is the number one cause of pediatric AIDS. Infection rates among women in the general population of many countries are far higher than in the United States. In some African countries, more than 1/3 of women of childbearing age are HIV-infected. In Cote d'Ivoire, approximately 12-14% of women in the general population are infected with HIV. In Thailand, the rate of infection in the general population is somewhat lower but varies by location in the country. In the absence of cost effective therapy, we can expect about 25% of children born to HIV infected mothers to be infected themselves. The CDC-sponsored studies are being carried out in CDC-supported field stations, representing long-term collaborations between CDC and the host country health ministry. These collaborations have, for a number of years, focused on public health issues of importance to both the host country government and to the United States (NIH 1997: http://aidsinfo.nih.gov/news/363/cdc-studies-of-azt-).

In the Thailand placebo-control trial, women participating in one study arm were given placebo while the other arm were given one zidovudine 300 mg twice per day for 36 weeks and every three hours during labor (Shaffer et al 1999). Placebo-control trial would be difficult to ethically justify today, unless there is no available treatment.

In a 1997 Lurie and Wolfe published an editorial in the *NEJM* criticizing these trials as unethical pointing to several ethical problems. They argued that two clinical trials were being conducted in the US where all participants had unrestricted access to AZT or other antiretroviral drugs. Additionally, Lurie and Wolfe argued that the trials were ethically flawed because they applied different ethical standards in developing countries. Under federal regulations, US-funded research should not exposed individuals to unnecessary risk (Lurie and Wolfe 1997). A series of debates was spurred by Lurie and Wolfe's editorial (Harvard 2013) and the studies were compared to TSS.

CDC's Response to OPRR

As parts of the corrective actions in response to OPRR's investigational report, CDC constituted six IRBs (A, B, C, G, and two more at NCHS and NIOSH), and set up an amnesty IRB (IRB S) to review all the protocols that OPRR required CDC to re-review, including the 96 suspended international studies. Afterward, IRB S became a permanent standing IRB on call to review emergency protocols. CDC leadership (Snider and Stroup 1997) published in an editorial in the *Public Health Reports* their rationales for how public health should define research and nonresearch and CDC followed with formal guidelines in 1999. Chapter 3 describes the social process that CDC took to develop the 1997 editorial and the 1999 Guidelines, which had since been revised into a CDC policy, although the 1999 Guidelines were also considered official CDC policy. A human subjects manual was also developed and issued in 1997 highlighting CDC commitment to the ethical conducts of research and to abide with federal regulations (45CFR46). The results of the OPRR's investigation and restriction of CDC MPA ushered in a new era of stricter oversight and more stringent IRB review of CDC research, as well as the implementation of formal research determination process. The number of research protocols requiring CDC IRB approval dramatically increased after 1997 (Table 1). A former CDC colleague who worked in CDC HSA said, "[It] seems [like] investigators were coming out of the closet to have their studies reviewed by an IRB," sometimes for study protocols that may not have actually meet the regulatory definition of research. OPRR appeared to be encouraged by the changes they observed taking place at CDC. According to Thomas Puglisi, who was the Chief Compliance Officer at

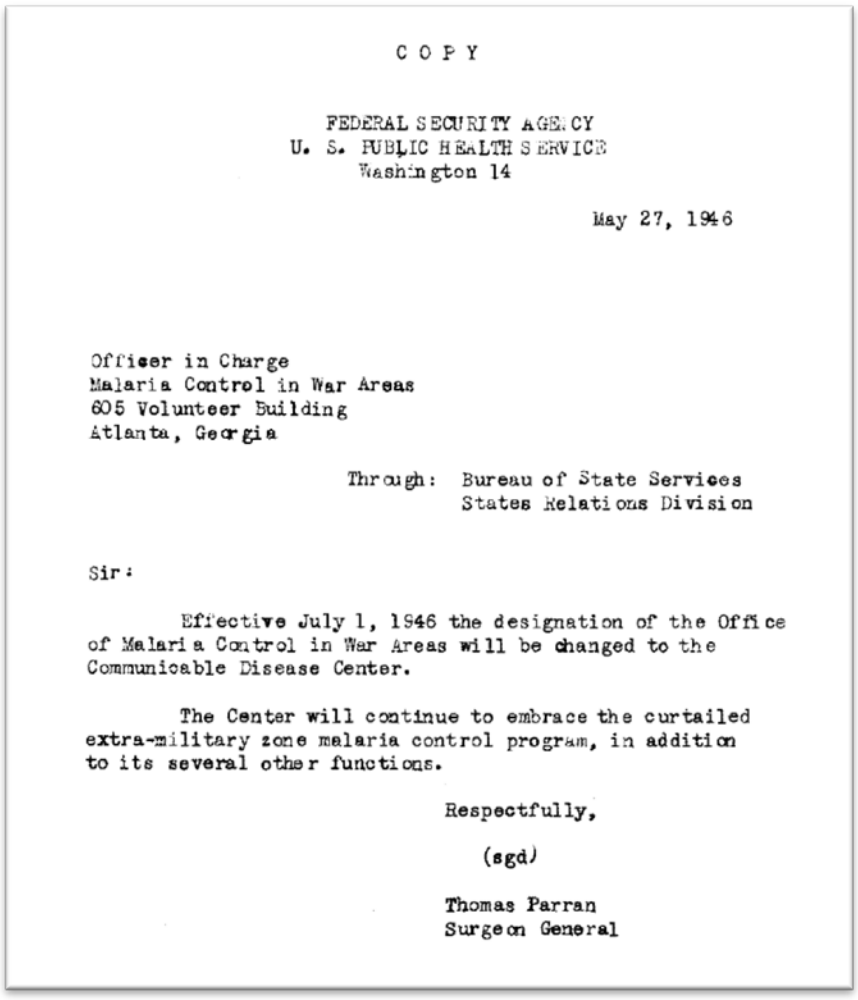
OPRR, "It takes a long time to change a culture, but there are people at the CDC now who are getting it. They're learning. But we've also learned when it comes to human subject protections, one has to be ever-vigilant" (Epstein and Sloat 1998).

Reorganization for Program Efficiency

One of CDC's most obvious cultural practice is the continual strive for improvement and efficiency through reorganization. In the early days in 1946 MCWA was renamed the Communicable Disease Center, which gave CDC its famous acronym (CDC Connect Story 2008: This Week in CDC History Timeline). The name changed several more times to National CDC in 1967, to the Center for Disease Control in 1970. CDC became an agency under the US PHS in 1973. An "s" was added to "center" in 1980 when major units were renamed as centers (CDC Connect 2013). In 1992 an act of Congress changed CDC's name to the "Centers for Disease Control and Prevention" in recognition of the agency's role in "prevention" (CDC 1992)[32].

[32] This reference is an internet article that has no page number.

Figure 4: Letter from Surgeon General Thomas Parran



C O P Y

FEDERAL SECURITY AGENCY
U. S. PUBLIC HEALTH SERVICE
Washington 14

May 27, 1946

Officer in Charge
Malaria Control in War Areas
605 Volunteer Building
Atlanta, Georgia

Through: Bureau of State Services
States Relations Division

Sir:

Effective July 1, 1946 the designation of the Office of Malaria Control in War Areas will be changed to the Communicable Disease Center.

The Center will continue to embrace the curtailed extra-military zone malaria control program, in addition to its several other functions.

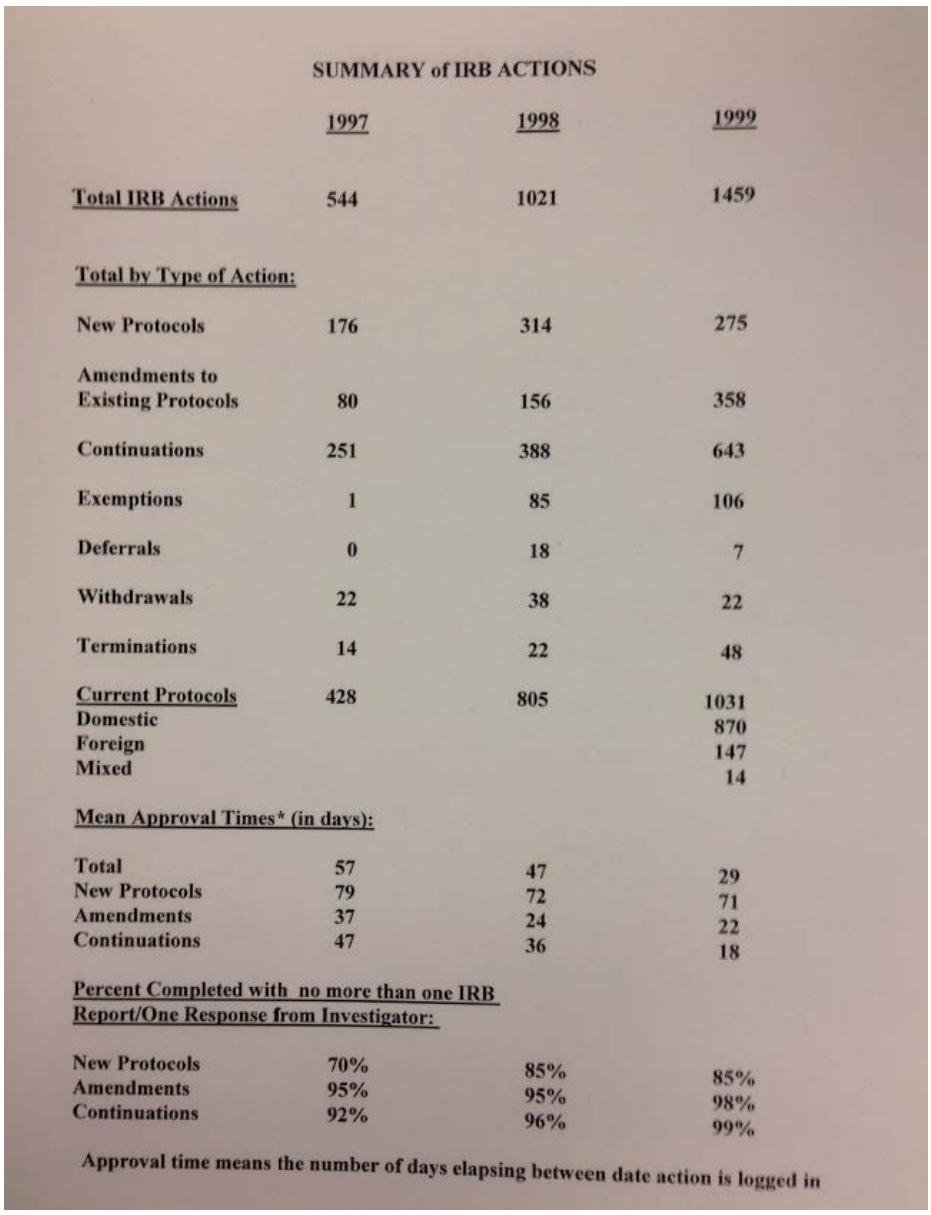
Respectfully,

(sgd)

Thomas Parran
Surgeon General

Source: CDC Repository of Organizational Changes (ROC) http://isp-v-maso-apps.cdc.gov/ROC/#

Table 1: CDC IRB Actions from 1997-1999



SUMMARY of IRB ACTIONS

	1997	1998	1999
Total IRB Actions	544	1021	1459
Total by Type of Action:			
New Protocols	176	314	275
Amendments to Existing Protocols	80	156	358
Continuations	251	388	643
Exemptions	1	85	106
Deferrals	0	18	7
Withdrawals	22	38	22
Terminations	14	22	48
Current Protocols	428	805	1031
Domestic			870
Foreign			147
Mixed			14
Mean Approval Times* (in days):			
Total	57	47	29
New Protocols	79	72	71
Amendments	37	24	22
Continuations	47	36	18
Percent Completed with no more than one IRB Report/One Response from Investigator:			
New Protocols	70%	85%	85%
Amendments	95%	95%	98%
Continuations	92%	96%	99%

Approval time means the number of days elapsing between date action is logged in

Source: CDC OADS Archive, Control # T7909A, Box 25, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294

According to an *MMWR* article about CDC history:

> CDC grew by acquisition. The venereal disease program came to Atlanta in 1957 and with it the first Public Health Advisors, nonscience college graduates destined to play an important role in making CDC's disease-control programs work. The tuberculosis program moved in 1960, immunization practices and the MMWR in 1961. The Foreign Quarantine Service, one of the oldest and most

> prestigious units of PHS, came in 1967; many of its positions were soon switched to other uses as better ways of doing the work of quarantine, primarily through overseas surveillance, were developed. The long-established nutrition program also moved to CDC, as well as the National Institute for Occupational Safety and Health, and work of already established units increased. Immunization tackled measles and rubella control; epidemiology added family planning and surveillance of chronic diseases. When CDC joined the international malaria-eradication program and accepted responsibility for protecting the earth from moon germs and vice versa, CDC's mission stretched overseas and into space (CDC 1996: 526-530).

Changes during reorganizations were not limited to just new names and acronyms. New programs with new priorities were created and whole programs were dissolved. People were relocated to other programs, documents were lost, including documentation about human subjects research, even though certain records were required to be kept and sent to the federal record archive. New programs were created through the coalesce of small units. Major reorganization occurred twice since OPRR's investigation in 1993. CDC has a history of undergoing constant changes and these changes affect its culture, people, and practices. During each re-organization people got reshuffled and new people brought in from outside of CDC. Everyone at the agency knew that re-organization is an expected fact of life at the agency, but each time there is a major re-organization, stress level and anxiety always ran high.

These reorganizations, large and small, contribute to and in many ways affirmed one of CDC long standing cultural values, a drive for organizational efficiency, although an efficiency that is biased towards achieving public health goals. Although these were the goals, these changes may or may not lead were improved efficiency and service. At CDC and likely true with many government

administration and agencies, one of the first noticeable signs of impending changes is the change in leadership, often starting with a new administration in the White House.

On April 21, 2005 CDC Director Julie Gerberding announced plan for a major reorganization of CDC. The reorganization was completed in 2007. In the recent re-organizations started in 2009, many people including well respected senior scientists within the agency believed that these changes were politically motivated. In each of the last two agency-wide reorganizations, the changes came when a new White House appointment took helm at CDC. When a new administration takes over, often previous changes had to be undone. The most recent re-organization, termed "organizational improvement" to distinguish it from the previous (2005) re-organization, was believed by many at the agency as a revert back to the pre-2005 CDC. The 2005 re-organization was viewed by many CDC staff, especially scientists, as particularly disruptive, but it was also thought to be necessary at the time in the aftermath of 911 and anthrax attacks in 2001. The world had changed and CDC became the frontline in bioterrorism defense.

A New York Times' (NYT) article describes CDC as the most changed agency during the Bush administration with entirely "new buildings, new managers, and new operating structure" (Harris 2010)[33]. The structure the article was talking about was the additional layer of bureaucracy created during the 2005 re-organization. Before the re-organization, centers' directors were direct reports to the CDC director. The re-organization grouped major centers together under a new

[33] This is an online article, which has no page number.

structure called “coordinating centers” (CC), effectively adding another level of bureaucracy at the agency sociopolitical structure (Figure 7). Centers’ directors who previously reported directly to CDC Director now reported to the CC directors, under which their centers were grouped. New non-scientist senior management official positions were created at various levels. The changes were not restricted to the center level. Divisions and offices were also reshuffled, new offices, branches, and divisions were created. The changes were often seen as disruptive, caused high stress level among employees, and to some, counterproductive to the agency’s missions. Harris, in the NYT article, describes how CDC reverted back to its old organizational structure after Tom Frieden took charge:

> A year into the Obama administration, only the new buildings remain. Dr. Thomas R. Frieden, the agency's director since June, has quietly scrapped nearly all the administrative changes that the previous director, Dr. Julie L. Gerberding, spent much of her six-year tenure conceiving and carrying out. Gone are the nonscientific managers whom Dr. Gerberding sprinkled throughout the agency's top ranks. Gone is a layer of bureaucracy, agency officials said. Gone, too, are the captain's chairs with cup holders from a conference room so fancy that agency managers dubbed it the Crown Room. In their place, Dr. Frieden has restored not only much of the agency's previous organizational structure and scientific managers, but also its drab furniture. And he has brought something new: a frenetic sense of urgency (2010).

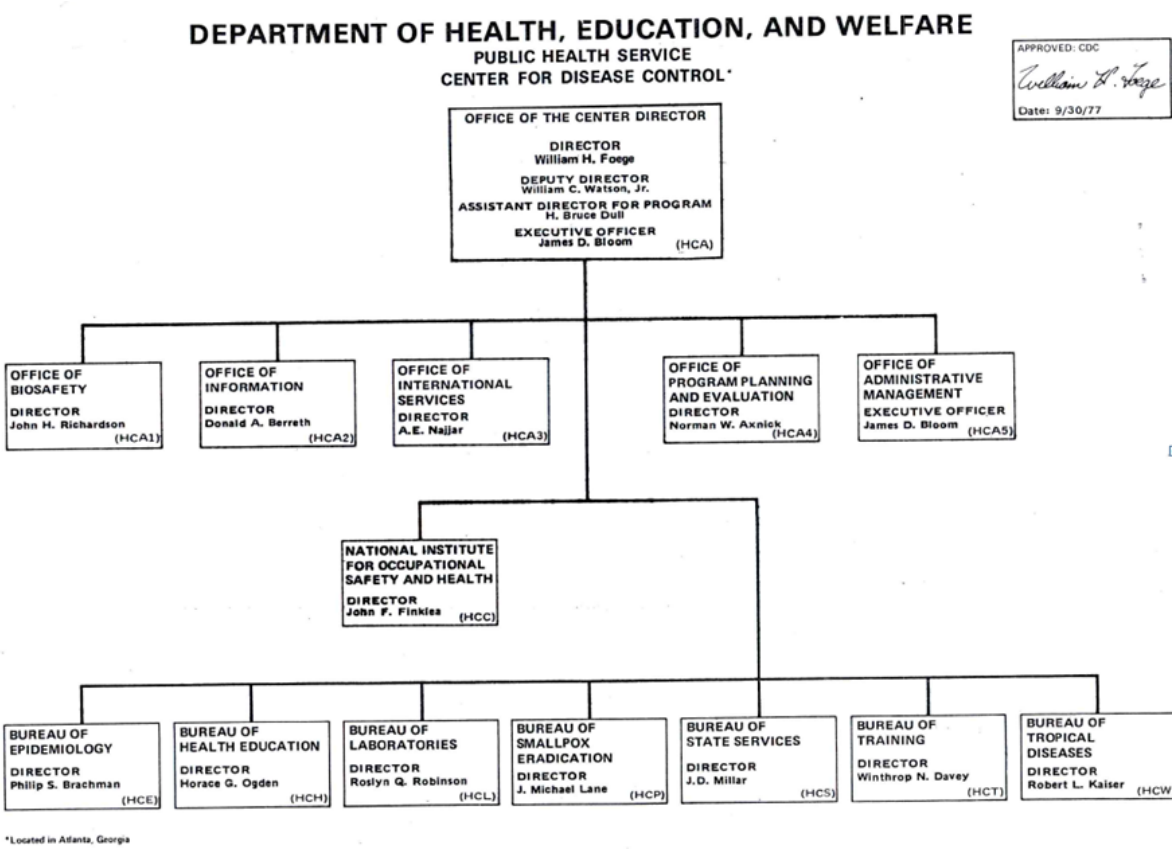
Harris also includes Dr. Gerberding’s email response to the reverted change:

> The 9/11 and anthrax attacks, SARS, and other global health threats altered the landscape of public health forever and made it necessary for C.D.C. to work faster and more synergistically to protect health than it had before. That was the intent of the reorganization. I'm sure the new ideas that Dr.Frieden is introducing are motivated by the same intent (2010).

Organizational Silos

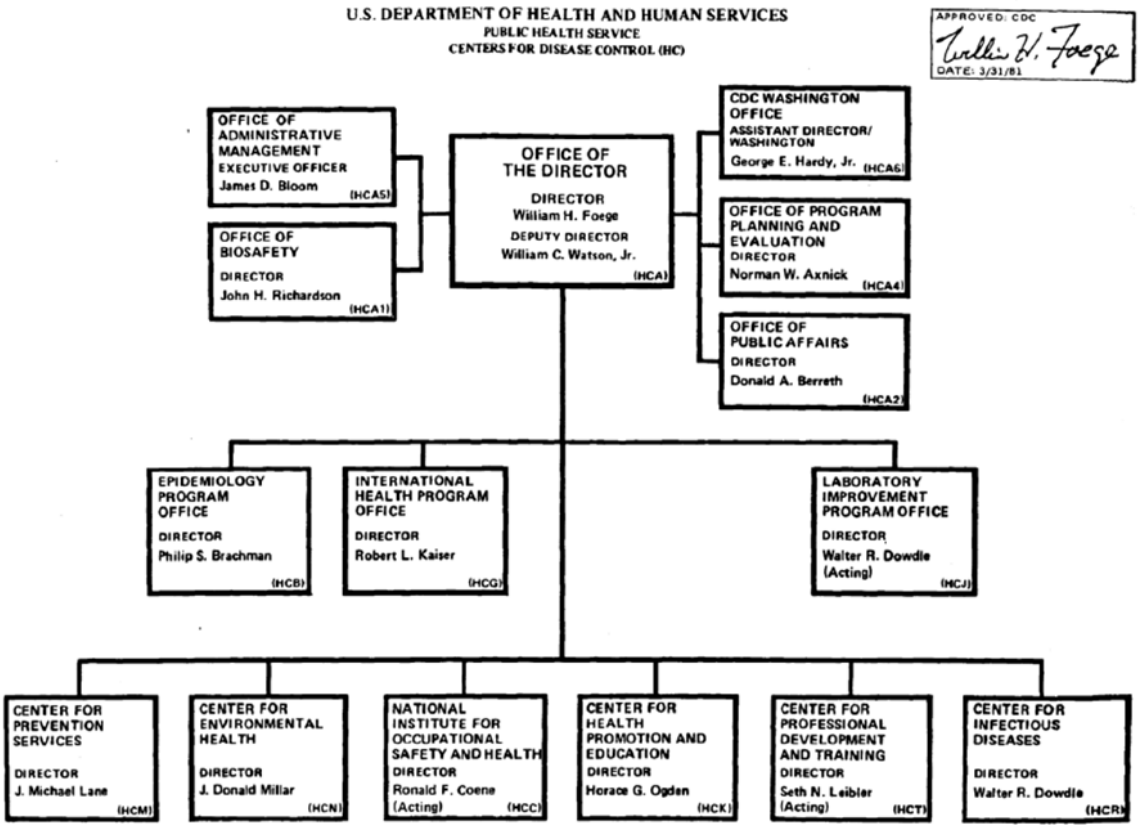
Historically, CDC has attracted other federal programs that later became divisions within CDC (See Etheridge's book *Sentinel for Health* for a detailed history), and in 1980 six major divisions, previously called "bureaus," were renamed "centers" and an "s" was added to CDC's name (Figure 5 and 6). Centers were traditionally organized according to specific disease or condition focus, e.g., in the current organizational scheme, there are National Center for Chronic Disease Prevention (NCCDP), National Center for Injury Prevention and Control (NCIPC), National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention (NCHHSTP), Center for Global (CGH) and so forth (Figure 8). Although this approach has served CDC well, having different centers with different leaders and missions, focusing on different diseases also created silos that can hinder cross-collaboration and reduce organizational efficiency. CDC silos, a term referring to farm equipment used to separate different types of grain, developed over time during CDC development and reorganization, grouping people according to their expertise. Major silos can be seen on CDC organizational chart, but smaller silos also exist within each major division, e.g., each center is made up of divisions and each division is made up of branches.

Figure 5: CDC Organization Chart, September, 30, 1977



Source: CDC Repository of Organizational Changes (ROC) http://isp-v-maso-apps.cdc.gov/ROC/charts.html.

Figure 6: CDC Organizational Chart, March 31, 1981

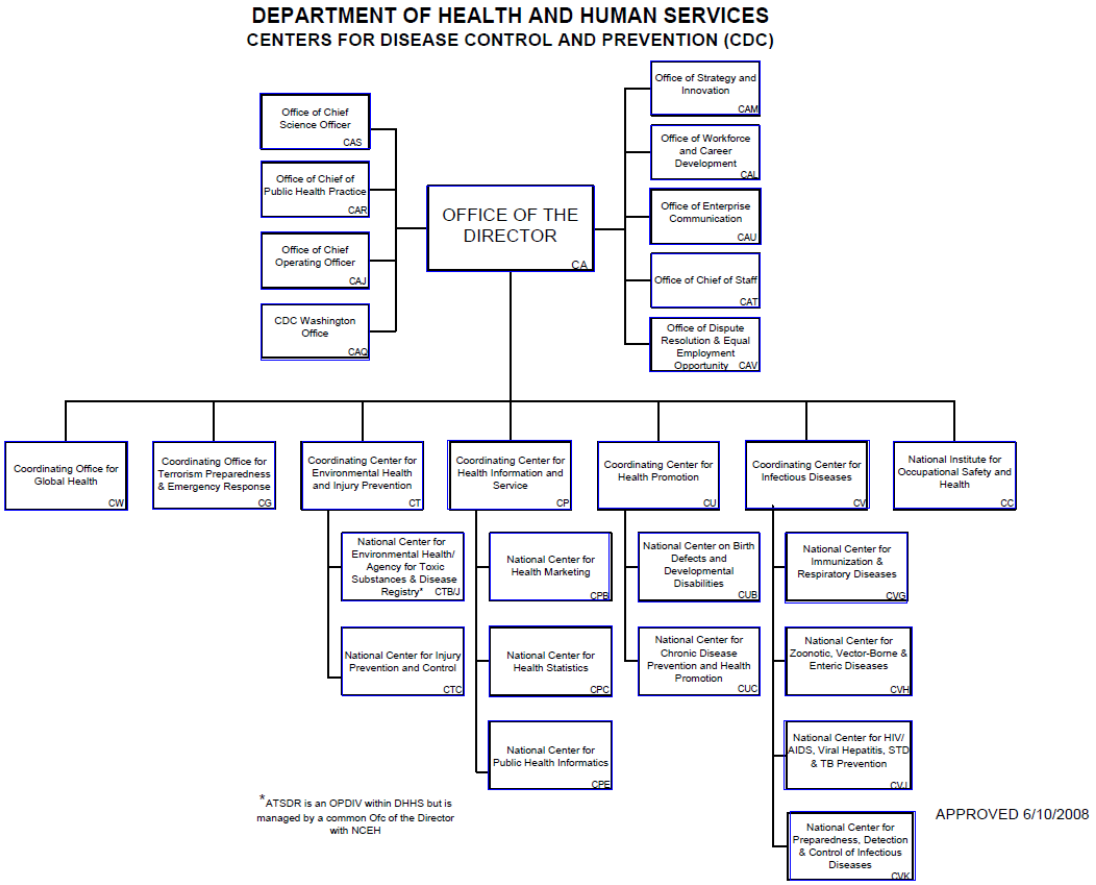


Source: CDC Repository of Organizational Changes (ROC) http://isp-v-maso-apps.cdc.gov/ROC/charts.html.

However, silos are here to stay and not always seen as a bad thing at CDC, although it can be a challenge to achieving public health goals. Former CDC Director Julie Gerberding was interviewed about the challenges she faced with organizational silos for an internal CDC article during emergency situations, such as the anthrax attacks, severe acute respiratory syndrome, and avian influenza outbreaks. In Gerberding's own words, Walsh describes how CDC leaders had "to bring people from a lot of silos together: communications, health informatics, all areas throughout the agency." In the article, Gerberding states that CDC scientists are

"some of the nation's most important national treasures. They need to go very deep into their field, and they find it distracting to look outside their scientific specialty. CDC developed extraordinary silos, but it didn't connect them" (Walsh 2005: CDC Connect Story). Although silos have their purposes, they create extraordinary challenges with communication, information sharing, and consensus, which contributes to its overall organizational cultures. Sometimes it is necessary to connect silos and the only way to do this sometimes is to force it, because people and programs usually feel too comfortable in their silos and they resist any change they feel will hinder their efforts or that takes too much work or resources.

Figure 7: CDC Organization Chart 2005-2009



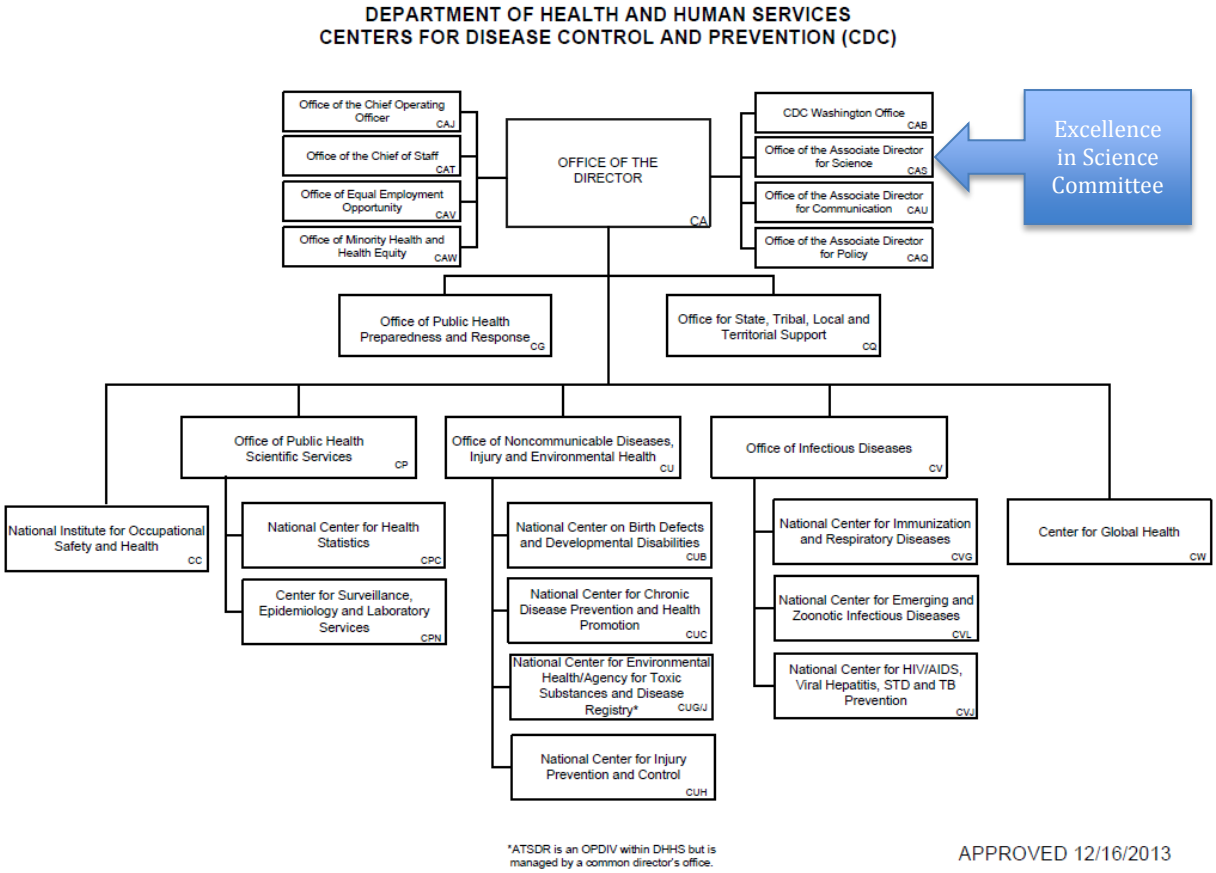
Source: http://www.nafv.org/PrintedDocuments/CDC+Organizational+Chart.pdf

To better understand the silo challenges on a smaller scale focusing specifically on the research determination practice, we can look at how organization silos affects the process at the Center for Global Health (CGH). The formation of CGH is reminiscence of how CDC was formed. CGH was established in 2010, although precursors to CGH have long been parts of CDC in various capacities and programs, e.g., Office of Global Health, Coordinating Office for Global Health, and International Public Health Program Office. CDC's foray into international health began early on when it joined the global malaria eradication campaign. CGH was established through a restructuring and reorganization of existing CDC programs. Initially four divisions were established and a fifth division later joined CGH. Two of the four divisions were programs or divisions previously resided with other centers. These are the Division of Global HIV/AIDS (DGHA), Division of Parasitic and Malaria (DPDM). DGHA was originally a division within the National Center for HIV, Hepatitis, STD, and TB Prevention (NCHHSTP). DPDM was originally a division within the National Center for Infectious, and Respiratory Disease (NCIRD).

The other two divisions, the Division of Public Health Systems and Workforce Development (DPHSWD) and Division of Global Disease Detection and Emergency Response (DGDDER) were also formed from acquisition of various CDC programs. A fifth division, Global Immunization Division, joined CGH later in late 2011, but was originally a division within the National Center for Immunization and Respiratory Diseases (NCIRD). Figure 9 shows the most recent organizational chart for CGH,

although it will be changed again in the near future.[34] The problem with having many silos is that each silo has their own way of doing things.

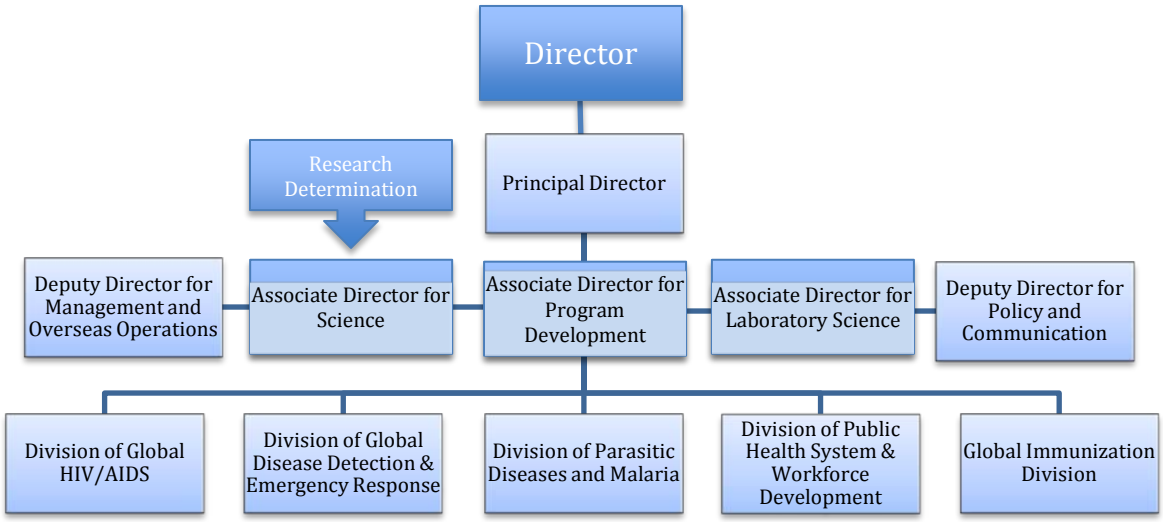
Figure 8: CDC Current Organizational Chart 2013



Source: CDC. Available at http://www.cdc.gov/about/organization/orgChart.htm.

[34] The divisions of Parasitic Diseases and Malaria and Division of Global Disease Detection and Emergency Response were merged into one, named Division of Global Health Protection (DGHP).

Figure 9: Center for Global Health Organizational Chart, CDC



Before October 2010 research determination for these various components were coordinated by HSCs from four other centers on behalf of CGH. Investigators were used to different processes and people they previously worked with. Two of the divisions came from centers where submitting projects for research determination was not a requirement, but a recommendation. When I spoke with their HSCs, I received basically the same response, that if investigators would like to have official support from their office, they can submit their project to receive an official determination. What this means is that if an investigator and their program are certain that their project constitute nonresearch then they have the option to implement the project without obtain an official letter stating that the project is nonresearch. This also means that the investigator and program make their own determination. However, if they do not obtain an official determination, then the investigators will be on their own. In this sense, receiving official determination

implies that they investigators will have some level of protection, or at least support, should they encounter problems later from OPRR, the media, or publisher if they choose to publish results from the project.

A Culture of Resistance

Investigators and programs' resistance to regulations and policies take many forms, which will be discussed in more details in chapter 4. Basically, resistance from programs and investigators to the overall IRB process may include any of the following nine strategies:

1. Submitting a summary of a protocol for determination when a complete protocol is available
2. Submitting research determination only after obtaining local approval
3. Getting local collaborators, including country Ministry of Health or local and state health department, to approve the project as nonresearch in hope that CDC would also approve it as nonresearch
4. Submitting a research determination after a project has ended (retroactive)
5. Being creative about study objectives (gaming the system) because of how CDC defined research based on primary intent
6. Obtaining a non-engaged status to avoid CDC IRB, if it suits their needs
7. Rationalize with reviewers whose hands are tied, thinking that if the reviewers give their blessing it's okay even if it's not in compliance
8. Implement program as nonresearch then later de-identified and use the data for research
9. Play ignorance

Programs and investigators believed it was advantageous to have a project determined as nonresearch. Results from the agency-wide survey show that among 335 respondents, 227 (83%) agreed that it can be advantageous to have a nonresearch determination for their project (Table 2). There are several reasons why this perception is pervasive at the agency. Top among these reasons is the

belief that the IRB review process is burdensome. Among 342 respondents to the survey question about how they perceive IRB, 239 (67%) believe that CDC employees considered the research determination and IRB process is burdensome (Table 2). The 70 individuals who checked "Not sure" were likely individuals who have not been involved in submitting a project for determination. This perceived burden can translate to the time and effort the investigators must take to revise the protocols to respond to the reviewer's comments, but most investigators see the burden extending beyond the impact on them, but to the populations they are trying to help. They viewed the delay due to the review and approval process that could result in the loss of life in some circumstances, for example, during emergency outbreak response.

Table 2: Survey Response on Perception of the advantageous if Determined Nonresearch

	Agree	Disagree	Not sure
At CDC it can be advantageous if a project is determined to be nonresearch	277 (82.7%)	58 (17.3%)	
Research determination and IRB review processes are generally considered burdensome by CDC employees	230 (67.3%)	42 (12.3%)	70 (20.5%)

The acronym "IRB" is a dreaded word for many CDC scientists, particularly junior ones, but it is not the only thing they dislike. IRB conjures up bureaucracy,

multiple forms, paperwork, and multiple layers of review and revisions of study protocols in people's minds (See Figure 1). Weber (1922) describes bureaucracy as the most efficient form of organization. According to Weber, bureaucracy is an impersonal, hierarchical system, managed by rules, organized by functions and missions. Individuals within a bureaucracy filled their positions according to their expertise. Unfortunately, there are bureaucratic hurdles that people at CDC detest and perceive as obstacles that delay their work, reduce their efficiency, and prevent them from achieving public health goals. Though CDC scientists generally do not talk about the power relations that come with bureaucracy, this can also play a role in the delays. CDC employees often speak about any new bureaucratic hoop they have to jump through with sarcasm. Throughout its history that began in 1942, bureaucracy at CDC is often seen as a hindrance to achieving public health objectives and improving health and saving lives. One of the integral parts of bureaucracy is filling out forms. Submitting a research protocol through CDC IRB requires filling out multiple forms. One CDC colleague viewed filling out forms as purely administrative, which has nothing to do with research ethics or human subjects protection.

> I think most things should have a protocol and oversight, but filling out forms on a regular basis is something I don't need. It has little to do with how you actually do anything, because you have to apply the same ethical standards whether it's research or not research. It's all administrative work. It doesn't--it should not ever impact how you interact with participant on whether you are collecting surveillance data from, you know information for program purposes or for research purposes.

At a science team meeting I routinely attended, one of the topics that were discussed was the implementation of a new system for approving CDC-sponsored

conferences and meetings. The system requires multiple levels of review. There was discussion about new, absurd restrictions on CDC staff attending conferences, for example, CDC employees cannot drink coffee or eat anything provided at a conference. People in the room spoke sarcastically of how wonderful and great this new system would be, knowing well that others understood that it is the total opposite.

To get a sense of what is behind this rhetorical question we need to visit CDC's historical roots. As with any federal agency, bureaucratic hurdles are routinely thrown at CDC from DHHS or from other parts of the government such as the Office of Management and Budget (OMB). These hurdles, for instance, having to go through different layers of red tape to access resources necessary to do one's job, make little sense to CDC employees. Some historical and contemporary examples are described below. CDC employees have a tendency to reject or resist any new system they have had no input in or find ways to make it economically sensible. Individuals also seem to weigh the broader public health benefits against potential risk, including personal risk, and it seems that this type of thinking was not only tolerated at CDC, but encouraged, a "negotiated culture" between what the individual feels as what may be "rule bending," but acceptable within the larger cultural context. CDC employees are encouraged to be innovative and think outside the box and this practice dated back to its early history. Some view this as CDC culture of rule breaking or gaming the system, but many at CDC see it as "getting the job done," "saving lives," "saving taxpayers' dollars." If rule bending is done for the greater good, but otherwise has no observable effect, then it seems that people will

tolerate such act.[35] Recently, Secretary of Health, Katherine Sebelius congratulated CDC on being named the "most trusted" agency in America (Sebelius 2013). CDC has consistently topped national surveys over the last several years and it reflects on the trust the American public has on the agency, which lends credence to its people and cultures.

[35] HHS has guidelines on institutional engagement in human subjects research as discussed in Chapter 3. Under this guidelines investigators from an institution that has been deemed non-engaged in human subjects research cannot interact with study participants or have access to identifiable data for research purposes, but IRB cannot enforce this policy in the field. Many investigators I spoke to said, in a hush-hush tone, said that does not happened. They have observed participants or have access to identifiable information in the research setting even when CDC was not considered engaged. People seemed to tolerate this apparent rule bending as long as there are local ethical oversights.

Chapter 3: Research Determination in Regulations and Policies

"OHRP believes that there are two problems with the reasoning in this document [referring to CDC 1999 Guidelines] regarding the distinction between research and nonresearch. The first concerns the use of the idea of "primary intent" as the basis for the distinction between research and nonresearch, and the second concerns the understanding of the generalizability of results. Both problems tend to lead to the conclusion that activities are nonresearch when they should be considered research as defined by Department of Health and Human Services (HHS) regulations at 45 CFR 46.102(d)."

OHRP Comments on CDC 1999 Guidelines (2005: 1)

The Common Rule defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (DHHS 2009: §46.102d). This definition is principally based on a definition socially-constructed by members of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission), which is encapsulated in the Belmont Report (Levine 1979).[36] The Belmont Report also attempts to articulate the differences between research and practice, but the language focuses primarily on biomedical research and practice. The Belmont Report states:

> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is

[36] The Commission, established on July 12, 1974 under the National Research Act, was tasked with identifying basic ethical principles for biomedical and behavioral research involving human subjects. The result of their deliberation was the Belmont Report, named after the Belmont Conference Center at the Smithsonian Institute (DHHS 1979).

> usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective (DHHS 1979).[37]

The focus on biomedical research, though understandable, is problematic for public health. The Belmont Report was developed following a series of medical abuses conducted in the name of science. This fact is universally recognized by practitioners and scholars alike (e.g., Snider and Stroup 1997, Santelli et al 2000, Burris et al 2003, Sankar 2004, MacQueen and Buehler 2004). Sankar notes:

> Whereas the goal of medical care is symptom relief or cure for the patient, the goal of research is hypothesis testing for the investigator. Thus, a *patient's treatment* is based on what is *best for* the patient's health, while *a subject's management* is based on what is *best for*, or required by, the research design (Sankar 2004: 430).

The Belmont Report does not allude to the term "nonresearch," which in public health is commonly equated to "practice." There is also no specific reference to public health, which views "patient" from a population level (Snider and Stroup 1997). Under the Belmont Report, it is not expected that a study protocol is written when commonly "accepted therapy" is implemented as part of medical practice. The same principle has been historically applied at CDC and in public health more generally. The Belmont Report also does not automatically consider every "experimental"[38] procedure to be research, however, it suggests that when "radical new procedures" are proposed, that formal research should be planned to determine its effectiveness. It also states that research and practice can be conducted simultaneously. In such case, "the general rule is that if there is any

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[37] The Belmont Report is a short document a few pages long and can be found in its entirety at http://www.hhs.gov/ohrp/humansubjects/guidelines/belmont.html.

[38] Experimental procedure refers to the use of new medical treatment or device on patient for a particular purpose that have not been approved by the FDA for such use.

element of research in an activity, that activity should undergo review for the protection of human subjects" (DHHS 1979). The Common Rule does not provide guidelines on how research determination is to be made and by whom, leaving it to the public health community to figure out for themselves.

In the Field

Most people I spoke to or interviewed over the last couple of years provided similar responses when I asked a seemingly simple question, "How do you define research?" Almost everyone, including non-US citizens, locally employed staff (LES) from other countries, attempted to regurgitate the Common Rule's definition, but usually with no further explanation of what it means. The 2012 survey also supports this fact. Two hundred nineteen (72%) among the 306 respondents who answered the question, "Which of the following is the regulatory definition of research?" correctly identified the Common Rule's definition (Table 3). Unfortunately, 126 of the 422 people who took the survey did not answer the question. My sense is that most people I have encountered, who work for CDC, must have been exposed to this definition, either through trainings they received or were educated by other CDC staff.[39] Their responses were not exactly the same, but they used similar terms in different orders. Usually their responses would be something like, "I think research is when the intent of a project is to develop generalizable information [knowledge] that goes beyond the study populations" or "research is a project designed to develop generalizable knowledge."

[39] A caveat to this is that most of the people I encountered were scientists or medical officers.

Table 3: Survey Response on the Regulatory Definition

Answer Choices	Responses	
A systematic investigation to develop generalizable new knowledge	16.34%	50
A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge	71.90%	220
A systematic method of evaluation designed to develop new knowledge	2.29%	7
A scientific method for developing new and generalizable knowledge	9.48%	29
Total		306

Often, people neglected to mention the term "design," but the term "generalizable" is almost always included on their take of the Common Rule's definition. One person assertively said, "If it's experimental design it's research."[40] Another person also assertively said, "A project is likely to be research if we include controls," but case-control studies are commonly used during emergency outbreak responses, which were mostly categorized as nonresearch. One of the most common outbreaks I have seen is related to food poisoning. Case-control method is commonly employed to determine the [culprit food] that might have been contaminated. One person, a LES doctor hired to serve as the CDC country ADS, stated what amount to be the regulatory definition, but then added, "I also think that when the researcher plan to publish their results that may be generalizing purpose and therefore the project is likely to be research." LES may not be as familiar with CDC policy. Intent to publish is not a defining criterion of research for CDC, although some people disagreed. According to CDC:

[40] In this case, experimental refers to anything new that has not been tested and shown to be effective. Any systematic study of new intervention, including drug, medical device, or behavioral intervention is considered research.

> Other attributes, such as publication of findings, statutory authority, methodological design, selection of participants, and hypothesis testing or generating, do not differentiate research from nonresearch, because these types of attributes can be shared by both research and nonresearch activities (CDC 1999 Guidelines: 4; CDC 2010 Policy: 3).

Three focus group discussions among HSCs and other CDC employees captured their thoughts on the general and shared characteristics of research and nonresearch (Table 3). Each focus group consisted of 5-7 individuals. Similar characteristics of research, nonresearch, and shared attributes were stated by all three groups. Table 3 simply lists these general characteristics. These characteristics mostly reflect the CDC Policy, showing their familiarity with the policy.

Table 4: General and Shared Characteristics of Research & Nonresearch

Research	Nonresearch	Shared
• Generalizability • New knowledge/evidence • Systematic investigation • Establishing Efficacy or effectiveness • Purpose/intent • Systematic comparison • Replicable • Experimental/ nonstandard • Hypothesis • Exploratory	• Evaluation (Gray as it is!) • Program improvement • Characterizing or monitoring disease • Beneficial to community • Use same methods as research • Program evaluation (mostly nonresearch) • Surveillance activity • Public health responses to solve immediate problem • Purpose is to benefit the populations • Program monitoring • Lab proficiency testing (to test equipment) • Standard, proven practices	• Evaluation • Methods/design • Systematic • Publications • Generalizable • Can involve risks • Consent for participation • Hypothesis testing

A center ADS had an interesting response about the term "nonresearch." He thought that the term nonresearch is part of the confusion in the CDC policy. He said:

> I think if it's not research, it's practice. It's public health practice. When I think of public health practice I think of the essential public health service that is well defined and that everybody understands or should understand. And even when you are doing public health practice there is ethical obligations to make sure that there aren't unintended harm to the people you are trying to help. So I see the duty or obligation of a scientist in public health practice to be no less than a researcher who is doing research and trying to protect research subject from harm. And if more scientists thought of things that way I think a lot of the confusion would drop away. I like the term essential. That word carries powerful meaning for me. It should for other scientists. It means you can't do without it. The fact that you can't do without it to me makes it NOT research, because we can do without research. Life will be not as good without research, but the essential public health services, I think heighten the sense of duty that I have that you are going to do things for people and risk people that they did not ask you to do and you are arguing it's essential and they can't do without it and that's maybe that true and maybe it's not. Then if they can't do without it, you have to make sure that it turns out as you expected and bad things is not happening to people by inadvertent.

A Pragmatist Approach to Research Determination

Charles R. McCarthy, first Director of OPRR, had a more pragmatic philosophy when it comes to determining what activity constitutes research. According to McCarthy:

> However, frequently before we even turn to the regulations, we often apply a pragmatic standard in order to estimate whether research is involved. For example, if an activity is funded by a research component within the department, such as one of the Institutes of the National Institutes of Health (NIH), the presumption is that the activity constitutes research, because the Institutes are authorized by law to support research, and not to support health care delivery (1984: 7).

This may explain the generally hand-off approach OPRR took with CDC's practice before the 1993 investigation. As already discussed, CDC was not historically seen as a research institution. CDC was envisioned as an agency that put science and research into practice. One can argue that almost every activity CDC undertook had practical purposes--to enhance the health and wellbeing of the populations CDC serves. The "design" or "intent" or "purposes," however it is termed, of most CDC activities have practical applications in public health. For this reason, as noted in the Belmont Report, one does not usually develop a study protocol for practice. Most CDC research studies were conducted for the purpose of developing knowledge that can be used to prevent or control diseases or illnesses.

The confusion over how to interpret the regulatory definition and put it into practice is not limited to CDC. Recognizing the inherent problems in applying the federal regulations to public health activities and the difficulties in determining when a project is research, Burris et al (2003) advocate for an exemption of public health institutions entirely from the federal regulations. Similar to CDC's rationales articulated in the 1999 Guidelines and 2010 Policy, they based their argument on several distinctions between public health and biomedical research. The Common Rule, they emphasize, was developed within the biomedical context brought on by abuses in biomedical research. They also pointed out that, similar to when physicians over the course of examining, diagnosing, and treating patients may develop new, generalizable knowledge, public health professionals in the course of conducting public health activities may also develop generalizable knowledge. Similarly, in both cases, other ethical principles and oversight system applied under

local laws and moral obligations. Although they see their argument as the beginning of the discussion, Burris et al noted that some US states, such as Virginia, have already taken this approach. Amoroso and Middaugh also recognized that:

> Nonresearch activities generally take the form of patient treatment, public health practice, program evaluation, or population surveillance" and "public laws provide for oversight of the collection of confidential information by public health authorities without consent, and confer special protection of the information from public disclosure" (2003: 250).

CDC has traditionally taken the view that most of its public health activities are not covered under the Common Rule and that other public health laws apply. The problem is that people were usually unfamiliar with which public laws apply within the locality, where they conducted their work. Written protocols often referenced local laws, but do not describe them in any details. In making research determination, reviewers and approvers often had no idea what public health laws are applicable and would have to trust that the investigators and their local collaborators would be able to address these issues.

The National Bioethics Advisory Committee (NBAC) also supported CDC's view, thanks in part to the advocacy from CDC and the public health community. Part of this support is attributable to NBAC's view that other public health laws also apply in case of nonresearch. NBAC understood the confusion and difficulties in making research determination. In its 2001 report, NBAC states:

> In some cases, the knowledge gained from public health practice could be used to develop or refine knowledge. Although the individuals who participate in these activities rarely benefit directly, the intent of public health practice is always to prevent or control disease and improve health or to improve a public health program or service in a specific population (i.e., 'the public health patient'). Usually these activities are carried out under local statutes (2001: 36).

Burris et al argues that although exempting public health activities from the Common Rule does not obviate the needs to be ethical in carrying out public health activities, it could:

> …afford the opportunity to craft new methods of oversight and accountability…as well as a new definition of research where traditional IRB review of investigations conducted by public health agencies may be warranted, based on methods or risks…rather than intent (2003: 641).

This position is echoed by many at CDC, that the ethical review should be based on risk level and methods used rather than whether a project is research or nonresearch. One seasoned CDC investigator told me:

> Despite two decades of research experience, I've never understood why CDC differentiates between research and nonresearch. The fundamental goal of an ethical review, as I see it, is to determine whether a project adequately protects the rights of the subjects. Unethical projects could be in research or program evaluation. Why not divide protocols into whether or not they pose a minimal risk to subjects? You could then do expedited reviews of the minimal risk projects, and require a full review for everything else. With such an approach, one could completely avoid the 'Is it research?' question.

Another person, a division ADS and HSC, said that, "The ethical part of what the scientists are doing will still need to be there whether it is considered research or not." Although many people agreed that studies should undergo review based on the level of risk, most people did not advocate sending everything to the IRB as suggested. However, no one really knows what could be an alternative to the IRB, and no guideline exists on how risk level should be determined. The only existing guideline is the Common Rule's vague definition of "minimal risk," which is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or

during the performance of routine physical or psychological examinations or tests" (DHHS 2009: §46.102i).

Federal Mandates under the Common Rule (45CFR46)

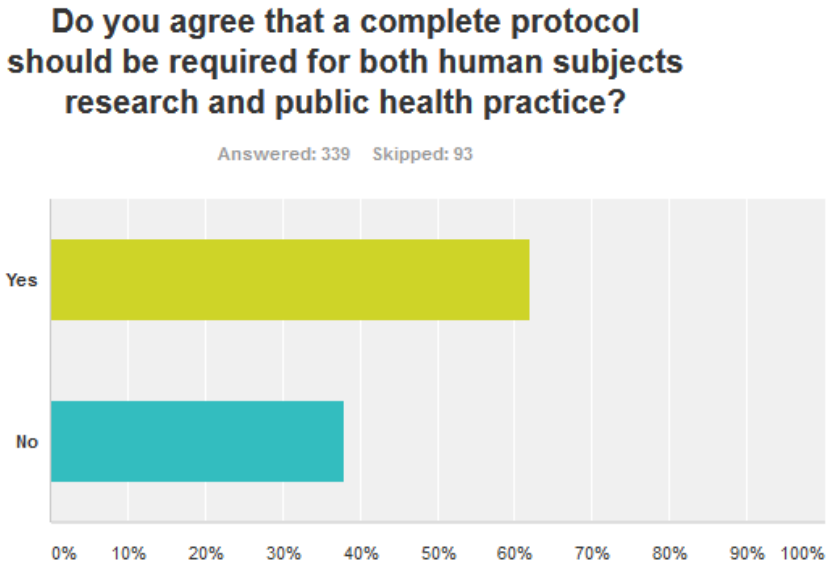
In 1995 CDC agreed to comply with OPRR's mandate that it needs to develop a guidelines and process to help investigators understand and determine when a public health activity is research (CDC 1995). Burris et al noted, and CDC knows well that:

> The problem with this view is….the day-to-day difficulty of drawing satisfactory line between research and practice using the definition of research in the Common Rule….The short version of the story, repeated again and again in all sorts of fields of study, is that the implementation of law is a transformative process: the people and institutions enforcing the law transform the law, the law transforms the people and institutions applying it, and in both cases the result may bear little relation to the intended outcome (2003: 641).

It is not so much that the policy or law literally transformed, but that the law (regulations) and policy derived from the regulations is interpreted and re-interpreted differently by different actors. They are not always in agreement. For research determination, investigators are generally biased towards having their projects determined nonresearch, because of the perceived or real bureaucratic burdens associated with the IRB process. In the few years after OPRR's visit, there was a major cultural shift in the determination practice. Policies in the form of the 1999 Guidelines were implemented and research determination process became formalized, although varied by centers, and investigators became more aware of the requirement to submit their projects for determinations. CDC policy, however, does not describe what information is necessary for research determination or whether a

complete protocol describe the project is needed. Most CDC centers do not require complete protocol for determination. HSCs often argued that they do were not provided with sufficient information to make research determination. Although many people were against requiring complete protocol[41] for both research and public health practice, in the 2012 survey, 210 (62%) of the 339 respondents to the question, "Do you agree that a complete protocol should be required for both human subjects research and public health practice?" selected "Yes" that a complete protocol should be required (Figure 10).

Figure 10: Complete Protocol for Research and Nonresearch



Answer Choices	Responses	
Yes	61.95%	210
No	38.05%	129
Total		339

[41] Complete protocol usually refers to a suggested format for scientific study and may include the following categories: Project Overview, Introduction, Procedures and Methods, Ethical Considerations, References, and other appendices.

The regulatory authority that governs the human subjects protection and research determination process is mostly derived from the Common Rule (45CFR46), although human subjects protection in clinical investigations (trials), for both research and nonresearch, is also regulated by the Food and Drug Administration (FDA), Title 21, Code of Federal Regulations, Parts 50 and 56. CDC has very few studies that fall under the FDA regulations; therefore the discussion to follow is focused on the Common Rule. The Common Rule was last revised in 2009, and is currently undergoing another revision. Section 45CFR46.101a dictates that the policy "applies to all research involving human subjects conducted, supported or otherwise subject to regulations by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research." This includes research conducted by Federal civilian employees or military personnel. Each "department or agency heads may waive the applicability of some or all of the provisions" (45CFR46.101b2i) of the Common Rule. "It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States" (45CFR46.101a). This applicability language, as we will discuss later, does not necessarily mean a public health project funded by CDC will required CDC IRB approval. CDC and any institution engaged in human subjects research covered by the Common Rule, namely federally-supported[42] research, must have the following in placed:

1. Assurance as dictated under 45CFR46.103a;

[42] Federally-supported refers to when an institution received direct funding from the US government, identifiable private information, or other tangible support. It does not include federal staff time in providing technical assistance.

2. If the institution supports (funds) another institution that is engaged, the funded institution must also have assurance in placed as dictated under 45CFR46.103b;
3. Sufficient staff to support IRBs review and record keeping as dictated under 45CFR46.103b2;
4. Have an IRB with varying background to promote the completeness of review as dictated under 45CFR46.107.

There are several exemptions defined in 46CFR46.101b. Exempt researches are not covered under the regulations and do not require IRB approval, although for CDC, exemption must be made by and approved by HRPO. Research that may be exempted from 45CFR46 include the following:

1. Conducted in established or commonly accepted educational settings, involving normal educational practices, such as (1) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricular, or classroom management methods;
2. Involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation;
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter;
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects;
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:(i) Public benefit or

> service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs;
> 6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
>
> (DHHS 2009: 45CFR46.101a)

Of note, section 45CFR46.101c places "final judgment as to whether a particular activity is covered by this policy" on the agency heads and section 45CFR46.101f and 45CFR46.101g noted that the regulations does not have any effect on state, local, or foreign laws or regulations that may provide additional protection. "Agency head" is defined in section 45CFR46.102a as the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.[43] Section 45CFR46.101h additionally permits, when research is conducted in foreign countries, the substitution of the foreign institution process if the agency determines that the institution "afford protections at least equivalent to those provided in this policy." Section 45CFR46.101i permits agency to waive the applicability of some or all of the provisions under the regulations. The Common Rule also required a notice for any of these actions to be submitted to the Federal Register.

[43] At CDC the delegated authority is with the CDC Deputy ADS.

The Source of the Confusion

CDC attributes the confusion and difficulty in defining research to the traditional view of public health and to the Common Rule, which does not directly address public health. According to the 1999 CDC Guidelines:

> The difficulty in classifying some public health activities as research or nonresearch stems either from traditionally held views about what constitutes public health practice or from the fact that 45 CFR 46 does not directly address many public health activities. In addition, the statutory authority of state and local health departments to conduct public health activities using methods similar to those used by researchers is not recognized in the regulations. Human subject protections applicable for activities occurring at the boundary between public health nonresearch and public health research are not readily interpretable from the regulations (CDC 1999 Guidelines: 1)

This excerpt from the guidelines captured an enormous amount of frustration and discussion at CDC. As noted earlier, the source of the Common Rule's definition goes back to the Belmont Report that was released in 1979. Much to CDC's disappointment, the Belmont Report focuses strictly on biomedical (therapeutic) intervention at the individual level. There appeared to be as much external frustration with the Common Rule's definition as there were within CDC. Beauchamp (2011) points out that there are many inherent problems in the Common Rule's definition. Even though the Belmont Report and the Common Rule were written within the context of biomedical research, the definition of research was not clear. According to Beauchamp:

> First, it uses the notion of research to define the term 'research,' creating problems of circular definition. Second, it does not define any of the several important terms (the key conceptual conditions) used in the definition, such as 'systematic investigation,' 'testing' and 'generalizable knowledge,' and these terms can be understood in several ways. Third, the definition is vague and overly broad because it is not clearly confined to biomedical research, clinical research and behavioural research – or even to *scientific research*,

> more generally. Its scope is left unclear. Fourth, and perhaps most importantly, it does not preclude 'research' from having a very close tie to 'practice (Beauchamp 2011: 384).

Among Beauchamp's concerns is the unnecessary overprotection, when in some cases "unnecessary delays" may cause unnecessary deaths and morbidity, a view that CDC had long held and had used in defense of its interpretation of the regulatory definition of research during OPRR's investigation.

> Because the definition is so nonspecific, regulatory requirements that use the definition may judge that some activities that are questionably research involving human subjects nonetheless must be treated as such. Government requirements are today commonly applied even if 'human subjects' may not need to be protected by the rules of human subjects research. A sweeping– that is, all-inclusive conception– of 'human subjects research' can have immediate and unjustifiable practical impact on attempts to up-grade medical care (Beauchamp 2011: 384).

Beauchamp cited the case of Peter Pronovost's (Pronovost et al 2006) catheter infection study where the confusion over the interpretation of the regulatory definition was seen at the highest level at OHRP. In response to a non-compliant complaint (no IRB review and no informed consent), OHRP opened an investigation into the study that according to Beauchamp (2011) was a quality improvement program looking at known effective interventions, such as hand washing, that have been recommended by CDC for such settings. Beauchamp believes that such study does not need IRB review and was not research involving human subjects. According to a senior CDC official (internal communication) the Pronovost's catheter study was perhaps the first time that "any national appreciation of the fact that even outside the public health realm, when you get to talking about group of

people, you have this difficulty of trying to classify things as to whether they are research or not research."

OHRP later acknowledged that the intervention was not medical research (OHRP 2008)[44] and issued the following statement, "the regulations do not apply when institutions are only implementing practices to improve the quality of care." Further, OHRP states, "We do not want to stand in the way of quality improvement activities that pose minimal risks to subjects…..HHS regulations provide great flexibility and should not have inhibited this activity…." In its resolution of the Pronovost's catheter case, OHRP acknowledged that the Common Rule permits great flexibility. By admitting that it was wrong and that there is flexibility, OHRP also acknowledged that there were confusions as well as disagreement among staffs within the federal office that regulates human subjects protection under the Common Rule.

The flexibility that OHRP referred is a reflection of the relatively strict requirements for an activity to meet the regulatory definition of research. An activity must be "systematically designed to develop or contribute to generalizable knowledge" before it can be called research under the Common Rule. If a study is not "systematic" and not "designed" to develop or contribute to "generalizable knowledge," it is not likely to meet this definition, although as Beauchamp pointed out, OHRP has not defined these key terms used in the definition. Seligson (2008) considers this definition unfortunate, precisely because of these exclusionary and strict requirements. It is unfortunate, he believes, because it would subject very

[44] Reference is from OHRP/DHHS archived web announcements; therefore there is no page number to cite for the quotes.

little risk research that meet the requirements, but also exclude other higher risk activities that do not meet the requirements. If a study is not systematically designed and the risk level is high, but it could potentially lead to important generalizable knowledge, it would not be subjected to formal ethical oversight. An example of such a case might be the off-label use of drugs for treating a new disease where the effectiveness and risks are unknown. Providing such treatment, e.g., treating nodding disease[45] patients with anti-epileptic drugs, on a case-by-case basis does not meet the regulatory definition of research.

Federally-supported

Under the current version, the Common Rule applies only if a "federally-supported" activity is deemed as "systematic investigation designed to develop or contribute generalizable knowledge" that involves human subjects. Human subjects is defined under the Common Rule as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information" (45CFR46.102f). According to the 2012 CDC-wide survey, most respondents understood that federally-supported means US government providing funding to a project. Federal employee staff time in providing technical support and expert analysis of research data are not considered as federally-supported (Figure 6). However, almost 50% of the respondents also incorrectly checked that providing

[45] Nodding disease is a syndromic illness characterized by head nodding among children between 5 – 15 years old. Cases have been reported since the 1960's, occurring only in parts of Uganda, Tanzania, and South Sudan. There is no known cause and is fatal. Anti-epileptic drugs have been used to treat cases. More information can be found at http://www.cdc.gov/globalhealth/noddingsyndrome/.

technical support, data analysis, and report writing as constituting federal support. HRPO also considered providing material support as constituting federally-supported.

Table 5: What does federally-supported mean?

Answer Choices	Responses
US government providing funding to a project	96.75% 327
US government official provide technical support (no federal funding)	47.93% 162
US government official participate in data analysis and report writing (no federal funding)	44.67% 151
Other	2.96% 10
Total Respondents: 338	

The issue of an activity federal support was linked to the engagement policy that was later instituted. According to a former HSM, "I consulted fairly frequently with OHRP, especially trying to understand the definition of conducted or supported, so that is where a lot of the discussion of engagement had its roots."

Institutional Engagement in Human Subjects Research

An important aspect of the human subjects protection practice is whether an institution is engaged in human subjects research. According to OHRP's Guidelines on Engagement of Institutions in Human Subjects Research posted on its websites, engagement is defined as followed:

> "In general, an institution is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable

> private information about the subjects of the research; or (3) the informed consent of human subjects for the research" (OHRP 2008).

These criteria apply only to non-exempt research, because exempt research is not covered and does not have to follow the requirements under the Common Rule. Another criterion an institution is considered engaged even if these three criteria are not met is when an institution received direct funding from a federal agency for the purpose of human subjects research even if all research-related activities are contracted out to another institution. For example, if CDC receives direct funding from HHS for the purpose of human subjects research, then CDC would be considered engaged, even if, CDC contracted out all research related activities and only receives anonymous data. Similarly, if CDC funds an institution to conduct human subjects research, the funded institution is considered engaged even when they contracted out the research to another institution. The funded institution is still required to hold a FWA, their IRB must be registered with OHRP, must approve the research. On the other hand, CDC's decision to fund human subjects research from its general appropriation does not automatically make CDC engaged.

Barring the last criterion about receiving direct funding for human subjects research as being engaged, in cases where investigator has access to linked data, a non-disclosure agreement can render the investigator and institution non-engaged. If an institution is not officially engaged in human subjects research, the institution is not required to hold a FWA and does not need to have its own IRB approves the research. Their involvement would be limited to providing technical assistance, participating in analysis of de-identified data, and co-authoring papers and

manuscripts, but their investigators cannot interact with participants and cannot have access to identifiable data for research purposes. For example, CDC investigators are often invited to participate in data analysis and report writing for a research study that has received local IRB approval. To be considered non-engaged in human subjects research, they can only have access to de-identified data. They can have access to linked data and be considered non-engaged only if there is a non-disclosure agreement. Often, determining whether an investigator is engaged involves trust. Protocols do not always spell out what role(s) collaborating institutions and investigators have.

Determining whether an institution is engaged in a particular human subjects research project has important ethical and administrative implications. When CDC is not officially engaged in human subjects research, but engaged in other aspects, such as through funding or providing technical expertise, CDC still has ethical obligations beyond the regulatory requirements, to ensure that the research is conducted ethically, even when CDC IRB approval is not required. In this case there is less administrative burden for CDC staffs, including HRPO and IRB staffs. Investigators often prefer to go this route, because they view it as less burdensome, even though they are still required to respond to any comments and requirements from their center HSC or ADS. Protocols often undergo multiple-level review which may include review by their supervisor, branch chief, division ADS or director. Some programs subject their protocols through other internal review for subject matter expert and technical review. According to a senior CDC official, “CDC may remain

unengaged and still contribute substantial intellectual input, provide funding, and participate as co-authors on publication."[46]

CGH, for example, (Table 6), received five times more requests that are non-engagement than for engagement that need to be sent to HRPO and CDC IRB. There is a general feeling among programs and investigators, including non-CDC investigators, that CDC IRBs are stricter than local IRBs, including international ethics committee. According to a former CDC HSM, there was also a claim that "CDC IRB trumps local IRB."

> There was a claim once at a meeting, at a presentation, before I was in that role that was, CDC IRB trumps local IRB. There is no basis for that. I can kind of understand the intuitive basis for it, because CDC is the funding agency, but that conflates the role of CDC as an institution with the CDC IRB as reviewing not really on behalf of the institution, but reviewing sort of CDC as an institution may carry out the research.

Obtaining non-engagement approval will reduce the time to getting a project implemented. On the other hand, non-CDC collaborators also often feel that having CDC IRB approval provides better protection for research subjects, which also helps to protect them as researchers, such as helping to avoid noncompliant with the regulations or protecting their reputation. A problem, as I will discuss later, is that often projects have already been implemented before a determination request are submitted and formal approval was given by CDC.

[46] This is a quote from someone I consider as one of my informants; therefore I cannot identify the person.

Table 6: Types of Research Determination Requests Received by CGH in 2013

	Engaged Research Approved by HRPO or IRB	Nonresearch	Research but no Human Subjects	Research but no CDC engagement
# of Research Determination Requests	33	191	37	159

Before July 30, 2007, HRPO and CDC IRBs accepted all protocols for review regardless of whether or not the Common Rule required CDC to review them. On July 17, 2007 CDC OADS issued a memo describing a new policy. The policy states that HRPO would no longer accept protocols for review when CDC is not engaged in human subjects research. The rationale for instituting the non-engagement policy was, according to a former CDC HSM, was that that CDC IRB does not have a "say about what happened at another institution."

> I came to understand, you know, hierarchy of authority with the regulations, departmental policy, agency policy, agency practice, and so and distinguishing between what is it that under the purview of CDC as an institution or CDC IRB and other activities that happen outside of CDC. So what can CDC IRB say about what happen at another institution. It turned out that a lot of what people had been thinking was wrong.

However, the rationale that was used to justify this change was largely an economic one. According to the memo:

> Temporary staffing shortages in HRPO have reduced the office's capacity to offer services that exceed requirements under regulations and agency policy. Therefore, as of Monday, July 30, 2007, HRPO will no longer accept protocols for extra-regulatory review. This memorandum summarizes regulatory and policy requirements, revised acceptance criteria, and real and perceived consequences of these decisions. This practice will be in effect until HRPO is again fully staffed, at which point it will be reevaluated (HPRO 2007).

Additionally, the memo points out that HRPO would no longer accept exemption determination request if CDC is not engaged nor will HRPO execute deferral agreement with a non-CDC IRB if CDC is not engaged. In an internal presentation, a senior OADS official pointed out that the bottom line is that, "CDC scientists gain no additional legal or ethical protection from having CDC IRB review protocols when we are not engaged, and devoting staff time to this diverts from tasks that we are legally obligated to complete." This argument is potentially controversial, particularly for CDC-funded research, because the role of IRB is not to ensure legal or ethical protection for investigators or institution, but to protect human subjects in the research. The Common Rule was developed essentially for the purpose of protecting individuals from being harmed in research. It was not meant to provide legal protection for researchers or institution nor does it place any value in the importance of the research. Because under OHRP guidelines, an institution is not required to subject a research protocol through their IRB if the institution is not engaged, CDC sees it as an "extraregulatory" activity. According to the memo, discussion with OHRP had reassured HRPO that this new policy would not impact CDC's ability to conduct or support research nor will it impact CDC scientists' ability to author or co-author any published manuscripts. The memo also states that a discussion with the Association for the Accreditation of Human Research Protection Programs (AAHRPP) had assured that the policy will not affect CDC's ability to be accredited. CDC is currently in the process of obtaining accreditation for its human subjects protection program.

Despite these assurances, some center HSCs see the non-engagement policy as a problem, even a "loophole". One person I interviewed said:

> When I first came into this position I had some issues with that and I am sort of accepted how the situation is, but I feel there are times when by a strict regulatory definition, but the guidelines, OHRP guidelines leaves leeway for the institution to say there are circumstances that makes you engaged. I think in some cases where CDC has so much oversight so involved and has developed the protocol, I think sometimes not engaged is a loophole. **I think it's a little ridiculous that we can pay for the study, we can design the study, we can write the protocol we can do everything and overseeing the study and then be saying that we're not engaged. I mean we're up to our neck in it.**

The issue of engagement sometimes presents ethical dilemma in practice when a project met CDC definition of research, but was not determined as research locally either at a local health department, state health department, a country Ministry of Health, or other collaborating partner. Collaborating institutions make their own research determination. The non-engagement policy can lead to a slippery-slope situation where a study that meets CDC definition of research, but deemed nonresearch by a collaborator, will have no ethical oversight. Even though the memo states that HRPO might make an exception in certain circumstances and accept a non-engaged research for IRB review, in practice this has not been my experiences. HRPO has rejected every single request I made on behalf of my center's investigators. My rationale for at least making the request, not only because the programs and investigators are requesting it, is because often, there will be no formal ethical oversight, because the projects were locally determined as nonresearch. In other cases, CDC's collaborator wanted to rely on CDC IRB, though CDC had no need to interact with study participants or have access to identifiable data for research purposes, or being official engaged.

The solution for investigators and programs, though ethically questionable, is to make CDC engaged even when that engagement is unnecessary for research purposes. An investigator can simply check a box on the CDC IRB form that indicates either 1) CDC interacts with participants or 2) CDC will obtain identifiable or linked data for research purposes. Personally, I do not condone this practice, but if an investigator or program choses to go this route, I have no way of knowing, and would be obligated to submit the request to HRPO for assignment to one of CDC's IRBs. Usually, if it is the case that being officially engaged is viewed as more burdensome, investigators may simply obtain local ethics approval and choose the non-engaged route. Having access to identifiable or linked data would make CDC engaged. However, for linked data, a non-disclosure agreement that prohibits the release of identifying code to CDC can be signed and executed, rendering CDC non-engaged. No CDC IRB approval is necessary as long as the research has received local IRB approval. If the research is funded by CDC, then the local institution must hold a FWA and the local IRB registered with OHRP. If CDC is engaged, the protocol would be accepted by the IRB, and HRPO would accept a nonresearch determination letter from an appropriate local official in place of the IRB approval if they view the project as nonresearch. In essence, the decision to become non-engaged in a study is effectively determined by the investigator.

Interpreting the OHRP 2008 guidelines on engagement is not straight forward. A former center deputy ADS and HSC believes that CDC had misinterpreted OHRP guidelines on engagement.

> If you look at the first paragraph under heading III: Interpretation of Engagement of Institutions in Human Subjects Research, you will see that an

> agency is engaged if their employees or agents obtain identifiable data, informed consent, or data or specimen through interaction with or intervention on the subjects. Thus if we pay contractors or awardees to conduct a study they are operating as our agents and we are engaged. This is the standard that OMB [Office of Management and Budget] applies. However if you look at example B.7 which describes a situation parallel to a coded data/specimen project, you would conclude that the agency is not engaged in research for any study where the agency does not interact with people or obtain identifiable data or specimens. I would argue that the earlier language takes precedence and so the agency is engaged in studies where the agency has defined the research interactions or interventions and caused them to take place because in those situations the contractor or grantee is operating as our agent.

The meaning of the term "agent" has caused some confusion at CDC. Under the OHRP guidelines if an individual acts "on behalf of the institution, exercising institutional authority or responsibility, or performing institutionally designated activities" the individual is considered a CDC "agent" and therefore CDC would be considered engaged in human subjects research. So if the agent does not represent CDC nor performs CDC designated/initiated activity, then the person is not a CDC agent. HRPO simply defined agent as "an on-site CDC contractor." "On-site" usually means a CDC facility, which would limits the term to someone who works at a CDC facility. One HSC, at a branch level, I interviewed said that she considered a CDC agent as someone on CDC payroll. Simply funding an activity or providing a protocol may not make CDC engaged, unless CDC initiated the activity. Under OHRP guidelines, CDC can be considered engaged without interacting with participants or having access to identifiable data, e.g., if CDC received direct funding from DHHS for human subjects research even if CDC contracts with another institution to conduct the research. On the other hand, CDC's decision to fund human subjects research from its general appropriation does not automatically make CDC engaged.

An example of when the issue of engagement was a problem for CDC is the EZ measles case discussed in Chapter 2. Since there was no CDC policy on engagement at the time, engagement did not factor into the issue of whether CDC IRB would review the study. However, under current CDC policy, CDC would have been deemed non-engaged. If CDC investigators had access to linked data, CDC could have easily been rendered non-engaged with the use of a non-disclosure agreement, and according to current policy, CDC would not have had regulatory responsibility under the Common Rule. According to one CDC scientist at the time of the EZ measles study, "CDC provided technical assistance, funding, and had the original idea. Kaiser was the PI." This scenario has played out over and over again in my experience reviewing determination requests. CDC often, but not always, initiated a study, wrote the protocol, had administrative, financial, and technical oversight, but is not by definition engaged in human subjects research. Investigators are generally happy with the non-engagement policy because their perception is that it reduces the burden that would have been placed on them by the CDC IRB. The perception is that obtaining local approval is easier and because the Common Rule permits IRB a certain degree of flexibility, HSCs cannot question the local decision without really good reason. In cases like these, it is expected that HSCs would approve the non-engagement, unless there are major problems that the local IRB had missed. As long as there are local approval, approving these requests made life easier for HSCs than disapproving or requiring revision.

Of course, centers would not approve a human subjects research study if there is no ethical approval or if it was locally considered nonresearch, some form of

approval from the appropriate institutional authority. If CDC funded the research, CDC is required to ensure that the engaged collaborator has a FWA filed and their IRB registered with OHRP. One problem with non-engaged approval in the current practice is that usually, once an investigator gets their non-engaged approval there is no follow up, because of the lack of resource and staff person. Currently, there is no policy requiring incident reporting for non-engaged studies. The only time when investigators are required to follow up is when they make major changes to the protocol.

In the EZ measles case, the proposal for the study was submitted to CDC, as a response to a funding opportunity announcement, from the Los Angeles County Health Department and Kaiser Permanente and was conducted at three local Kaiser health-care facilities (Internal CDC Document: Measles Vaccine Timing Study Background). Specimens and data with unique patient ID were sent to CDC, but no personal identifiers were kept at CDC. If this was to take place today, a non-disclosure agreement with Kaiser would have rendered CDC non-engaged in human subjects research. Regardless of CDC level of engagement, CDC was held fully accountable for the study's ethical shortcomings by OPRR, the media, and the general public. CDC issued an apology to the parents of the children recruited to be in the study, and admitted to being noncompliant with the Common Rule. CDC admitted that it failed to inform parents that the vaccine was an investigational new drug (IND), although the issue of whether it was considered experimental was unclear given that the vaccine had been approved for use in other countries. It had not been licensed by FDA for use in the US, but a statement in a questions and

answers document prepared by CDC, "CDC did not consider the EZ vaccine experimental because of its wide use [internationally] and demonstrated safety worldwide" (Internal Document). The public outcry played out in the media was largely aimed towards CDC and the US government in general. The study was compared to the TSS that CDC inherited in 1957 by default when the Venereal Disease division of US PHS became a part of CDC.

Should problems arise in CDC-funded, non-engaged study, CDC will be held accountable, if not by OHRP, certainly by the media and general public as in the case of the EZ measles study. There will be program oversight and investigators ultimately bear ethical responsibility, but if CDC initiated, funded, provided oversight, authored or co-authored a paper, involved in a non-exempt human subjects research study, CDC must have greater ethical responsibility and oversight of such study regardless of whether CDC is officially considered engaged in such study. All HSCs I interviewed share this belief, as one person said, "We are up to our neck in it." In the current practice it is difficult to find out whether changes have been made to a study or whether incidents involving risks to participants have occurred in non-engaged research studies. CDC requires that major amendments be reported, but CDC does not currently have a mechanism for reporting incidents involved in non-engaged studies or for nonresearch.

Social Construction and Interpretation of the Regulatory Definition

As previously discussed, CDC was originally envisioned by its founders to be the agency that applies scientific knowledge to practice, and CDC traditional

activities since its inception were outbreak investigations (emergency response), public health surveillance, program evaluation, capacity building, guidelines and policy development. According to a former senior CDC official, every member of the committee (the Commission) that drafted the Common Rule never imagined that the regulations would apply to public health agency such as CDC or to state or local health department. Historically, until the 1990s, "the thinking within the Department [HHS] was that CDC rarely conducted research activities" (Former CDC official).

> These regulations were intended primarily for academia, everybody who was involved in development agreed they had academia in mind. They didn't have public health department or CDC in mind when they put those regulations together, but the question was; is that set of regulations really implementable in the context of certain public health activities like Epi Aid?" You know when you have an emergency event going on in the population, can you really delay that to go through this process over here that many people feel is not really applicable because the main rationale you have for an Epi Aid is to determine what's causing the disease cluster and stop it, not really to generate generalizable knowledge (Former CDC official).

This section describes some of the rationales behind CDC cultural interpretation of the regulatory definition, beginning with Epi-Aid.

Request for Epidemiological Assistance (Epi-Aid)

Epi-Aid is a mechanism CDC uses to assist local, state, and international public health partners, including countries' ministry of health (MOH), to provide technical assistance in investigating and responding to urgent public health problems which require epidemiological expertise, such as disease outbreak (Brachman and Thacker 2011). It is one of CDC earliest cultural practices and a

defining symbol of CDC. The most prominent CDC program affiliated with the Epi-Aid process is the two-year Epidemic Intelligence Service (EIS) training program created by Alexander Langmuir in 1951 at the beginning of the Korean War to protect the US against manmade epidemics (Koo and Thacker 2010, CDC Connect Story, CDC 2013, CDC 1996). The creation of the EIS program expanded CDC's mission to include other disease epidemics including non-communicable diseases and environmental hazards. The EIS program logo is globally recognized as the symbol of the program. The logo consists of the sole of a shoe with a hole on the bottom, representing what CDC called "shoe-leather epidemiology," or "field epidemiology" or "intervention epidemiology" (Koo and Thacker 2010). The hole in the sole symbolized EIS officers or other field epidemiologists prolonged walking, sometimes door-to-door, tracking down the causes of disease outbreak, and literally wearing down the sole of their shoes. According to Koo and Thacker, "All 3 terms imply investigations initiated in response to urgent public health problems and for which the investigative team does much of its work in the field" (2010: 737).

Figure 14: EIS Logo

Source: http://www.cdc.gov/eis/index.html

In principle, CDC does not interject itself into an emergency situation until a formal invitation is received, although when there is an outbreak of interest, CDC can initiates contact with the relevant authority who could make the invitation. It is generally accepted that the primary "intent" of an Epi-Aid is to response to emergency situations, and any new or generalizable knowledge that may result from the investigation should not define the nature of the activity. According to a CDC senior official:[47]

> That should be a secondary or a tertiary or whatever benefits, but it's not really the reason that the whole thing is instigated. So I think it was around Epi Aid or emergency response we might say more generally today, that people felt like, this is just so far removed from what the regulations were intended to regulate that there needs to be not letting people off the hook from an ethics standpoint, but it needs to be a separate ethical process for looking at these and not the same bureaucratic framework. Once you start talking about it for Epi Aid and naturally working in this organization the question comes up what about surveillance in general? Not every case of surveillance! What about program evaluation? Etc. So it began with Epi Aid and then it branch out into this other activities and so we found at least it's been my experience continuing today that it was difficult to separate these groups of activities and say they [are] never research. Just like it would be inappropriate from my standpoint to say they are always research, so what we try to do was to say when they are research and by implications if they don't do that then, they are not research (Former CDC official).

This was the cultural model or mindset at CDC at the time it put together its response to OPRR and in developing its general guidelines (1999 Guidelines) to assist investigators in making research determination. Responding to OPRR and developing the guidelines was a social process that involved internal CDC staff as well as its public health allies and supporters. In one case, an external, academia supporter was recruited and joined CDC as a permanent staff to coordinate and

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[47] This senior official has retired from CDC since our interview in 2013.

defend CDC strategies in research determination practice. In many ways, it was a call to arms, because CDC was being challenged from the outside by public complaints, the media, and OPRR. CDC rounded up its troops and called out to its friends in the public health community to join in the battle to preserve traditional public health principles and practices. The war metaphor of public health's battling diseases was certainly relevant to the ways CDC strategized in its response to the threat to CDC's "way of life". According to an internal communication, it was literally a threat from OPRR, which was seen by one senior official as setting the agenda for CDC. According to the official, "I'm having the feeling that we are letting OPRR define our agenda." Another senior official said, "They were absolutely unmovable and threatened to make life even more difficult for us if we didn't comply with what they wanted. I think the best leverage we have is with constituents like CSTE."

In 1996, at the urging of CDC staff, CSTE wrote a position letter voicing its concern over the confusion of the definition of research, calling for OHRP and CDC to address the problem (Amoroso 2003, CSTE 1996). The argument CSTE made was that essential nonresearch public health activities such as public health surveillance and outbreak investigations were not addressed by the Common Rule. Additionally, these activities have legal mandates under local or state laws to be conducted to protect the community and therefore should not be considered as research that needs to go through the IRB process. Doing so could be detrimental and harmful to the public's health. CSTE's position letter was welcome by CDC. One senior official said that he was glad that CSTE wrote the letter, but he suggested other strategies to address the problems with OPRR. Other strategies suggested include: contacting

other constituents, writing an editorial for the *Journal of Public Health*, or meeting with other OPRR staff who might be more supportive of CDC's position.

The most significant response by CDC was the editorial published in 1997 in *Public Health Reports* entitled, "Defining Research When it comes to Public Health" (Snider and Stroup 1997). Amoroso and Middaugh called the editorial a "groundbreaking document" that "attempts to differentiate research from nonresearch," but feels that "considerations should be given to the creation of a new 45CFR46 category or categories of exempt activities performed by federal agencies or states under legal authority derived from the US Constitution" (2003: 252). The resulting discussions from the social process that went into developing the editorial also provided the rationale and content for the 1999 Guidelines. Some examples of the discussions found in CDC historical documents at the national archive among CDC staff that manifested in the 1999 Guidelines include:

- I'm having the feeling that we are letting OPRR define our agenda. While realize the lengthy discussions you have had with them, think it is critical to revisit this surveillance distinction. Numerous articles in the literature discussing public health research do not mention the term "surveillance." The example you mention, BRFSS[48], illustrates what I believe is a fallacy in OPRRs reasoning. By this example, every management analysis we undertake should have OPRR clearance because we generalize from the findings. I am happy to discuss this further at any time, but I think this a critical issue on which to articulate how CDC does it's work.
- I agree that an informational campaign to help shape OPRR's thinking on this may be appropriate. It would make life very difficult for us if our routine surveillance required human subjects review, and I agree that the distinction between "routine surveillance" (ie Legionnaires' disease) vs systematic surveys (ie BRFSS) is a fine one. The idea of an editorial is a good one – it

[48] BRFSS is the Behavioral Risk Factor Surveillance System, which have been deemed as exempt research by CDC. It is an annual telephone survey conducted by the National Center for Health Statistics (NCHS), which is a part of CDC. http://www.cdc.gov/brfss/about/about_brfss.htm

might discuss both the Epi-Aid issue and surveillance within the context of human subjects review.

- I agree that OPRR is setting the agenda, but it is difficult to do otherwise. ----, -----, and I went to meet with them in Washington about this and other issues. They were absolutely unmovable and threatened to make life even more difficult for us if we didn't comply with what they wanted. I think the best leverage we have is with constituents like CSTE. I'm glad they wrote the letter. I have a couple of ideas besides getting some additional constituents to write (without saying we contacted them). One is to write an editorial for the *American Journal of Public Health* on Public Health Practice, Public Health Research, and Human Subjects Review (or some better titled topic)…. The other idea is to go up to meet with ___ (OPRR) ONLY, without ___ in the room. I was thinking that one or two ADSs might be willing to go with me.
- My major reaction is that this is an unusual topic for a commentary in the *AJPH*.[49] Also, it strikes me that writing an article is not the best way to get resolution of this knotty problem. I found myself as a reader wondering why someone does not just get a dozen or so of the key persons needed to hammer this out and put them to work as a group to come up with a proposed answer that we could use. This semantic kinds of difficulties are not likely to be resolved by invoking the input of the general community of public health and human subjects professionals. I do not think you will get consensus that way. It seems like what we need is a decision that we can try to implement. None will be perfect but I think we are better off with some decision now that could be refined later on if the need exists. I think the answer ultimately may lie in what the intent of the investigation is—research of no immediate use or public health related with immediate application in disease prevention. From the human subjects point of view, it is the same and therein lies the difficulty.
- First, it reads a little like an apologia for CDC's record in this area and not an in-depth presentation of a real problem. It seems to me that it should be the latter. It reads as though the visit of the OPRR stirred things up a bit. It is not good to seem to be on the defensive without stronger arguments.

(Internal Communications)[50]

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[49] The commentary ended up being published in *Public Health Reports* even though there was discussion about publishing it *AJPH*.

[50] Source for internal communications: CDC Archive, Control # T7909A, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294

After OPRR sent the investigational report to CDC in 1995, senior officials did not refute the fact that there were confusions at CDC about how to define research. One official I interviewed stated:

> There was really a misunderstanding of the regulations and therefore is not complying with it and you can appreciate that the thinking had not gone very deeply into trying to decide in this environment at CDC and public health what is research and what is not research. There were a lot of discussion that wasn't only internal, but external discussion with OPRR and then with OHRP and with ethicists on the outside[51] who eventually over the years have gotten very comfortable with public health and talking about public health.

The challenge for CDC was to develop an approach to distinguishing the differences between research and nonresearch that would be easy for CDC investigators to discern and also remain in harmony with traditional public health practices. Some of the contentious and confusing issues seen as arising from the Common Rule that sent CDC staff reeling are discussed below.

Contentious Issues

The four most contentious issues regarding CDC's approach include the issues of distinguishing research from nonresearch based on the "primary intent," "systematic investigation," "generalizability," and "intent to publish." The case of "public health surveillance," which encapsulated all of these issues, sent CDC staff scrambling to make a case for support of CDC's practices. These issues remain as confusing to CDC staff now as they were when OPRR visited CDC in 1993.

[51] Among some of the ethicists whom this senior official had discussions with were members of the Commission which developed the Belmont Report.

Primary Intent

AS mentioned earlier, "primary intent" is CDC's take on the term "designed" found in the Common Rule's definition of research. The concept of "primary intent" evolved within the context of Epi-Aid, which became the most problematic, controversial, and criticized aspect of CDC's interpretations. Following OPRR's visit, there were some discussions about requesting an umbrella exemption for Epi-Aids, but one person affiliated with the EIS program countered against such exemption stating:

> We're already struggling to prevent abuse of the Epi-Aid mechanism. This would only increase pressure on Epi-Aids as a funding source. It was believed that there were occasions when an event was urgent enough to be called an epi aid. Criteria for meeting an epi aid include "(1) urgency and (2) severity of the problem. Urgency >95% of the time means that there is pressing public health need that would require an investigation no matter what (i.e., that this is primarily public health "treatment" of the community as a patient, not research. So >95% of the time, Epi-Aids are nonresearch and don't need IRB review anyway, and the waiver is not necessary (Internal communication).

Though for the most parts Epi-Aids have been deemed nonresearch, there believed to be occasions when the opportunities exist to conduct research. EIS officers often sought opportunities to conduct research and publish their findings. According to one person:

> I think that there are ethical reasons for requiring IRB review of these situations, and I would prefer NOT to exclude them by means of a waiver. We want to prevent real abuse, which could happen because after releasing funds to the investigators, we have no control over how they conduct the investigation. The situations where IRB review of Epi-Aids is indicated are few enough that they should not clog the IRBs with lots of cases, and don't represent an inordinately onerous burden on our investigators (Internal Communication).

Another person echoed this sentiment:

> Perhaps the most interesting interface of research and public health at CDC is the Epi-Aids/health hazard evaluation. Young bright researchers are sent out wanting to make a name for themselves and come back with publishable material. Relatively inexperienced investigators are sent out by supervisors who often supply the research ideas. One of my EIS classmates was famous for not going out "unless it was publishable!" There is therefore pressure to do research and push the envelope (Internal Communication).

Though Epi-Aids rarely get submitted to IRB, they provided the rationale for the concept of "primary intent." The 1999 Guidelines incorporate "primary intent" as the main distinguishing factor between public health research and nonresearch, stating:

> The major difference between research and nonresearch lies in the primary intent of the activity. The primary intent of research is to generate or contribute to generalizable knowledge. The primary intent of nonresearch in public health is to prevent or control disease or injury and improve health, or to improve a public health program or service (CDC 1999: 2).

In 2010, when the 1999 Guidelines were revised and became an official CDC policy, the word "intent" was replaced by the word "purpose." Although the meaning remain unchanged, the new term seemed less subjective than the term "intent." "Intent" seems too closely related to personal's intent, whereas purpose seems more related to the purpose of a project. Focus group discussions provided CDC employees' takes on what the term "design" meant to them. Both the terms "intent" and "purpose" were among the responses. There were other terms and phrases that came up, but no one was highly argumentative about what others came up with. The term "objective" also came up during the discussion, and in practice, "research objectives" are what usually mentioned. One participant noted that "We [CDC] give a lot of passes for secondary objectives."

- Intent
- How intent or objective influence how the project is conducted
- Constructed to answer a specific health problem
- Primary purpose (secondary objective might make it research)
- Design=intent=purpose=objectives?
- How you are going to do something (protocol)
- Intent to do something
- Purpose
- Reason for collecting the data
- Why are you doing this? Stated purpose

Criticisms of this approach to the interpretation were not limited to external individuals, but also internally. "Research by intent" could mean that some creative investigators who do not want to go through the IRB process could write a protocol that would be nonresearch under CDC policy. One possible tactic is simply not stating what the research intents are, and stay focused on what the program benefits would be, even if there may be hidden research objectives. For people who are in the position to make research determination, namely HSCs and ADSs, sometime they have to interpret (mind reading, if you will) the information submitted for determination to get behind what the real intents are. Because defining research by "intent" or "purpose" can appear subjective, it is a politically difficult decision for HSCs and ADSs to make a decision that is counter to the program's preferences.

One of my colleague conducted a field visit to one of CDC country offices in Africa learned that field staffs always want nonresearch determination. In discussing the issue with field staffs about a project that appeared to be research, one person said, "Oh, we'll get it changed to nonresearch." The question I posed to my colleague is, "Can the original research objectives be achieved if the project was

revised so that it could be categorized as nonresearch?" We both agreed that it is likely not possible to achieve the same objectives.

OHRP did not agree with CDC's interpretation that focuses on the primary intent of an activity. In July 2005, OHRP sent comments to CDC about the 1999 Guidelines highlighting the problems it had with CDC's interpretation. Over the next several years, CDC and OHRP engaged in ongoing communications about OHRP's concerns. The ensuing discussions with OHRP led to the revision of the 1999 Guidelines that became the 2010 Policy. The CDC position statements are the same in both the 1999 Guidelines and 2010 Policy, but "primary intent" became "purpose," which remained the principle criteria for distinguishing research from nonresearch.

Regarding primary intent, OHRP states:

> The problem with this approach is that the designation of primary intent is arbitrary. Primary could mean (a) first in temporal order, (b) ultimate, (c) most influential, or (d) most important to the designer. The effect of introducing the idea that if an activity has multiple purposes it is only research if the primary purpose is generalizable knowledge, is to reduce the number of activities considered to be research. Wherever there is clear practical objective in an activity that objective becomes the primary intent of the activity, which makes it be classified as nonresearch. Since applied (as opposed to basic) research activities have practical purposes, this seems to lead to the result that many - if not all - applied research activities are mistakenly designated nonresearch. CDC, whose mission is an applied one, is likely to support a large proportion of applied research activities (OHRP 2005: 2).

OHRP considered an activity as meeting the definition of research even if research is a secondary intent. The Belmont Report states:

> This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in

> an activity, that activity should undergo review for the protection of human subjects.[52]

For CDC, "If a project includes multiple components and at least one of those components is designed to generate generalizable knowledge, then the entire project is classified as research unless the components are separable" (CDC 1999: 5). CDC's position slightly differs in that only if a project has different components and if one of the components is designed to generate generalizable knowledge will CDC view the entire project as research. Primary intent or purpose is typically determined by assessing the study objectives. In practice, secondary objectives are also assessed, but if an investigator neglects to mention their secondary research objectives and only focuses on the primary nonresearch objective, then it is likely that the project will be deemed nonresearch.

OHRP's concerns led to their effort to develop guidelines that were sent out to federal agencies for comments in 2007. The guidelines were meant to represent OHRP's thinking on the regulatory definition of research, but were never finalized. For reasons unknown, whether it was due to staff change or change in OHRP's thinking, the draft guidelines that OHRP had developed was not pursued. It cannot be found either on the internet or CDC intranet, but I was able to obtain a copy. A HSC told me that CDC and other federal agencies were not happy with the document.

> No, it was never finalized. It was never even made available for public comment. The HHS agencies commented the first week of Jan 2008, and the sense I got was that CDC and the other agencies were not happy with the proposed guidelines.

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[52] The Belmont Report is a short document and can be found at (http://www.hhs.gov/ohrp/humansubjects/guidelines/belmont.html).

Another issue was related to the change in leadership at OHRP. Another HSC stated:

> There was another change in leadership at OHRP and this was relegated to the back-burner. The current leadership at OHRP is (in my opinion) far more flexible, so I'm not sure that this document accurately reflects the current position of OHRP.

While the draft OHRP's Guidelines was tabled and not pursued and will probably never get resurrected, some HSCs found the guidelines to be useful and continued to use it as a guide in research determination. One colleague said:

> I do find the approach to definition to be very useful, and it is sometimes helpful for evaluating projects that don't fit into the current CDC policy very cleanly. If anything, I think this document is more conservative than OHRPs current position, so it is a reasonable baseline for supporting decisions.

Another colleague said:

> Starting around 2005 maybe 2006, OHRP started to draft what look like it might become departmental level guidelines on the differences [between research and nonresearch]. As far as I know it never saw the light of days, except that elements of it, discussions that happened around those several versions did come to inform the events that support the notice for proposal rulemaking in the current NPRM that is under development. But the way it informed the advanced notice and the actual notice are quite different from how things were shaping from the development of the guidelines itself, which is to say, OHRP came to see the value to curving out certain activities as nonresearch.
>
> I asked my colleague further, "Why did OHRP abandon it?"
>
> He responded, "I don't know."

Another colleague states, "I think that, you know, OHRP tried to put out Guidelines on that. They couldn't come to any agreement on it, so that's why they let it sort of dropped." An EISC's meeting minutes dated 9/19/2006 noted CDC's main disagreement:

> CDC's formal response highlighted one primary point of contention and

> disagreement with OPHR's guidance document. The OHRP document defined public health practice as research, which would apply to most of CDC's surveillance and program evaluation activities. CDC, along with several other agencies, disagreed with this guideline; CDC offered the following rationale: a) redefining public health practice activities as research would impede CDC's mission and the conduct of public health activities and b) the new definition would offer no increase in the protection of research participants.

Systematic investigation

Another key term used for defining research is that an investigation must be "systematically" designed to generate generalizable knowledge before an activity is deemed research under the Common Rule. CDC and other public health institutions such as state and local health departments and CSTE found that to be problematic, because nonresearch public health activities also employ systematic methods to investigate disease outbreaks, conduct program evaluation and surveillance activities. If every systematic study with human beings that generates generalizable data, even if as secondary outcomes, is research under the Common Rule, then more of CDC's public health activities might have to undergo IRB review. Many at CDC have argued that it would "cripple the agency." It is generally accepted that public health activities employed systematic methods in both research and nonresearch. Both the CDC 1999 Guidelines and 2010 Policy include languages to this effect:

> Scientific methods are used in both public health research as well as public health practice activities. Knowledge is generated in both cases. Furthermore, the extent to which knowledge is generalizable might not differ greatly in research and nonresearch. Thus, nonresearch and research activities cannot be easily defined by the methods they employ. Three public health activities – surveillance, emergency response, and evaluation – are particularly susceptible to the quandary over whether the activity is research or nonresearch (1999: 2).

> Scientific methods are used in both public health research as well as public health practice activities. Knowledge is generated in both cases.

> Furthermore, the extent to which knowledge is generalizable might not differ greatly in research and nonresearch. Thus, nonresearch and research activities cannot be easily defined by the methods they employ (2010: 2).

A former senior official had argued that OPRR in the 1990s had not accepted this interpretation in regards to systematic investigation. He believes that systematic investigations such as surveillance, that sometimes obtained and used data and specimens without consent, but done under public health laws by public health authorities with full knowledge of the legal system and the public were not something OPRR was comfortable with. "The idea that they were systematic investigations, but they weren't necessarily research was novel to them [OPRR]" (Former CDC Official).

The meeting minutes from an internal discussion among CDC senior scientists notes that, "CDC maintained its position that surveillance activities should be evaluated according to their primary intent, whereas according to OHRP, activities are evaluated according to their design" (Internal CDC Document). The document also noted that OHRP did not agree with CDC's practice of dual designation, where a project can be determined as nonresearch by one institution and as research by another institution. This usually occurs when CDC worked with its local, state, and international partners. CDC routinely obtained and used program data for research purposes, but these projects were not considered research by local collaborators. Often these projects were deemed as surveillance or public health program activities by local partners.[53] In these cases, CDC often contended that local

[53] For examples, CDC conducts ongoing surveillance systems including the Youth Risk Behavior Survey (YRBS), the Behavioral Risk Factor Surveillance System (BRFSS), and the Pregnancy Risk

partners have legitimate public health program uses for information derived from surveillance or program activities, but that CDC uses this information to develop generalizable information for the country.

Generalizability

As we were discussing the history of CDC human subjects protection a former CDC HSM said to me, "Generalizability is considered after taking into account after what the primary purpose is."

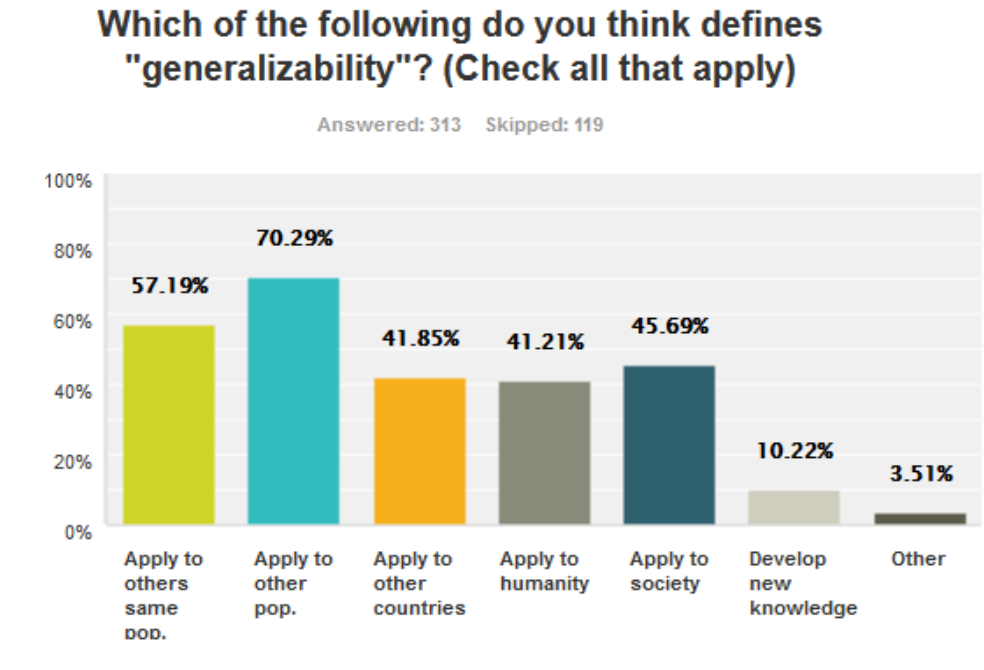
It is understood among HSCs that the primary purpose of an activity supersede generalizability and systematic method. Even if there was clear agreement on the issue of "primary intent" and "systematic method," there were still confusions on the issue of "generalizability." The confusions played out on a daily basis, project by project, because the 1999 Guidelines and 2010 Policy have not clarified the term. Both documents include ambiguous language that interpret "generalizability" one way in one place and later contradict. Generalizability is an important distinguishing factor in determining if a public health project is research. According to the Common Rule's definition, if an investigation is systematically "designed to develop or contribute to generalizable knowledge" then the activity meets the regulatory definition of research. According to the survey that I conducted CDC-wide in the summer of 2012, there was no consensus on what the term "generalizability" means (Figure 15). The option that was checked most was that generalizability is when results from a study are "applicable to other populations,"

Assessment Monitoring System (PRAMS), where CDC uses data derived from these systems to generate generalizable information about the conditions for the US.

but a significant percentage of people also checked the other options. One former center ADS whom I interviewed on several occasions stated that during her time as ADS, her thinking was that, "generalizability meant generating results applicable to populations in other countries." In focus group exercises that I conducted in 2012, various responses were provided to the question, "How do we define generalizability?" Participants' responses include:

- Outcomes transfer/use in different populations
- When we know we are collecting information from a statistical standard hold true or more reliable
- Designing the study in order upfront to generalize
- Results broadly apply
- Predictability – can information be used to predict something about another group? Predictability of what is under study.
- Draw conclusions about other groups
- Furthering knowledge

Figure 12: CDC-wide Survey Response: Generalizability



One participant asked the group, “Does anything CDC conducts qualify as research under the Common Rule?”

Another person asked, “Project has to be tailored to the study population, so can we say any results from that study generalizable?”

The assumption is that if results cannot be transferred to a different population from which study participants are drawn then the study cannot be said to be generalizable. Participants acknowledged that there may be disagreements on how “population” is defined and when generalizability applied. Participants and people at CDC in general did not considered publication as being related to generalizability. CDC believes that lessons learned from nonresearch are worth publishing.

The 1999 CDC Guidelines defines the general attributes of public health research as the:

> Intent of the project is to generate generalizable knowledge to improve public health practice; intended benefits of the project may or may not include study participants, but always extend beyond the *study participants*, usually to *society*; and data collected exceed requirements for care of the study participants or extend beyond the scope of the activity (CDC 1999: 4).

The same statement with the term “purpose” replacing the term “intent” is found in the 2010 Policy. This statement is confusing in that it can be interpreted in different ways. The term “society” is not defined in the guidelines. Society may be taken to have different meanings. One way society has been defined is “a body of individuals living as members of a community” (Dictionary.com). This appears to be the case, because the term “study participants” just preceding “society” means individuals who are recruited to take part in the study are the study population, but they are

also members of the "society." If CDC goes by this interpretation, and a study is being conducted with the intent to generate information that is applicable to any person in the society other than the study participants, the study would be considered "generalizable." This may be the interpretation from a biomedical research perspective, but some bioethicists (Casarett et al, 2000) also extend this interpretation to quality improvement public health program. In 2005 when OHRP sent its comments about its concerns of CDC 1999 Guidelines, this was also their interpretation. According to the OHRP:

> …when the document reviews the classification of an activity in which generalizability is limited by the nature of the sample, or there is significant overlap between study participants and the population to which the results are generalizable, the document does not acknowledge that generalization has occurred. As a result, when coupled with the idea of "primary intent", some activities are misclassified as nonresearch…describing the activity at the program level seems to suggest that the population of people who were studied in the evaluation is identical to that of the people who will benefit from the results of the evaluation of the program (OHRP 2005: 3).

CDC generally views public health "patient" from a population level and that if the results apply to the same population it would not be considered generalizable, but the 1999 Guidelines and 2010 Policy are both ambiguous. One of the most frequent questions from programs and investigators is, "How do you apply the policy's definition of generalizability when the policy is unclear?" It is a difficult dilemma for HSCs or anyone in the position to make research determination.

Surveillance

The early HIV sero-prevalence surveillance studies in the US, as discussed in chapter 2, were among the events that lead to OPRR (now OHRP) investigation of

CDC human subjects protection system. At the time CDC conducted a series of surveys that were considered surveillance. OPRR did not have a definition of surveillance. According to internal CDC communication, OPRR considered all surveillance as research that should be approved by an IRB. Even though CDC considered the surveillance as nonresearch, these surveys were submitted and approved by CDC IRB. Out of precaution, CDC asked OPRR to review the studies, and as already discussed, OPRR did not considered the studies as meeting the regulatory definition of human subjects research.

In a 1994's draft guidelines for CDC scientists entitled, "Decision Making About Human Subjects Review Requirements" CDC described surveillance as followed:

> Surveillance refers to the regular ongoing collection and analysis of health-related data (in terms of time, place, person). If the surveillance activity is conducted solely to monitor the frequency of occurrence and distribution of disease or health condition in the population, it is not considered research. Such activities are the public health equivalent of a private physician checking the vital signs of an individual patient. Examples of nonresearch surveillance projects include (1) the routine reporting of cases of notifiable diseases by State health departments to the *Morbidity and Mortality Weekly Report* and (2) other routine monitoring of the occurrence of diseases and conditions in a population for the purpose of detecting conditions for which research is or may be needed, or to determine whether public health action is needed to decrease the incidence of these diseases and conditions. (CDC 1994a: 11).

Although CDC appeared to have satisfied OHRP's predecessor (OPRR) in laying out how CDC and others within the public health community viewed public health research and nonresearch, including surveillance, in its 1999 Guidelines, OHRP continued to receive complaints about how CDC defines research. In January 2002, a public citizen complaint was filed with OHRP about the Hawaii Youth Risk Behavior

Survey (YRBS), which CDC had determined as nonresearch, public health surveillance activity (Internal CDC memo). In response OHRP contacted CDC about the complaint. OHRP pointed out the regulatory definition, "research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Although OHRP agreed that the activity was a program, it believes that in part, the program was developed to contribute to generalizable knowledge. OHRP's conclusion was based on the following statement in the State of Hawaii Department of Education's letter to parents of children randomly selected to take part in the survey:

> The survey will gather information about the drug use, nutrition, tobacco use, physical activities, intentional and unintentional injuries, and sexual behaviors or practices that result in HIV infection, other sexually-transmitted diseases, and unintended pregnancy will be on the survey…The findings of the survey will be used to strengthen our health education and other related programs. They will also be used by other state agencies and community-based organizations to assess and access resources to meet the needs of our youth (Internal document).

OHRP argued that the study appeared to be a systematic investigation designed to contribute to generalizable knowledge about:

> (i) the drug use, nutrition, tobacco use, physical activities, intentional and unintentional injuries, and sexual behaviors or practices that result in HIV infection, other sexually-transmitted diseases, and unintended pregnancy in Hawaii school children; and (ii) the adequacy of state resources for addressing the needs of Hawaii school children with respect to the above behaviors.

In response, CDC reminded OHRP of the 1999 Guidelines, that they were prepared with "extensive consultative process involving CDC staff, the Association of State and Territorial Health Officials, the Council of State and Territorial Epidemiologists, and other CDC partners, and consultations with expertise in public

health research and practice" (Internal memo). CDC also reminded OHRP that the 1999 Guidelines were also vetted and approved by OPRR. Of note, the CDC official tried to clarify the agency's view on the issue of generalizability:

> Previously when discussing data obtained using survey methodology, I have noted a discrepancy in how some persons interpret the term generalizable in the definition of research. Specifically, some persons interpret the term such that at any time that data are obtained from some proportion of persons in a group other than 100%, and comments are made about the group as a whole, you are generalizing and thus conducting research. However, others rely on the standard usage of the terms as defined as external validity—that is the ability to utilize data from the population from which data are collected to make inferences about other groups or populations. We would argue that learning how well a state immunization program has done in delivering the second dose of measles vaccine to children prior to school entry (whether that information is obtained from all children or a representative sample) tells you nothing about how well other states are doing in this regard. Such information is needed by the state to evaluate the effectiveness of its program, identify areas of weakness, and develop and target appropriate remedial measures. We regard all these uses as responsible public health practice activities, not research. Similarly, if an HMO uses a survey to access customer satisfaction in its service population or monitor for and correct medical errors, mere use of a survey methodology does not make this effort research. Therefore, use of survey methodology in conducting surveillance or program evaluation activities—essential components of public health practice—does not alter the determination that this [these] activities does not constitute research under 45CFR46 (Internal Communication).

The memo further notices that OHRP has confirmed that another similar survey, the Behavioral Risk Factor Surveillance System (BRFSS) is nonresearch. "Reclassification of surveillance and evaluation use of survey methodologies would have a major [impact] on CDC and State and local public health activities." Despite past concurrence with CDC guidelines, the new OHRP staff had difficulty accepting CDC's interpretation.

Meeting minutes from 2005 internal CDC's discussion notes that OHRP's interpretation had changed from its earlier assertion that all surveillance systems

are research. The minutes note that:

> OHRP formally stated that CDC's surveillance activities that are designed to assess trends in the prevalence of known health-risk factors (e.g., CDC's YRBS) do not meet the definition of research under 45 CFR part 46. In addition, OHRP agreed that surveillance activities designed to improve current scientific, clinical, or academic understanding about some issue of interest do meet the regulatory definition of "research," regardless of the governmental level at which they are conducted (Internal Document).

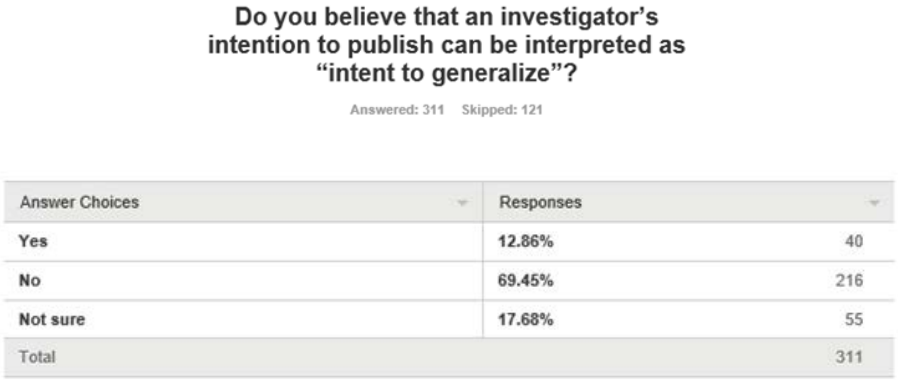
The key term here is "known health-risk factors." If a surveillance system involves unknown risk factors and etiologies, then it is likely that OHRP would consider such system as meeting the regulatory definition of research.

Intent to Publish

In the 1980's and 1990s, CDC historical archives appear to indicate that "intent to publish" was equated with "intent to generalize" at OHRP and in academia (Internal Documents). Some people at CDC agreed with the principle back then, but generally it was a problem, because nonresearch programs were thought to provide valuable lessons that should be shared more broadly. CDC staff felt that there were an ethical and public health responsibility to share those lessons learned. The belief that publishing findings from a study does not necessarily mean that the study is research was widespread throughout the agency, locally and internationally among locally employed staffed. Results from the 2012 survey show that 69.5% (216 of the 311 people responded to the question) of the respondents said that intention to publish cannot be interpreted as intention to generalize (Figure 13). Only 13% said yes it can be interpreted as intention to generalize. In my experience most projects

submitted for research determination described their intention to publish regardless of whether the requests were for research or nonresearch approval.

Figure 13: Intent to Publish



Do you believe that an investigator's intention to publish can be interpreted as "intent to generalize"?

Answered: 311 Skipped: 121

Answer Choices	Responses	
Yes	12.86%	40
No	69.45%	216
Not sure	17.68%	55
Total		311

Chapter 4: Research Determination in Practice

"Requiring emergency responses to include the traditional development of a written protocol and IRB review is not practical nor would it be in the best interests of either the individuals or the community affected by the problem because the resulting delays in identifying the nature and magnitude of the community health problem and in instituting control measures to take such a steps would frequently result in excess disease and death."

Snider and Stroup (1997: 31)

A colleague who was a deputy Associate Director for Science (ADS) and HSC described his view about research determination this way:

> "If no one complains you are not doing it right. In my job if people like me all the time, I'm not doing my job right, because people have to make hard decisions. Not everyone is always going to agree with me…I question OHRP's decision-making, because what experience [do] they have in the field and what [do] they really understand."

Determining what activities constitute research is indeed a difficult decision, not only because of the lack of clarity in definition, policy, and guidelines, but because of the ethical implications involved in making such decision. When an activity is deemed research that is not exempt under the federal regulations, it is routed to the IRB for review and approval. When it is not research or human subjects, it does not go to the IRB. The levels of approval and oversight vary by programs and centers. Because of the gray areas in the definition and policy, there is no guarantee of consistency in individual's distinction between what constitutes research and what constitutes practice.

Social Structure and Authority

Not until the late 1990s did a more formal research determination process and infrastructure became developed at CDC. The OPRR investigation that began in 1993 and subsequent restriction of CDC MPA and suspension of international research studies in 1997 forced a major response and shift in CDC research determination culture, one that I would argue has not significantly evolved since. After OPRR sent its investigational report to CDC in 1995, a social process ensued over a two-year period from 1995 to 1997 to develop a policy, infrastructure, and process for research determination. CDC's traditional practice placed responsibilities for research determination with investigators and programs; today, this is considered a conflict of interest. The culture war of the 1990s was disruptive, and drastically changing the agency's practice that has continued to this day.

The earliest CDC Human Subject Protection Manual (HS Manual) dated September 15, 1994. According to this manual, it replaced the last "Manual Guide-General Administration No. CDC-11, Protection of the Individual as a Research" dated August 10, 1983. I was unable to locate the 1983 manual. I searched all 41 boxes from the CDC OADS archive. Before the 1999 Guidelines, there was no policy or guidelines to aid investigators and programs in determining whether a project is human subjects' research is covered under the Common Rule. Research determination process was incorporated into the HS Manual. The 1994 HS Manual had relatively "lax language" (see below) suggesting that the policy was not very strict in terms of requirements and enforcement. Under the section describing the

steps for reviews and approvals, the responsibilities for the centers, institutes, and offices (CIO) was described this way:

> CDC investigators and managers should contact the CIO HSR [Human Subjects Review] Contact Person or ADS/CIO in accordance with internal CIO procedures, to discuss projects involving human subjects which might be construed to be research, to determine if the project is research involving human subjects which may require IRB review (CDC 1994: 11).

The use of the term "should" rather than the term "must" might have been construed to mean that research determination was not required, only that they should be submitted for review. Certainly, the literal interpretation was that only certain projects were subjected to review and most projects conducted by CDC were thought not to require such review. The term "should" was used throughout the manual which reinforced this cultural belief and practice. The sense I got from speaking and working with many CDC "old timers"[54] is that when CDC collaborated with outside partners, they would be responsible to obtain local ethics approval for projects which they deemed as research and then moved forward with implementation without seeking CDC IRB approval, whether, CDC was by definition engaged or not. This was particularly true in international settings, and some CDC assignees[55] in other countries still believe it is the case today.

There have been changes in CDC procedures, including changes in the number of staff persons (9 persons in HRPO and 25 HSCs in 20 CIOs) working on human research protection, new policy defining engagement, and the revision of the 1999 Guidelines into the 2010 CDC Policy. These changes do not equate to a change

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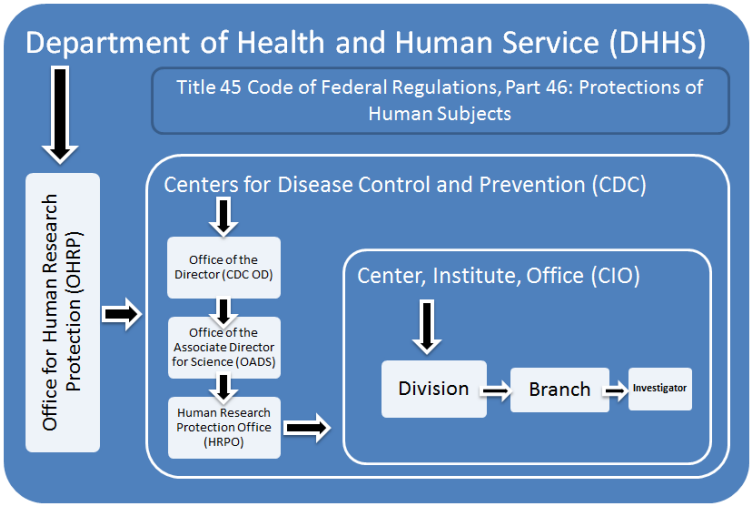
[54] By "old timers" I meant seasoned, senior scientists who have worked at CDC for several decades.
[55] "Assignee" refers to a CDC employee who has been sent to work in other location, such as local health department or in other country at a ministry of health or in CDC's country office.

in cultural beliefs and practice; in fact they might have reinforced the previous practice. Research determination is still being made by individuals through a bureaucratic process. Whether CDC realized it or not, many of the current efforts to improve the system are really continuing efforts to meet OPRR's 1995 mandates. CDC structure and approval process have not changed much since the 1999 Guidelines were released (Figure 17). The process essentially follows the CDC bureaucratic structure, top-down or bottom-up, whichever one prefers to view it, from the agency level (OADS, within the Office of the Director, CDC) to the investigators. From an institutional perspective, OHRP is the regulator of the Common Rule and therefore ultimately has the final saying on whether a study is research, although OHRP rarely intervenes in institutional decision-making, unless there were problems or complaints arise, such as during the EZ Measles and HIV surveillance cases. At CDC research determination responsibility had been with the OADS within the CDC Office of the Director, but was now re-delegated to the centers.

The 1999 Guidelines place the responsibilities for making research determination with the Center HSCs. The 2010 Policy was slightly revised, placing the responsibility with the Center ADSs, although ADSs have the discretion to re-delegate the authority to the other individuals within the centers, typically to the center HSCs. Not all HSCs have been re-delegated this authority, so the practice is not consistent among different centers. Some Center ADSs retained the final authority even though their HSCs usually review protocols submitted for research determination and made recommendations on whether the studies are research or nonresearch. CDC policy does not specify if the authority can be re-delegated

beyond the center level (Center OD) to the division or branch, but HRPO prefers that the authority remains at the center level (personal communication). It is theoretically possible to re-delegate the authority down further the bureaucratic chain.[56]

Figure 14: Human Research Protections Structure



Center level HSCs[57], who reside in the science offices within the center, are in essence the gatekeepers to HRPO and IRBs. Protocols are submitted to them for review and for determination of whether the protocol is research or nonresearch. HSCs' roles are broad, and include a critical regulatory function in making an initial research/nonresearch determination. Additionally, HSCs play an important

[56] Although HRPO would not agree to permit research determination to be re-delegated further down to the division or branch level, they did agree to allow determination of CDC engagement be made below the center level. This particular situation was related to a field training program, where CDC provides epidemiology training to fellows who were not CDC employees, but were employees of other institutions, such as the Ministry of Health.

[57] Although ADSs has the final authority at the center level for research determination, they typically do not intervene in their HSC's decisions, unless there are major problems. The discussion, therefore, is focused on HSC's.

unofficial role in the ethical oversight of nonresearch. However, during the initial research determination and protocol review, HSCs are not required to apply the same stringent requirements, e.g., addressing consent and other ethical and human rights issues, as they would if the project is determined human subjects research. Under CDC policy a complete detailed protocol is not required for research determination. HSCs may also provide ethical guidelines for nonresearch, although it is not possible to fully assess ethical issues involving a project if only a project summary is submitted.

In 2012, there were approximately 25 individuals who played the roles of HSCs throughout CDC, although often they also have other roles and responsibilities. HSCs may also serve in multiple other roles, such as also being the Office of Management and Budget (OMB) contact[58], public health ethics lead, deputy ADS, ADS, and other roles. HSCs also come from different backgrounds and have a wide range of pay scale under the federal salary structure. For most, their roles are similar, but their workload might differ, depending on the size of their programs. In some centers the ADSs retain the roles as HSCs, which reflects the wide salary gap shown in Table 5. The differences in salary may also depend on experiences, years in the federal government, and the type of position. Fifteen of the 21 HSCs during 2010 were in "general health science" position. This means that most HSCs at a minimum had a Bachelor of Science (BS) degree, if not higher level of science education. Many have master of public health degree or other higher education.

[58] OMB Contacts review projects under the Paperwork Reduction Act (PRA) to ensure that the federal government is not overburdening the public. OMB-PRA applies to standardized data collection by the US government on 10 people or more persons.

Table 7: CDC Human Subjects Contacts 2010 (Public Data)

Center	Official Position Title	Salary
A	GHS	$76,694
B	GHS	$99,749
C	AP	$69,550
D	GHS	$124,608
E	PS GHS	$111,148 $76,694
F	GHS	$88,677
G	GHS	$71,901
H	Medical Officer	$185,907
I	GHS	$130,731
J	Statistics	$211,315
K	GHS	$101,035
L	GHS	$142,616
M	GHS	$162,824
N	GHS	$61,987
O	GHS	$111,138
P	GHS GHS	$111,138 $107,770
Q	GHS	$94,049
R	GA	$138,654

Source: http://php.app.com/fed_employees11/search.php

GHS – General Health Science
PS – Program Specialist
AP – Administrative and Program
GA – General Arts & Information

ADSs have overall responsibilities for promoting science and ethics at the centers. For the most part, they are the supervisors to the center HSCs. Though HSCs mostly function independently, serving as the center regulatory experts in human subjects protection, ADSs serve as their overall guidelines. There are also division level ADSs, and some branches also have ADSs with similar functions at the division and branch levels respectively. Protocols often must be reviewed by the division ADSs before they go HSCs for review. CDC investigators are permitted to propose an initial determination on whether their project is human subjects research, but the final decision rests at the center level, often made by a HSC.

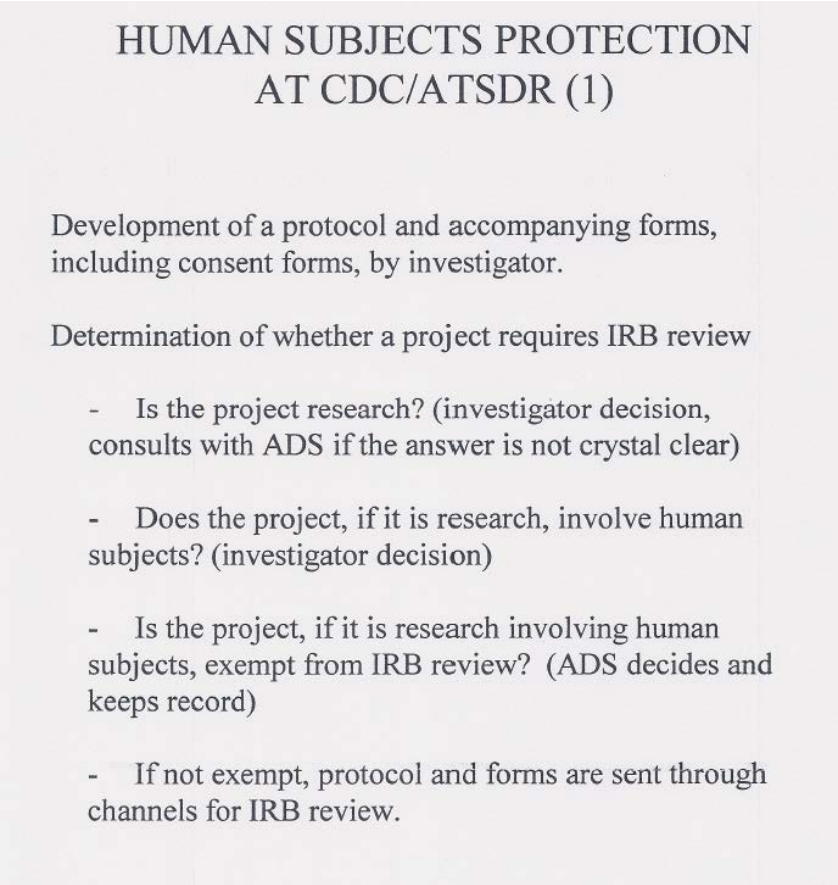
Research Determination Practice in the late 1990s

In 1997 there was no requirement and formal process for submitting projects for research determination, although some centers have begun developing formal process, but was not yet widespread. According to a former HSM:

> There wasn't a centralized, well, even after 1997, they weren't systematically documented, there were only some centers that had systematically approaches for that… I don't know if they still do, but they had a form going back many years. NCHHSTP also did. [One center] had an undocumented, but systematic process… It varied greatly by center, pretty much all CDC said in those guidelines was that it's up to the center to determine what is research and what is not.

This was two years after OPRR released its investigational report and restricted CDC MPA and two years before the 1999 Guidelines were released. In my discussion with staff in one center, I was informed that they were probably one of the first to implement a formal determination process, likely because the center was responsible for one of the two events that led to OPRR's investigation (HIV Seroprevalence and EZ Measles). Before this time investigators were largely left to decide on their own whether their project constituted research, and if the investigator determined that his/her project is research, the center ADS then determined whether it involved human subjects and whether it can be exempted or must be submitted to the CDC IRB. In going through archived documents at the Federal Records facility, I found an old document from around the time of the EZ measles, and one page (Figure 15) shows this simple process. This is now considered a conflict of interest, although this practice was also not exclusive to CDC at the time.

Figure 15: Early Determination Process around 1997



HUMAN SUBJECTS PROTECTION
AT CDC/ATSDR (1)

Development of a protocol and accompanying forms, including consent forms, by investigator.

Determination of whether a project requires IRB review

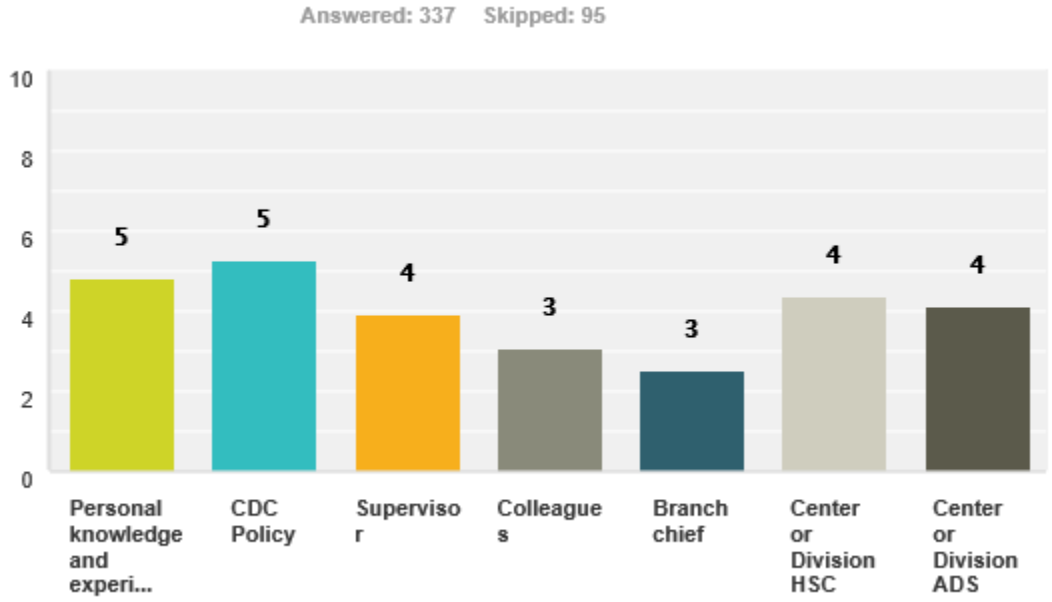
- Is the project research? (investigator decision, consults with ADS if the answer is not crystal clear)
- Does the project, if it is research, involve human subjects? (investigator decision)
- Is the project, if it is research involving human subjects, exempt from IRB review? (ADS decides and keeps record)
- If not exempt, protocol and forms are sent through channels for IRB review.

Source: CDC OADS Archive, Control # T7909A, Box 25, Available at the Federal Records Center, 4712 Southpark Blvd., Ellenwood, GA 30294

Investigators at the time were only submitting projects to HSA (now HRPO) when they and their programs were certain they were conducting human subjects research. They mostly depend on their senior colleagues, supervisors, and branch chiefs to help them navigate the various bureaucratic processes at CDC, including the human subjects review and IRB processes. Figure 16 shows the 2012 survey results confirming my ethnographic observation and experiences that CDC colleagues, branch chiefs, and supervisors were the most used resources.

Figure 16: Most used Resources in Research Determination Practice

Rank the following resources you refer to in helping you determine whether your project is research or nonresearch. (1= most use, 7= least use)



Similar Processes, Different Requirements

By the year 2000 research determination process became routine in many centers. Minimal information requirements were usually submitted via email from investigators to their supervisors to the center human subjects office. Figure 17 is an example of such email submission. For EIS program, the rule of thumb for when a project is required to undergo human subjects review was *"if an investigation or evaluation takes more than one day of an investigator's time*," which seemed arbitrary, but became a rule of thumb. Investigators were usually informed that they should consult their supervisors and if they were unsure, anyone else who has experience and expertise in human subjects protection, IRB, and ethics. Although

the processes were similar in different centers, the requirements differ more significantly as described below.

Figure 17: Example of Early email Research Determination

From: Human Subjects Review
To: Supervisor

Subject: Request for Human Subjects Review Tracking Number

Date: 2/3/2001

Investigator's project: "Legionnaires' Disease in a Nursing Home--State A" has been assigned HSR Tracking #1234.

_____

From: Supervisor
To: Human Subjects Review
Subject: Request for Human Subjects Review Tracking Number
Date: 2/2/2001
Dear HSR Reviewer,
Please see the Investigator's note to me. Here are the formal lines of info required for the record:

Decision Maker: Supervisor
Date Request Received from Investigator: 2/1/2001
Date of Decision: 2/2/2001
Decision Code: 1
Explanation: Although it involves an investigation of human subjects, this project is not primarily "research," because its primary purpose is to determine the cause and extent of this epidemic of presumptive Legionnaires' disease in order to control the outbreak and diminish the likelihood of a similar event recurring.

_____

From: Investigator
To: Supervisor
Subject: Request for Project Tracking Number
Date: 2/1/2001
I'm submitting the following on the L.D. outbreak that I mentioned to you earlier today:

Project Title: Legionnaires' Disease in a Nursing Home--State A
Principal Investigator: Investigator
Date Activity Began: 1/1/2001
Project Description:
State A Health Department notified by local authorities of 5 residents of a nursing home in Town A developing pneumonia over a period of 48 hours. Legionella serology reportedly positive in two patients. We will evaluate and implement control measures.

The research determination process usually begins with the investigator developing an interest in an issue or being assigned to develop and conduct an activity. Figure 1 found in Chapter 1 page 14 is a flow diagram that shows a typical process at most centers. In general, the first step in the human subjects review (HSR) process is the submission of a project determination request by an investigator to their supervisor along with the required center's request form and either summary of their project or a study protocol if available. Most centers do not require extensive amount of information and there is no single CDC-wide form. Each

center has their own form requiring different types of information (see Appendix E for an example). The investigator usually checks off one of the categories they believe their project would qualify, although some centers do not even allow their investigators to make this initial suggestion. Investigators simply submit their protocol or project summary and the centers' HSCs provide their written determination. This was the case in the outbreak investigation I participated in for three weeks in 2012. The investigation was led by another center, so the determination was made at the lead center, by their center HSC. For centers that do have forms, their determination typically includes the following categories, although may not be in the exact order:

Project Categories:

I. Not human subjects research;
II. Research, but not human subjects;
III. Research, but CDC not engaged;
IV. Research, CDC engaged.

Any project falling into category IV must be submitted to HRPO. Under each of these categories, there may be sub-categories. For example, under category I, there could be IB: program evaluation; IB: surveillance; IC: outbreak investigation; ID: laboratory proficiency testing. Other types of categories may be included on the form depending on the center's needs.

Once the supervisor has approved the request, it is sent to the Branch Chief or Country Director (or designee, usually country ADS) for any project originating in one of CDC country offices. The reviews within programs are to ensure both the

scientific and ethics quality of the project. Once the branch chief or country director has reviewed and approved, the request is submitted to the division ADS.

The Division ADS or division HSC reviews and forwards the request to the center Human Subjects Office for center's review and approval. The center reviews the request and determines if additional information and/or revision is needed. If the project falls under category I, II, and III, the center official (usually HSC and ADS) will sign the determination form confirming the category and return it, usually through email to the CDC PI, division and other relevant individuals. Category I, II, and III[59] does not require further review beyond the center and the investigators are informed that any major changes must be submitted as an amendment for further review.

If the project falls under category IV, human subjects research where CDC is by policy, engaged, it might fit into two types. First, the project might be considered "exempt" human subjects research that does not require IRB approval. In this case, HRPO makes the final determination. Second, the project might be "non-exempt" human subjects research. In this case, there are two possibilities for action. The study could be sent for CDC IRB review or the CDC investigator may be able to request that CDC rely on another IRB under an institution that has an FWA filed with OHRP. Under category IV, a complete protocol (if not already included) along with the appropriate IRB form(s) will be required. The requirements are usually less

[59] Category III also include exempt and non-exempt human subjects research where CDC investigators are not engaged, i.e., do not interact with participants and do not have access to identifiable or linked data for research purposes. If investigators wish to have access to linked data, but still remain non-engaged, a nondisclosure form can be signed prohibiting the engaged institution from releasing identifiable code to CDC.

stringent for exempt research than for nonexempt research requiring approval by an IRB.

Once investigators submit all the requirements to the center, the center will forward the request to HRPO. HRPO will review and grant approval on exemption, process reliance/deferral agreements, and assigns protocols needing CDC IRB review to one of seven CDC IRBs. IRB may request additional information from the investigator before the final approval is made. HRPO may return a request if inadequate information is provided or if the protocol is in very poor shape. In normal practice there will at least be one round of revision before CDC IRB granted final approval. The time from when HRPO received a request to approval by a CDC IRB depends on the type of IRB request. For exemption and reliance, it usually takes between two to three weeks for approval. For expedited, amendment, and continuation request, it takes four to six weeks. For convened IRB board review, it can take eight to ten weeks.

Failure of Research Determination to Evolve

The steps described above or slight variations of it have not changed since CDC implemented the research determination process in the late 1990s. There have been some changes as I have already discussed, but these changes, such as the new engagement policy, did not have any impact on the research determination process itself, although it did reduce the burden on HRPO and CDC IRBs. The process, policy, and confusion have not changed. I spoke to one of the main architects of the 1999 Guidelines and process for research determination and human subjects protections,

and he agreed. He told me that he was disappointed with the way the process has not evolved since it was implemented. The senior official said:

> You know when I was talking about a little disappointment on the evolution of the failure for things to evolve, there are several things that have been discussed that one point or another that as far as I know, we have really come back to which is the question of who should make those determination? If you are going to have certain data collection activity that are research and some that are not research then the question came up as to who should make that determination. There were a lot of discussion about whether the IRB should make that determination, but then people like [external ethicist] and others who had been involved with IRB felt like that was kind of defeating the whole purpose of making the determination anyway, because what they were trying to do is protect the IRB from being overwork with basically low risk things that they didn't really feel fell under that umbrella, but then it doesn't follow that just because the IRB doesn't do that determination that it has to be within the center. I think one of the reasons it just began that way was the resource issue (Former senior CDC Official).

Determination was pushed down to the centers because of funding issues. It seemed that CDC might have centralized research determination within HRPO if the funding structure made it possible to do so. Centers had their own budgets and there were individuals such as the ADSs who were responsible for scientific integrity and quality, who could make these determinations. The former CDC official told me that his intent was that how CDC went about in determining research would evolve over time and the process and procedures would evolve to handle the daily challenges to improve how CDC protects individual human rights.

> One of the things I wonder is, you know, we had two or three people in the central office making those determinations instead of the center, would it be better? And then another question came up and some work started on this and it never, it never really went anywhere was, the things you were talking about (Former senior CDC Official).

The "things you were talking about" he referred to was in reference to the initiative at CDC relating to human rights in 2002. He continued.

> We are going to have some questions, some activities going on that aren't research, but they need to be done ethically, what are the concerns that need to be addressed and should we, as the responsible public health people, then use some of the principles from, you know, some of the public health ethical things that have already been written and review those kind of things by an IRB-like group that was separate from IRB, but would still do the nonresearch review and that way, it accomplishes a lot of things. Most importantly, ensure that the nonresearch activities are being conducted in an ethical manner. That, you know, that the appropriate questions can be asked and answered. It also takes away potentially some of the benefits that you were talking about that people might feel they have if they get a nonresearch determination. So I in agreement that where we are now is basically, as far as I can see, is where we were more than a decade ago. And somehow this whole process needs to move along, not backtrack to where we were before, but needs to grow and mature from where it started (Former senior CDC Official).[60]

Some people may argue that the practice has evolved, because now CDC has more staff working in HRPO, there is the new policy for non-engagement, and the 1999 Guidelines and Human Subjects Manual has now been revised and become official CDC policies. Mainly, these changes were parts of an ongoing implementation of the agreements with OPRR's 1995 requirements. Given that there was no timeline for implementation in the OPRR Report, the slowness in which these changes took place made it appear as if they were part of an ongoing evolution of the practice. There are variations in practices now as there were variations when formal research determination began in 1999. These variations include:

- Variations in the process and requirements,
- Who makes the determinations, e.g., HSC or ADS,

[60] Quotes were written verbatim as spoken by my informant.

- What type of information is required, e.g., a paragraph or a complete protocol,
- The different tracking systems used by different centers and even by different divisions within a center,
- Whether research determination is even required for projects to move forward, and
- Variations in interpretation of the definition and policy.

There are some centers that do not require that projects be submitted for determination as dictated by CDC policy. These centers permit investigators and programs to implement their projects without first seeking formal determinations, although based on what their centers' HSCs told me; in general people do submit their project for determination. In cases where they do not submit formal determination requests, the program and investigators do not have the support and backing of the center's ADS and human subjects office. Should problems arise later, they are on their own. This means that the investigators will have to accept any potential consequences for implementing a project without formal approval. If an investigator implemented a project believing it was nonresearch, but turned out to be research, the consequences may include termination of the study, disciplinary action, and termination from CDC employment. Other consequences may include, not being able to publish, potentially facing criminal charges. There are of course risks to the agency. Should there be problems, for example, if a human subjects research was implemented and there were unethical conducts and harms reported, then the problem and liability are not limited to just the investigators. It might affect the whole center and CDC's ability to conduct research as a whole. CDC as an agency would be at stake and research participants might have been or will be placed in

unacceptable risks, whether physical or non-physical. Whatever procedural benefits the program and investigators might reap will not justify the risks placed on human participants. CDC policy states that

> CDC's human research protection program (HRPP) is comprised of every component throughout the agency that participates in planning, reviewing, executing, or administratively supporting research involving human participants. Ethical responsibilities for human research protections extend, for example, to CDC investigators who directly interact with research participants, project officers who provide technical assistance, associate directors for science who provide an early line of critique to assure high-quality science and ethics, management officials who direct the allocation of agency resources, institutional review board (IRB) members who carry out the charge for autonomous review, contract specialists who authorize the disbursement of funds for human research, and laboratorians who analyze specimens that can be traced to unique individuals. CDC's IRBs play a vital but limited role in this enterprise; all components of CDC's human research protection program must remain accountable to the public trust (CDC Policy 2010: 2).

The Beginning of Regulatory Audit

In June 2011, HRPO began requiring centers to submit all research determinations on a monthly basis. Although this new requirement created some consternation, every center essentially had to comply. HSCs I spoke to were not particularly thrilled with this new requirement. Although auditing is a frowned upon process by CDC employees, the HRPO process served several purposes. It was part of HRPO's efforts to obtain accreditation for CDC Human Research Protection Program with the Association for Accreditation of Human Research Participant Protection Programs (AAHRPP) and a requirement from OHRP to ensure that CDC is compliant with the Common Rule. One of the main goals of any audit is to develop consistency in practice, a desirable goal in the CDC research determination practice. However, achieving consistency can sometimes contribute to a system where

everyone is suspicious of everyone else and where auditing has become a cultural practice that unintentionally creates unnecessary stress and anxiety.

Audit often failed to achieve its stated goal. In an analysis of the National Bioethics Advisory Commission (NBAC) hearing, it is suggested that as:

> long as ethical accountability is only imaginable in the form of managerial auditing….practitioners [investigators and researcher] of divergent research styles will continue to simulate consilience with the regulatory ideal so as to appear compliant, cooperative, and transparent—therefore ethical (Lederman, 2007: 314).

Current CDC policy and practice certainly provides many ways to appear in compliant. Because public health is a diverse field which incorporated many disciplines, including their ethical standards, it seems that achieving consistency can create burdens, without actually contributing to ethical benefits and protection of the people they are meant to protect. Enforcing consistency means that we do not accept the variability in disciplines, interpretations and practices. Lederman questions the logic of consistency stating, "The consistency-seeking logic of bureaucratic oversight persistently refuses to recognize diverse professional ethical standards as ethical, suspecting them instead of self-interest" (Lederman 2007: 314). Particularly, the application of the biomedical model to socio-cultural and behavioral research in public health has been problematic ever since the creation of IRB. Unless we have different standards for judging different research as practiced by different disciplines, striving for consistency using a "one size-fits-all" approach might do little to achieve higher level of protection for human participants. Many people I spoke to believe that it is better that we focus on the risk level when determining the level of review. It does not matter whether it is research or

nonresearch, because there are so many different interpretations and variability in practice.

Agency-wide results of the total number of research vs. nonresearch projects approved by centers were available for the first time in CDC history in April 2013 (Table 8). Projects were broken down only as either research or nonresearch. Centers' names were not provided, perhaps as part of HRPO's effort to maintain confidentiality.[61] For HSCs, it would be relatively easy for them to identify which center has how many projects, because they were the ones who provided the determinations. The newer centers were likely to be the ones with the fewer number of research determinations, with the exception of my center, CGH, which was formed from the merging of established CDC programs previously housed in other centers. The center that reported "zero" determination is likely the center whose activities are mainly related to emergency response. The more established centers were more likely to report more projects. Although, based on Table 6, the percentages of projects that were determined by centers to be nonresearch were higher than those determined to be research, I would have expected it to be much higher. It is likely that investigators from the newer centers were more likely to submit projects that they perceived as research for determination, skewing the numbers towards research. It is also possible that individuals who identified themselves as researchers were more likely to submit projects for determination, increasing the percentages of research vs. nonresearch. Since these were not broken down by subcategories, for examples, for research, whether they were

[61] Typically, there are only one or two HSC's for each center, therefore it is more likely that HRPO is attempting to protect HSC's confidentiality.

human subjects, non-human subjects research, it is possible that many of the projects determined as research were not covered under the Common Rule, and therefore were not subjected to IRB oversight. They would also include research where CDC was not officially engaged, and therefore do not go to CDC IRB.

Table 8: Project Determinations at CDC July 1, 2010 – June 30, 2011

CIO[62]	No. of Projects	No. of Projects Determined as Research	No. of Projects Determined as Nonresearch
1	225	113	112 (50%)
2	97	74	23 (24%)
3	194	76	118 (61%)
4	16	6	10 (63%)
5	105	28	77 (73%)
6	135	77	58 (43%)
7	0	0	0%
8	11	5	6 (55%)
9	108	48	60 (56%)
10	29	6	23 (79%)
11	1	1	0%
12	294	7	287 (98%)
Totals	**1215**	**441 (36.3%)**	**774 (63.7%)**

Source: CDC Human Research Protection Office

Despite the lack of details, Table 8 provides a lot of information about the research determination practice at CDC. CDC policy requires that "all CDC activities must be reviewed to determine whether they are research involving human participants" (CDC 2010: 2). The only possible guess as to why some centers have very few determinations is that they were noncompliance or that they did not document their determinations, and therefore had few reports to submit. Whatever the reason is, it does not seem possible that these centers had only these few

[62] CDC's organizational units comprised of centers, institutes, and offices or CIO's. CIO's and centers often used interchangeable and supposedly enjoy the same status under CDC organizational hierarchy, although this can be debated.

projects that fell under the policy; therefore noncompliance is the likelier answer. To be familiar with the research determination practice a new CDC investigator is usually introduced to the process by their supervisors, colleagues, through training; therefore it is possible that staff from newer centers have not yet been enculturated.

Research Determination of this Dissertation

It makes sense to describe the process that I went through to obtain official approvals (determinations) from CDC and from Emory IRB for this dissertation, because it is related to the study objectives. As it turned out, both CDC and Emory IRB deemed this dissertation as not requiring IRB approval. Although their decisions had the same outcome, the approval languages were slightly different. The dissertation was approved at CDC as non-research/program evaluation. At Emory, the dissertation was determined to not meet the regulatory definition of research.

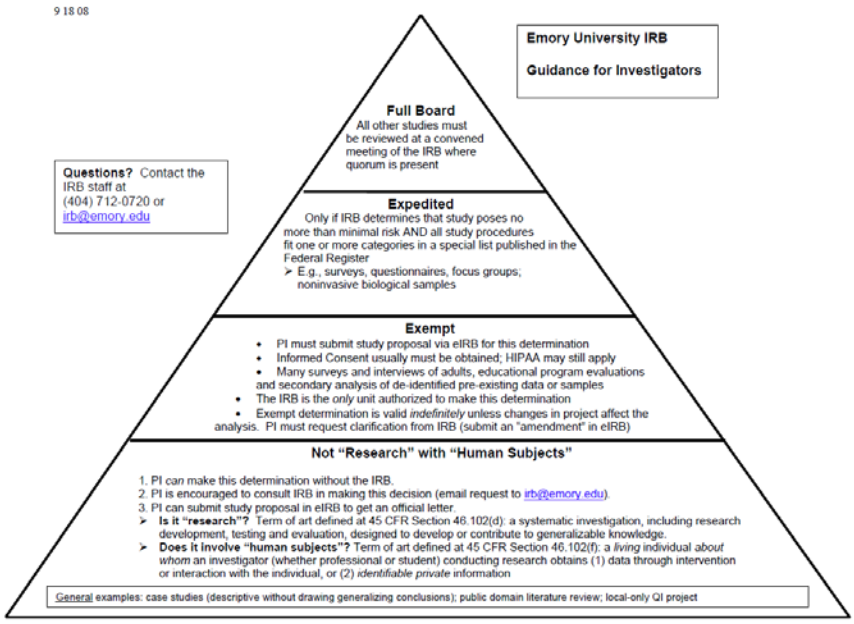
Because of where I was organizationally-situated at a center office of the director (OD) level, the only review I was required to go through was with the center Associate Director for Science (ADS), who made the official research determination for my project. Had I been in a program at the branch level, I would have to go through two additional levels of review. I had requested that the proposal be considered for non-research, program evaluation under CDC policy (2010). I did not have to provide a rationale of why I requested a non-research/program evaluation determination. In practice, although an investigator can make an initial recommendation on the category, it is considered under CDC policy to be a conflict of interest for an investigator to make formal research determination. Investigators

cannot make such determination of their own project. The documents I had to submit include the center's determination form, which lists a number of possible research and non-research categories, and a summary or protocol of the proposal. The center does not required a complete protocol to be submitted for a research determination, although if it was determined to be non-exempt human subjects research, a complete protocol will be required for submission to CDC Human Research Protection Office (HRPO), who will assign the protocol for review by one of CDC seven IRBs. The center's ADS determined that my dissertation proposal was non-research under the program evaluation subcategory.

As an Emory University graduate student, I also had to submit my proposal to the Emory IRB for approval. At Emory it was the IRB administrator who makes the official determination, although the department has to approve the proposal prior to submission to the IRB administrator. At the time I submitted the proposal to the Emory IRB in November 2011, the Human Subjects Decision Charts (Figure 18) found at the IRB website (Emory 2008) appears to permit the investigator/researcher to make a research determination, but it is not clear whether non-research project had to be submitted for official determination. The guidelines states that if an investigator wants a formal determination letter from the Emory IRB, they can obtain one by submitting the proposal for review, which was what I did. The letter I received from the Emory IRB states:

> The above-referenced study has been vetted by the Institutional Review Board (IRB), and it was determined that it does not required IRB review because it does not meet the definition of 'Research' under applicable federal regulations. Accordingly, IRB review is not required (Emory IRB 2011).

Figure 18: Emory University IRB Human Subjects Decision Chart



Source: Emory IRB (Permission Obtained from Emory IRB Director)

The letter stating that the determination was made by the IRB is not technically accurate, because the decision appeared to be made by the Senior Research Protocol Analyst (IRB administrator under CDC lingo) who analyzed the protocol and made the official determination. The letter then states the Common Rule's definition of research as the reason why IRB was not required, "research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." The letter cited my overall study objective:

> …study is to examine the historical, socio-cultural, and political factors that influenced CDC cultural practices in human subjects protection and ethical oversight of public health research and program and to describe the (pre-IRB) review and approval processes, including the decision-making processes, criteria, and guidelines for determining whether a project is research or nonresearch. Through this study, the PI will evaluate the current (pre-IRB) human subjects protection program at the CDC and develop

> recommendations for improving current program and practice at CDC. The results of this study are specific to the CDC and are not generalizable beyond this organization.

Unlike the CDC determination, the Emory IRB letter does not state that the study is not research, only that it did not meet the regulatory definition of research. This may imply that the Emory IRB considered the project as research for other purposes. Before I officially submitted my dissertation proposal to the Emory IRB, I requested a consultation with the IRB administrator, but never got a response. After I received the determination letter I sent another email to the Emory IRB requesting an opportunity to discuss their thoughts and decisions about how they view my proposal and elaborate on their deliberation on why they feel it did not meet the regulatory definition of research. Unfortunately, I received no response a second time. The letter appears to hinge the decision on the issue of "generalizability," that the study results "are not generalizable beyond" CDC. Emory based their decision on "generalizability," which as discussed in previous chapter, is one of the most confusing terms and concepts for CDC.

I had assumed that my proposal provided sufficient details of the ethical issues involved in the study. In addition to providing details about the study methods, I also described the plan for protecting individual rights, privacy, and confidentiality. Even so, protecting individual confidentiality and privacy in an ethnographic study at one local or community is difficult, because many of the people I interacted with, interviewed, or participated in focus group discussions knew one another. Though I was wary of people being concerned about responding to my questions, most of them were open to sharing their thoughts with me. I made

extra effort to make sure that as many people as possible knew what I was doing. I did not want it to be a secret study. I wanted them to know that I was not spying on them, although I am certain that there were some people who were wary and suspicious of my presence in meetings, conferences, and other avenues, if not at least annoyed.

Determination Requirements

The Common Rule does not dictate who at an institution should be given the authority to make research determination only that it be made, although at most institutions research determinations are made by the IRB (McCarthy 1984). This implies that determination can be made by individual researcher and program, and this has been the assumption and practice at CDC before the formal processes were developed in the late 1990s. Charles R. McCarthy stated in an article that "in case of doubt within an institution the matter must be submitted to an IRB, which shall then determine whether or not all of the requirements of the HHS regulations apply to the activity" (McCarthy 1984: 8). CDC policy was meant to be flexible, allowing centers to develop their own internal procedures and processes for research determination. This flexibility has led to variations in processes and inconsistency in interpretation. Research determination is not really about distinguishing whether a project is research or nonresearch, but whether a project is "research" under the Common Rule's definition that was constructed in 1974 by the Congressionally-mandated Commission. An activity may be considered research for other purposes. The challenges lie in the interpretation of this definition.

Investigators and programs were generally happy that CDC policy does not specifically require that a complete protocol is submitted for research determination. This led to many centers' practices where investigators only need to complete a short form, usually identifying the category they believe their activity falls under, and a summary of the activity for determination. A summary may be as short as a few sentences and usually no more than a few pages. Many questioned whether anyone can make a determination with such little information. All HSCs I spoke to agreed that it is insufficient to address the ethical aspects of the activity, such as taking into account the informed consent requirements. Although all HSCs understood the rationale behind the policy of not requiring comprehensive information for research determination, they were also frustrated by the inability to ethically assess the activity, because of the amount of information provided to them. Some centers required complete protocols for research determination, but that seemed to be the exception, and the practice varied even within centers, where some programs (divisions) required complete protocols, whereas other centers did not, and others did not required research determination. One center HSC told me:

> Basically, our rule of thumb is if you want a written determination you need a written protocol. So I mean if it's something they consulted with the division and the division ADS agree and say I agree it's not research, it doesn't need a determination, then we don't give them a formal determination….If they want a written determination for any reason, then they have to have something written down, a protocol. It doesn't need to be long, but it needs to satisfy all of our questions, and answers everything we need to know about it. So and sometimes we have things that were really straight forward that they need a written determination for some reasons and in that case, we always give them one if they need one, want one, or feel better to have one, whatever.

Issues Related to Research Determination Practice

Retroactive Approval

Except for emergency protocol, a project should not be implemented before receiving appropriate approval whether it is considered research or non-research. A review of past determinations I received shows that almost all of the time, projects indicated starting dates that have passed, arousing my suspicion that many of these requests were mostly retroactive review requests. In some cases, the starting dates were tentative and the reasons they have passed when I receive them was due to the delay in the review process in the divisions. The delay could be due to many factors, slowness of reviewer to take a look, investigators to respond to comments from reviewers, often related to poor quality protocols, or it could even be related to the government shutdown, or in some cases instability in the country. An endless list of factors can cause a delay in protocol approval, delay that frustrated investigators, which perpetuate the practice of implementing projects before receiving formal approval from CDC and program condoning the practice by not raining down on the noncompliant.

On many occasions the projects have already been implemented or ongoing, some, for many years before a protocol is submitted for research determination. Given, if these were program evaluations, then those dates may refer to the dates that the projects were implemented, and not the dates that the evaluations started. Investigators and programs should understand that a project being submitted should indicate the starting date of the project, whether it is an evaluation of an existing project or new project or research. If a new program is being developed and

implemented then the starting date should be in the future, after the determination has been made. If it is an evaluation of an existing, ongoing program, then the starting date should be when the evaluation will be implemented. Retroactive review should be reserved for very unusual circumstances.

Record keeping

One of the reasons why OPRR restricted CDC MPA was for the poor record keeping at CDC, which was related to the allocation of financial and human resource for human subjects oversight. Record keeping had been a challenge at CDC, both in the past and in the present. Two instances I have already mentioned based on my experiences are 1) related to my quest for archival documents (minutes) from the EISC meetings. I was not successful in obtaining the EISC minutes; and 2) when I joined CGH, I had very poor and incomplete records of the research protocols I was supposed to oversee. Both of these situations were related to the organizational changes and transitory nature of CDC employees and positions. CDC employees often moved from position to position within CDC, and records are not always passed on to the next person. In the case of the EISC minutes, they appeared to be lost or were destroyed.[63] In the case of the research records for CGH protocols, records, mostly in the forms of emails, were being transferred from three different centers to CGH, and they were not always complete. Essentially, I had to create my own record and obtained research protocols as they were being submitted for renewal. When I first joined CGH in 2010, I did not even know what research

[63] I have not given up on finding them.

protocols belong to the center. I asked HRPO for a list of CGH protocols, but it took over a year before I was given a list, and it was horribly inaccurate.[64] Protocols were missing and others did not belong to CGH. Poor record keeping will continue to be one of the problems at CDC, because of the constant reorganization and staffing change, unless a cultural and technical solution is implemented to insure that records are appropriately transferred from one custodian to the next, and that people are committed to doing so.

Engagement

As already discussed, in July 2007, HRPO issued a new policy stating that CDC IRB no longer accepts research protocols for review if CDC is by definition "not engaged" in human subjects research. Putting this policy into practice significantly reduced the number of research protocols going to CDC IRB. For example, in calendar year 2013, CGH had 159 protocols determined as human subjects research, but CDC was not engaged. Only 33 protocols were determined to be engaged and were submitted to HRPO for exemption approval, deferral/reliance, or approval by one of CDC seven IRBs (Table 9). This means that only 33 (17%) of the 192 (159 non-engaged + 33 engaged) protocols that could potentially go to HRPO, actually went to HRPO, a reduction of 83%.

[64] I am not blaming the staff in HRPO, because they inherited a poorly developed tracking system. It was also difficult to identify individual protocol, because CGH was new and it took time for investigators' affiliations to be determined in the system. However, the current IRB tracking system was poorly developed.

Table 9: CGH Project Determination Requests for Calendar Year 2013

Measure	Total
Non-research	191 (45%)
Research but no human subjects	37 (.09%)
Research but no CDC engagement	159 (38%)
Research CDC Engaged	33 (.08%)
Total Determinations	422

In term of the protocols that were submitted to HRPO, 6 were exempted, 11 received expedited review, 3 were reviewed by a convened (full) CDC IRB board, and 13 were deferred/reliance to other non-CDC IRBs (Table 10). This means that only 14 (42%) protocols out of 33 that were submitted to HRPO actually received CDC IRB approvals. If we account for the total number of protocols (engaged and non-engaged protocols, n=192) that could have potentially gone to CDC IRBs, only 7% were approved by CDC IRBs. These calculations only account for one center (CGH) and CGH is unique in that the center has staff working in over 50 countries globally. It is not likely that other similar-sized centers will have the same number of deferral/reliance protocols, although it is possible that they have similar percentages of non-engaged.[65]

[65] Unfortunately, I do not have data to calculate for other centers.

Table 10: CGH Research Protocols Submitted to HRPO in 2013

Measure	Total
Exempt	6
Expedited	11
Convened	3
Reliance	13
Total	33

The rationale for the non-engagement policy was related to staffing shortage in HRPO, an economic one, but some HSCs believed it has more to do with personality and interpretation of the OHRP guidelines on engagement. Many HSCs find the policy troubling in practice and a few have told me that they have voiced their concerns to HRPO to no avail. One HSC I interviewed was particularly unnerved when we discussed the non-engagement policy.

> They're (HRPO) wrong on that…If we define the interaction with the participants, we pay for the work to be done. We get de-identified data, because we don't have direct interaction, and because we have de-identified data, they say that we are not engaged, but we are driving the whole research activity. How can we be NOT engaged?
>
> When [name of HRPO staff] was in place, [HRPO staff] has been upset about all the data from [a center], but otherwise not engaged and the data would come back to CDC and [HRPO staff] said we don't want to review all these things, so we are going to say CDC is not engage in these, so we are not going to review anything where CDC is not engaged. And I have lots of talk with [HRPO staff] about this and the center's perspective was we want to make sure that there's IRB approval and that there is appropriate protection for people and for the agency. And this was a fair consideration and I think [HRPO staff] was wrong.

The problem is that in practice, the issue of engagement can be used to avoid submitting human subjects research protocols to CDC IRB. If CDC IRB will not accept protocols where it is not necessary for CDC investigators to interact with study participants or have access to identifiable data, then investigators may prefer to go a

non-engaged route. It is true that if CDC funds the study or provided material support that the engaged institution must have an FWA and their IRB must be registered with OHRP. In that scenario, there will be formal ethical oversight even if it is not by CDC IRB. For studies where CDC does not provide funding and material supports it can be ethically problematic. If the local institution insists that they will not consider the study as research and by definition CDC is not engaged, there will be no formal ethical oversight of the study that meets CDC definition of research. HRPO has repeatedly refused to accept any request where CDC was not engaged by definition, but have significant interests and could provide substantial intellectual input to the study. Another HSC also voiced this concern. Below is the conversation I had with one HSC.

> AL: There have been several instances where I asked HRPO to accept protocols for non-engaged, because, for one reason, the local MOH doesn't consider it as research.
>
> R: Right!
>
> AL: So they are not going to send it to the IRB.
>
> R: Right!
>
> AL: And CDC is not going to be engaged.
>
> R: Right!
>
> AL: And so HRPO won't accept it.
>
> R: Yep, had that happen too!
>
> AL: We are going to have a study where…
>
> R: Nobody review it!
>
> AL: Nobody review it. Do we have the authority to say, "No, you can't do it!"?

> R: We don't really! If you say we're not engaged then we don't.
>
> AL: If I say that, they would go somewhere else, they would go to the ADS, to the center Director.
>
> R: Right, yeah! No, I agree and I think that a loophole, that's a problem. You know, I mean, I think the other…yeah, I think that's a problem where nobody reviews it. And the whole exemption engagement thing is the other thing surrounding that I believe that OHRP makes it clear that exemption is applied before engagement. Not the other way around.

This was an interesting exchange. Some of my other center counterparts have been involved in human subjects protections for many years, were having to address issues that appears to present an ethical dilemma, and were sometimes frustrated. HSCs cannot really disapprove a protocol submitted, although they can request revisions. They were never really the final authority, because their decisions can always be appealed.

Problematic Practices

Investigators who do not want to have to go through CDC IRB have some options available to them during the research determination process to have a decision made that does not require submission to HRPO and subsequently to CDC IRB. They can obtain a non-research, research but no human subjects, or a non-engaged approval.

1. Submitting summary of protocol for determination when a complete protocol is available

I have encountered several occasions where investigators submitted summaries of research protocols for studies where complete protocols were already developed, in hope that I would approve the project as nonresearch. This was usually when CDC investigators were being invited to take part in existing studies. Sometimes, out of suspicion that there is a protocol, I asked the investigators whether complete protocols were available and whether local ethics approvals have been obtained. In some cases, the summaries were written in a way that the project appeared more like nonresearch, but when I read the complete protocol, the language was completely different and the projects ended up being determined as research. Permitting investigators to submit summaries of projects for research determination can leave room for dishonesty and even deceit, if there is strong enough desire to avoid going through CDC IRB. When they found that there is the option to be involved, but CDC remains non-engaged, in all such cases, the investigators usually chose to go the non-engaged route, where they rendered themselves non-engaged by promising to not interact with study participants nor access identifiable data.

2. Submitting research determination only after obtaining local approval

In many cases investigators have already obtained local IRB approval or have submitted their protocol to local IRB review, before submitting it to the center for review and submission to CDC IRB. When this happened, it doesn't make sense for the center to request changes to the protocol during the review pre-IRB review process and defer any changes to the IRB. Although this practice helps facilitate the

process and shorten the timeline for project approval and implementation, the investigators or program effectively bypass the center's review process. As the center level reviewer I am hesitant to demand changes even though those changes may be required under CDC policy or under regulations. The hope is that CDC IRB conducts an appropriate review and requests any additional changes. Unfortunately, due to the numbers of protocols I have to review, I am not able to thoroughly review every protocol to ensure that investigators respond appropriately to any requirements.

3. Getting local collaborators, including country ministry of health or local and state health department, to approve the project as nonresearch in hope that CDC would also approve it as nonresearch

CDC cannot dictate to collaborating partners when an activity is research or nonresearch. In principle, research determination is made by each institution involved in the project and CDC would honor the decision of the institution. Under CDC policy, a public health activity can be considered research by one institution and nonresearch by another institution; a project that is categorized as research by CDC may be categorized as nonresearch by another institution. Ethics committees in many countries may not have the same standards as in the US, and sometimes approval letters can be obtained only for convenience. Many involved in human subjects protection know that local IRB approvals in some countries are just simple rubberstamps.

4. Submitting a research determination after a project has ended (retroactive)

Another way to avoid having to respond to the reviewers in the research determination process is to submit a project after the study has ended. Usually if the study is human subjects' research, investigators would obtain local IRB approval and then worked with local partners to implement the study. Although the investigators took a huge gamble in that their study may not be approved, this practice defeats the whole purposes of the system. Retroactive submission should be reserved for very rare occasions, such as in emergency outbreaks, but even in emergency, the project can meet the regulatory definition of research. In terms of approval, if CDC was engaged, then it is usually not possible for CDC to approve such project if it was human subjects research. If CDC was non-engaged, HSCs often trust the investigators that they were indeed non-engaged, and if there were documentation of local ethics approval, then CDC can provide retroactive, non-engaged approval. Investigators can take advantage of this practice, because it permits them to bypass CDC IRB.

5. Being creative about study objectives (gaming the system) because of how CDC defined research based on primary objectives

As already discussed, the most criticized aspect of CDC interpretation of the regulatory definition of research is the issue surrounding primary intent. Primary intent is usually captured in the study objectives. It has been argued both internally and externally that a creative investigator can write research objectives to appear as if they are nonresearch objectives. Better yet, investigators can simply leave out any research objectives from the written materials they submitted for determination.

For nonresearch, there is usually no follow up. One possible way to find out whether research was conducted is to review the published materials from the study.

6. Rationalize with reviewers whose hands are tied, thinking that if the reviewers give their blessing it's okay even if it's not in compliance

The most dreadful part for HSCs in making a research determination is that their decision might be wrong, particularly when there was insufficient material to assess the ethical components of the study. Research determination is a part of the human subjects review process, and should not be considered simply a process to determine whether a project is research. Under CDC policy, everyone involves in human subjects have responsibility to ensure that research is conducted ethically. More dreadful than making a wrong decision is probably running into an investigator who is adamant about their project, and who would not accept the decision of the HSC. For an investigator who has some clout, HSCs determination has little meaning, because their decision can be challenged and often reversed. Although this is rare, there have been two cases in my personal experiences. A center ADS discussed how investigators would argued with his staff and how only selected protocols were submitted for formal research determination.

> People will argue strenuously with [staff] and with me and with [staff]. You know [staff] does most of the formal assessment of research vs. practice using the form, there is a standard form, standard procedures, but only selected protocols that the divisions choose to send forward are subjected to that formal determination process as you know.

7. Implement program as nonresearch then later de-identified and use the data for research

In the 1990s, one of OPRR's criticisms of CDC's interpretation of the regulatory definition is in relation to collecting data in nonresearch activity such as

surveillance and later use de-identified data for research purposes. From OPRR's perspective at the time, all surveillance projects were research. Many program evaluation projects would be research even if CDC definition of research is based on the primary intent of the project, because part of the intent could imply that collected data would be used for research. There is no follow up on what the investigators actually do during project implementation and data analysis. Projects almost always change during the implementation phase and the intent uses of data also change. Reviewers often have to interpret what the intentions of the investigators are, trying to "read their mind" in a sense. Use of existing program data for research purpose later is fair and legitimate use, but if a project is implemented as nonresearch only to avoid going through IRB, but data would be used for research purposes, then it should be categorized as research. The use of de-identified data where it is no longer linked to individuals would not be considered human subjects research and would not need to go to the IRB, effectively bypassing the system and another tactic that defeats the purpose of the process.

8. Play ignorance

I am not going to say much about ignorance, because something is better left unsaid and are simply understood. Some of the statements I heard through the years I have been involved in human subjects protection work include:

- "We didn't know we had to submit our project for review" when asked why the project was not submitted before implementation.
- "We assumed that the local partners had gotten their approval" when asked why there was no local approval.

- "We submitted our project, but it must have gotten lost through the process." Email systems can be unreliable particularly in developing countries, but it is the responsibility of the investigator to follow up.

Efficiency

Efficiency helps CDC fulfills its promised to be a "diligent steward of the funds entrusted to it" (Walter R. Dowdle, 1990), but efficiency can come at a price, which may, ironically, include an erosion of public trust in the case of human subjects protection. One scientist I spoke to said:

> I think our [project] is best fit for section IIIa [human subjects research, but CDC is not official engaged] under the project determination for USCDC. The full USCDC IRB process would take months and we would still be required to have the IRB process done……..anyway. So for international projects, it makes the most sense to go under section III if possible to avoid the long IRB process in the US. That is my understanding.

Since the implementation of the non-engagement policy CDC scientists believe it is a more efficient for them to have their collaborating partners obtain local IRB approvals than to go through CDC IRB. Rendering CDC non-engaged is a relatively simple process. They just cannot interact with study participants nor have access to identifiable data for research purposes. Access to linked data is also permissible with the execution of a non-disclosure agreement that prohibits the release of identifying code to CDC investigators. The issue of CDC initiating a project is simply an undiscussed topic, because as discussed earlier, an alternative interpretation of OHRP guidelines is if CDC initiates, funds, and caused data to be collected for research, regardless of whether CDC interact with participants or have access to identifiable information, then CDC is engaged. This is the definition that the Office of Management and Budget use for paperwork reduction. Non-

engagement has certainly helped reduce the workload for CDC IRB, but when the scenario above arises, it does not release CDC of its ethical obligations. For programs, it is a more efficient way for projects to get implemented, and in many cases, projects are implemented before a formal determination is made. Programs permitting this practice to continue not only condone such practice, but encouraged continuing practice. If policy is to be taken seriously, investigators cannot, must not implement projects until formal approval is obtained, but policy does not always get implemented the ways it was intended. Closser states:

> The ideal represented by policy does not determine what happens on the ground….. David Mosse has argued that in development projects, policy is not even designed to reflect what is happening in implementation. The function of policy, he argues, is to get multiple stakeholders on board and, speaking in the same terms, to frame projects for donors; it does not necessarily deeply shape how projects are implemented (2010: 143).

CDC policy, without strict enforcement, certainly functions the same way. There are many reasons why this is the case. Because of the continuing culture of reorganization often causes staff turnover, there is often a lack of continuation of the previous administration's priorities and goals. A new administration brings forth new priorities and goals, and what was previously done often get toss aside. Things are not followed up and even get loss in the chaos of reorganization. The lack of sufficient and effective systems, such as for tracking of protocols, contribute to a cultural practice that is messy at best, unethical at worse, and no one to blame in term of accountability.

An individual can be overwhelmed and as mentioned earlier, "something" will be placed in the backburner. That "something" is not always trivial, and in the

case of CDC human subjects protection, that something was as simple as having a good monitoring and tracking system and filing and processing assurance, which led to the restriction of CDC MPA and suspension of CDC research. It makes little sense to force individuals to take on more work than one person can normally carried out, but this is often the case at CDC and not only with work related to human subjects. The opposite may also be true.

In the research determination process, requiring less information will obviously improve efficiency at many levels. In an ideal world this scenario would play out perfectly, the approval timeline will be shorter, the project can be implemented sooner, and investigators will be able to write up and share and/or publish their results, but ultimately, the health of the individuals and community would improve, health crisis averted and lives saved, with no or few significant risks or harms to the participants. But in the real world, it can also lead to unethical conducts and harms to individuals and communities.

Research Determination for External Funding Proposals

An anomaly in the human research determination practice is the verification process used by CDC Procurement and Grant Office (PGO) to ensure that no CDC (federal) funds for nonexempt human subjects research are disbursed unless awardees hold valid FWA and certified that IRB approvals have been obtained. PGO relies on the centers to make this determination and HSCs are usually the individuals to sign off. The problem with this process, which is slightly different from the routine research determination, is that the documents submitted for

review, which usually consisted of the funding proposals, were never sufficient to make an informed determination. PGO has a human subjects tracking form that, according to some informants, was developed in collaboration with CDC OADS for this purpose, but centers do not find it useful, because of the insufficient information contains in the funding proposal.

The process is similar to the routine research determination process described earlier, except that instead of a CDC investigator initiating the request, a project officer (PO) who oversees the funding disbursement submits the request along with the PGO form. Most of the time the requests were submitted in the last minutes and the PO usually wanted approval as soon as possible, expecting the HSCs to drop everything and without consideration of other priorities. To add to the problem, several years ago, CDC decided to separate research and nonresearch funding mechanisms e.g., research cannot be funded through nonresearch cooperative agreement, although nonresearch can be funded under research agreement. HSCs are supposed to determine and verify whether the submitted nonresearch proposals were indeed nonresearch, and if the submitted proposals are for research, then verify that appropriate IRB approval have been obtained. If no IRB have been obtained, then a funding restriction (a percentage of the total award, usually 50%) is imposed.

The fact that insufficient information was usually provided to HSCs means that the process was essentially ineffective, if not useless. It was simply a rubber stamp and at least one center protested. Other centers just signed off, and simply

stated that they do not conduct formal determination through this process. One center HSC said:

> There simply is not enough information. The sign-off on the tracking form (for a non- research award) is simply an acknowledgement that an authorized individual has reviewed the application and not identified anything that is inconsistent with nonresearch.

From a program perspective, one person said to me that in the past, "Our branch never announced a research funding opportunity. We always fund projects through nonresearch, and they can do whatever they want with the money. We don't monitor or follow up with ethical approval." Fortunately, when a CDC investigator becomes engaged in a project, which is usually the case for cooperative agreements and contracts, they usually submit each project for formal research determination.

Chapter 5: Research Determination Case Examples

"The applicability of the HHS regulations to an activity depends on the nature of the particular activity. It is sometimes difficult to determine whether the regulations apply to a particular activity. The determination requires familiarity with the regulations, the basic features of research design, and the details of the particular activity in question. **There is no single criterion that can always be relied on to distinguish activities that meet the regulatory definition of *research* from those that do not**."

OHRP Unpublished Guidance (2007: 3)

An unpublished drafted OHPR guidance states that making research determination "requires familiarity with the regulations, the basic features of research design, and the details of the particular activity in question," because "there is no single criterion that can always be relied on to distinguish activities that meet the regulatory definitions of research from those that do not" (OHRP 2007: 3).[66] I would also add that because the definition and interpretation of the definition of research were socially constructed, it would also be helpful for anyone having to make such determination to be familiar with the historical underpinning of how they were developed. Understanding the history will at least give a sense of how we got here.

This chapter is a continuation of the previous chapter on practice and will explore several cases in more details to understand the processes and rationales behind CDC research determination. These cases are not meant to provide clear examples on whether they are research or nonresearch, but to describe the difficulties and complexities involved in making such determinations. They are based on real events, but the topics have been made generic in my effort to protect

[66] In 2007 OHRP circulated a draft guidance on their "current thinking" of the regulatory definition of research. This guidance was never finalized and released to the public.

the privacy and confidentiality of individuals and programs involved. Individuals who were participants in the activities will certainly be able to identify the events and recognize themselves in the descriptions. Any interpretation and inaccuracy I described are certainly mine and I take full responsibility for them.

Case 1: Emergency Outbreak Investigation

In late July 2012, a medical epidemiologist walked into my office to inform me of an ongoing outbreak of severe respiratory and neurological illnesses among young children, mostly less than 3 years of age, in a developing country. The illnesses were caused by an enterovirus that is commonly found worldwide, but was unexpectedly deadly in this particular country. It was the first known outbreak of this particular strain of the virus in the country. The fatality rate was 98 percent among the approximately 10 dozen initial reported cases. The first few dozen cases were identified between April and June 2012. There were 61 cases of the disease reported in 14 of the 23 provinces in the country. An initial investigation led by another institution was inconclusive about contributing factors to the unusual fatality rates. After describing the situation, he asked me if I would be interested or willing to be on the CDC team requested by the country's ministry of health (MOH) to help investigate the outbreak. I would be a part of a four-member CDC Atlanta team to assist the country MOH and CDC country office in the emergency outbreak investigation.

I later learned that the reason I was invited was because someone familiar with my background had suggested that the team could benefit from my help in the

investigation. It was obvious to me why they had approached me. It was not because I had extensive experience investigating outbreaks, but because of my cultural knowledge and language skills. This was how CDC usually put together investigation teams. The program with the subjects matter expertise usually takes the lead and team members are recruited based on expertise to ensure the best possible outcomes. Usually fellows accompany outbreak investigation teams as part of their training. In this case, an EIS officer participated in the investigation. Initially I hesitated to join the team, because of an ongoing family crisis, my father-in-law was losing battle with adenocarcinoma (stomach cancer), but the opportunity was too good to pass up. It was a chance for me to take part in an important outbreak investigation with global implications. It was also a serendipitous opportunity to be both a participant from the standpoint of an investigator, and an observer from the standpoint of my dissertation study, and to develop ethnographic experience and understanding behind the rationales already discussed in previous chapters for why most emergency responses/outbreak investigations at CDC have been determined to be nonresearch and when they might be research.

Before I even said "yes," I was quickly introduced by email to the people coordinating the outbreak response efforts across CDC's programs in Atlanta, CDC country office, the country MOH, and other local and international partners. It was an urgent public health emergency and the situation called for quick, coordinated actions and responses. Decisions had to be made quickly, because lives were at stake. Although the email introduction to the people involved expressed my uncertain response, I was already copied on the message. I barely had a chance to

discuss with my family, because the investigation would mean I will be away for at least several weeks. Leaving my wife home alone with three small children was not something I would take lightly. I am sure that the medical officer who met me in my office was fairly certain that my answer would be "yes." In his message to other CDC staff involved he wrote, "Dear all, I spoke with Aun Lor (copied) who is interested in supporting the investigations from HQ and potentially available for travel." It would be difficult to refuse after that message.

CDC had been on alert since April 2012 when 61 initial cases were reported from two local pediatric hospitals. A few CDC staff persons both stationed within and in a neighboring country were involved in the initial investigation lead by the local MOH and their international partners. Because patients were reported coming from fourteen of the 23 provinces, CDC was interested in conducting a community-based investigation looking at the potential unknown risk factors associated with severe outcomes, generating hypotheses that might be tested in a later study, and provide recommendations to the MOH on current and future outbreaks. Those were as it turned out, the final primary purposes (intents) of the CDC investigation, although they have evolved a bit from the initial thinking of the lead program.

The CDC program leading the investigation was based at different center, but the funding for the team came from my center. This means that the project must be submitted to the other center for research determination. One of the first things I noticed when I joined the team was that no one had thought about submitting the project for an official research determination, even though the program had been on alert since April, for about three months. A possible reason I found out later,

although I am only speculating, for why there had not been a determination was that the policy of the lead center did not require that an activity is submitted for determination.[67] If the investigators and programs were certain the project was not research they can implement the study without formal research determination. When I spoke to the Center's HSC who eventually provided a determination for the project, she said that if investigators would like to have official backing of the center ADS and their human subjects office, they can submit their projects for official determination. There is no requirement that they do, but if they do not, she said, "They are on their own."

Once I became more involved in the planning and before we left for the field investigation I asked the team whether a research determination had been submitted for the investigation. This was sometime in early August 2012 and by the end of August the program submitted a request to their center's HSC asking whether an official determination was needed. The request indicated that the investigation was an Epi-Aid, an emergency response request. A brief two-page proposal was submitted with the center's determination form, indicating that the activity was "public health nonresearch" and the goal of the activity was to "identify, control or prevent disease, illness, disability, or death in response to an immediate public health threat." Further the form indicated that informed consent will be sought from participants. The summary proposal indicates that the investigation proposed to collected clinical data from patients' medical records, interview family members,

[67] This was the first time I learned that some centers still do not require projects to be submitted for research determination. I also found that at least one other center held the same view—that if an investigator does not submit, they are on their own if they get into trouble.

and health care providers, either clinicians or pharmacists, who treated the patients. The summary also indicates that risk factors for severe outcomes of the illness were unknown, therefore one of the purposes of the investigation was to identify potential risk factors so that this information can be "used to control the extent and scope of the outbreak" (Internal document). Among the potential risk factors might be the use of traditional medicine or unknown host risk factors, certainly knowledge that would be new as they relates to the cause of high mortality associated with the illness.

In response to the request, the center HSC relayed her concerns about the investigation, particular as it relates to risk factors and hypothesis generation. In her response, the HSC states:

> Typically, the data collection that is acceptable for the purpose of hypothesis generation is limited to surveillance systems as opposed to individual investigations. Also, it is very clear that when risk factors are not known or there is a need for etiologic exploration, that the project is considered research.

Further, she continued:

> However, whenever there is an immediate threat to health or safety, it is reasonable to conduct investigation that allows you to identify (which you know which virus is causing the problem) and characterize the extent of illness in order to invoke the necessary public health mechanisms to control the outbreak in that context and help prevent future outbreaks. The issue is the data collected should be limited to understand the problem before us in this specific [country] outbreak. So within that context there is latitude to assess why it arose in this context, how to prevent transmission in this context (Internal communication).

The center HSC further expressed her thoughts about the proposed investigation. She felt that the investigation should be limited to collecting only data critical to determine the extent of the outbreak so it can be stopped. She pointed out

that the data collected, depending on the quality, might be later used for research purposes and IRB approval may be required then. She also states that if a case-control is foreseen in the investigation, that the team might develop a protocol and obtain approval beforehand if the opportunity presents itself during the outbreak investigation. This would permit a more systematic and in-depth assessment of the unknown risk factors, information that would be new and generalizable beyond the study population. Although this would have been ideal, there was no existing standard protocol that the team could have adapted for this case, and there was certainly no time to develop a new protocol before leaving for the field. She also explained that the needs for informed consent even if the investigation was nonresearch must be considered, but that consent needs not follow the specific conventions of research and requirement according to the Common Rule, as well as suggesting additional protocol related issues to include, though not a requirement.

The HSC expressed her concerns to another team member about the "slippery slope" of making research and nonresearch determination when an investigation involves limited knowledge about risk factors and when the collection of data is to determine the causes of disease severity and risk factors. If the investigation was to be conducted as initially written, to identify unknown risk factors associated with high fatalities, then she felt it was research. She wanted to meet the team to clarify what the actual purposes of the investigation would be. Parts of a HSCs roles is to assist investigators and programs in developing study proposal, so it was not an unusual practice that while her job was to make an unbiased determination, she was also helping the team understand when they might

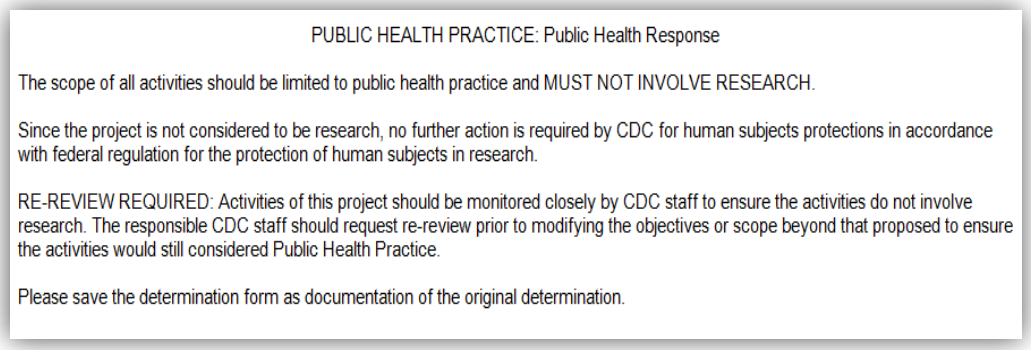
cross the research/nonresearch line, at least according to her interpretation and understanding. Another HSC might have had a different approach as well as interpretation of the situation. Whether a protocol or a summary of an activity is submitted for determination, it usually is not a guarantee that the first draft proposal would be approved without revision. If it turns out that the language in the initial draft does not lead to a "desirable" outcome for the investigator, the HSC usually helps investigators revise it to a point that they feel would meet the criteria for the desired outcome, usually when the investigator believe that they are not conducting research, and wanted a nonresearch determination.

The comments from the HSC lead to a revision of the initial draft proposal. The team responded that the investigation would inform disease outbreak control and that the findings would be communicated to partners. The team also responded that they had no idea what they will find and therefore do not know how the results might be used for disease control. The HSC was satisfied with the response and approved the investigation as "public health nonresearch, identify, control or prevent disease, illness, disability, or death in response to an immediate public health threat" under category I on the center's form.

The approval note (Figure 19) indicates that any changes in objectives and scope are required for re-review, which is a typical requirement, although often not followed upon. Outbreak investigations are particularly fluid on the ground, and no one really thinks about changes made along the way. It is considered essential. It is the responsibility of the lead staff to ensure this happens. On the center's form, she also provides her rationale for the determination. She noted that:

> Between April and June 2012, several cases of severe neuropulmonary disease [occurred in country]. In response, CDC has been asked under an Epi-Aid to assist the [country] MOH to investigate this [deleted] epidemic by further characterizing the extent and scope of this outbreak and providing data to inform containment strategies to prevent further transmission…. Clinical and epidemiologic data will be collected about cases to inform the investigation.

Figure 19: Comments from HSC



PUBLIC HEALTH PRACTICE: Public Health Response

The scope of all activities should be limited to public health practice and MUST NOT INVOLVE RESEARCH.

Since the project is not considered to be research, no further action is required by CDC for human subjects protections in accordance with federal regulation for the protection of human subjects in research.

RE-REVIEW REQUIRED: Activities of this project should be monitored closely by CDC staff to ensure the activities do not involve research. The responsible CDC staff should request re-review prior to modifying the objectives or scope beyond that proposed to ensure the activities would still considered Public Health Practice.

Please save the determination form as documentation of the original determination.

With this approval in hand, the team made other logistical preparation and head out on a long, full-day flight to the field. Besides the summary of the proposed investigation, there was no time to develop a detailed study protocol, at least at the time when I joined the team. My initial thought was that the program, if not the team, could have developed a draft protocol after learning about the outbreak in the few months before the team was put together. It was theoretically possible that, because one of the team members was an EIS officer, that one of the goal of the investigation was to provide training to the EIS officer, and part of that training could be to take part in developing a study protocol. Another possible reason for not having a prepared protocol is that we needed to have some initial understanding of the situation on the ground before we could develop a detailed plan. Whatever was the reason we did not have a detailed study protocol ready when we boarded the

plane for a long tiring (coach seats) flight to the field. We were expected to begin work immediately when we arrived, despite any jetlag symptoms. Even had it been determined as research and we had submitted a prepared protocol and obtained IRB approval beforehand, it might not have been possible to implement the exact protocol. Submitting an amendment from the field might have been next to impossible as timing was critical. We traveled across the country in four-wheel drive vehicles to remote and hard-to-reach areas, where internet connections were often nonexistent or unreliable. Data collection tools, questionnaires, consent forms, data abstraction tools, were all developed while we were in the field, usually at night in the hotel rooms, because the days were spent in briefing meetings with country officials in ritualistic "meet-and-greet" between foreign and local officials in such a collaborative and important effort. Fortunately, the team was supported by an outstanding CDC field team, which included locally employed staff. They planned the logistics in the country and were the guides for the team during the investigations.

The "meet-and-greet" rituals with local officials were important. They were courtesy calls on our part and a welcome and blessing on their part. Without local official approval and guides we would not have been able to do our work. One high level local official said to the team, "You need to have a protocol and an approval letter to show to the people, and then they would agree to participate." The approval letter he was referring to was not the IRB approval letter, but an official government approval for the team to carry out the investigation. The letter was the invitation letter from the MOH. Even with this letter and local guides, we still encountered challenges, such as not finding the local clinics or clinicians not around when we

arrived, sometimes purposely because of fear for being blamed for the deaths, and difficult to get to areas because of rough roads and terrains. One health center allowed us to review medical records, but would not let us record the information unless we had a study protocol that was approved by an IRB. That was a surprise to me, because this was a poor, developing country, but they were familiar with the requirements for conducting human subjects research, even though we told them we were not there to conduct research, but to investigate and hopefully stop an outbreak. We showed the letter from the MOH. This speaks to the importance of having a prepared, "generic" protocol that could quickly be revised and submitted for ethics committee and IRB approval before heading to the field.

One local pharmacist refused to talk to us even though we showed him the letter from the MOH. He said that the letter does not mention that we could talk to local pharmacy and that if we want to talk to him we need to obtain a letter from the provincial hospital director. We did not anticipate this, therefore, although we could have asked the provincial health director for such a letter, who likely would have provided one, we did not have enough time to do so. It was 5:30PM after the interviews with families. It was getting dark and it was better to head back to our hotel for safety concerns. The refusal was not over any ethical concern, but probably over suspicion that we were there to monitor his practice, an invasion of his privacy. He stated over and over that the MOH letter does not authorize us to talk to him and that he would only abide if he was required to. That was certainly his right and we left.

Early on during the investigation at one of our team dinners, I informed the team about my dissertation project and asked them if it is okay that I was observing the investigation from the perspective of an observer. No one objected. I asked the team lead for his perspectives about the investigation and whether in his mind, he has any thought that it might be research. He responded:

> The usefulness of the study at this point is that we may be able to develop some hypothesis that may lead to a case-control study that will provide generalizable information and be useful to other population. That would be research. There is no hypothesis at this point.

We were collecting risk factors data so we can contribute to halting the outbreak, current and future. This case shows that during an emergency situation, obtaining a research determination for the investigation was not initially seen as a priority.[68]

Case 1a: Problems with Publishers

The report of the findings from the above investigation were shared with the country MOH and partners, but have not been published in a peer review journal, although there have been several presentations given by team members and program staff at various professional conferences. I have not participated in these presentations, although I provided feedback and was listed as a co-author on the presentations and report. Other than contributing to the on-the-ground investigation and providing input when asked, I refrained from any further involvement. I am not sure of any plan to draft an article for publication in a peer

[68] I wonder had I not mentioned that the team should submit a determination request to the lead center's HSC, if it would have been submitted? I found out during an interview that this center does not strictly require research determination.

reviewed journal, but if that was to happen, sometimes the publisher will ask about what human subjects protection process the project went through. Below is a description of another real case when the results from another outbreak investigation was written up and submitted for publication.

This investigation started out very similar to the one I participated in. It was approved as nonresearch, emergency response/outbreak investigation by the center that led the investigation. Although the particular disease have been known for several decades, the etiology of the disease is not known, therefore there was potential for research to be conducted along with the investigation. Any finding about risk factors and etiology was certain to contribute to generalizable knowledge, but as already discussed, CDC does not define research based on generalizable knowledge alone. The study findings were written up and submitted for publication in a peer review journal. According to the center HSC, the journal contacted the CDC lead author requesting "more information about the consent and ethics procedures for your study" (Internal Communication).

The journal asked the author, "Could you provide a reference citation or web link to more details about the CDC Human Subjects Review policies and procedures, to support your comment that this is a common practice in public health response?"

The CDC author contacted the center HSC for advice. The center HSC asked for the article submitted to the journal and pointed out apparent problems with the article. As it turned out, there was no written protocol when the project was submitted for research determination, because this was not required under CDC policy, and many centers, including my center, do not require comprehensive

written protocol for research determination. Informed consent was obtained orally with no pre-approved script as typical for research. The investigation appeared to have evolved on the ground during the conduct of the investigation, similar to the one I was involved in. In my investigation, we had drafted a simple informed consent script before we left for the field, but the final consent was written and translated on the ground. It certainly was not one that was submitted and approved by the center, and if we were to write up an article for publication, similar concern may arise.

The problem with the article according to the center HSC was that it was written up like a research study. According to the HSC, "…from the beginning through the discussion, this investigation is presented as a systematic investigation that was prospectively designed to develop/contribute to generalizable knowledge." She pointed out to the author/investigator that, because an activity was an outbreak investigation it was not automatically considered nonresearch. In outbreak investigation she said:

> It is the activities that are conducted to identify, characterize, or control an immediate public health threat that are considered to be nonresearch. Those activities may very well result in a contribution to generalizable knowledge – but what matters is whether the contribution to generalizable knowledge was implicit in the design.

This rationale is basically the same as the one provided by the HSC from the center that determined the investigation I participated in. For an outbreak investigation to be determined as nonresearch, the focus or purpose must be on characterizing the immediate problem within the context of the outbreak with the purpose to invoking public health mechanisms to control the outbreak and prevent future outbreaks.

Any objective beyond the immediate problem to include etiologic testing, that might include case-control study, and generating knowledge that could apply in other settings and contexts would likely lead to research. In both cases, little was known about the risk factors, so both investigations focused on risk factors, and in both cases, the HSCs indicated that generalizable knowledge may well be generated from the investigation. Their determinations were in compliant with CDC policy.

The HSC made several suggestions to the author/investigator on how the situation can be fixed. The original manuscript refers to the outbreak investigation as a "study." She suggested that the term "study" should be reserved for research, and offered that the term "investigation" should be used instead. She also suggested that the manuscript should focus on characterizing the outbreak in order to develop appropriate control measures:

> ....in the context of an immediate health threat, activities that are undertaken for the purpose of identifying, characterizing and controlling that threat are generally considered to be nonresearch. The reason is because they are generally not *designed* to contribute to generalizable knowledge – they are *designed* to address an immediate threat.

One of the core requirements of the regulatory definition is that the investigation must be "designed" in such a way that reduce bias and can lead to generalizable knowledge. If the design does not meet these relatively stringent criteria, they may not meet the regulatory definition of research even if it is considered research for other purposes, and therefore, would not be covered under the Common Rule. If scientific characteristics such as the study being replicable, objective, and systematic are strictly held, then it seems that many anthropological research studies would not meet the regulatory definition of research. The general design is

there, but one can argue that it is impossible to duplicate anthropological study. How do one duplicate ethnographic observation?

Case 2: Public Health Surveillance

As already discussed in previous chapters, the issue of when surveillance activity is research has been one of the major debates at CDC. A high level CDC official once told a division level ADS that "surveillance is surveillance," hinting that CDC should considered every surveillance activities as nonresearch. However, a former CDC Deputy ADS once told me that when surveillance is conducted for the first time, e.g., to determine the prevalence rates of a particular disease or condition, then that first implementation of the surveillance should be considered research, because one of the purposes (intents) must be to develop new, generalizable knowledge. Subsequent ongoing implementation of the surveillance would become routine surveillance activity, because it would verifies and updates the previously determined prevalence rates. This has been the litmus test I used in the past in making determination of whether surveillance activity constitutes research, because often surveillance implemented in a country for the first time is initiated with the purpose of developing new, generalizable knowledge about the population. I have already discussed in previous chapters that this is not necessarily the case. If a new surveillance is conducted with the purpose of monitoring known disease or condition and known risk factors, then it may not be considered research. This debate occurred at the highest level within CDC and OHRP. CDC 2010 policy characterizes public health surveillance as:

> …a series of ongoing systematic activities, including collection, analysis, and interpretation of health-related data essential to planning, implementing, and evaluating public health practice closely integrated to the dissemination of data to those who need to know and linked to prevention and control. Public health surveillance is predicated on the need to address a defined public health problem or question and aimed at the use of data to guide efforts to protect and promote population health. Surveillance systems can be either research or nonresearch, depending whether the purpose is to identify and control a health problem or to contribute to knowledge beyond the system's participants, to society…… Surveillance systems are likely to be research when they involve the collection and analysis of health-related data conducted either to generate knowledge that is applicable to populations and settings other than the ones from which the data were collected or to contribute to new knowledge about the health condition (CDC 2010: 4).

It is difficult to justify a project as surveillance if it is a "one time" survey. A one time survey, including the department of health seroprevalence survey (DHS), may meet other requirements and can be approved as nonresearch, but it is probably not surveillance by the accepted definition of surveillance, which was defined as:

> The ongoing systematic collection, analysis and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated to the dissemination of these data to those who need to know and linked to prevention and control (CDC 2010: 13).

DHS surveys were frequently CDC-funded activities in developing countries and often were conducted for the first time in the countries, but if they were conducted for the purpose of providing ongoing monitoring of known disease and known risk factors, they were likely not considered research.[69]

DHS surveys are similar to CDC-conducted surveillance activities in the US, such as the National Health and Nutrition Examination Survey (NHANES, http://www.cdc.gov/nchs/nhanes/irba98.htm), the Behavioral Risk Factor

[69] As already discussed, this was the position of OHRP at one point, but is not at all settled. More recent experiences, as discussed below, hint at a flip-flop in OHRP's perspective on the issue.

Surveillance System (BRFSS, http://www.cdc.gov/brfss/), and the Pregnancy Risk Assessment Monitoring System (PRAMS, http://www.cdc.gov/PRAMS/). For these three surveillance systems, CDC had taken the view that they can both be considered research and nonresearch at the same time. All three systems were initially approved as research, because CDC was and still is using the data for research purposes, to develop generalizable knowledge about the health status of the US population. CDC also determined that local and state health departments, who were often funded to conduct the data collection activities, would not be engaged in the research activities, and that the use of these data to improve the population's health would not be considered as research. CDC left it to the local and state partners to decide whether they would submit the studies to their IRBs, which they often did. DHS surveys are designed to assess populations' health. They may be conducted through a telephone survey, such as PRAMS, or by household survey, and may include specimen collection and biometric measurements. In developing countries, they are often funded by CDC and conducted for the first time by local partners, usually led by the MOH. They are often funded under nonresearch cooperative agreements, which usually determined whether they will be categorized as research or nonresearch. This often presents a problem for HSCs who must interpret the project under CDC policy. Below, is an example of a real case made generic to protect the privacy and confidentiality of individuals involved in the decision-making process.

Non-communicable Diseases Survey (NCD's)

In the last few years, CDC included NCD's, such as heart disease, hypertension, and stroke, to its global health priorities, although the focus remained on infectious disease. One of the most common CDC-funded NCD activities is the cross-sectional population-based survey to assess the risk factors associated with NCD's involving thousands of individuals across a nation. These surveys were often deemed as surveillance activities, although data about these risk factors simply do not exist and therefore new, generalizable data will be generated. Objectives of such survey generally include to:

- Assess the distribution of life-style factors and anthropometrics measures of selected NCD's
- Identify dietary practices which are risk factors for selected NCDs.
- Determine the prevalence of selected NCD's
- Provide up-to-date data on NCD risk factors for program planning and evaluation

Individuals and programs involved in funding and conducting the project did not always agree on the research and nonresearch status of the project. On one particular case, one center funded a survey in a developing country through a nonresearch cooperative agreement, but employees from another center with subject matter expertise were also involved in developing the protocol and providing technical input. However, the center with the subject matter expertise insisted that such surveys are nonresearch, public health surveillance, while the division within the center with the lead CDC investigator considered the survey as research that should have gone to an IRB, if not to CDC IRB. The division would not

agree to approve the protocol as nonresearch and would not allow it to go to the center level for determination.

> A further complication is that the [Division] Science Office does not see that we can sign off on the current protocol as nonresearch, although the center ADS would be willing to do so. Previously OHRP has informed us…..that population-based surveys involving diagnostic testing and return of test results require IRB review[70] (e.g., as for NHANES in the U.S). All of the DHS and AIDS Indicator Surveys that [division] has been involved with and supported have gone through IRB review. If CDC staff are not engaged in the study through interaction with participants or analysis of identifiable data, CDC can accept the local IRB approval.

The division/program funding the survey suggested that the center with subject matter expertise take the lead and have determination made by that center.[71] However, that center was not willing to take primary responsibility for protocol oversight. I suspected that the real reason for this suggestion has nothing to do with subject matter, but with the disagreement about the research/nonresearch issue. The division ADS further stated:

> In our experience OHRP has taken a more conservative approach to research determinations in the last few years and some projects such as PRAMS that were considered nonresearch at the state level are now announced, competed and managed under a research FOA. This change in the funding announcement type for PRAMS was dictated to us by OHRP. Currently it appears that the announcement for BRFSS is nonresearch.

The other major issue that caused some tensions regarding this case was that several years ago, CDC decided to separate research and nonresearch funding mechanisms e.g., research cannot be funded through nonresearch cooperative

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[70] This was new to me. I was not previously aware of what year OHRP had made this demand of CDC, but it appears that the requirement is beyond the issue of research/nonresearch.

[71] The usual practice is that the center with the lead investigator makes the final research determination, so the assumption that the center with SME makes the determination is not typical, although it is possible if everyone agrees to it.

agreement, although nonresearch can be funded under research agreement. According to the center with the SME, it is possible to fund an activity that CDC considered as research under a nonresearch agreement if locally the activity is not considered as research, because research determination is in principle said to be independently made. If so then the distinction between research and nonresearch agreement has no useful function, which seems to be the consensus among HSCs. Another related problem is if an activity is funded under a nonresearch agreement, must CDC also determine the project to be nonresearch? Can CDC determine it as research and permit funding to be released because locally it is considered nonresearch? This presents a dilemma and HSCs sometimes are pressured to categorize the survey as nonresearch even though they may not agree with the decision. This also may impact CDC's strive for consistency in determination. The determination audit conducted by HRPO might determine that the program was not in compliant with the CDC Policy, and thus with the regulations, but being compliant, it seems is the least of CDC's problem. Compliance is only a bureaucratic illusion when it comes to research determination. It provides no meaningful way to move the issue forward and improve human subjects protection.

Case 3: Program Evaluation

Program evaluation or quality improvement as it is sometimes called, is defined by CDC as:

> A management tool to monitor and improve a public health program; often a component of the regular, ongoing program. The purpose is generally to assess the success of an established program in achieving its objectives in a

> specific population, where the information gained from the evaluation will be used to provide feedback to that program (CDC 2010: 6).

Theoretically any program evaluation that was not included as a part of the original program development plan is suspect as research and must be carefully reviewed. If it is an evaluation plan for a new untested program or intervention, it is almost certain that it would meet the regulatory definition of research even if the evaluation was part of the plan. Implementation and evaluation of new program is considered experimental and is usually categorized as research at CDC until it is proven to be effective.

I often wondered about the nature of public health program and if it is true that only implementation of a successful program is nonresearch. It is almost like the "chicken and egg" dilemma. Which came first? Any new public health program if not based on previously evaluated to be effective must be viewed as research in some respect or at least the evaluation of the program must be viewed as research. Sometimes programs are implemented hastily, e.g., during emergency or because of political pressure, but was not said to be designed to be generalizable. Those programs were often implemented without formal ethical review, which presents ethical challenges in research determination. Individuals tasked with the authority to make such determination must assess whether the intervention was based on known effective intervention or something new. Often a new intervention is implemented as a pilot without formal ethical review and later a more in-depth evaluation plan is submitted for determination and the investigators almost always wanted it to be approved as program evaluation/nonresearch. One HSC told me that "Before I came into this position [referring to a previous HSC] if you said something

was pilot she said pilots are research." The HSC continued that investigators may try to convince HSC that their pilot projects are nonresearch saying something to the line, "Well this is a limited implementation to inform or work out the logistical issue before we go wide scale." I often told the investigators that this was not how it works. You cannot implement a new program first and come back and submit an evaluation of the program and say this is "program evaluation" if the evaluation include a design that will reduce biases and improve generalizability, such as the use of random sampling method. Public health program should not be implemented before undergoing some form of review, except in an emergency situation. Even in emergency, if the program is experimentally designed to generate generalizable knowledge, it should be categorized as research and undergo ethical review. Often, new public health programs were not systematically designed to generate generalizable knowledge, and therefore do not meet the regulatory definition of research. According to one HSC, in a case of limited implementation of a pilot project targeting only a few individuals and the purpose is to determine the logistics for implementing such project, it is unlikely to be generalizable and therefore would not meet the regulatory definition of research. "It's not furthering the understanding….of the methods." A full scale implementation of a new project is likely research.

Case Summary

A generic case based on many real examples is the pilot testing of a new public health intervention program. A new intervention was developed and

implemented by local CDC partners. CDC may or may not have had a role in the implementation of this new intervention program, but was requested by the partners to conduct an evaluation to see if the intervention was effective in reaching its targeted population. A protocol was developed by CDC and its partners with the objectives to assess the effectiveness of the intervention and evaluate the program implementation (process evaluation)[72]. The evaluation would randomly sample individuals in the intervention area and individuals in a non-intervention area (control) for comparison. The process evaluation included focus group exercises and interviews with key stakeholders implementing the intervention.

Investigators' Perspectives

Investigators, both CDC and local investigators, often argued that the evaluation is nonresearch. From their perspectives, they considered the project as an evaluation of an existing intervention already implemented by local partners. The communication and debate between investigators and the center HSC are usually through a proxy, either the division ADS or program staff, although sometimes directly with the investigators. Programs tend to support their investigators' perspectives.

[72] Process evaluation, which assesses the implementation and logistics of a program, is almost always considered as nonresearch. However, when the evaluation is conducted with the aim to assess the efficacy of a new intervention or of an intervention that have never been previously assessed even if it has been an ongoing program, then it is considered research.

CDC Policy perspectives

Under CDC policy program evaluation may be human subjects research covered under the Common Rule if they were systematically designed to generate generalizable or new knowledge. Evaluation of new, untested intervention is automatically research under CDC policy if it is designed to develop new or generalizable knowledge.

Problematic Issues

No matter what the reason is, a program's support of their investigators' preferences in obtaining a nonresearch determination can be a source of problem for research determination practice. The program's support essentially condoned and facilitated, and contributed to an ongoing cultural practice.

Case 4: Non-engagement: Research with no formal ethical oversight

The implementation of the non-engagement policy in 2007 created a slippery-slope practice at CDC. As seen in the EZ Measles case, being non-engaged did not resolve CDC of its ethical and legal obligations. When CDC funding is involved, being non-engaged will not shield CDC from public scrutiny and criticism. When an activity is determined to be non-exempt human subjects research that has received an IRB or ethics committee approval, there is at least a formal ethical oversight of the study even if CDC was deemed non-engaged. A potentially serious problem arises when CDC is not engaged in an activity that is non-exempt human subjects research, but determined as nonresearch by local partners. I have not been

able to identify any fallout from such a case, but this situation occurred relatively frequent, because of the principle of independent determination by collaborating institutions. The separation between research and nonresearch funding mechanisms should have partially resolved that problem, but there are differences in interpretation and disagreements about what constitutes research at all level at the agency. The non-engagement policy also created a practice where if an investigator or program wanted CDC IRB approval, they must make themselves engaged even if that engagement is not necessary or else lie about it, something I certainly do not condone, but cannot assess if that is the case.

Case Summary: Urgent Malaria Study

CDC investigators were invited to participate in a study to assess malaria hotspots in a country in Africa in order to help the Ministry of Health conducts a final push to eradicate malaria in the country, which has seen the prevalence rate declining dramatically in the last few years. CDC participation would greatly increase the chance of success, and according to the program, results from the study would be generalizable and useful in other countries. The program considered the study as human subjects research, while none of the partners did. There was no CDC funding involved, but the study received funding from the U.S. Agency for International Development (USAID). CDC investigators would not need to interact with study participants nor have access to identifiable data. The program was leaving the option for CDC to do so, because none of the partners will submit the study to their ethics committee for review and approval. Because the study involved

federal funding, the program felt that CDC has an obligation to submit it to CDC IRB, even though they have no need to be officially engaged. If not, there will be no ethics oversight of a research study that met the regulatory definition of research.

Outcomes

Even though the program was adamant that the study was non-exempt human subjects research, the study was not accepted for CDC IRB review. HRPO cited the contents of the CDC non-engagement policy for their decision to deny the request. According to HRPO:

> Our office uses the research determination and CDC's role in activities to determine whether or not a CDC IRB review is needed, not the funding mechanism. Based on the information that has been provided, we've determined that CDC is not engaged in the activity and therefore CDC IRB review is not required. Documenting CDC's determination fulfills our obligations. If at any point the program decides to become engaged in the activity, the project can be re-submitted and we will send it forward for an IRB to review.

As it turned out the program did not have a need to be officially engaged, and saying so would basically be untruthful. The study was withdrawn from submission to CDC IRB, and was initiated by local partners without CDC official engagement.

Chapter 6: Conclusion
Moving Beyond Regulatory Compliance

"An abstract term is like a box with a false bottom: you may put in it what ideas you please, and take them out again with-out being observed."
-Kidd quoting Alexis De Tocque-Ville (1959: 368)

Social Construction of Research and Practice

The confusion over what constitutes research is pervasive throughout CDC. There is no simple or best solution to resolving what appears to be a problem of human differences manifested in their interpretation of the regulatory definition of research that was socially-constructed during a different time, by different individuals, and under different circumstances. Applying a multi-method anthropological approach to studying CDC human subjects protection and research determination culture provides a holistic understanding of the roles CDC history and public health culture influenced how the agency socially-constructed its own policy and interpreted the regulatory definition of research.

CDC research determination was constructed through a social process and cultural consensus. The regulatory definition itself was socially-constructed through group consensus by the Commission that developed the Belmont Report. CDC's interpretation, as in the 1999 Guidelines, of the regulatory definition was also developed through a social process among CDC officials and public health professionals outside of the agency with the aim of advocating for a wider understanding and acceptance of the public health perspective, which tends to favor broad societal benefits over individual's rights. The 1999 Guidelines were also developed in response to the many requests from the public health community for

CDC to take the lead and to provide such guidance, because CDC was seen globally as the premier public health agency. This was, as the 1999 Guidelines describe, because the regulatory definition was constructed without taking into consideration the public health perspectives. CDC had also collaborated with CSTE and commissioned a report that addresses public health research and nonresearch (Hodge and Gostin 2004). In 2006, through a similar social process, OHRP drafted avguidance on their interpretation of the regulatory definition of research. The guidance document was tabled and never pursued due to apparent disagreements with other federal agencies.

Research Determination Culture of CDC

The development of the CDC research determination culture hinged on Epi-Aids (outbreak investigations), even though Epi-Aids make up only a small proportion of CDC's activities. Epi-Aids became an ideal cultural model that was used by CDC leaders to support the notion that "primary intent" or "purpose" of the activity should define whether the activity is research or practice. Early CDC's historical attributes help strengthen this interpretation and creation of research determination reality for CDC. These attributes include:

- CDC being envisioned as the center of excellence that would put scientific research and knowledge to practice;
- The urgent nature of CDC public health missions to prevent and control diseases;
- Resource shortages that encourage innovation and hard work;
- The distance from the politics of Washington, D.C., giving CDC a certain degree of freedom;

- A public health culture that values population benefits over individual's rights, and
- A public health institution that values applied science over basic research.

These characteristics of CDC culture influenced the social construction of research determination cultural domain, which include:

- Defining research based on "primary intent" or "purpose,"
- Placing special emphasis on traditional CDC activities, including surveillance, program evaluation, and outbreak investigation (Epi-Aid),
- Reserving specific terms for referring to research and nonresearch, e.g., investigation is a preferred word in referring to nonresearch, and study is a preferred word for research.

Despite all of these efforts, CDC continues to struggle with the daily task of interpreting and re-interpreting the regulatory definition of research whenever a new public health activity is initiated. Investigators, supervisors, ADSs, and HSCs re-enact their ritualized process with each new initiated activity pondering on the question, "Is it research or nonresearch?" For an activity that is ambiguously difficult to distinguish whether it is research or nonresearch, a cultural debate might ensue each time a research determination request is submitted for review. A former CDC HSM once said, "What might be true is any activity that has ambiguity you might be able to use CDC policy and say it's nonresearch." The tendency then, is to categorized ambiguous activities as nonresearch.

Organizational culture and resource scarcity also means that CDC continues to strive for efficiency and improvement through organizational improvement initiatives and perpetual reorganizations, even though sometimes those efforts were counterproductive. Recent reorganizations have not had much impact on the research determination process, essentially because CDC is still in the process of

implementing the OPRR (OHRP) 1995 mandates.

Another major evolution of the human subjects protection culture is about to occur. In July 2011 DHHS announced the Notice of Proposed rulemaking (NPRM) to revise the Common Rule that will have major impact on human subjects protection and research determination practice (DHHS 2011). When implemented, NPRM will force another major cultural shift in CDC human subjects protection practice, but the issues surrounding research determination will remain a challenge ahead.

Institutional Structure and Bureaucracy

As CDC continues to cherish or at least reminisce on its physical distance and freedom from the watchful eyes of Washington, D.C., the gap has narrowed over the last two decades. Within the human subjects protection culture, CDC and OPRR (OHRP) experienced their first culture clash over the differences in interpretation of the regulatory definition of research in the 1990s. It appeared that this was also a result of the culture change in Washington at OPRR—a shift from a minimal intrusion and pragmatic approach to regulatory oversight under its first director, Charles McCarthy, to an increased in regulatory investigation in the 1990s under a new director, Gary Ellis. In the 1990s, OPRR asserted its regulatory authority over other institutions and agencies and was more keened on investigating public citizen complaints and claims of noncompliance and abuses in research.

The nature of being under a US government bureaucracy means that any review and approval process, including the research determination process would be dictated by bureaucracy. As discussed in details in previous chapters, CDC

employees do not have a positive view of bureaucracy, which is seen as hindering their importance public health work. Although Weber (1922) describes bureaucracy as the most efficient form of organization, bureaucracy has also been criticized as a threat to individual autonomy and freedom (Ritzer 2004, Swedberg 2005). Resource limitation and power relation at different level of the research determination process also contribute to the bureaucratic delays, which was a major reason why CDC investigators wanted to avoid the CDC IRB.

The problem of resistance was mainly due to the frustration with the delay or perception thereof, caused by the review and approval process, which many investigators viewed as burdensome. This belief was confirmed by both the ethnographic observation and the agency-wide survey conducted in the summer of 2012. No one I spoke to or worked with said that they wanted to be able to do whatever they want. Investigators understood their responsibilities, and have a craving for clearer information and guidelines. Resistance due to bureaucratic hurdles and delays is different from resistance in principle. The resistance I observed may be resolvable through system improvement and responsiveness of the different actors in the system. This is partly related to the political economic situation, e.g., lack of funding, lack of effective tracking system, but is also related to efficiency and training.

As a result of this cultural perception, perceived or real, investigators found creative ways to bypass the CDC IRB. Some of these alternative routes were officially and legally sanctioned, such as the non-engagement policy, while others may be ethically questionable. As these alternative routes may be sensitive in nature,

figuring out what they were required more than a simple checklist survey to extricate. They required long term ethnographic participant-observation and interpretation of stylized actions and practices. These include:

- Submitting a summary of a protocol for determination when a complete protocol is available, because CDC policy does not require a complete protocol;
- Submitting research determination only after obtaining local approval;
- Getting local collaborators, including country Ministry of Health or local and state health department, to approve the project as nonresearch in hope that CDC would also approve it as nonresearch;
- Submitting a research determination after a project has ended (retroactive);
- Being creative about study objectives (gaming the system) because of how CDC defined research based on primary intent;
- Obtaining a non-engaged status to avoid CDC IRB, if it suits their needs;
- Rationalize with reviewers whose hands are tied, thinking that if the reviewers give their blessing it's okay to proceed;
- Implement program as nonresearch then later de-identified and use the data for research, or
- Play ignorance.

Current CDC's Efforts for Improvement

Two major agency-wide projects were initiated across CDC beginning in 2010 and are still ongoing. The first is known as the Science Services Support Project (S3P). S3P is described as:

> …an agency-wide project, led by the Office of Scientific Integrity (OSI), for supporting CDC science. The overarching S3P goal is to streamline the processes for compliance with Federal regulations that are required for the conduct of federally sponsored scientific and programmatic work via process improvement and information technology. S3P will deliver an IT system specifically designed for all CDC staff to submit, track, review, approve, and update the status of any project activities associated with human subjects protection, the Paperwork Reduction Act, and/or confidentiality protections including but not limited to protocols, requests, applications, amendments, and determinations" (S3P Website CDC Intranet).

One of the goals of S3P is to have research determinations processed through this new system beginning in late 2014. Currently, CDC is working on the funding issues, software development, and logistics.

S3P is not an entirely a new initiative even though the system to be developed will be new. In 1995, OPRR/OHRP mandated that:

> CDC-ATSDR should address the need for increased support for the office of the Human Subjects Review Coordinator. Particular care should be taken to ensure adequate staffing, at both the professional and administrative levels, for the IRB recordkeeping and human subjects education functions of this office. CDC-ATSDR should also ensure that the office is provided with sufficient work space and computer tracking systems to perform its functions effectively (OPRR 1995: 14).

CDC had implemented two previous computer tracking systems that were not up to task, so S3P in my opinion is a continuing effort to improve CDC efficiency and consistency in order to meet OPRR's mandates. My understanding from participating on the S3P initiative as a subject matter expert is that a sort of guided questionnaire will be developed to facilitate the determination process. This will certainly help improve efficiency, but many people agreed that making a research determination requires much more. Making research determination that is consistent with the current regulations and policies requires knowledge and experiences that can only be obtained through many dedicated years doing the task. It cannot be performed through simple checklist as one center's workgroup noted:

> Distinguishing research from practice requires collective professional experience and judgment as well as familiarity with…..policies, CDC policies and guidance, and HSRB practices. The exercise is not amenable to simple "check list" determinations by clerical staff (CDC Internal Working Group 2009).

The second major initiative as already mentioned is the beginning of regulatory audit (initiated in 2011) of ten percent of the research determinations made at CDC. Routine auditing is being conducted by a Determination Review Group (DRG) that consists of five members and two alternates, with HRPO holding two permanent slots. Since this study began, two rounds of audit have been conducted and for the most part the final results showed that CDC is in compliant with the federal regulations in determining whether a project is research or nonresearch, at least based on the interpretation by the five-member DRG. A group composes of different individuals is likely to derive at slightly different results. The auditing process caused much anxiety among HSCs and programs when it was first announced. People were questioning the purpose(s) of the audit and what the outcomes would be if a program is found to be non-compliant.

One HSC asked, "Is there an attempt to standardize how we are doing the determination?"

HRPO responded, "This is not intended to make center change the way they do business, but the outcomes may result in some guidance or training."

Many complained that the process was just putting extra burden on individuals who were already thinly stretched, because the outcomes would not change how CDC does things. After the first round, the discussion appeared to quiet down, and it appeared that auditing has now become a routine part of the research determination culture. If the results of the auditing were accurate, it shows that there was consistency at least among HSCs and ADSs about how they interpret the CDC policy. There were certainly debates about these results (see Table 8 on page

160). Before the results from the first round of audit were released, there were discussions that there may be twenty to thirty percent discordant in determination between the centers and the DRG's determinations, therefore a result of almost 100% accuracy was a surprise to many HSCs. The procedure for appeal if there was a discordant is a meeting between the program and center representative with the DRG. Based on my own and another HSCs experience, the appeals have been successfully in favor of the centers and programs.

The 2012 survey results (Table 12 on page 252) show that most respondents believe that CDC should strive for consistency, but they were not in favor of achieving it through audits. Training, streamlining, and centralizing research determination were checked more often as other means of achieving consistency. Even if consistency was obtained through the current process as it appears based on the results from the agency-wide audit, there were loopholes in the system that could potentially place research participants in unacceptable risks. Compliance does not equate to better protection. The policy on non-engagement, as discussed, could be a major pitfall for CDC and other federal agencies. Many at CDC support a system of ethical review based on the risk levels, though the only existing guidance for determining risks is the OHRP definition of "minimal risk." Dr. Greg Koski (2002), former director of OHRP states in his resignation letter,

> To preserve public trust in research, the scientific community must go beyond a culture of compliance--it must strive for a culture of conscience--one in which we do the right thing not because we are required to, but because it is the right thing to do, a refrain now echoed frequently through the research community.

The Future –Notice of Proposed Rulemaking (NPRM)

The regulatory investigations of CDC and other institutions, and the general debates about the applicability of the federal regulations to public health activities over the past two decades have contributed to OHRP's recognition of the need to revise the Common Rule.

> The current regulations governing human subjects research were developed years ago when research was predominantly conducted at universities, colleges, and medical institutions, and each study generally took place at only a single site. Although the regulations have been amended over the years, the human research enterprise has evolved, experiencing a proliferation of multi-institutional clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics. This rule is an effort to modernize, simplify, and enhance the current system of oversight….While traditional biomedical research conducted in academic medical centers continues to flourish, many studies are now also conducted at community hospitals, outpatient clinics, or physician-based practices (DHHS 2013: 1).

> The rapid growth and expansion of human subjects research has led to many questions about whether the current regulatory framework is adequate and appropriate for the protection of human subjects in the 21st century. Addressing these considerations now is timely and consistent with the President's Executive Order requiring federal agencies to review existing significant regulations to determine whether they should be modified, streamlined, expanded, or repealed to make the agency's regulatory program more effective or less burdensome in achieving the regulatory objective (DHHS 2013: 4).

CDC and other federal agencies participated in meetings and conference calls with OHRP providing ongoing comments and suggestions to the proposed changes in the Common Rule. Currently, NPRM is in the clearance phase at various agencies within DHHS, although there is no certain timeline of when the new rules will go into effect. NPRM caused some anxieties among HSCs, because it proposes some major changes to the Common Rule that will have an impact on their life and work.

HSCs' concerns stemmed both from economic and ethical reasons. The changes will affect their jobs and roles in some capacity and they are concerned that some research will fall through the cracks. At one of the HSCs meetings people were deeply concerned about their jobs, that some of the changes will mean a reduction in the amount of work, and perhaps causing some program to reduce the number of staff. They were also concerned about whether the changes will affect human subjects protection and increase risks for participants in research, because as discussed below, one of the changes will mean investigators will be able to make some research determination on their own. According to DHHS:

> Over the 2015-2024 period, we estimate present value benefits of $1,880 million and annualized benefits of $214 million using a 3 percent discount rate, and present value benefits of $1,439 million and annualized benefits of $191 million using a 7 percent discount rate. We estimate present value costs of $8,522 million and annualized costs of $970 million using a 3 percent discount rate, and present value costs of $6,123 million and annualized costs of $815 million using a 7 percent discount rate. Non-quantified benefits include improved human subjects protections in clinical trials and whole genome sequencing research not currently subject to oversight, as well as in research reviewed by independent IRBs; increased uniformity in regulatory requirements among Common Rule agencies; standardization of human subjects protections when variation among review IRBs is not warranted; improved informed consent documents and processes; reduced time to obtain informed consent in some future research studies; improved protection of individually identifiable private information, individually identifiable specimens, and whole genome sequencing data; and increased transparency of HHS-supported clinical trials to inform the development of new consent forms. Non-quantified costs include the time needed for consultation among Common Rule agencies before federal guidance is issued, and the time needed by investigators to obtain consent for secondary use of whole genome sequencing data (DHHS 2013: 6)

NPRM is another social process that will revise the applicability criteria of the Common Rule, delineating what types of public health activities will be covered under the regulations. The regulatory definition of research will not change,

however, but it proposes some major changes in the scope and interpretation of what constitutes research under the regulations.

> First, the definition is clarified by the statement "Activities that are not designed to produce information that advances the knowledge base of a scientific discipline or other scholarly field are not considered research for purposes of this policy." This statement limits the scope of the definition in that some activities that are designed to develop or contribute to some types of generalizable knowledge are not to be considered research for the purpose of this policy, if they are not also designed to advance the knowledge base of a scientific discipline or other scholarly field (DHHS 2013: 35).

Initially, "exempt" research was reclassified as "registered" research, which caused for some concerns or at least of keen interest to CDC HSCs (Emanuel and Menikoff 2011). In the version submitted for departmental approval, the term "exempt" was retained, but the concept of a registration remains. "Instead of the registration requirement that was proposed in the ANPRM, a web-based tool will be implemented by OHRP. Investigators can complete the online registration and if it indicates a study qualifies for exemption, then that will constitute a "safe harbor" eliminating the possibility of compliance actions relating to that determination" (DHHS 2013). NPRM will:

> …require that researchers file with the IRB a brief form (approximately one page) to register their exempt studies, but generally allow the research to commence after the filing; and clarify that routine review by an IRB staff member or some other person of such minimal risk exempt studies is neither required nor even recommended" (DHHS 2013: 10).

As discussed in earlier chapter, currently only HRPO can grant exemption approval at CDC. This change would permit the investigators to register their research in an electronic repository system. An institutional authority, to be identified, would have 14 days to review and either confirm or disagree with the

categorization. However, if the institutional authority does not get back to the investigators in 14 days, the investigators can move forward and implement their research. In essence the determinations would be made by the investigators. The rationale behind this change is that it would lessen the burden on IRBs and human subjects protection programs of research that present very little risk to human subjects, mostly informational risk. This change would address some of the concerns from many at CDC that public health activities should be reviewed based on the level of risk and not whether they are research or nonresearch. It will be a welcome change to investigators at CDC. They also do not have to submit for annual renewal. Renewal for minimal risk research would also not be required under NPRM. It is theoretically possible that investigators will end up registering their studies even if the studies do not meet the regulatory definition of research. This registry would provide more transparency for public health activities that might otherwise not be submitted into any oversight system.

Other proposed changes include the exclusion of some public health surveillance activities from the regulatory definition of research even if they had in the past meet been considered as research, a data security provision, extending coverage to all research at an institution that receives federal funding, and requiring a single IRB for oversight of all domestic research. CDC in general prefers that public health surveillance is broadly defined, rather than attempting to identify different types of surveillance. The proposed rule would also exclude quality improvement activities (program evaluation) from the regulatory definition of research, unless there is experimental design and randomization of participants. A data security

provision currently does not exist and for international research, collaborating institution can provide written assurance to the federal agency without having to file an FWA with OHRP (DHHS 2011).

Currently the proposed rule would not require auditing of "registered" research, but that could change during the clearance process, and many questioned whether the 14-day waiting period is sufficient and how that would be enforced. This change will in some way reverse the practice whereby it will no longer be considered a conflict of interest for investigators to make determinations of their own studies. NRPM when implemented will also mean that new guidelines and policies will be implemented. Changes will come and I am certain CDC will adapt and its culture will evolve, albeit, slowly. Although NPRM is in the clearance stage, there may still be some revisions taking place during the process and final implementation date is not certain.

Public Health Ethics: Constructing a new Cultural Domain

Moving towards a risk-based ethical oversight will require a paradigm shift in human subjects protection and research determination at CDC. New cultural domain will emerge, new guidelines on how risk levels are defined will be needed, and alternative approaches to protecting individuals and communities in nonresearch activities will need to be explored. While CDC was trying to differentiate the differences between research and nonresearch, there were always ethical consideration and discussions about the ethical issues surrounding nonresearch:

> One of the point we had to make along the way was just because an activity doesn't fall under the regulations doesn't mean there is not ethical issues that have to be addressed and that was another step, you know as you keep moving towards greater understanding, you first have to get everybody attention comply with the regulations, but then as we already touched on, it was critical to begin to talking about conducting the rest of our activity in an ethical manner even if they didn't fall under the definition of research that we finally can feel comfortable with what is research and not research (Former CDC Official).

Burris et al (2003) argues that "Exempting public health agencies entirely from the Common Rule would provide an opportunity for the development of new approaches to assuring human subject protection, approaches that could be models for changes in the Common Rule" (2003: 641). Others have suggested alternative approaches or deviations from the usual practices, such as only requiring IRB review for qualitative improvement (program evaluation) research when "1) the majority of patients involved are not expected to benefits directly from the knowledge to be gained" or "2)additional risks or burdens are imposed to make the results generalizable" (Casarett et al, 2000). MacQueen and Buehler, referencing the NBAC 2001 Report, suggests that "reviews are commensurate with the levels of risk, and to appropriately situate the regulation of human subjects protections relative to public health more broadly" (2004: 931). They believe that CDC's interpretation, although legally derived from the federal regulations (Common Rule) may not be readily accepted outside of public health, but noted that public health in general is already "heavily regulated through formal means as well as indirectly through the operation of political authority." Strictly applying the Common Rule requirements in every case may not be practical or necessary.

Although an alternative approach to the IRB process has not been developed through regulations, at CDC there are ongoing efforts to ensure and improve ethical practices at the agency. There was an Ethics Subcommittee to the Advisory Committee to the Director (ACD), composed of external ethicists from around the U.S. I am not certain when this committee was first formed, but a review of archival documents indicated that the subcommittee dated back to at least 1997. When I first heard about this subcommittee I was among a few individuals recruited by CDC OADS to rethink public health ethics at CDC and to help coordinate an internal public health ethics committee (PHEC). This was sometimes in 2005. The internal PHEC would work with the external Ethics Subcommittee as partners to develop public health ethics initiatives at CDC. I became the first chair of the Education Subcommittee for PHEC and over two and a half years, coordinated public health ethics training at CDC. One of PHEC subcommittees is the consultation subcommittee, which has developed a process for investigators and programs to submit ethical consultation requests for the subcommittee to consider. The consultation can be requested for ethical issues related to both research and nonresearch, although the subcommittee does not take that distinction into consideration.

Each CDC center, institute, or office has a public health ethics lead, which is one of my roles in my center. The lead serves as the center's representative to PHEC and coordinates the consultation process for the center. The consultation request must be approved by the center's director before being accepted by PHEC. The request is usually reviewed by and deliberated on by PHEC Consultation

Subcommittee and one external ethicist, who was a member of the external Ethics Subcommittee to the ACD. The external ethics subcommittee was dissolved in 2013 by the ACD citing only that the internal PHEC is now capable of addressing any ethical issues the agency may faces. Future consultations will likely involve an external ethicist in an informal, voluntary basis.

A deliberation process (Table 11) was developed by PHEC for addressing consultation requests. Various ethical principles and guidelines are considered for any particular request, e.g., the Common Rule, The *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (developed by the Council for International Organizations of Medical Sciences (CIOMS)). At least one meeting will be scheduled with the program and investigator(s) during the deliberation. After the meeting the consultation subcommittee drafts a report about the deliberation and possible recommendations for the investigators and programs to consider. The committee does not dictate the action(s) to be carried out. The final decision would be left up to the program.

Although PHEC does not provide ethical oversight of public health activities, it does provide much needed ethical insights to the programs and investigators, who wish to engage the committee for additional input on tough ethical questions. The consultation process provides many benefits to the investigators and programs and helps ensure protections for individuals and communities involved.

The Benefits of the Consults include:

- Provided a forum for discussion and raising ethical concerns with PHEC and an external ethicist;

- Informed program and investigators of ethical guidelines and importance of community involvement;
- Provided useful and timely feedback and recommendations for program and investigators to consider;
- Re-affirm and remind our own staff's concern and commitment to populations we serve, and
- Develop trust.

Programs that have requested and underwent public health consultations often find them very useful. They felt that the consultations have a high degree of impact on their programs and added value to the policy decision-making. They were usually extremely satisfied with the timelines and response of the CDC process and with the outcome. Other comments from programs include, the process help them feel:

> …more comfortable about the current plan, quick and high quality, help clarified the importance of community role, practical recommendations, and grateful for the quick consultation, which help us move forward with our plans (Internal Communication).

The ethical consultation process was not meant to be an alternative to the IRB review, and has not been well used by CDC programs. It does not view public health activities from a research and nonresearch perspective, but it can provide a safety net for protecting individuals and communities for both research and nonresearch. For public health research that fell through the loophole, such as non-exempt human subjects research where CDC is not engaged and locally determined as not research, the ethics consultation can provide additional assurance that subjects are protected. PHEC has also established an ethics desk at the CDC Emergency Operations Center to provide ethical consultations to CDC staff during times of emergency.

Table 11: Public Health Consultation Process

	Public Health Ethics Consult Process	
Identify	The identification phase identifies the issue and gathers relevant information, identifies the stakeholders and their values, and clarifies the public health ethics question.	
	Steps	**1. Identify the Issue and Gather Information** **2. Identify Stakeholders and their Values** **3. Clarify the Public Health Ethics Question**
Analyze	The analysis phase evaluates the gathered information, considers ethical perspectives, and critically weighs all factors.	
	Steps	**4. Evaluate Gathered Information** **5. Consider Ethical Perspectives** **6. Critically Weigh All Factors**
Resolve	The resolution phase identifies alternatives for resolving the public health ethics issue, weighs the pros and cons for each option, and develops recommendations.	
	Steps	**7. Identify Alternatives** **8. Weigh Options** **9. Develop Recommendation**

*Source: CDC Public Health Ethics Committee (PHEC)

Final Thoughts

The debates, criticisms, and controversies over CDC's use of primary intent/purpose to distinguish public health research from nonresearch are that it can be used to "game the system" and allows investigators to bypass the IRB. The regulatory definition of research is an abstract term, socially constructed and continually reconstructed through interpretations by individuals and groups. If we accept that individuals come from different backgrounds, have different lives, make different choices, have different opinions and beliefs, then it is easier to understand

that there will always be variations and disagreements in the interpretation of the definition of research.

One HSC compared research determination to Major League Baseball's infield fly rule, stating, "My personal opinion…whether or not something is research will always come down to a judgment call, sort of like the infield fly rule -- CDC's policy on distinguishing research versus nonresearch is flawed." There were few people at CDC who thought they know exactly what constitute research. The most common thought is that people would like to shift from procedural compliance toward reviewing public health activities according to the level of risk. An additional criterion to determine the type and level of review is to also assess the benefits, whether the activity benefits the individuals or communities. Studies, either research or nonresearch, which provide little or no benefits to the individuals or communities should have a higher level of review and protection. This is necessary in public health because the patients in public health are the populations; and individuals do not always directly benefit from a public health intervention or study. In principle, public health always favors population over individuals. According to Taylor, the Institute of Medicine (IOM) has:

> …encouraged institutions and regulators to look beyond the review of research proposals conducted by the IRB when considering the protection of research participants and to move toward establishing accountability within an ethical culture (2007:9).

An over-emphasis on compliance has led to a community of mistrust and lack of confidence in IRB. As the numbers of research studies continue to grow, the human subjects protection system may be challenged and overburdened. It appeared that

DHHS has heard the calling from the public health community in proposing changes to the Common Rule that would reduce these burdens.

Among the proposed changes are the exclusion of certain activities from the definition of research and the clarification of what research is exempt from the Common Rule in an effort to "to better calibrate the level of review to the level of risk" (DHHS 2013: 5). The new Common Rule when implemented will be more "risk-based" protections and oversight. CDC has blamed the Common Rule for its problems and has advocated for many of the changes proposed in NPRM. When implemented the new Common Rule is certain to lead to another major cultural shift in CDC human subjects protection and research determination practice. NPRM will reduce the burden created by the current regulatory compliance and oversight, but there will be new challenges, education, and training. For those like Wedeen who support greater oversight, NPRM might be a disappointment. However, their disappointment can be reassured if public health institutions work to promote and create an ethical culture in an atmosphere of trust, transparency, and collaboration.

Appendix A: Interview Guide

This is a general interview guide. Actual interview may vary depending on individual participant, their roles in research oversight, background, and other factors. Not every question will be asked of every individuals and the order of the questions will depend on how each interview progresses. These questions may be drawn on during individual contact with participants during participant-observation setting and will be presented to participants at various times and setting (typical of ethnographic study). The target populations include various individuals and groups who have a role in research oversight and human subjects protection. These may include human subjects contacts (HSCs), associate directors for science (ADSs), IRB administrators, IRB members.

Demographic information:

Before we begin the interview, please fill out this short demographic survey to the best of your knowledge. If you do not wish to respond to a particular question, please skip and go to the next one.

1. Gender
    a. Female
    b. Male
    c. Prefer to not respond
2. Educational background
    a. Science
    b. Social science
    c. Business
    d. Medical
    e. Public health
3. Degree (s)
    a. Undergraduate
    b. Master
    c. Doctoral
    d. Other _____
4. Career
    a. Early
    b. Mid-career
    c. Late
5. Official Job Title
    a. Health Scientist
    b. Public Health Analyst
    c. Public Health Adviser
    d. Program Analyst
    e. Policy Analyst
    f. Other _____
6. Functional Title
    a. Center HSC
    b. Division HSC
    c. Branch HSC
    d. ADS (center, division)
    e. Others

    _____
7. Years in Position
    a. Less than a year
    b. 1-5 years
    c. 6-10 years
    d. More than 10 years

Introduction:

As you already know, this is a part of a broader ethnographic evaluation of CDC human subjects protection process. As part of this evaluation, we want to learn more about your roles in order to get an in-depth understanding of how we at CDC protects human subjects in both our research and nonresearch projects. Before we get start, do you mind if I audiotape our interview? This is strictly for my note taking to ensure accuracy of your responses. The recording will be kept in a secure location and once, a transcription is made, the recording will be permanently destroyed. Your name or any other information that may identify you will not be recorded in the transcription.

Is this okay with you?

Background:

The interview may take 1.5-2 hours and we may take a short break depending on how it goes. Although there are some specific questions I want to ask you, I want you to feel free to talk about whatever you like that relates to your roles and feelings about human subjects protection at CDC or in general. Feel free to interrupt me or ask question if you have one.

Confidentiality:

You may refuse to response to a particular question if you feel uncomfortable, but I want to assure you again that your responses are strictly confidential. The main goal is to understand the various perspectives and roles in protecting human subjects in our research and nonresearch projects. Any information that will be shared or published will not contain anything that may identify you as a person.

Guiding Questions

Do you have any question before we start? If not, please feel free to bring up any question during the interview. I would like this to be more like an informal discussion/conversation, so please feel free to share any thought that may come to mind when we discuss any particular issue.

Background: Personal, educational, and professional

You may have already provided some information to some of the questions, but I would like for you to elaborate if they are repetitious.

1. First, tell me a little bit about yourself. What are your interests? Personal, professional? Have you always known what you wanted to do when you were

growing up? When you were younger, did you ever imagine what you would be when you grow up? Do you think that at least part of that came true?
2. What is your educational background? Do you have a graduate degree?
3. How long have you worked at CDC? How long have you been in your current position?
4. What were your previous positions? Were they at CDC? Outside? What organizations?
5. How do you feel about your current position? How is the workload? Are you happy with the compensation and benefits you get? Are you happy / satisfied with the roles you play in the position?

Knowledge and Experience: *Human subjects protection and ethics trainings and experiences*

6. Can you tell me about the specific trainings you have received that are related to your current roles? What do these training cover? Federal regulations, history, public health ethics, human rights?
7. What other experiences do you have that you believe help you in doing your job effectively? Clarification: this may include your participation in workgroups, association, previous jobs, teaching, etc.
8. Were there specific trainings that you were required to take? Are these sufficient for your current role?
9. Do you go to regular meetings or trainings provided by HRPO, other CDC programs, or at outside institutions that are related to your current roles? Are you required to go to any specific training? How would you describe existing training opportunities? Are they sufficient in quantity/quality?
10. Can you tell me what/who are most helpful to you in doing your current job?
11. What else do you think you need to do your job more effectively?

Beliefs, Perceptions and Practices

Human subjects, Research, Nonresearch

Please answer the following questions without consulting any reference or CDC guidelines policy

12. In your own understanding of the term, how would you define “human subjects”?
13. In your own understanding of the term, how would you define “research”?

a. How do you distinguish "human subjects" from "non-human subjects" research?
b. In your understanding of CDC policy, what types of research require approval by CDC IRB?

14. How would you define "nonresearch"?
    a. Do you apply the same level of scrutiny for nonresearch project? For example, does your center require a complete detailed protocol for nonresearch determination?
        i. If not, do you normally request that investigators address ethical and human rights issues in their protocols/submissions?
        ii. Have you encounter resistance or frustration from the investigators when you ask them to address these issues?
    b. Does your center have guidelines (brochure, guidelines document, etc.) to help your investigator in developing their protocol or proposal? If so, is there specific guidelines for nonresearch request?
    c. What key information or criteria do you personally look for in defining a project as nonresearch? What guidelines do you give investigator?
    d. What happened after you have determined that a project is "nonresearch"?
        i. What kind of follow up or requirements does your center have for nonresearch determination?
        ii. If the nonresearch proposal involved contact with and/or collection of data from human subjects, does your center require a written description of the consent process for review?
        iii. What specific elements do you require in the informed consent?
    e. Does your center require or request that investigator submit a progress or final report for their nonresearch project?
    f. If human subjects are involved, what other monitoring is/are in place to protect individual rights, privacy, and confidentiality?

Human subjects review process and system

15. How would you describe the human subjects review process in your center (program/branch/division for others than HSCs)?
16. Does your center have a project determination form? Do you like the form? Is it useful? Did you develop the form? If not, who/how was it developed? Any plan to update the form?

17. Does your center have a project tracking system? What are the main functions? Who can access the system? Is the system sufficient? Tell me how you feel about your center system?
18. What is your role in the human subjects review and protection process? What is most frustrating, rewarding about the process?
19. How would you characterize "minimal risk"? How would you view minimal risk for biomedical/clinical research? What about qualitative research, which involves interviews or ethnographic study?

Informed consent, minimal risk, human rights, and public health ethics

20. What is your perspective on informed consent?
    a. Do you feel that informed consent is a sufficient tool for protecting human subjects in research?
    b. What about research in developing countries? Do you see any problem with informed consent in developing countries? What about cultural and socioeconomic factors?
    c. Do you address informed consent issues in nonresearch activities that engage with human subjects? What about in research that CDC, by definition, is not engaged in human subjects research?
21. How would you define minimal risk?
22. What is your understanding of human rights principle? What is your perspective on human rights and human subjects research, particularly in developing countries?
23. What is your perspective on public health ethics?
    a. Do you participate on the CDC Public Health Ethics Committee?
    b. Has you consulted or been involved in a consultation with a PH ethics committee? Tell me more about the consultation.

Final Thoughts

24. Is there anything else that we have not discussed that you would like to mention or anything you would like to discuss further?
25. May I contact you if I have any more questions or need clarification on something you have said during this interview?
26. Thank you again for talking to me.

Appendix B: CDC Human Subjects Protection Practice Survey

Background

This anonymous survey is part of a larger qualitative assessment of CDC human subjects protection and ethical practices pre-IRB. Most often the questions below will not have a correct response, so please answer the questions as best you can.

1. Gender

- ● Female
- ● Male
- ● Prefer not to respond

2. Which center or program office do you work in?

Select one

3. Education

- ● Undergraduate
- ● Master
- ● Doctoral (MD or equivalent)
- ● Doctoral (PhD)

4. Educational Background (Check all that apply)

- ☐ General science
- ☐ Social/behavioral science
- ☐ Medicine
- ☐ Public health
- ☐ Economics
- ☐ Engineer
- ☐ Business
- ☐ Other

5. Position Title

- Medical Officer
- Health Scientist
- Public Health Analyst
- Program Analyst
- Policy analyst
- Other

6. Years in Position

- Less than a year
- 1-5 years
- 6-10 years
- More than 10 years

7. Years at CDC

- Less than 1 year
- 1- 5 years
- 6 to 10 years
- 11 to 15 years
- 16 to 20 years
- 21 to 25 years
- More than 25 years

8. What is the most significant role you have played in a research or major public health program activity? (Check one)

- Principal Investigator
- Primary Contact
- Project Officer/Administrator
- Project Staff
- Reviewer/approver
- Other

9. Are you a locally hired staff (non-US citizen)?

- Yes
- No

Please identify country

Human Subjects Protection Practices

The following questions address human subjects protection practices throughout CDC. Please answer to the best of your knowledge and practice.

10. Have you been involved in the determination of research and nonresearch?

- Yes
- No

11. If you are a locally-hired staff, does the ministry of health in your country distinguish research from nonresearch when submitting a proposal for ethical review?

- Yes
- No
- Not applicable

12. Do you agree that a complete protocol should be required for both human subjects research and public health practice?

- Yes
- No

13. Please rank the following resources you refer to in helping you determine whether your project is research or nonresearch. (1= most use, 7= least use)

- o Personal knowledge and experience
- o CDC Policy
- o Supervisor
- o Colleagues
- o Branch chief
- o Center or Division Human Subjects Contact
- o Center or Division Associate Director for Science

14. To your knowledge, who in your center has the authority to make the final determination as to whether a project is research or nonresearch? (Check all that apply)

- ☐ Branch chief
- ☐ Division Associate Director for Science
- ☐ Division Human Subjects Contact
- ☐ Center Associate Director for Science
- ☐ Center Human Subjects Contact
- ☐ Other
- ☐ Don't know

15. What is/are the main reasons why a project is submitted for human subjects review? (Check all that apply)

- ☐ CDC policy
- ☐ Regulatory requirement (US and other country)
- ☐ Funding requirement
- ☐ Program requirement
- ☐ Ethical obligation
- ☐ Other

16. Are you happy with the current human subjects review process including the research determination process?

- ● Yes
- ● No
- ● Not sure

17. In your opinion, does your program address human subjects protection and ethical issues for nonresearch activities?

- ● Yes
- ● No
- ● Don't know

18. Please rank the following ethical guidelines that you refer to most in addressing ethical issues in your study protocol? (1= refer to most, 5 = refer to least)

- o 45 Code of Federal Regulations Part 46: Protection of Human Subjects (aka, The Common Rule)
- o Belmont Report
- o Helsinki Principle
- o Council for International Organizations of Medical Science Guidelines (CIOMS)
- o Other

19. What do you think "engagement" in human subjects research means? (Check all that apply)

- ☐ Interacting with individuals for research
- ☐ Obtaining and analyzing identifiable data for research
- ☐ Obtaining individual consent for research
- ☐ Analyzing linked data for research
- ☐ Observing interview or intervention with participants
- ☐ Other

20. In your opinion what does “federally-supported” activity mean? (Check all that apply)

- ☐ US government providing funding to a project
- ☐ US government official provide technical support (no federal funding)
- ☐ US government official participate in data analysis and report writing (no federal funding)
- ☐ Other

21. At CDC it can be advantageous if a project is determined to be “nonresearch.”

- ● Agree
- ● Disagree

22. If a project is determined to be nonresearch, from a program standpoint, most ethical concerns about the potential impact on participants are irrelevant.

- ● Agree
- ● Disagree

23. For nonresearch, oversight of human subjects' rights and safety is beyond the scope of CDC responsibilities.

- Agree
- Disagree

24. CDC is not equipped to monitor potential human rights problems in nonresearch projects.

- Agree
- Disagree

25. Human subjects protections and IRB are considered to be very important by most CDC employees.

- Agree
- Disagree

26. Research determination and IRB review processes are generally considered burdensome by CDC employees.

- Agree
- Disagree
- Not sure

27. You are invited by a local ministry of health/health department to provide technical assistance on a study that they do not consider research, but the study fits the CDC definition of human subjects research. You do not interact with participants for any reason nor have access to identifiable data. Does your program permit you to participate in such study?

- Yes
- No
- Don't know

What is research?

The next set of questions assesses how research is defined, interpreted, and understood throughout CDC. Please answer based on your own experience and knowledge.

28. It is easy to determine the difference between research and nonreserch.

- Yes
- No

29. Which of the following is the US regulatory (45CFR46) definition of research? (Select one)

- A systematic investigation to develop generalizable new knowledge
- A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- A systematic method of evaluation designed to develop new knowledge
- A scientific method for developing new and generalizable knowledge

30. For CDC what do you think is the most important criterion for defining research? (Please rank 1=most important, 6=least important)

- Generalizability
- New knowledge
- Intent to publish
- Standardize methods
- Hypothesis testing
- Purpose of the activity

31. Which of the following do you think defines "generalizability"? (Check all that apply)

- Applicable to different people of the same population as the study subjects
- Applicable to other populations
- Applicable to other countries
- Applicable to humanity as a whole
- Applicable to society in general
- Developing new knowledge
- Other

32. If the purpose of a surveillance system is etiologic testing (finding the cause of disease or condition) do you consider the system as research?

- Yes
- No
- Don't know

33. Do you agree that a study can be seen as research by one collaborator and as nonresearch by another collaborator?

- Yes
- No
- Not sure

34. What do you think are the most important factors distinguishing research from practice? (Please rank 1=most important, 7 = least important)

- The design of the activity
- Experimental
- Development of new knowledge
- Generalizability of results
- Standardize methods
- Publication
- Benefits to participants

35. Do you believe that an investigator's intention to publish can be interpreted as "intent to generalize"?

- Yes
- No
- Not sure

36. Do you believe CDC should strive for consistency in research determination across the agency?

- Yes
- No
- Don't know

37. If you answered "yes" above, in your opinion, how should we develop consistency in the way CDC makes research determinations? (Check all that apply)

- ☐ Through routine audits
- ☐ Through training
- ☐ By streamlining the determination using well defined criteria for research
- ☐ By centralizing research determination
- ☐ Other

38. When conducting research involving human subjects please rank the following ethical considerations in term of what you think are most importance? (1= most important, 5= least important)

- o Informed consent
- o Benefit to participants
- o Privacy and confidentiality
- o Protecting human rights
- o Well-designed methods

39. In your view, what is the most important function of a human subjects protection system including IRB? (Rank 1= most important, 5= least important)

- o Protecting individual autonomy and rights
- o Protecting community rights
- o Minimizing research risks
- o Protecting vulnerable populations
- o Protecting researchers and institutions

40. In your view, what do you think the current human subjects protection system including IRB, achieve (rank 1= achieve most, 5=achieve least)

- o Protecting individual autonomy and rights
- o Protecting community rights
- o Minimizing risks
- o Protecting vulnerable populations
- o Protecting researchers and institutions

41. If you are planning a surveillance activity for the first time in a particular country and the activity involves going out to communities interviewing individuals and collecting blood and other biological specimens for testing to determine the prevalence and incidence of various diseases and conditions in the population. New knowledge about the population will be generated, but the primary purpose is to plan public health activity. Would you consider this activity research or non research?

- Research
- Non research
- Don't know

42. Thank you for taking the time to do this survey. Would you be willing to be interviewed in person? The interview will focus on specific cases.

- Yes (Please contact Aun Lor at alor@cdc.gov or call 404-398-2681)
- No

Appendix C: Excerpts Comparing CDC 1999 Guidelines to 2010 Policy

	1999 Guidelines	2010 Policy
Why is it difficult to classify an activity as research or nonresearch?	The difficulty in classifying some public health activities as research or nonresearch stems either from traditionally held views about what constitutes public health practice or from the fact that 45 CFR 46 does not directly address many public health activities. In addition, the statutory authority of state and local health departments to conduct public health activities using methods similar to those used by researchers is not recognized in the regulations. Human subject protections applicable for activities occurring at the boundary between public health nonresearch and public health research are not readily interpretable from the regulations (page 1).	For other activities the classification is more difficult, because 45 CFR part 46 does not directly address many public health activities. In addition, the statutory authority of state and local health departments to conduct public health activities using methods similar to those used by researchers is not recognized in the regulations. Appropriate protections applicable for activities occurring at the boundary between public health nonresearch and public health research are not readily interpretable from the regulations (page 1).
What differentiates research from practice?	The major difference between research and nonresearch lies in the primary intent of the activity. The primary intent of research is to generate or contribute to generalizable knowledge. The primary intent of nonresearch in public health is to prevent or control disease or injury and improve health, or to improve a public health program or service (page 2).	The major difference between research and nonresearch lies in the purpose of the activity. The purpose of research is to generate or contribute to generalizable knowledge. The purpose of nonresearch in public health is to prevent or control disease or injury and improve health, or to improve a public health program or service (page 2).
What is CDC policy?	All CDC activities must be reviewed to determine whether they are research involving human subjects. When an activity is classified as research involving human subjects, CDC and its collaborators will comply with 45 CFR 46 in protecting human research subjects (page 3).	All CDC activities must be reviewed to determine whether they are research involving human participants. When an activity is classified as research involving human participants, CDC and its collaborators will comply with 45 CFR part 46 in assuring human research protections (page 2).

	1999 Guidelines	2010 Policy
What is the ultimate criterion for defining research?	Although general guidelines can be given to assist in classifying these activities as either research or nonresearch, no one criterion can be applied universally. The ultimate decision regarding classification lies in the intent of the project. If the primary intent is to generate generalizable knowledge, the project is research. If the primary intent is to prevent or control disease or injury or to improve a public health program, and no research is intended at the present time, the project is nonresearch. If the primary intent changes to generating generalizable knowledge, then the project becomes research (page 3).	Although general guidelines can be provided to assist in classifying these activities as either research or nonresearch, no one criterion can be applied universally. The ultimate decision regarding classification lies in the purpose of the project. If the purpose is to develop or contribute to generalizable knowledge, the project is research. If the purpose is to prevent or control disease or injury or to improve a public health program, and no research is intended at the present time, the project is nonresearch. If the purpose changes to developing or contributing to generalizable knowledge, then the project becomes research (page 2).
Who is responsible for making research determination?	The Human Subjects Contact (HSC) in each Center, Institute, or Office (CIO) determines whether the project constitutes research. If the HSC is unclear about classifying a project, the HSC should consult with the CDC's Deputy Associate Director for Science (page 4).	The Associate Director for Science (ADS) in each National Center (NC) has been given the responsibility to determine whether a project constitutes research involving human participants. This authority may be redelegated at the discretion of the ADS (page 3).
What are the general attributes of public health research?	Intent of the project is to generate generalizable knowledge to improve public health practice; intended benefits of the project may or may not include study participants, but always extend beyond the study participants, usually to society; and data collected exceed requirements for care of the study participants or extend beyond the scope of the activity. Generalizable knowledge	The purpose of the activity is to develop or contribute to generalizable knowledge to improve public health practice; intended benefits of the project can include study participants, but always extend beyond the study participants, usually to society; and data collected exceed requirements for care of the study participants or extend beyond the scope of the activity. Generalizable knowledge means new information that has relevance beyond the population or program from

	means new information that has relevance beyond the population or program from which it was collected, or information that is added to the scientific literature. Knowledge that can be generalized is collected under systematic procedures that reduce bias, allowing the knowledge to be applied to populations and settings different from the ones from which it was collected. Generalizable, for purposes of defining research, does not refer to the statistical concept of population estimation or to the traditional public health method of collecting information from a sample to understand health in the population from which the sample came. Holding public health activities to a standard of studying every case in order to classify an activity as nonresearch is not practical or reasonable (page 4).	which it was collected, or information that is added to the scientific literature. Knowledge that can be generalized is collected under systematic procedures that reduce bias, allowing the knowledge to be applied to populations and settings different from the ones from which it was collected. Generalizable, for purposes of implementing the definition of research, does not refer to the statistical concept of population estimation, or sampling, which is collecting information from selected individuals in order to understand health in the population from which the sample came. Holding public health activities to a standard of studying every case in order to classify an activity as nonresearch is not practical or reasonable, nor is it necessary for nonresearch activities (page 3).
What are the general attributes of nonresearch?	Intent of the project is to identify and control a health problem or improve a public health program or service; intended benefits of the project are primarily or exclusively for the participants (or clients) or the participants' community; data collected are needed to assess and/or improve the program or service, the health of the participants or the participants' community; knowledge that is generated does not extend beyond the scope of the activity; and project activities are not experimental (page 4).	The purpose of the activity is to identify and control a health problem or improve a public health program or service; intended benefits of the project are primarily or exclusively for the participants (or clients) or the participants' community; data collected are needed to assess or improve the program or service, the health of the participants or the participants' community; knowledge that is generated does not extend beyond the scope of the activity; and project activities are not experimental (page 3).

	1999 Guidelines	2010 Policy
What are the shared attributes of public health research and nonresearch?	Other attributes, such as publication of findings, statutory authority (see discussion in next section), methodological design, selection of subjects, and hypothesis testing/generating, do not necessarily differentiate research from nonresearch because these types of attributes can be shared by both research and nonresearch projects (page 4).	Other attributes, such as publication of findings, statutory authority (see discussion in next section), methodological design, selection of participants, and hypothesis testing or generating, do not differentiate research from nonresearch, because these types of attributes can be shared by both research and nonresearch activities (page 3).
Can nonresearch develop generalizable results?	A nonresearch project may generate generalizable knowledge after the project is undertaken even though generating this knowledge was not part of the original, primary intent. In this case, since the primary intent was not to generate or contribute to generalizable knowledge, the project is not classified as research at the outset. However, if subsequent analysis of identifiable private information is undertaken to generate or contribute to generalizable knowledge, the analysis constitutes human subjects research that requires IRB review (page 4).	A nonresearch activity can develop or contribute to generalizable knowledge after the project is undertaken even though generating this knowledge was not part of the original purpose. In this case, because the purpose was not to develop or contribute to generalizable knowledge, the project is not classified as research at the outset. However, if subsequent analysis of identifiable private information is undertaken to develop or contribute to generalizable knowledge, the analysis constitutes human research that now requires further consideration under 45 CFR part 46 (page 3).
What if a project has multiple components?	If a project includes multiple components and at least one of those components is designed to generate generalizable knowledge, then the entire project is classified as research unless the components are separable (page 5).	If a project includes multiple components and at least one of those components is designed to develop or contribute to generalizable knowledge, then the entire project is classified as research unless the components are separable (page 4).

Appendix D: Key Findings from an Agency-wide Survey, Summary for Sharing with Relevant CDC Staff

Survey

- 41 Questions via Survey Monkey

Type of Questions**:** Definition of research; Interpretation of CDC policy and other guidelines; Distinguishing research from practice, Ethical principle and guidelines**;** Perception on Human Subjects Review (HSR) and IRB**;** Perceptions on traditional criteria for defining research**;** Central focus on HSR**;** Issues of engagement.

- Timeline: July – September, 2012
- CDC employees and locally hired staff overseas
- Recruitment through internal CDC announcements, listserves, words of mouth, etc.

Sampling

- Sample size ≈ 4,000-5,000 CDC FTE's, including locally employed staff (LES)
- Respondents N = 432 (≈ 10%)
- Number completed survey n = 317 (73.4%)
- Female (269, 63.4%); Male (151, 35.4%), No response (5, 1.2%)
- LES from 18 countries representing 14 CIO's, n=70; Female (41, 60%); Male (27, 40%)

Summary of Major Findings

- Most respondents agreed that a complete protocol should be submitted for research determination.
- There is no general consensus on what "generalizability" means.
- Most respondents considered research determination and IRB processes to be burdensome.
- Colleagues and Branch Chiefs were the most used guidelines for research determination.
- Not clear whether they know who can make research determination for the center.
- Ethics, regulation, and CDC policy were cited most as the reasons why they submit projects for human subjects review.
- Protecting human rights was seen as the most important in human subjects research and should be the most important function of the IRB.

Cultural Finding

- CDC Human Subjects Protection and research determination practice have not significantly evolved since the release of the 1999 Guidelines.

Short Term Policy and Training Issues for Resolution

- There may be little resistance, especially among LES, if complete protocols are required for research determination.
- Move forward with S3P.
- Colleagues and branch chiefs are the main guidelines, so training might be focused on Branch Chiefs and others with supervisory roles.

Medium Term Policy, Training, Guideline Issues

- There are still confusions about what constitute public health research, so dealing with this seems to require addressing and clarifying CDC policy, training, and better guidelines in general.
- Develop nonresearch protocol guidelines to highlight what is expected in terms of science and ethics.
- Address ethical gaps for when CDC is involved, but not engaged, in research that has no formal (IRB) ethical oversight, where locally is not considered research.
- Explore the possibility of requiring incident reporting for nonresearch and for research where CDC is not engaged and locally considered as nonresearch.

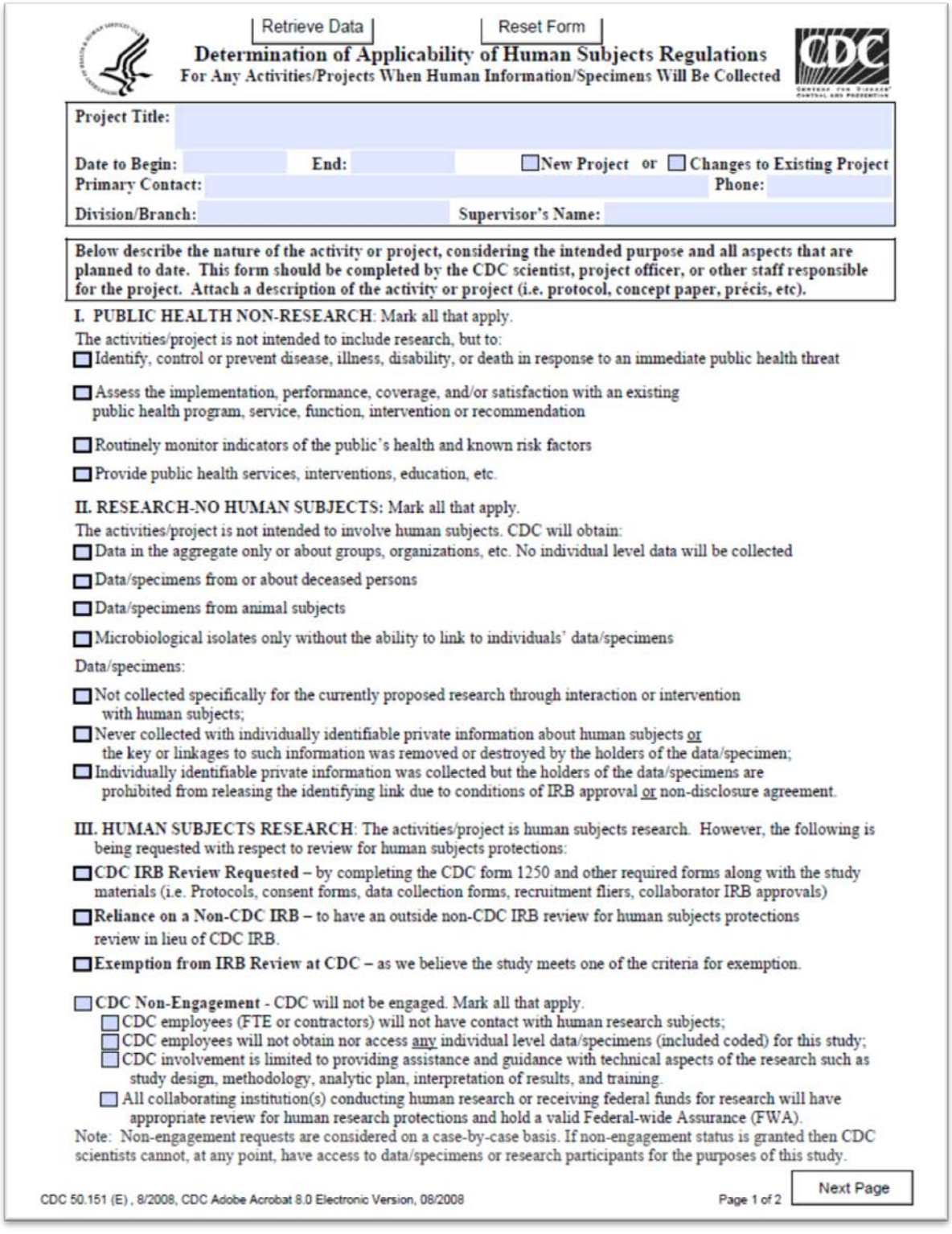
Long Term Challenges

- Foster an environment that ensures ethical cultural practices, despite of the confusions over how to define research.
- Explore the possibility of developing a nonresearch review committee to address ethical issues among the tougher cases (protocols).
- Allocate sufficient resources for human subjects and ethical oversight, including staffing, consultation, and site visits at all level.

Table 12: Key Survey Findings

	CDC-wide, N=432	Locally Employed Staff, n = 70
Gender (F, M)	63% (269) vs. 36% (151) M	60% (41) vs. 40% (27)
Have you been involved in the research determination process? (yes vs. no)	74% (256) vs. 26% (90) (n=346)	60% (28) vs. 40% (19)
Does the MOH distinguish research from nonresearch when submitting for ethical review?		44% (20) vs. 13% (6)
Do you agree that a complete protocol should be required for both human subjects research and public health practice? (Yes vs. No)	62% (210) vs. 38% (129)	85% (40) vs. 15% (7)
Most important resources to help with research determination (1-7, Rank, lower means most used)	Branch Chief 2.51 Colleague 3.07 Supervisor 3.91 Center of Div ADS 4.11 Center or Div HSC 4.34 On own 4.82 CDC Policy 5.24	Colleague 2.85 Branch Chief 3.28 Center or Div HSC 3.77 Center of Div ADS 4.02 On own 4.04 Supervisor 4.68 CDC Policy 5.36
At CDC it can be advantageous if a project is determined to be nonresearch. (Yes, No)	83% (278) vs. 17% (58)	69% (31) vs. 31% (14)
Research determination and IRB processes are considered burdensome by CDC employees (Agree, disagree, unsure)	67% (231) vs. 12% (42) vs. 20% (70)	54 (25) vs. 15% (7) vs. 30% (14)
It is easy to determine the difference between research and nonresearch. (Yes, No)	28% (88) vs. 72% (224)	42% (17) vs. 58% (24)
Which of the following do you think defines generalizability? (check all apply)	Other in same pop. 57% (179) Other pop. 70% (220) Other countries 42% (131) Humanity 41% (129) Society in general 46% (143) New knowledge 10% (32) Other 4% (11)	Other in same pop. 49% (20) Other pop. 46% (19) Other countries 29% (12) Humanity 51% (19) Society in general 51% (21) New knowledge 12% (5) Other 0 (0)
Do you agree that a study can be viewed as research and nonresearch by different collaborators? (Yes, No, Not sure)	88% (273) vs. 7% (21) vs. 6% (17)	80% (32) vs. 18% (7) vs. 3% (1)
Do you believe that intention to publish means the same as intention to generalize? (Yes, No, Not sure)	13% (40) vs. 69% (216) vs. 18% (55)	22% (9) vs. 54% (22) vs. 24% (10)
Do you believe CDC should strive for consistency? (Yes, No, DK)	86% (271) vs. 6% (18) vs. 8% (25)	88%(35) vs. 3% (1) vs. 10% (4)
What is the best way to achieve consistency?	Routine audits 30% (82) Training 65% (179) Streamline 87% (240) Centralize 32% (89) Other 4% (12)	Routine audits 32% (12) Training 76% (28) Streamline 92% (34) Centralize 46% (17) Other 0% (0)

Appendix E: Sample Research Determination Form



Retrieve Data | Reset Form

Determination of Applicability of Human Subjects Regulations
For Any Activities/Projects When Human Information/Specimens Will Be Collected

Project Title:

Date to Begin: **End:** ☐ New Project or ☐ Changes to Existing Project
Primary Contact: **Phone:**
Division/Branch: **Supervisor's Name:**

Below describe the nature of the activity or project, considering the intended purpose and all aspects that are planned to date. This form should be completed by the CDC scientist, project officer, or other staff responsible for the project. Attach a description of the activity or project (i.e. protocol, concept paper, précis, etc).

I. PUBLIC HEALTH NON-RESEARCH: Mark all that apply.

The activities/project is not intended to include research, but to:

☐ Identify, control or prevent disease, illness, disability, or death in response to an immediate public health threat

☐ Assess the implementation, performance, coverage, and/or satisfaction with an existing public health program, service, function, intervention or recommendation

☐ Routinely monitor indicators of the public's health and known risk factors

☐ Provide public health services, interventions, education, etc.

II. RESEARCH-NO HUMAN SUBJECTS: Mark all that apply.

The activities/project is not intended to involve human subjects. CDC will obtain:

☐ Data in the aggregate only or about groups, organizations, etc. No individual level data will be collected

☐ Data/specimens from or about deceased persons

☐ Data/specimens from animal subjects

☐ Microbiological isolates only without the ability to link to individuals' data/specimens

Data/specimens:

☐ Not collected specifically for the currently proposed research through interaction or intervention with human subjects;

☐ Never collected with individually identifiable private information about human subjects or the key or linkages to such information was removed or destroyed by the holders of the data/specimen;

☐ Individually identifiable private information was collected but the holders of the data/specimens are prohibited from releasing the identifying link due to conditions of IRB approval or non-disclosure agreement.

III. HUMAN SUBJECTS RESEARCH: The activities/project is human subjects research. However, the following is being requested with respect to review for human subjects protections:

☐ **CDC IRB Review Requested** – by completing the CDC form 1250 and other required forms along with the study materials (i.e. Protocols, consent forms, data collection forms, recruitment fliers, collaborator IRB approvals)

☐ **Reliance on a Non-CDC IRB** – to have an outside non-CDC IRB review for human subjects protections review in lieu of CDC IRB.

☐ **Exemption from IRB Review at CDC** – as we believe the study meets one of the criteria for exemption.

☐ **CDC Non-Engagement** - CDC will not be engaged. Mark all that apply.

- ☐ CDC employees (FTE or contractors) will not have contact with human research subjects;
- ☐ CDC employees will not obtain nor access any individual level data/specimens (included coded) for this study;
- ☐ CDC involvement is limited to providing assistance and guidance with technical aspects of the research such as study design, methodology, analytic plan, interpretation of results, and training.
- ☐ All collaborating institution(s) conducting human research or receiving federal funds for research will have appropriate review for human research protections and hold a valid Federal-wide Assurance (FWA).

Note: Non-engagement requests are considered on a case-by-case basis. If non-engagement status is granted then CDC scientists cannot, at any point, have access to data/specimens or research participants for the purposes of this study.

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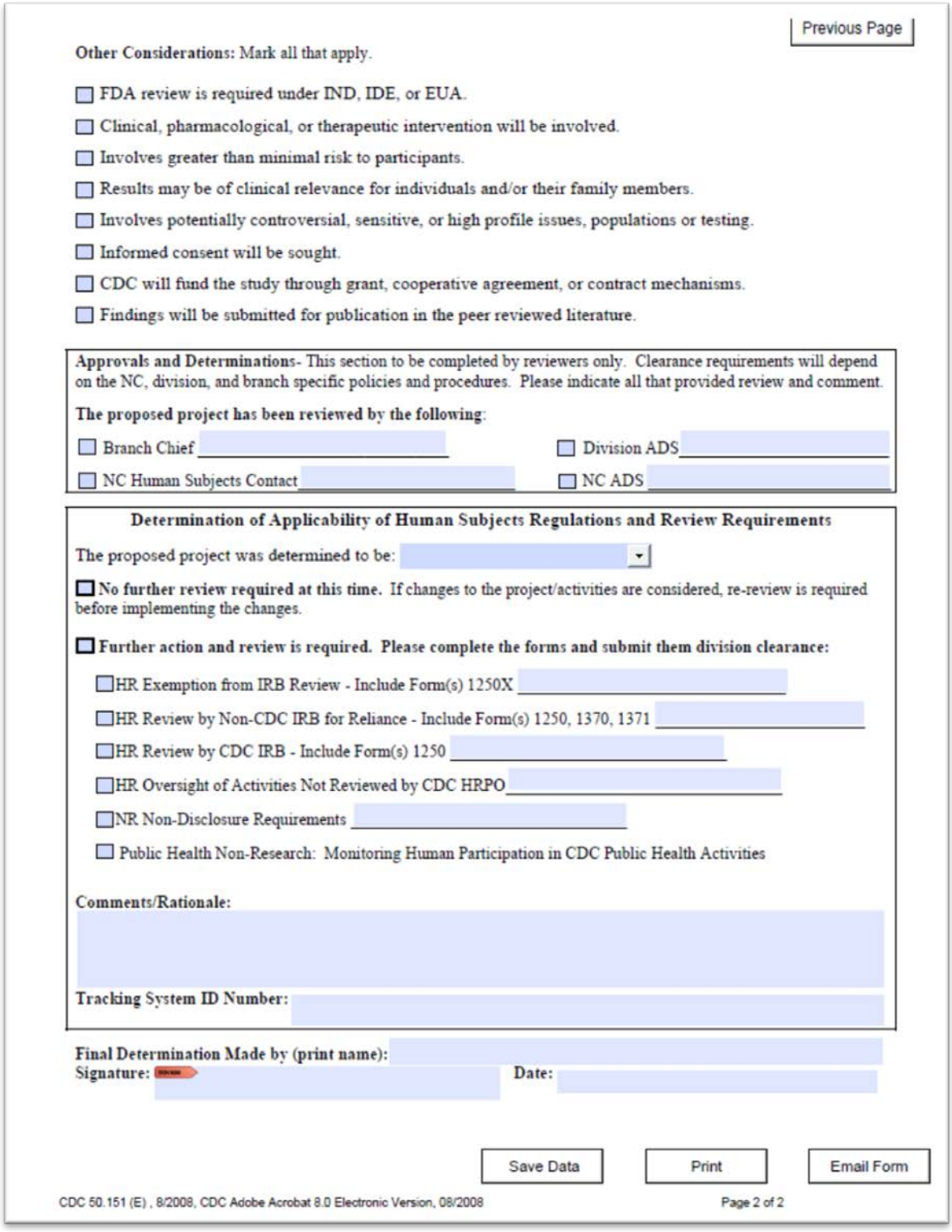

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Other Considerations: Mark all that apply.

- ☐ FDA review is required under IND, IDE, or EUA.
- ☐ Clinical, pharmacological, or therapeutic intervention will be involved.
- ☐ Involves greater than minimal risk to participants.
- ☐ Results may be of clinical relevance for individuals and/or their family members.
- ☐ Involves potentially controversial, sensitive, or high profile issues, populations or testing.
- ☐ Informed consent will be sought.
- ☐ CDC will fund the study through grant, cooperative agreement, or contract mechanisms.
- ☐ Findings will be submitted for publication in the peer reviewed literature.

Approvals and Determinations- This section to be completed by reviewers only. Clearance requirements will depend on the NC, division, and branch specific policies and procedures. Please indicate all that provided review and comment.

The proposed project has been reviewed by the following:

☐ Branch Chief _____ ☐ Division ADS _____

☐ NC Human Subjects Contact _____ ☐ NC ADS _____

Determination of Applicability of Human Subjects Regulations and Review Requirements

The proposed project was determined to be: _____

☐ **No further review required at this time.** If changes to the project/activities are considered, re-review is required before implementing the changes.

☐ **Further action and review is required. Please complete the forms and submit them division clearance:**

- ☐ HR Exemption from IRB Review - Include Form(s) 1250X _____
- ☐ HR Review by Non-CDC IRB for Reliance - Include Form(s) 1250, 1370, 1371 _____
- ☐ HR Review by CDC IRB - Include Form(s) 1250 _____
- ☐ HR Oversight of Activities Not Reviewed by CDC HRPO _____
- ☐ NR Non-Disclosure Requirements _____
- ☐ Public Health Non-Research: Monitoring Human Participation in CDC Public Health Activities

Comments/Rationale:

Tracking System ID Number:

Final Determination Made by (print name):

Signature: **Date:**

Save Data Print Email Form

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Source: CDC Human Research Protection Office

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