Meeting the Challenges: Bringing Evidence-Based Treatment to the Pregnant Patient

Anna R. Brandon, PhD, MSCS, ABPP

Clinical Assistant Professor

University of North Carolina at Chapel Hill

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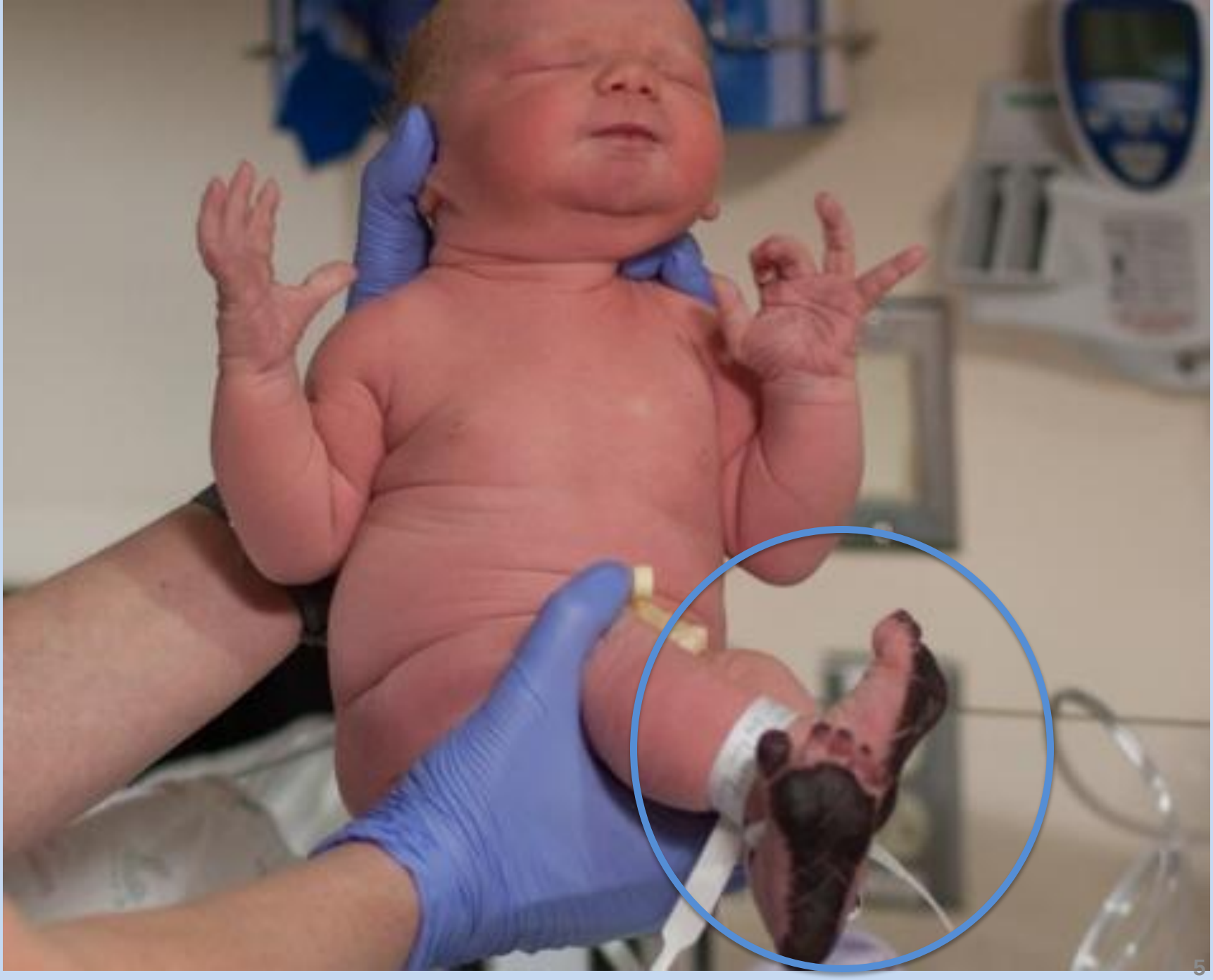
Where the skies are…



There’s no place like home

Still interested in this problem:

- More than 500,000 women annually suffer with a psychiatric illness predating or with onset during pregnancy
- More than a third take psychiatric medications during pregnancy
- None of these are approved by the FDA for use during pregnancy

ACOG Practice Bulletin, 2008

Objectives Today

- Identify the key themes of ethical concern
- Explore the beliefs and experiences of those "in the trenches"
- Discuss appropriate points of emphasis in informed consent processes
- Report the willingness of pregnant women to be randomized

Current Issues

- Nearly half of all prenatal women reported the use of one or more medications during their pregnancy
- Approximately half of all pregnancies are unintended, with unintended fetal exposure to substances in the first trimester
- Untreated or undertreated diseases have fetal consequences too

Cooper et al, 2007; Lorenzo et al, 2011

We Do Have:

- Observational and descriptive studies
- International pregnancy registries
- A growing cadre of researchers who regularly communicate
- Conferences and organizations

But there are few RCTs

- Still considered the “gold standard”
- Essential in areas of equipoise?
- Diseases like perinatal depression less appropriate for “no treatment” or “wait-list” control groups

Study One

University of Texas Southwestern Medical Center

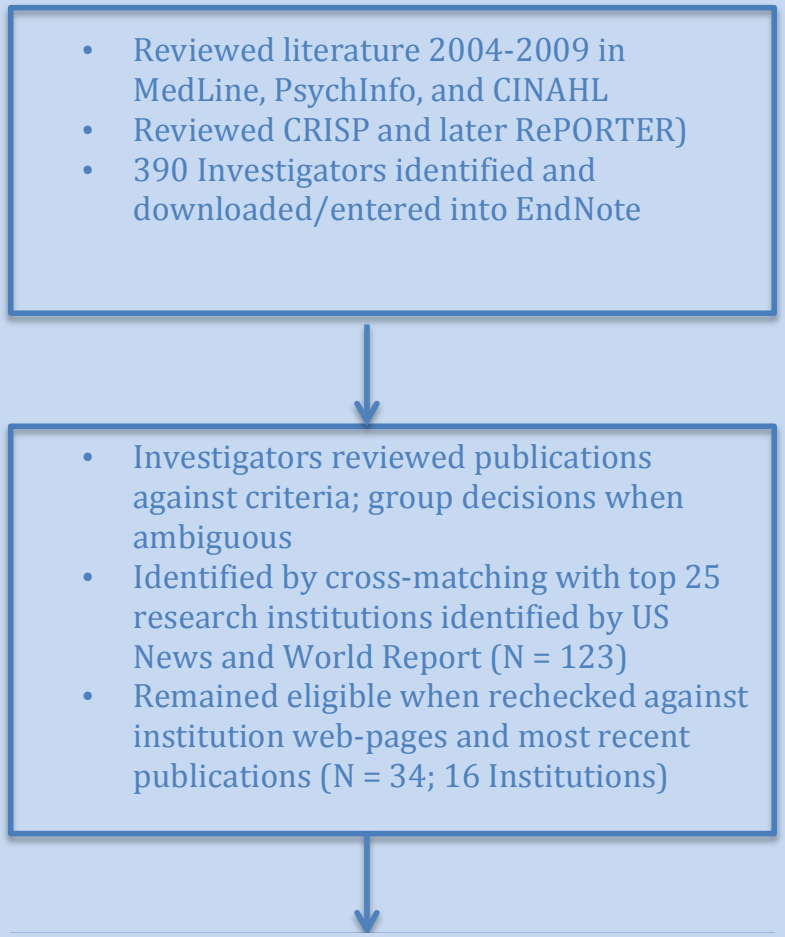
Geetha Shivakumar, MD
Stephen Inrig, PhD
Simon Craddock Lee, PhD
Nadia Ceccotti, PhD
John Sadler, MD

Study One: Specific Aims

- Identify the ethical issues faced by investigators and IRB administrators in practice of perinatal mental health research
- Compare and contrast the viewpoints
- Catalogue the range of issues
- Present a reconciliation of pluralistic views

Study One: Research Design

Qualitative Analysis


• Reviewed literature 2004-2009 in MedLine, PsychInfo, and CINAHL
• Reviewed CRISP and later RePORTER)
• 390 Investigators identified and downloaded/entered into EndNote
• Investigators reviewed publications against criteria; group decisions when ambiguous
• Identified by cross-matching with top 25 research institutions identified by US News and World Report (N = 123)
• Remained eligible when rechecked against institution web-pages and most recent publications (N = 34; 16 Institutions)

- Participated in first instrument refinement interviews (N = 2)
- Participated after first email invitation describing study and requesting interview (N = 3)
- Participated after first conference presentation (N = 10)
- Declined/no longer qualify (N = 7)
- No response (N = 12)
- Total = 15 Investigators from 12 Institutions

- Twelve Institutional IRBs contacted
- Participated after first contact (N = 2)
- Participated after CTSA referral (N = 4)
- No response (N = 6)

IRB Representatives	N (%)
Gender	
	Male 0 (0.0)
	Female 6 (100.0)
Credentials	
	JD 2 (33.3)
	MD 2 (33.3)
	PhD 1 (16.7)
	MS 1 (16.7)
Open Protocols with Perinatal Participants	
	Yes 5 (83.3)
	No Knowledge 1 (16.7)
Areas of past/current research*	
	Pharmacology 4 (66.6)
	Psychotherapy 4 (66.6)
	Complementary/Alternative 3 (50.0)
Types of Research Designs Reviewed*	
	Clinical Trials 4 (66.6)
	Observational Studies 3 (50.0)
	Pharmacokinetic Studies 3 (50.0)
	Safety trials 1 (16.7)
	Psychotherapy/behavioral 4 (66.6)
Approximate Years Reviewing Perinatal Protocols	
	Unknown 2 (33.3)
	Median: 13.5 4 (66.6)
	Range: 5.5-15
Academic rank	
	Associate Professor 2 (33.3)
	Assistant Professor 1 (16.7)
	No Appointment 3 (50.0)
Participating in Protocol Reviews	
	Routinely 4 (66.6)
	Occasionally 2 (33.3)

Clinical Investigators	N (%)
Gender	
	†Male 1 (6.6)
	Female 14 (93.3)
Credentials	
	MD 7 (46.7)
	MD, MPH 1 (06.7)
	MD, MS 1 (06.7)
	PhD 4 (26.6)
	PhD, MS 1 (06.7)
	PhD, MSW 1 (06.7)
Open Perinatal Protocols	
	Yes 13 (86.6)
	No 2 (13.3)
Areas of research*	
	Pharmacology 8 (53.3)
	Psychotherapy 9 (60.0)
	Complementary/Alternative 8 (53.3)
Research designs*	
	Clinical Trials 12 (80.0)
	Observational Studies 9 (60.0)
	Pharmacokinetic Studies 4 (26.6)
	Safety trials 3 (20.0)
	Psychotherapy/behavioral 9 (60.0)
	Other 5 (33.3)
Years in research	
	m = 11.56, *sd* = 5.46; range (years) = 3.5-23 15 (100%)
Academic rank	
	Professor 5 (33.3%)
	Associate Professor 6 (40.0%)
	Assistant Professor 3 (20.0%)
	Lecturer 1 (06.7%)
IRB Participation	
	Yes 4 (26.6)
	No 9 (60.0)
	Unknown 2 (13.3)

Data Analysis

- Interviews audio-recorded and transcribed
- Entered into Nvivo software
- Answers coded then analyzed for themes
- Study team cross-compared themes, consolidating into four themes and fifteen subthemes

Major Theme 1

Study Design/Methodology

- Use of Placebo
- Use of Comparison Groups
- What is “Standard of Care”

Major Theme 2

Safety Concerns

- Risk to mother of untreated disease
- Risk to fetus of treatment
- Determining minimal risk to fetus
- Risk of using psychosocial treatments in Axis I illness
- Differentiating Congenital from Developmental teratogenic risks

Major Theme 3

Participant selection and recruitment

- Exclusions based upon disease severity
- Blurred boundary between clinical care and research

Major Theme 4

Autonomy

- Clear and understandable consent forms
- Maternal competency and comprehension
- Status of paternal consent
- “Double” vulnerable populations
- Confidentiality

	First		Second		Third	
***Respondents**	**PCI** N=15	**IRB** N=5	**PCI** N=14	**IRB** N=5	**PCI** N=12	**IRB** N=5
Safety	**7**	**1**	**6**	**2**	**1**	**2**
Total	**46.6%**	**16.6%**	**42.8%**	**40.0%**	**8.3%**	**40.0%**
Fetal	4	1	1		1	
Maternal	3		3	1		2
Maternal/fetal unit			2	1		
Research Design	**4**	**1**	**3**	**2**	**3**	**2**
Total	**26.7%**	**16.6%**	**21.4%**	**40.0%**	**25%**	**40.0%**
Placebo/comparison groups	2		2	2	3	1
Randomization	1	1	1			
Standard of care						
Cross-sectional vs. longitudinal	1					
Undefined						1
Participant Selection/Recruitment	**2**				**2**	
Total	**13.3%**				**16.7%**	
Severity of illness	1					
Underage mothers	1					
Inclusion/exclusion criteria					1	
Women in poverty					1	
Autonomy	**2**	**3**	**2**	**1**	**2**	**1**
Total	**13.3%**	**60.0%**	**14.3%**	**16.6%**	**16.7%**	**16.6%**
Informed consent	2	2	1	1		
Conflicts of interest		1	1			
Vulnerability status					1	1
Privacy/confidentiality					1	
Other Concerns			**3**		**4**	
Total			**60.0%**		**33%**	
Split in field (Pharm vs. non-pharm)			1			
Stigma			2			
IRB “issues”					1	
Minimal patient collaboration					1	
Lack of attention to family context					1	
No accommodations for minimal risk					1	

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§ 46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ 46.121 [Reserved]

§ 46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§ 46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§ 46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B — Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§ 46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at § 46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of § 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in § 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Definitions.

The definitions in § 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§ 46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§ 46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater

Of the 10 criteria investigators must fulfill in research including pregnant women, 4 involve the informed consent process:

- Must obtain informed consent
- Must include full disclosure regarding the foreseeable impact on fetus or neonate
- If research is to benefit the fetus and father is available and competent, must include his consent
- Pregnant minors are to give assent

Double Whammy: Pregnant and Depressed

① Able to comprehend the risks of participation?

② Competent decision makers?

③ Full disclosure by investigators?

STUDY TWO

University of North Carolina at Chapel Hill

Rebecca Siegel, PhD

Anne Drapkin Lyerly, MD

Study Two: Specific Aims

- Test comprehension of the basic elements of informed consent
- Test delivery and interest in an audio/visual enhancement to the informed consent process
- Compare levels of comprehension
- Inquire about willingness to participate

Study Two: Research Design

Randomized Trial

- Standard process of consent (SP; N = 20)
- Process enhanced by audio/visual presentation covering the proposed study (EC; N = 20)

Study Two: Participants

- 40 pregnant women in waiting areas of UNC OB/Gyn clinics
- Partners included when present
- Exposed to a “pretend” study

Expert in the Field

Research Coordinator

Participant (Actress)

Definitions

"Randomization" means:

The treatment of the individual patient is decided by chance

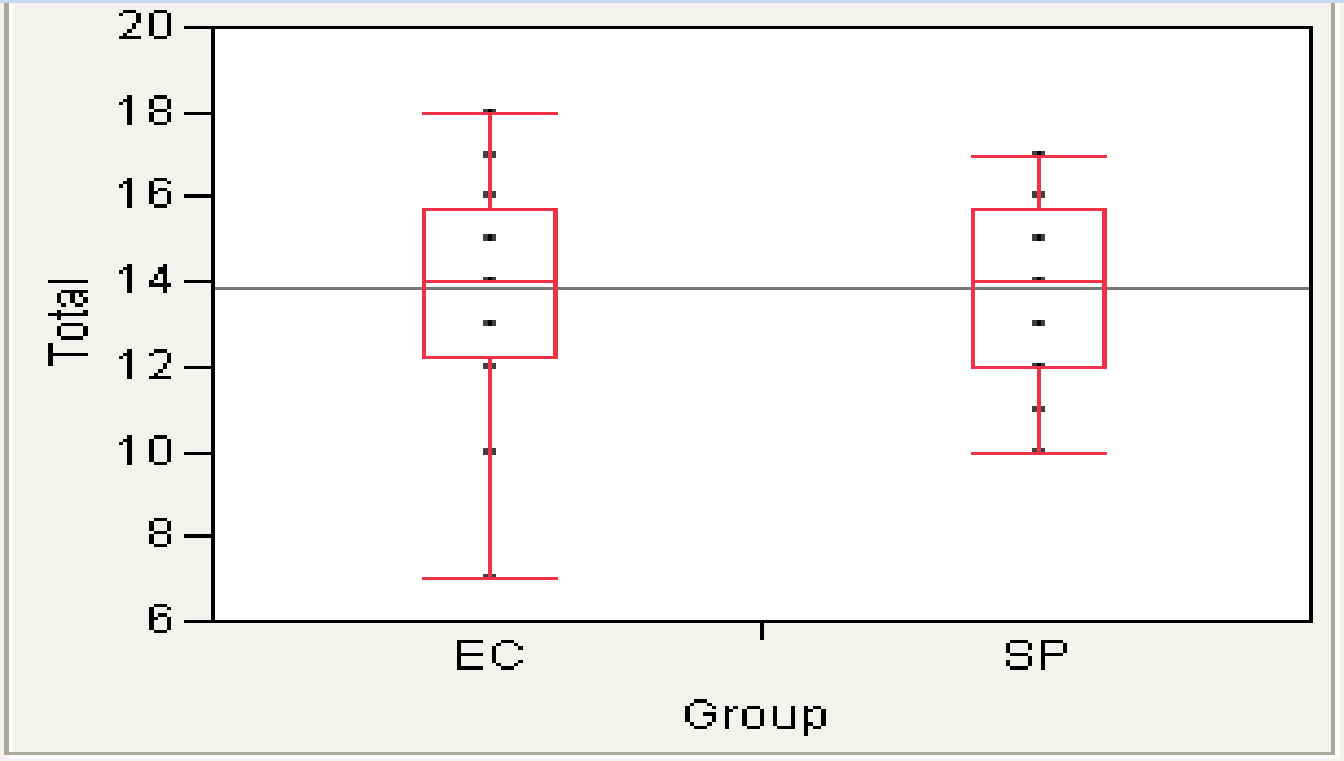
Illustrations

Principal Investigator

SPECIFIC AIM ONE:

TEST COMPREHENSION OF THE BASIC ELEMENTS OF INFORMED CONSENT

Comprehension by Group



EC = ENHANCED CONSENT SP = STANDARD PROCESS OF CONSENT

EC: *n* = 20, *m* = 13.65, sd = 3.25
SP: *n* = 20, *m* = 13.70, *sd* = 2.23

p = 0.995

Question	TOTAL
	%
1. The main reason for carrying out research…	90.00
2. Research is only carried out when…	82.50
3. In a randomized clinical research trial treatment is…	87.50
4. The main aim of a randomized trial is to…	92.50
5. When a study is randomized…	95.00
6. It is OK for doctors to carry out a randomized study when…	72.50
7. In this study women will be randomized to…	87.50
8. Babies of mothers who take antidepressants during pregnancy…	47.50
9. As far as we know psychotherapy effects upon fetus…	55.00
10. Patients are chosen for this study if…	85.00
11. Taking part in this study means…	100.00
12. Women in the antidepressant group will come to the clinic…	72.50
13. Women in the Partner-Assisted Therapy group will see their therapist…	50.00
14. You can leave the study if/when…	95.00
15. If you do not want to take part in the study you can…	65.00
16. In research, pregnant women are considered…	57.50
17. Research done so far has found…	85.00
18. Women who are in this study may/may not get/be…	62.50

Adapted from Hutchison, 2007

TEST DELIVERY AND INTEREST IN AN AUDIO/VISUAL ENHANCEMENT TO THE INFORMED CONSENT PROCESS

Two-sample t-test $p = 0.598$

Outcome Measures

Did this information...

	Not at all	A little	Somewhat	Quite a bit	A great deal
Help you understand the decision about participating in the study?	○	○	○	○	○
Prepare you to make a decision to participate or not participate?	○	○	○	○	○
Help you think about the risks and the benefits of being in the study?	○	○	○	○	○
Help you organize your thoughts about what being in the study would mean?	○	○	○	○	○
Help you identify any questions you want to ask?	○	○	○	○	○
Interest you?	○	○	○	○	○
Bore you?	○	○	○	○	○
Irritate you?	○	○	○	○	○
Waste your time?	○	○	○	○	○
Make you want to know more about research with pregnant women?	○	○	○	○	○

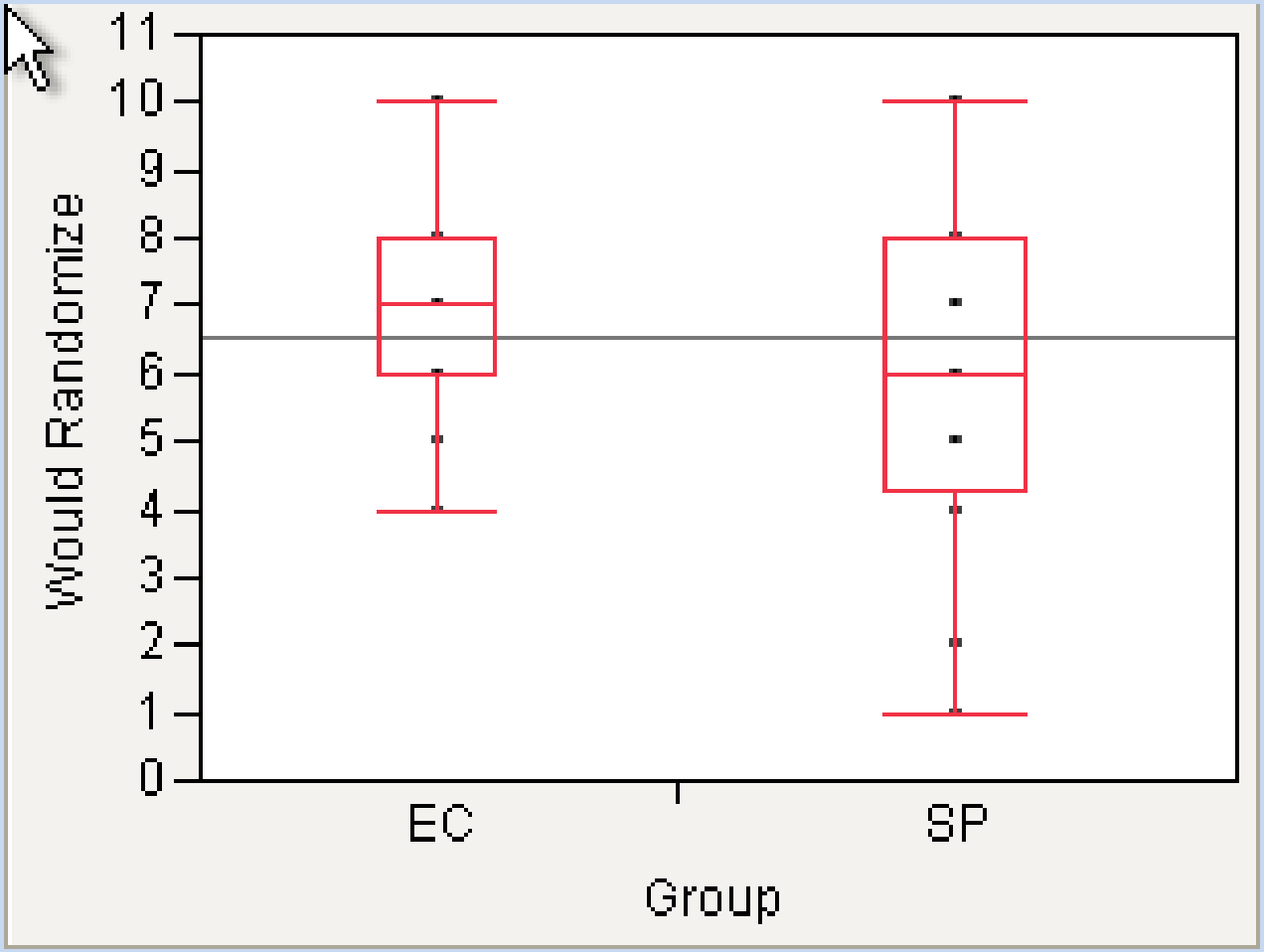
P < 0.0001

SPECIFIC AIM THREE:
INQUIRE ABOUT WILLINGNESS TO PARTICIPATE

Three Questions

Wouldn't Participate | **Not Sure** | **Would Participate**

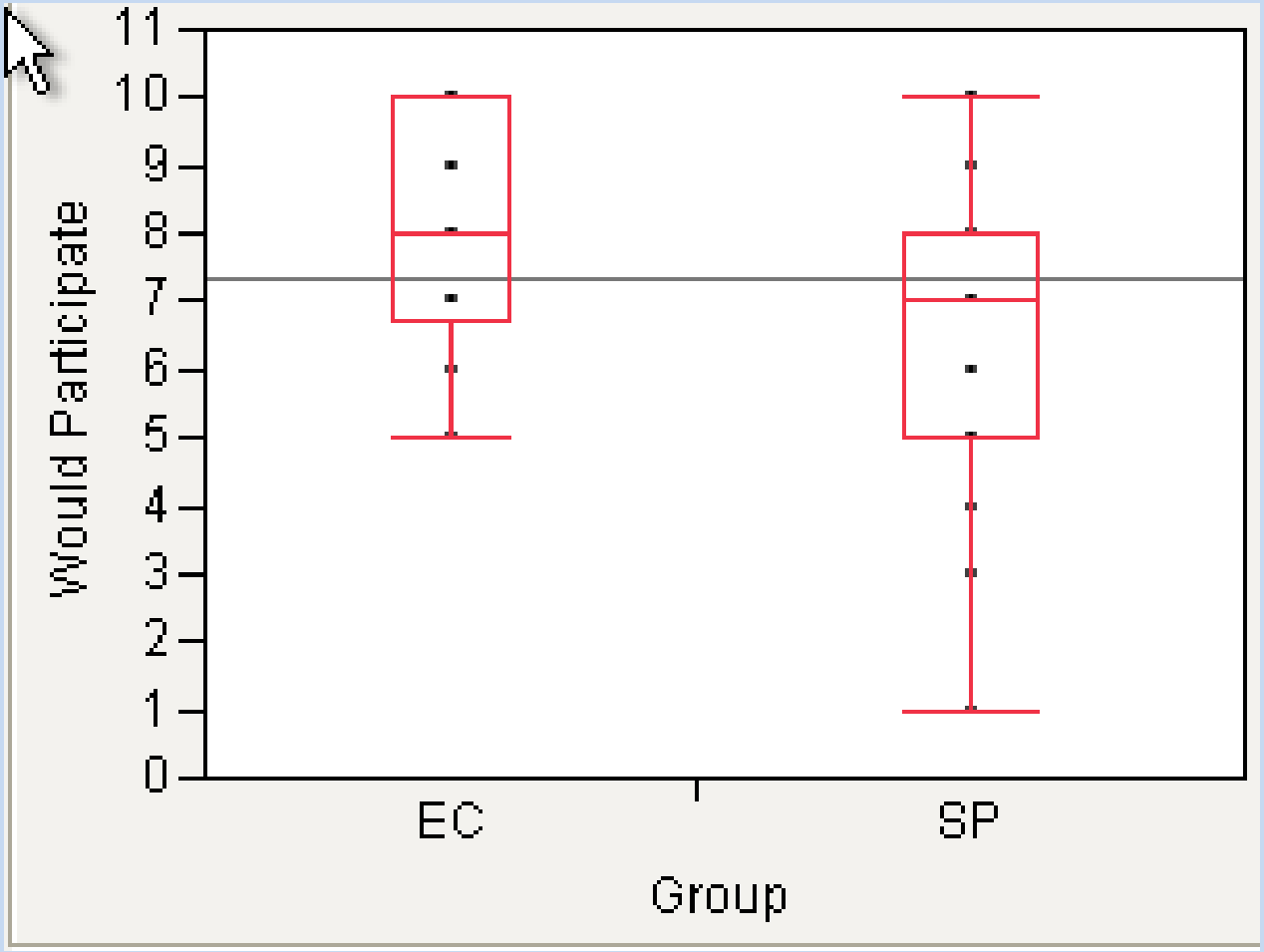
Willingness to be randomized…



EC (n=18): *m* = 7.22, *sd* = 1.66
SP (n=20): *m* = 6, *sd* = 2.49

p = 0.087

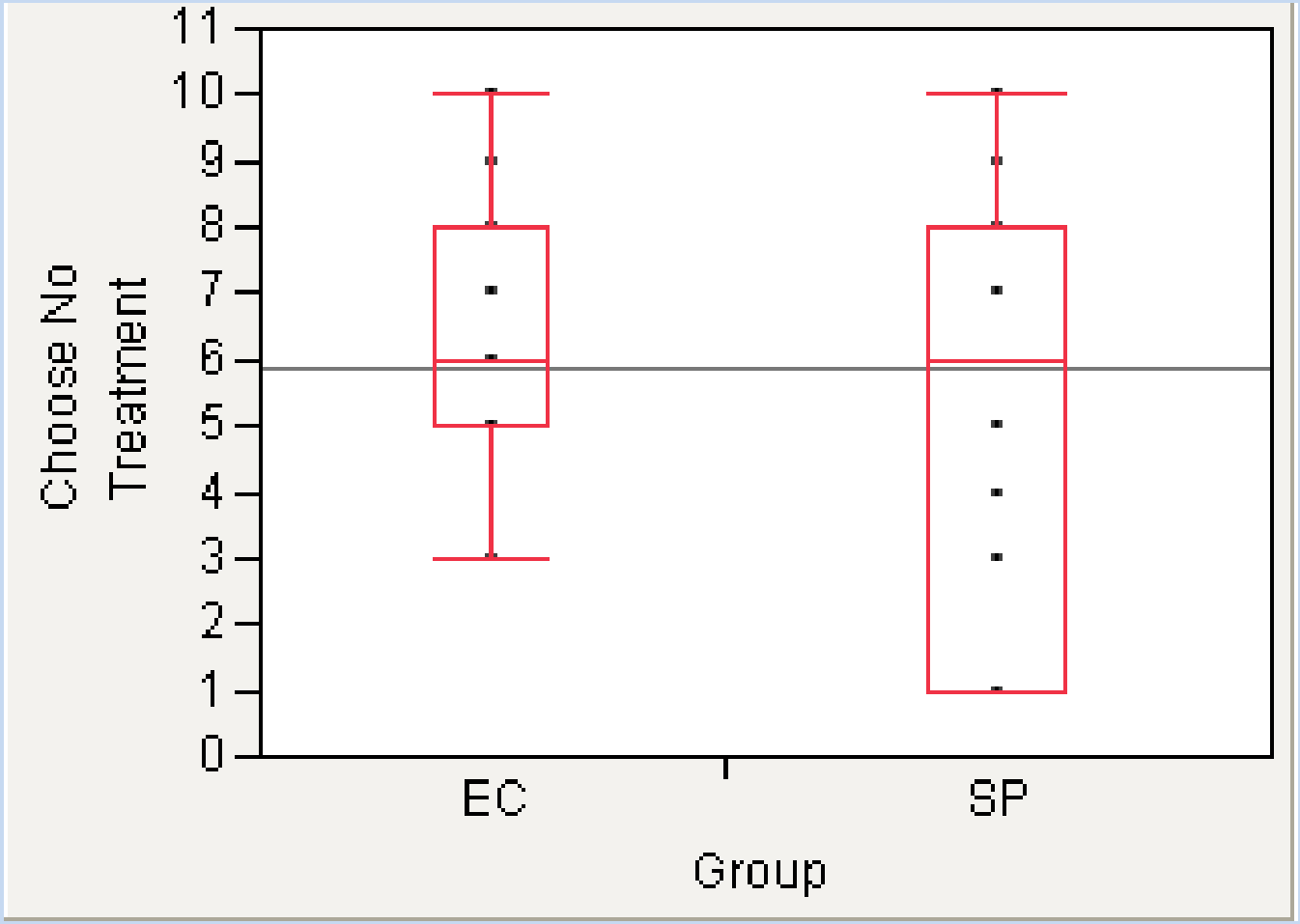
Would Participate with No Randomization



EC (n = 19): *m* = 8.00, *sd* = 1.795
SP (n = 20): *m* = 6.6, *sd* = 2.46

$p < 0.05$*

Would Choose No Treatment



EC (n = 18): *m* = 6.66, *sd* = 1.878
SP (n = 20): *m* = 5.15, *sd* = 3.407

p = 0.095

Limitations

- Hectic environments
- Gathered no demographic or clinical characteristics
- Representative of UNC public clinics but may not be generalizable to other communities
- Small sample

Implications

- Is it all about about comprehension?
- Diversity in learning styles?
- Does seeing/meeting the Principal Investigator affect the decision to participate?

Study Three: Specific Aims

- What are the public beliefs about perinatal research?
- What is the public understanding of randomization and placebos?
- What is the public judgment about pregnant women and medication research?

Study Three: Research Design

Descriptive Survey Study

- Consent implicit by participation
- English and Spanish
- Web-based

Study Three: Participants

- Webpage visitors:

http://www.mededppd.org

- Word of mouth:

English:
https://unc.qualtrics.com/SE/?SID=SV_3qvlW3os9JfVUKE

Spanish:
https://unc.qualtrics.com/SE/?SID=SV_6Sg1ICk0lCwI5IV

Thank You!

anna_brandon@med.unc.edu