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Influence of clinical research investigator fraud on clinical trial participation

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Influence of Clinical Research Investigator Fraud on Clinical Trial Participation

by

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DEDICATION:

This thesis is dedicated to my inspiration, my gods, and most importantly my loving father, Haribabu Garimella, and mother, Durgadevi Garimella.

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ABSTRACT

The number of clinical research investigators whom the Food and Drug Administration (FDA) has disqualified or totally restricted has been increasing since 1964. In addition, several public polls and surveys indicate a major dilemma in clinical trial participation and public perceptions of clinical research. This research investigates how clinical investigator fraud or misconduct influences public perceptions of participation in clinical trials. To meet this challenge, a well-designed electronic survey was developed for the faculty at Eastern Michigan University (EMU). The survey results indicate that 79% of respondents were "very likely" to be influenced by fraud committed by their own physicians. However, when the fraud has been committed at a hospital elsewhere, only approximately 20% of respondents reported that they were "very likely" to be influenced. These results, however, reflect only a select group of people. Further studies on larger populations are recommended to learn about the impact of investigator fraud on patient recruitment.

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Chapter I: Introduction

"While scientific misconduct is rare, when it does occur, it affects public confidence in the clinical trial process and raises questions about the effectiveness of trial monitoring and its follow-up by sponsors." Stan W. Woollen[1]

"Although the public clearly holds positive attitudes about the general importance of clinical research, the same cannot be said for public trust in the professionals who oversee, manage, and support that research." Kenneth A. Getz[2]

The two statements above indicate the long-term effects of research misconduct on public confidence in the clinical research. The first quotation is from a Food and Drug Administration (FDA) deputy director at a Drug Information Association (DIA) meeting and indicates the major repercussions of clinical research misconduct and fraud. In the second quotation, Kenneth A. Getz states that the public has an optimistic perception of clinical trials and their importance in the advancement of medicine. However, Getz also insists that the public may not have the same confidence and trust levels in the people who conduct and supervise clinical research studies.

While clinical research organizations have numerous major challenges, patient or subject recruitment is most crucial. If research misconduct and investigator fraud continue to occur, there will eventually be a very small percentage of people who have trust in clinical trials.

Nevertheless, since 1964, the number of clinical investigators disqualified by the FDA due to research misconduct has slowly increased, which may show influence on public awareness of clinical trial knowledge. In addition, polls and surveys conducted by market research companies have indicated many reasons for public reluctance to participate in clinical trials (Harris Interactive, 2002). This research study aims to find out how knowledge of investigator fraud might change public perceptions and whether investigator fraud or misconduct might affect public participation in clinical trials. If successful, these findings could alter the way that public awareness campaigns are managed and may lead to a better understanding of the negative impact of reporting on fraud without proper context.

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[1]Deputy Director, Division of Scientific Investigations, Center for Drug Evaluation and Research, FDA - June 14, 2000

[2]Founder and Chairman of the Non-Profit Organization CISCRP and a Senior Research Fellow at the Tufts Center for the Study of Drug Development - ACRP: September, 2008

Chapter II: Background and Problem Statement

Definitions

Research Misconduct or Fraud:

According to the Office of Research Integrity, U.S. Department of Health and Human Services and 42 CFR Part 93.103

a. *Fabrication* is making up data or results and recording or reporting them.
b. *Falsification* is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
c. *Plagiarism* is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
d. *Research misconduct* does not include honest error or differences of opinion.

Clinical research misconduct or fraud means, according to the FDA, "falsification of data in proposing, designing, performing, recording, supervising, reviewing, analyzing, collecting clinical research or reporting clinical research results, outcomes and endpoints" (Mauriello, 2010).

The FDA uses fraud and misconduct interchangeably and includes acts of omission, which means consciously not revealing all data and commission which means consciously altering or fabricating data (Below, March, 2003).

Early History

The FDA's various offices regulate all phases of clinical research studies that are intended to develop evidence to support safety and effectiveness of new or generic investigational drugs, devices, and biological products. In addition, the FDA has provided statutes, regulations, and guidance documents for conducting these clinical investigations. All clinical investigators and other study staff associated with investigations must comply with these procedures to ensure the integrity of the clinical data. Based on this clinical and non-clinical data, product approvals are further decided by the FDA.

The FDA's Office of Regulatory Affairs (ORA) mainly oversees inspections and enforcement actions, along with other regulatory activities. The ORA has a list of various categories of clinical investigators who have been completely "disqualified" or "totally restricted" from clinical investigations, or received necessary "enforcement actions" by FDA due to non-compliance with regulatory requirements. The graph below shows the number of clinical investigators per decade in those categories.

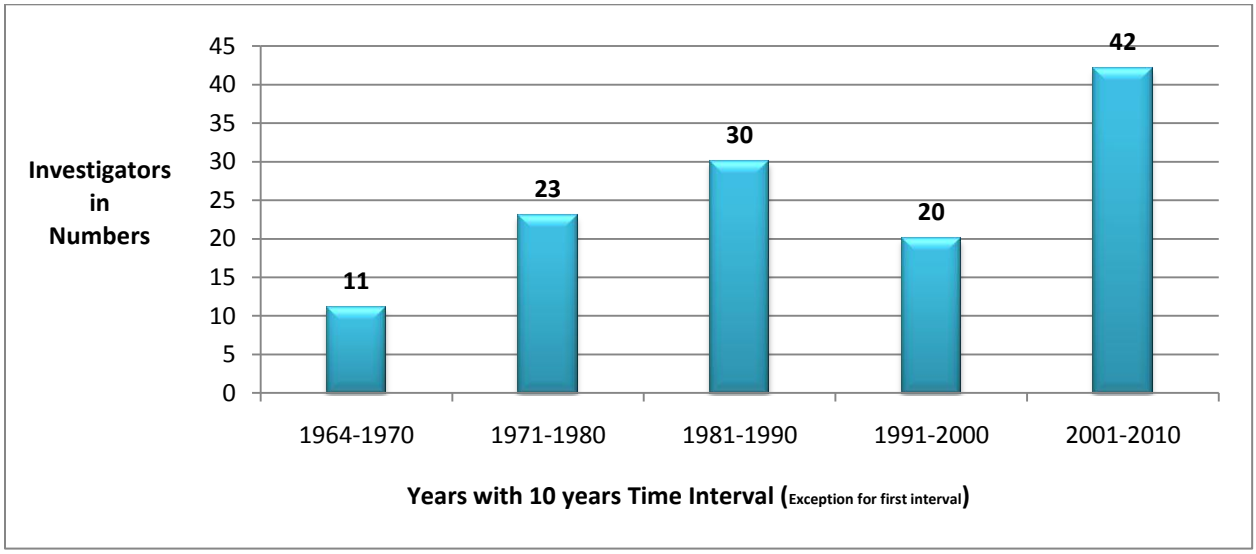

Figure 1 Disqualified Clinical Investigators by the FDA (07.15.11)

Description of Graph:

The FDA initiated its disqualification process in 1964. The total number of clinical investigators who were disqualified or totally restricted from clinical investigations between the years 1964 to 2010 was shown in Figure 1. According to the graph, the number increased gradually each year, beginning in 1964. From 1964 to 1990, the number of investigators increased; from 1991 to 2000, on the other hand, the number decreased slightly. From 2001 to 2010, however, this number increased dramatically to 42 investigators.

Case Studies

From the FDA's disqualified clinical investigators list, three investigator cases were selected, and the available literature on their misconducts and disqualification was reviewed. The related information was obtained mainly from the FDA's warning letters and the media coverage on those investigators. The investigator (*who*), his misconducts (*what*), and the FDA's response to the misconducts (*how*) were presented here as three case studies.

The reason for selecting these case studies was not only that they were renowned, but also that, in all three cases, the misconduct seems surprising given the researchers' experience and prestige of their institutions. Since 1964, the FDA has either disqualified or totally restricted many other investigators from conducting research-related activities. Some of these investigators, however, contend that stringent federal regulations were responsible for their misconduct.

Case Study 1

Who was the researcher?

Dr. Robert Alan Fiddes, physician, researcher and president of Southern California Research Institute, Whittier, California.

What was the misconduct?

Beginning in the early 1990s, Dr. Fiddes was involved in over 200 clinical studies and extensively fabricated and falsified his clinical data. In his studies, fictitious patients were enrolled, as well as ineligible ones. He also fabricated lab results, by substituting clinical specimens and manipulating lab instrumentation.

According to the *New York Times*, "Dr. Fiddes's coordinators were paid bonuses for recruiting patients into the studies. Thereafter they also began improperly enrolling themselves and members of their family. Over time, the frauds orchestrated by Dr. Fiddes grew ever more audacious. Eventually, according to government documents, it was not just the records that were being falsified, instead, the medical tests were rigged -- and at times, patients simply invented. Outside monitors reviewed the documentation, but since there were real lab records for the rigged tests, they had no clue that they were being deceived" (Kolata, 1999).

The former chief financial officer of Dr. Fiddes's research center commented in an interview that Dr. Fiddes was putting the health of all his participants at risk and was skewing samples that could affect the whole American public.

How was it handled?

- On June 11, 2002, Dr. Fiddes, along with three of his study coordinators, was debarred from participation in drug research subject to FDA regulation for 20 years.
- Debarment followed upon entry of a guilty plea in a criminal case arising from fraud and false statements related to several clinical trials.
- Dr. Fiddes was sentenced to 15 months in federal prison and ordered to pay $800,000 in restitution.
- The Medical Board of California permanently revoked Dr. Fiddes's medical license in 2000.
- On May 17, 1999, a *New York Times* headlines read, "A Doctor's Drug Trials Into Fraud."

Case Study 2

Who was the researcher?

Dr. J. Michael McGee, physician and practitioner of otolaryngology at University of Oklahoma, Tulsa, Oklahoma.

What was the misconduct?

As a principal investigator, Dr. McGee conducted clinical trials of an experimental vaccine for malignant melanoma, in which he failed to fulfill the responsibilities of a clinical investigator, by violating FDA regulations governing investigational new drugs.

According to the FDA warning letter, Dr. McGee failed to adequately protect the safety and welfare of human subjects, by enrolling several ineligible subjects in the study and not obtaining proper Institutional Review Board (IRB) approvals of protocol modifications. In addition, Dr. McGee was accused of not having exercised control over the investigation, not

directly supervising patients who took the investigational drug, and keeping inadequate study records. Additionally, improper storage of test vaccine may have resulted in its contamination.

Moreover, Dr. McGee did not follow certain protocol requirements, such as removing from the study severely sick patients who were concurrently undergoing other treatment methods (the protocol required that such patients be excluded). Worst of all, however, Dr. McGee concealed adverse side effects data, disclosing it neither to the FDA, the sponsor, nor to the proper IRBs.

How was it handled?

- In January 2009, the FDA permanently debarred and disqualified Dr. McGee from serving as an investigator in any research.
- The FDA field investigator, Cherlynn Mathias said of the fraud: "It was a perfect lesson in how not to run a clinical trial."

Case Study 3

Who was the researcher?

Dr. Alfred E. Chang, physician, professor and chief of surgical oncology department at University of Michigan, Ann Arbor, Michigan.

What was the misconduct?

According to the FDA warning letter, Dr. Chang failed to fulfill the responsibilities of a clinical investigator for studies utilizing unlicensed biological investigational new drugs. The violations were as follows:

- Recruiting subjects who were ineligible to participate in the research

- Failing to obtain informed consent from the participants in accordance with the provisions of 21 CFR Part 50, as well as performing study-related procedures prior to consent from the subjects
- Failing to conduct research in accordance with the investigational plan
- Failing to follow the protocol in the management of toxicity related to the infusion
- Not submitting proper initial and continuing reviews of the clinical studies to the IRB
- Failing to maintain adequate and accurate records of the disposition of investigational drugs and case histories of individuals treated with investigational drugs

How was it handled?

- On April 7, 2010, the FDA permanently debarred and disqualified Dr. Chang from serving as an investigator in any research.

Discussion of Public Trust and Confidence

Although various acts, regulations, and guidance documents are available to serve the clinical investigation process, research misconduct remains a persistent problem. The rise in the number of investigators disqualified or totally restricted each year influences the general public's perceptions of clinical trials. Currently, most clinical research organizations depend on the Internet and social media for promotions and patient recruitment. Yet these very tools have been responsible for spreading research misconduct. In addition, people's awareness of clinical trials is influenced by word-of-mouth publicity. This may adversely affect public perceptions about volunteering or participating in a clinical trial.

The Harris Interactive group, a market research company, has conducted numerous surveys and public opinion polls regarding clinical trials and has presented significant findings regarding public opinion. First, a survey study conducted in 2008 indicated that most practicing physicians usually fail to follow clinical guidelines (Harris Interactive , 2008). In addition, this survey strongly suggests that financial incentives to physicians might have encouraged physicians to follow these guidelines. Secondly, another study conducted in 2007 showed that public confidence and trust in the clinical research enterprise has gradually decreased (Harris Interactive , 2007). Moreover, a study conducted in 2002 revealed that a majority of people do not agree with how patients were treated in clinical trials (Harris Interactive, 2002). Finally, a nationwide survey conducted by a non-profit organization called the Center for Information and Study on Clinical Research Participation (CISCRP) uncovered that only a small percentage of participants considered clinical trials to be safe (Surveys on Public Opinion on Clinical Research, 2004 to 2008).

One challenge of clinical research is to persuade people that they will not suffer as a result of participating. Historical research misconduct cases such as Nuremberg trials (1948), Thalidomide tragedy (1962), and the Tuskegee syphilis study (from 1932 to 1972) have had negative effects on public confidence in clinical research. The current surveys and public polls reveal a dilemma in the public perception of clinical trials. So the present research will focus on clinical research investigator fraud's possible effect on the public and to find out how it influences participants' opinions of clinical trials.

Thesis Statement

An attempt will be made to answer these following questions:

Specific Aim / Problem Statement:

1. How might fraud on the part of clinical research investigators influence the participants' perception and likelihood of participating in clinical studies?

   Hypothesis:

   - Knowledge of fraud committed by clinical research investigators affects people's perception of clinical trials and their likelihood of participating in them.
   - Geographic proximity of fraud cases may contribute to people's reluctance to participate in clinical trials.

2. Do factors such as socio-demographics, education level, general health knowledge, and previous clinical study experiences influence the public's perception of participation in clinical studies?

   Hypothesis:

   - The awareness of clinical research knowledge varies depending on a participant's socio-demographics, education level, general health knowledge, or previous clinical trial experience. However, it is not expected that socio-demographic factors will significantly affect the influence of investigator fraud on people's likelihood to participate in clinical trials.

Chapter III: Methodology

Sample Size Design

This research has been conducted in order to determine how fraud by clinical research investigators might influence public perceptions and a person's likelihood to participate in clinical trials. Assessing the role of geographic proximity to investigator fraud is also part of the study objectives. To meet these research goals, a well-designed electronic survey was developed to obtain the views of faculty within Eastern Michigan University (EMU). The population of interest for this study was faculty employed by Eastern Michigan University.

There are approximately 1,396 faculty members at EMU. These include 692 regular faculty, 97 lecturers and 607 adjunct faculty members. The faculty data (as of 2011) was obtained from EMU's Institutional Research and Information Management (IRIM) department. All of these faculty members were sent an electronic survey with opinion questions having a five-point Likert rating scale.

Research Design

Pre-Study Phase

- Power analysis to determine appropriate sample size
- Extensive review of literature on research misconduct and clinical investigator fraud
- Develop study design, questionnaire, informed consent, and intervention plan
- Approval from thesis committee and EMU's University Human Subjects Review Committee (UHSRC)

Study Phase

The descriptive quantitative method of research design was developed for this research survey. Defining descriptive research, Creswell (1994) stated that "the descriptive method of research is to gather information about the present existing condition" (Creswell, 1994). The descriptive method of research is also used to describe the nature of a current situation or condition and to explore its causes. Moreover, it is flexible, quick, and appropriate for this survey, as this method is used for gathering prevailing conditions.

The eligibility criteria for this survey research consist of:

- Inclusion Criteria:
    a. Age 21 or over (EMU faculty)
- Exclusion Criteria:
    b. Non-EMU faculty

The EMU faculty was selected as the target population for this study. Following approval by the UHSRC (Appendix A), an electronic mail (e-mail) was sent to all participants. The UHSRC-approved informed consent document (Appendix B) was used as the content of the email, briefly describing the study procedures and requesting recipients' participation. The survey questionnaire (Appendix C) was used as the main and primary data gathering source for this study. In the survey questions, the participants were asked five study-related questions, followed by five response options, involving a case scenario of a disease or condition. Additionally, the participants were asked four general demographic questions. The five response options represented, for each question, the extent to which clinical investigator fraud was likely to influence the respondent.

Data Management and Analysis Plan

Two weeks after sending out the survey, the survey was closed and the study data analysis phase began. The primary data analysis included all data collected from the respondents within this two-week period. To preserve anonymity, the survey database did not collect any information or data (such as Internet Protocol (IP) addresses) that might identify participants.

After obtaining the completed surveys from the participants, responses for each question were obtained and tabulated. From the responses, percentages for each response were calculated. The average weighted mean and standard deviation values were calculated for Likert scale questions.

Based on the responses to first survey question, the other four study-related questions were cross tabulated. The cross tabulated information provided a clear method of understanding results qualitatively and quantitatively and for examining the study hypothesis.

Human Subjects Protection

According to the Code of Federal Regulations, 45 CFR 46 entitled "Protection of Human Subjects," research projects involved with use of human subjects are subject to federal policies. As this research involves human subjects participation (specifically, among the EMU population), this study falls under federal regulations. This research complies with all applicable regulations in all cases of survey procedures involving human subjects.

Institutional Review Board (IRB)

Appropriate notification and approval from the IRB was obtained before proceeding with any study-related activities. The research proposal, survey instruments, and informed consent

document were submitted to and approved (Appendix A) by the University Human Subjects Review Committee (UHSRC) at Eastern Michigan University.

Informed Consent Form (ICF):

Every selected study participant received an informed consent document (Appendix B). The consent form clearly explained the study purpose, procedures, voluntariness, and contact information. The informed consent form was mailed electronically to all selected participants, since this was an electronic survey. Finally, the survey questions were free from all materials that might alter participant perceptions.

Chapter IV: Results and Discussion

Demographics of Respondents

A total of 156 people out of 1396 responded to the survey for a response rate of 11.2%. The response rate also varies by colleges (Appendix D). In addition to the five study-related questions, the respondents were asked four optional demographics questions: their gender, their age, their college of the university, and their preferred sources of health care information (the last question allowed for more than one response). Only three participants refused to provide their demographic information.

The four tables below present tabulations of the demographics responses.

Gender

Table 1 *Survey respondents by gender*

#	Answer		Response	%
1	- Male		61	40%
2	- Female		92	60%
	Total		153	100%

Age

Table 2 *Survey respondents by age*

#	Answer		Response	%
1	- 21 to 30		8	5%
2	- 31 to 40		22	14%
3	- 41 to 50		38	25%
4	- 51 and above		84	55%
	Total		152	100%

College of University

Table 3 *Survey respondents by college of University*

#	Answer		Response	%
1	- College of Arts and Sciences		66	43%
2	- College of Business		11	7%
3	- College of Education		20	13%
4	- College of Health and Human Services		33	22%
5	- College of Technology		16	10%
6	- Other		7	5%
	Total		153	100%

Most Trusted Sources for Health Related Information:

Table 4 *Survey respondents by source preferences*

#	Answer		Response	%
1	- Physicians (Surgeons or Doctors)		134	88%
2	- Print media, e.g., newspapers, magazines		45	29%
3	- Broadcasting media, e.g., television, movies, documentaries		23	15%
4	- Social networking media, e.g., Facebook, MySpace, Twitter,		0	0%
5	- General Internet media, e.g., news websites, discussion forums		13	8%
6	- Health specific Internet media, e.g., medical news sites, medical discussion forums		118	77%
7	- Friends and/ Family members		72	47%
8	- Other		29	19%

Note: Multiple Response Question

Presentation of Research Question Responses:

The five tables and charts below present the responses to the five research questions.

Q-1: Clinical Trial Participation - Past and Future:

From question 1, participants' prior clinical trial opportunities, experience, and likelihood to participate in future clinical trials were obtained.

According to results in Table 5, 20% of respondents had previous clinical trial experience, and 61% of those respondents would be willing to participate in the future, given the opportunity. On the other hand, 10% of respondents had had opportunities to participate but had chosen not to. And the remaining 10% of respondents would not consider participating, even in the future.

Table 5 *Clinical Trial Participation: Past & Future*

#	Answer		Response	%
1	Those who had an opportunity and participated in clinical trials		31	20%
2	Those who had an opportunity but DID NOT participate		15	10%
3	Those who NEVER had an opportunity, but will consider participating		95	61%
4	Those who NEVER had an opportunity, and WILL NOT consider participating		15	10%
	Total		156	100%

Base: All Adults (age: 21 and above)

Q-2: Fraud Occurring Somewhere in U.S.

Question 2 captures participant perceptions on the influence of investigator fraud on a clinical study conducted somewhere in United States.

From Table 6, it appears that 45% respondents report that investigator fraud somewhere in United States would "not likely" influence them. Conversely, the second-largest portion of respondents (21%) said fraud would "very likely" influence them.

Table 6 *Extent of Influence on Decision to Participate: If Fraud Occurs Somewhere in the U.S.*

#	Answer		Response	%
1	- Not likely		69	45%
2	- Less likely		18	12%
3	- Somewhat likely		23	15%
4	- Moderately likely		12	8%
5	- Very likely		33	21%
	Total		155	100%

Q-3: Michigan Investigator Fraud

The third question in this series asked about the extent to which respondents would be influenced by investigator fraud committed in the state of Michigan.

Table 7 displays the percentages for all responses. In this case, 35% of respondents reported that Michigan investigator fraud would "not likely" influence their decision to participate in local clinical trials, whereas 23% of respondents reported that Michigan investigator fraud would "very likely" influence them. This type of fraud was "somewhat likely" to influence 17% of respondents, and 15% of respondents answered "less likely."

Table 7 *Extent of Influence on Decision to Participate: If Fraud Occurs in Michigan*

#	Answer		Response	%
1	- Not likely		54	35%
2	- Less likely		23	15%
3	- Somewhat likely		26	17%
4	- Moderately likely		16	10%
5	- Very likely		35	23%
	Total		154	100%

Q-4: Local Hospital Investigator Fraud

The influence of local hospital investigator fraud on the decision to participate in a clinical trial conducted by another investigator was obtained from question 4.

The results demonstrated in Table 8 were quite interesting. Misconduct or fraud by an investigator at a local hospital would "not likely" influence 21% of respondents in deciding whether to participate in a clinical study by another investigator. Nevertheless, it would "very likely" influence 21% of respondents and "moderately likely" influence 22%. In addition, this misconduct would "less likely" influence 21% and "somewhat likely" influence the remaining 21%. Responses to this question were dispersed almost uniformly among all five options.

Table 8 Extent of Influence on Decision to Participate: If Fraud Occurs in a Local Hospital

#	Answer		Response	%
1	- Not likely		32	21%
2	- Less likely		28	18%
3	- Somewhat likely		27	18%
4	- Moderately likely		34	22%
5	- Very likely		33	21%
	Total		154	100%

Q-5: Research Fraud by Patient Physician

The influence of fraud committed by a patient physician on respondents' likelihood to participate a clinical trial was determined from the last question.

Table 9 shows that fraud committed by a patient physician would "very likely" influence 79% of respondents. In addition, this type of misconduct would "moderately likely" influence 6%, "somewhat likely" influence 5%, and "less likely" influence 1%. This fraud would "not likely" influence 8% of respondents. From the results, it appears that fraud committed by a patient physician is more likely to influence clinical trial participation than other location-determined frauds.

Table 9 Extent to Influence Participation: If Fraud Is From Patient Physician

#	Answer		Response	%
1	- Not likely		13	8%
2	- Less likely		2	1%
3	- Somewhat likely		7	5%
4	- Moderately likely		10	6%
5	- Very likely		122	79%
	Total		154	100%

4.3 Cross Tabulation of Results

The survey respondents can be grouped according to the four major special classes of participation. It is illustrative to cross tabulate the results of these four classes of respondents, since their responses to other misconduct/fraud questions differ appreciably on certain fraud questions as shown in Table 10.

Table 10 *Clinical Trial Participation vs. Extent of Fraud's Influence*

Fraud/Misconduct- Response		Q1: Clinical Trial Participation				
		With Experience	**Would Participate**	**Didn't Participate**	**Wouldn't Participate**	**Total**
Q2: Somewhere in U.S.	Not likely	18	37	8	6	**69**
	Less likely	7	10	1	0	**18**
	Somewhat likely	3	18	1	1	**23**
	Moderately likely	2	6	2	2	**12**
	Very likely	1	23	3	6	**33**
	Total	**31**	**94**	**15**	**15**	**155**
Q3: Michigan	Not likely	15	29	7	3	**54**
	Less likely	4	15	2	2	**23**
	Somewhat likely	6	16	2	2	**26**
	Moderately likely	4	9	0	3	**16**
	Very likely	1	25	4	5	**35**
	Total	**30**	**94**	**15**	**15**	**154**
Q4: Local Hospital	Not likely	10	17	2	3	**32**
	Less likely	6	18	3	1	**28**
	Somewhat likely	7	14	5	1	**27**
	Moderately likely	4	24	1	5	**34**
	Very likely	3	21	4	5	**33**
	Total	**30**	**94**	**15**	**15**	**154**
Q5: Patient Physician	Not likely	2	5	3	3	**13**
	Less likely	1	1	0	0	**2**
	Somewhat likely	2	5	0	0	**7**
	Moderately likely	1	6	0	3	**10**
	Very likely	24	77	12	9	**122**
	Total	**30**	**94**	**15**	**15**	**154**

Table 10 Explanation

Cross tabulated information among all five research questions presents an idea of data distribution among participants. The above table differentiates responses of all participants depending on their likelihood to participate in clinical trials.

From the table, three major categories of respondents were chosen for discussion. Category 1 includes those participants who initially participated in clinical trials. Given their experience in clinical trials, their responses to fraud/misconduct-related questions are significant. Category 2 includes those participants who would consider participating in future clinical trials if given the opportunity. Category 3 consists of those participants who have neither participated in the past nor wish to participate in the future. This latter category will not be discussed further for data analysis.

Category 1 - "With Experience"

Of those responding, 20% were category 1 respondents—individuals who had participated in clinical trials before. The investigator misconduct/fraud somewhere in U.S. would *not likely* influence 58% of category 1 respondents. It would *very likely* influence 3% of category 1 respondents, which in this case means only one respondent. Investigator misconduct/fraud in Michigan would *not likely* influence 50% of category 1 respondents and would *very likely* influence 3% (again, only one respondent). Fraud in a local hospital would *not likely* influence 34% and would *very likely* influence 10% of category 1 respondents. Fraud committed by a consulting physician would *very likely* influence 80% of category 1 respondents and would *not likely* influence 7%. In sum, it appears that research fraud is *not likely* to influence most category 1 respondents, unless it is committed by the patient physician; research fraud by a patient physician is *very likely* to influence most of the category 1 respondents.

Graphical Presentation:

The graph presents the distribution of survey responses for each fraud location. The graphs were drawn between the percentages (%) of each category of respondents and their responses regarding the influence of investigator fraud.

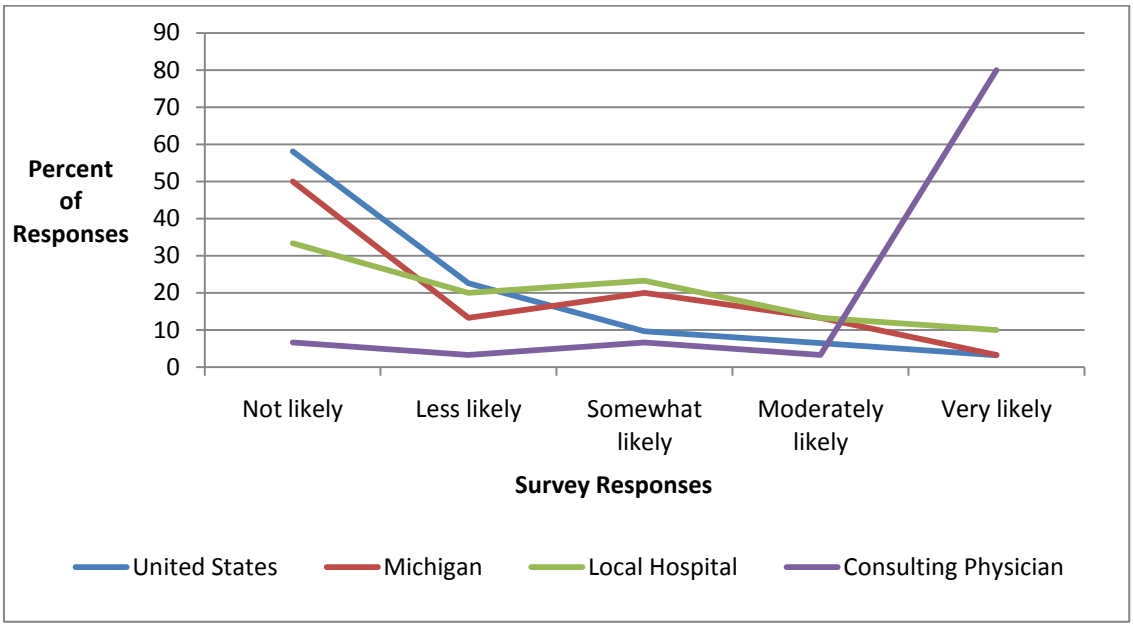

Figure 2 Extent of Fraud Influence on Decision to Participate for Category 1 ("With Experience") Participants by Location

Category 2 - "Would Participate"

The survey respondents who would consider participating in future clinical trials (category 2) account for 61% of total respondents. Investigator misconduct occurring somewhere in U.S. would *not likely* influence 40% of category 2 respondents, whereas 25% said fraud would *very likely* influence them. In cases of fraud in the state of Michigan and in a local hospital, category 2 respondents' answers differed. Fraud occurring in Michigan would *not likely* influences 30% of respondents, while 27% said it would *very likely* influence them, and 17%

said *less likely*. In contrast, fraud in a local hospital was *not likely* to influence 18%, *less likely* to influence 19%, *somewhat likely* to influence 15%, *moderately likely* to influence 26%, and *very likely* to influence 22% of respondents. Fraud by a patient physician was *very likely* to influence 82% of category 2 respondents and *moderately likely* to influence 6.4%. Fraud committed by a patient physician would *not likely* influence 5.3% of respondents. In sum, the majority of category 2 respondents said fraud committed by a patient physician would *very likely* influence them, while fraud somewhere in U.S. was *not likely* to influence them.

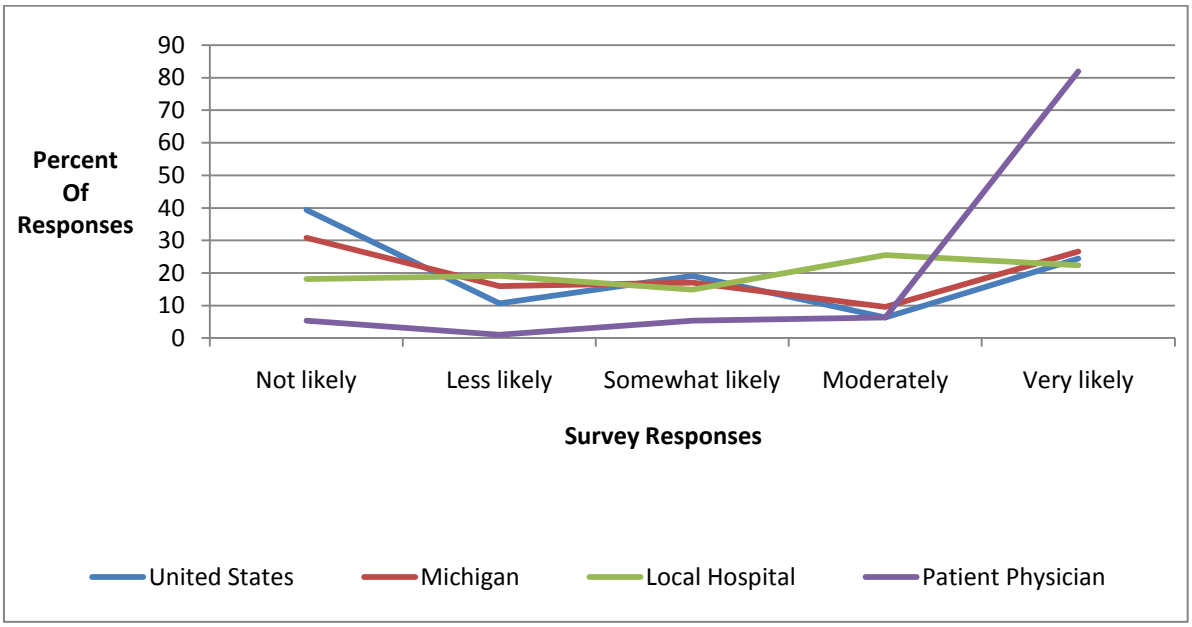

Figure 3 Extent of Fraud Influence on Decision to Participate for Category 2 ("Would Participate") Participants by Location

Comparing Means for Category 1 – "With Experience" and Category 2 – "Would Participate"

The above graphs indicate the distribution of investigator fraud influence based on the location of the fraud. However, the likelihood of investigator fraud influence on a respondent's decision to participate in clinical trials was determined by calculating the mean of each section of

response, since the extent to which investigator fraud influenced respondents changed in each case, depending on the location of the investigator or fraud.

Since these survey questions were designed and developed using a 1 (not likely to influence) to 5 (very likely to influence) Likert scale for responses, the mean for each question could be determined. Finally, the extent of investigator fraud influence in each of the four situations presented—somewhere in the U.S., in Michigan, in a local hospital, and by a consulting physician—was obtained. A graph drawn between category 1 and category 2, with these calculated mean values of fraud influence (with scale on Y-axis: 1-not likely, 2-less likely, 3-somewhat likely, 4-moderatelty likely and 5- very likely), gives an exact and final distribution of investigator fraud influence.

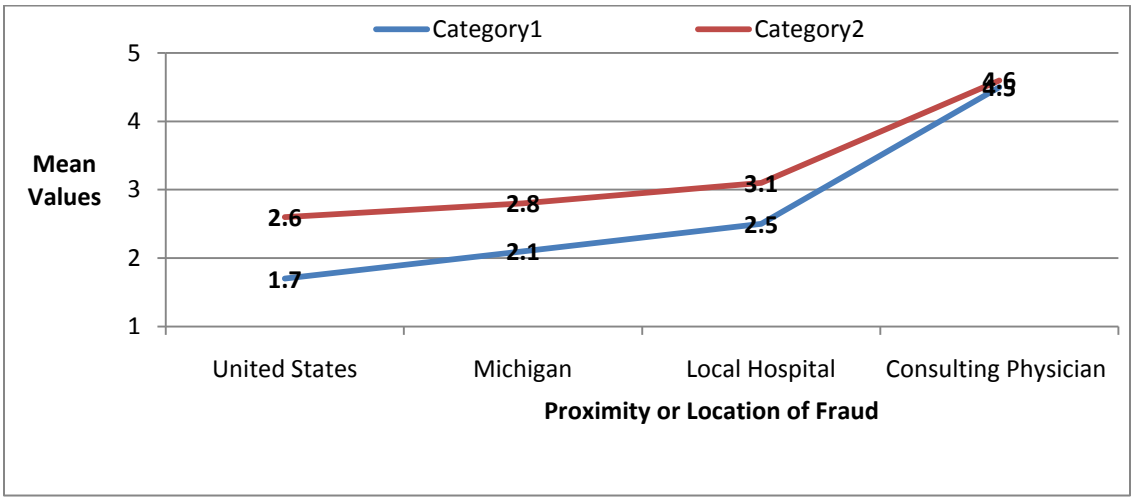

Figure 4 Mean values vs. Location of Fraud for Category 1 ("With Experience") and Category 2 ("Would Participate") Participants

Category 1 vs. Category 2

Of the 33 respondents who said fraud occurring somewhere in U.S. would *very likely* influence them, 70% were in Category 2. Of the 35 respondents who said fraud in Michigan would *very likely* influence them, 71.4% were respondents from Category 2. Likewise, of the 34 respondents who reported that fraud in a local hospital would *moderately* or *very likely* influence, the majorities were in Category 2. The Category 1 responses to cases involving fraud committed in Michigan or somewhere in the U.S were constant, differing in fraud cases occurring in a local hospital or involving a consulting physician.

Mean Fraud Extent for All Respondents

The mean values were calculated using the 1-not likely to 5-very likely scale. The graph drawn between mean values vs. locations of investigator fraud did not give a consistent increase in the slope, as expected in the hypothesis. However, from the graph it appears that the average likelihood of fraud influence gradually increased, the closer the proximity of the fraud.

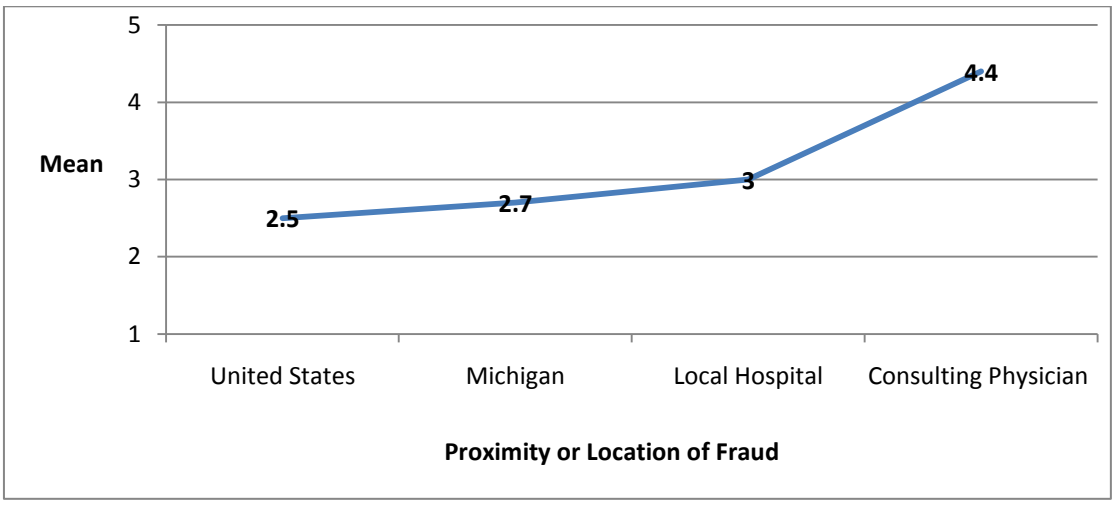

Figure 5 Mean Extent of Fraud Influence by Fraud Location

Chapter V: Summary of Findings

The participants in this survey research were faculty members at Eastern Michigan University. As stated in the methodology section, these faculty members included lecturers and adjuncts of Eastern Michigan University. This suggests that all of the respondents were well educated and held doctorates and/or master's degrees. In addition, the population was diverse, including faculty from all colleges within the university. The majority of respondents (81%) were age 41 and above, and 55% of this segment were over 50.

From the survey results, respondents considered physicians the most trustworthy source of health-related information, followed by health-specific Internet media (such as medical news sites and medical discussion forums), family and friends, and, finally, print media. Social networking media, on the other hand, was not selected by a single participant as a trusted source for health related information.

The majority of survey respondents stated that they would consider participating in other clinical trials, given the opportunity. Knowledge of fraud, irrespective of where it occurred, would discourage 25% of this group from participating in clinical trials. Therefore, it seems that knowledge of investigator fraud or misconduct, regardless of where it occurred, may *very likely* discourage the general public from participating in clinical trials. In addition, as investigator fraud occurs geographically closer to the respondents, they gradually grow less inclined to report that the fraud would *not likely* influence them. Of respondents who were interested in participating in clinical trials, 40% said that fraud occurring somewhere in U.S. would *not likely* influence them. The closer the geographic proximity of the fraud, the less often respondents reported that knowledge of the fraud would *not likely* influence them: 31% if the fraud occurred in Michigan, 18% if the fraud in occurred in a local hospital, and only 5% if their own physician

committed the fraud. Again, these values suggest that the location of a known instance of fraud affects respondents' willingness to participate in clinical trials. It is not geography, however, but the knowledge of fraud and of who committed it, that discouraged respondents from participating in clinical trials.

Wherever it may occur, research investigator fraud influences people's likelihood to participate in clinical trials. Those who have already participated in clinical trials were nearly consistent about their decision to participate, when they heard about the investigator fraud. The perceptions of those who had never before participated but would consider participating in future changed with any fraud knowledge and also changed rapidly with their investigator fraud. On the other hand, the results represented people's immediate reaction to learning of investigator fraud. But how long this fraud knowledge will have the public/participant attention was another important research question to consider. Hence, further studies are recommended to study the time of impact.

From the results outlined above, it appears that as the location of the investigator fraud approaches the location of the individual, its likelihood to influence that individual's decision to participate in clinical trials also increases. Therefore, we see the public's likelihood to participate in clinical trials decreasing. However, the differences among the averages were small in cases of fraud occurring somewhere in the United States, in Michigan, and in a local hospital. The influence of fraud in these three cases is mild compared to the last case—fraud committed by a patient physician. The influence of research investigator fraud or misconduct may depend on the location of the fraud, and this geographical impact is less compared with knowledge of fraud committed by a patient physician.

Chapter VI: Conclusion

Patient recruitment and retention is a constant challenge for clinical research organizations. To rise to this challenge, every organization must secure and maintain public trust and confidence in clinical research. The current results from this pilot study show that knowledge of investigator fraud has greater impact on the participant's perceptions than knowledge of where the fraud occurred.

The present findings address only a select group of highly educated members of the community. Further studies involving larger populations are recommended to learn more about clinical research investigator fraud and its influence on the public perception of clinical trials. In addition, further studies are necessary for developing and organizing new clinical awareness strategies, in order to earn back public trust and confidence in clinical trials. Additional data will also be necessary to extrapolate to other populations and to discover the transient nature of fraud impact on recruitment to studies.

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Appendix A: University Human Subject Review Committee (UHSRC) Approval Letter

EASTERN MICHIGAN UNIVERSITY
Education First

COLLEGE of HEALTH & HUMAN SERVICES
www.emich.edu/chhs

Dear Purnachandra Garimella,

After careful review, your proposal and revised consent form for ""Clinical Research Investigator Fraud": How Does it Influences Public Perception to Participate in Clinical Trials?" have been accepted by the College of Health and Human Services Human Subjects Review Committee. This approval extends over a period of one year from this date.

The current version of your paper is available here:
http://commons.emich.edu/cgi/preview.cgi?article=1038&context=chhs_hs

You may also view the referee reports and preview your material on that page. Should any revisions be required in the future,use the Revise Submission link on that page. Please include reference number 1038 on future inquiries or submissions.

Congratulations and best wishes in the completion of your investigation.

Sincerely,

Gretchen Dahl Reeves, PhD.
Chair, CHHS Human Subjects Review Committee

303 Marshall Building, Ypsilanti, MI 48197• 734.487.0077 • Fax: 734.487.8536

Appendix B: Informed Consent Form / Survey Email

Dear faculty member,

As a part of my master's thesis, I would like to request your participation in a survey research.

You have been selected by the Eastern Michigan University to complete this survey about research investigator (physician) fraud or misconduct in clinical trials. Participation in this study is completely voluntary and you may choose to quit the survey at any time. Please be assured that your answers are anonymous. No Individuals response to the survey will ever be identified in any report. All data will be compiled in the aggregate, and no individual respondents will be identified. This survey (six multiple choice questions) will take you approximately 5 to 10 minutes to complete. There is no known risk involved with your participation.

Web Survey-Link: https://umichumhs.qualtrics.com/SE/?SID=SV_0juiXIZXsmOL79O

By clicking on the **link above**, you are indicating your consent to participate in this survey. There is no direct benefit in your participation but your input is valued and I hope you will respond. If you have any questions or concerns about the study, I encourage you to contact Irwin Martin Ph.D., Associate Professor, College of Health and Human Services, Marshall Building, imartin2@emich.edu.

"This research protocol and informed consent document has been reviewed and approved by the Eastern Michigan University Human Subjects Review Committee for use from 10.17.2011 to 10.31.2011. If you have questions about the approval process, please contact Dr. Gretchen Dahl Reeves, PhD, Chair, CHHS Human Subject Review Committee at 734.487.0077"

Appendix C: Survey Questions

Case Scenario:

"You have a disease or condition.

You are being treated adequately, but improvement is possible.

You are informed of a clinical study of a new, but not yet approved drug."

Q-1: Have you ever had an "opportunity to participate" or to volunteer in any clinical study before?

- Yes. And, I agreed to participate in a clinical study
- Yes. But, I did not agree to participate
- No. I never had an opportunity. But, I would consider participating
- No. I never had an opportunity. And, I would not consider participating

Q- 2: Suppose that you learned that an investigator in "another part of the U.S." was involved in research misconduct*. To what extent would this misconduct influence your decision to participate in a clinical study conducted locally?

- Not likely
- Less likely
- Somewhat likely
- Moderately likely
- Very likely

**Misconduct may include actions such as falsification of data or improper consent of subjects*

Q- 3. Suppose that you learned that an investigator “from Michigan” was involved research misconduct*. To what extent would this misconduct influence your decision to participate in a clinical study conducted locally?

- Not likely
- Less likely
- Somewhat likely
- Moderately likely
- Very likely

**Misconduct may include actions such as falsification of data or improper consent of subjects*

Q- 4: Suppose that you learned that an investigator “from your local hospital” was involved in research misconduct*. To what extent would this misconduct influence your decision to participate in a clinical study conducted by ANOTHER investigator?

- Not likely
- Less likely
- Somewhat likely
- Moderately likely
- Very likely

**Misconduct may include actions such as falsification of data or improper consent of subjects*

Q- 5: Suppose that "your physician" was involved in research misconduct*. To what extent this would influence your decision to participate?

- Not likely
- Less likely
- Somewhat likely
- Moderately likely
- Very likely

**Misconduct may include actions such as falsification of data or improper consent of subjects*

Q-6: Demographic Questions:

Q-6a: What is your gender?

- Male - Female

Q-6b: What is your age?

- 21 to 30 - 31 to 40 - 41 to 50 - 51 and above

Q-6c: In which college do you teach or research primarily?

- College of Arts and Sciences
- College of Business
- College of Education
- College of Health and Human Services
- College of Technology
- Other (Please specify)

Q-6d: With respect to health related information, what are your trusted sources of information? (Check all that apply)

- Physicians (Surgeons or Doctors)
- Print media, e.g., newspapers, magazines
- Broadcasting media, e.g., television, movies, documentaries
- Social networking media, e.g., Facebook, MySpace, Twitter,
- General Internet media, e.g., news websites, discussion forums
- Health specific Internet media, e.g., medical news sites, medical discussion forums
- Friends and/ Family members
- Other (Please specify)

Appendix D: The Survey Population Profile

The Survey Population Profile by their Colleges (2011 data)

#	College	Faculty	Lecturers	Adjuncts	Total	%
1	College of Arts and Sciences	363	51	319	733	9.0%
2	College of Business	73	10	37	120	9.2%
3	College of Education	90	18	61	169	11.8%
4	College of Health and Human Services	89	13	118	220	15.0%
5	College of Technology	54	3	62	119	13.4%
6	Other	23	2	10	35	20%
	Total	**692**	**97**	**607**	**1396**	

% means, the survey response rate with respect to each college

(Source: Institutional Research and Information Management (IRIM), EMU)