## S1 Appendix. CTTI pregnancy testing in clinical trials project survey.

Firs	First, we would like to ask a couple of background questions about you.				
Wh	nich of the following best describes your organization? Please check all that apply.				
	Academic Medical Center  Non-academic Clinical Research Site  Clinical Research Organization  Institutional Review Board  Industry  Government (FDA, NIH, VA)  Other, please specify				
If a	pplicable, which do you consider your PRIMARY area of clinical experience/expertise?				
O	Women's health/obstetrics & gynecology				
O	Family medicine				
$\mathbf{O}$	Internal medicine (including subspecialties)				
$\mathbf{O}$	Surgery (including subspecialties)				
$\mathbf{O}$	Neurology/psychiatry				
$\mathbf{O}$	Nursing				
$\mathbf{O}$	Pharmacology or pharmacy				
O	Other, please specify				

Before continuing on to the main part of the survey, we would like to provide you some background.

The main purpose of pregnancy testing as part of a clinical research protocol is to minimize risk to an embryo or fetus from exposure to potentially harmful study interventions. The specific goal of testing may be to prevent exposure completely (by testing prior to any study interventions), or to minimize the duration of exposure during early pregnancy (by periodic testing during the study).

The negative predictive value (NPV) of a particular pregnancy testing protocol is the probability that a negative test result in a given patient population represents a true negative pregnancy test. The higher the negative predictive value of the pregnancy testing protocol, the less likely a false negative pregnancy test result will occur and in turn, the less likely a prolonged unintended exposure of the study intervention to the embryo or fetus will occur.

The NPV of any pregnancy testing protocol is a function of the subject's baseline probability of pregnancy (primarily related to age) and contraceptive method. (For purposes of this survey, the term "highly effective contraception" refers to methods that, when used consistently and correctly, have a failure rate <1 per 100 woman-years. Examples include male or female sterilization, long-acting reversible contraceptives such as hormonal implants or intrauterine devices, or the combination of oral contraceptives and barrier methods). Negative predictive value is also affected by the following factors:

- The sensitivity of the assay used to detect human chorionic gonadotropin (hCG)
  - Serum tests are able to detect lower levels of hCG than urine tests
- The timing of the assay relative to when a pregnancy started
  - Neither serum nor urine tests will be positive if performed prior to implantation in the cycle in which a subject becomes pregnant

Different choices of tests (urine or serum assays), timing of tests relative to expected menses, and frequency of testing may result in different negative predictive values in different subject populations. Conversely, in a given population, there may be several potential testing protocols that result in similar negative predictive values, but have different implications in terms of potential burden on the subject, burden on the study team, and testing costs.

For the following questions, we will describe a clinical study scenario and ask you a series of questions about the acceptable risk of an unintended fetal exposure to a drug, the importance of several factors going into clinical study design, and the type of pregnancy testing protocol that you would recommend.

required to use two methods of highly effective contraception.
Would you recommend excluding pregnant women from this study?
O Yes
O No
If No Is Selected, Then Skip to End of Block
Please answer some additional questions about the previous scenario, restated below
A Phase III study of a new analog of thalidomide (a drug known to be associated with a very high risk of birth defects). Study drug is administered for 12 months. Assume that all subjects are required to use two methods of highly effective contraception.
In your opinion, what is the acceptable risk of a false negative pregnancy test resulting in exposure to study drug to the embryo or fetus?

Less than 1 in 100,000 (0.001%)
 Less than 1 in 10,000 (0.01%)
 Less than 1 in 1,000 (0.1%)
 Less than 1 in 100 (1.0%)

Scenario: A Phase III study of a new analog of thalidomide (a drug known to be associated with a very high risk of birth defects). Study drug is administered for 12 months. Assume that all subjects are

	Not important at all	Not very important	Moderately important	Very important	Extremely important
Negative predictive value (minimizing false negatives)	0	•	•	•	0
Burden on subjects	•	•	•	•	0
Burden on study team	•	•	•	•	O
Testing Costs	<b>O</b>	•	•	•	O

For	this scenario, which type of pregnancy test would you recommend using? (Choose 1)
O	Serum hCG performed in lab
$\mathbf{O}$	Urine hCG performed in lab
$\mathbf{O}$	Point of care urine hCG performed by study personnel
$\mathbf{O}$	Home test performed by patient
For	this scenario, how do you recommend scheduling the pregnancy test(s)? (Choose 1)
O	Whenever convenient for subject
0	Timed to expected menses

A Phase III study of a new analog of thalidomide (a drug known to be associated with a very high risk of birth defects). Study drug is administered for 12 months. Assume that all subjects are required to use two methods of highly effective contraception.

	this scenario, at which study time points do you recommend a pregnancy test be formed? (Choose 1)
O	Before study only Before and during study Before, during, and after study exposure completed
The	e final two questions on this page are only shown if applicable to the answer above.
Pri	or to study drug administration, when do you recommend testing for pregnancy? (Choose 1)
O	At screening visit Immediately before administering study drug At screening visit and immediately before administering study drug
Но	w often do you recommend testing for pregnancy during the study?
О О	Every month  Every other month  Every three months  Other (Please Specify)
	w long after study exposure is completed do you recommend continuing to perform pregnancy ting?
O O O	1 month 2 months 3 months 6 months 12 months

Scenario: A Phase III study of a new indication for a currently marketed drug administered for 6 months, currently classified as Pregnancy Category C (the relative risks and benefits in humans are unknown, because of positive data in animals only, no human data, or no data at all). Assume subjects are using a highly effective method of contraception as specified by the protocol.

Would you recommend excluding pregnant women from this study?
O Yes O No
If No Is Selected, Then Skip to End of Block
Please answer some additional questions about the previous scenario, restated below
A Phase III study of a new indication for a currently marketed drug administered for 6 months, currently classified as Pregnancy Category C (the relative risks and benefits in humans are unknown, because of positive data in animals only, no human data, or no data at all). Assume subjects are using a highly effective method of contraception as specified by the protocol.
In your opinion, what is the acceptable risk of a false negative pregnancy test resulting in exposure to study drug to the embryo or fetus?
<ul> <li>Less than 1 in 100,000 (0.001%)</li> <li>Less than 1 in 10,000 (0.01%)</li> <li>Less than 1 in 1,000 (0.1%)</li> <li>Less than 1 in 100 (1.0%)</li> </ul>

	Not important at all	Not very important	Moderately important	Very important	Extremely important
Negative predictive value (minimizing false negatives)	0	•	•	0	•
Burden on subjects	•	•	•	•	0
Burden on study team	•	•	•	•	0
Testing Costs	O	•	•	<b>O</b>	O

FOI	this scenario, which type of pregnancy test would you recommend using? (Choose 1)
O	Serum hCG performed in lab
$\mathbf{O}$	Urine hCG performed in lab
$\mathbf{O}$	Point of care urine hCG performed by study personnel
$\mathbf{O}$	Home test performed by patient
For	this scenario, how do you recommend scheduling the pregnancy test(s)? (Choose 1)
O	Whenever convenient for subject
$\mathbf{O}$	Timed to expected menses

A Phase III study of a new indication for a currently marketed drug administered for 6 months, currently classified as Pregnancy Category C (the relative risks and benefits in humans are unknown, because of positive data in animals only, no human data, or no data at all). Assume subjects are using a highly effective method of contraception as specified by the protocol.

	this scenario, at which study time points do you recommend a pregnancy test be formed? (Choose 1)
O	Before study only
O	Before and during study
0	Before, during, and after study exposure completed
The	e final two questions on this page are only shown if applicable to the answer above.
Prio	or to study drug administration, when do you recommend testing for pregnancy? (Choose 1)
O	At screening visit
$\mathbf{C}$	Immediately before administering study drug
O	At screening visit and immediately before administering study drug
Ho	w often do you recommend testing for pregnancy during the study?
O	Every month
O	Every other month
	Every three months
O	Other (Please Specify)
	w long after study exposure is completed do you recommend continuing to perform pregnancy
tes	ting?
O	1 month
O	2 months
	3 months
	6 months
O	12 months

Scenario: A 1 month Phase II study of a new intravenous antiemetic agent for prevention of postoperative nausea and vomiting, where exposure is limited to the perioperative period, drug elimination half-life is 6 hours, and preclinical studies show no signs of reproductive toxicity. Assume subjects are using a highly effective method of contraception as specified by the protocol.

Wo	ould you recommend excluding pregnant women from this study?
O	Yes
O	No
If N	lo Is Selected, Then Skip to End of Block
Ple	ase answer some additional questions about the previous scenario, restated below
and and	month Phase II study of a new intravenous antiemetic agent for prevention of postoperative nausead vomiting, where exposure is limited to the perioperative period, drug elimination half-life is 6 hours, depreclinical studies show no signs of reproductive toxicity. Assume subjects are using a highly ective method of contraception as specified by the protocol.
	your opinion, what is the acceptable risk of a false negative pregnancy test resulting in exposure to dy drug to the embryo or fetus?
O	Less than 1 in 100,000 (0.001%)
O	Less than 1 in 10,000 (0.01%)
O	Less than 1 in 1,000 (0.1%)
$\mathbf{O}$	Less than 1 in 100 (1.0%)

	Not important at all	Not very important	Moderately important	Very important	Extremely important
Negative predictive value (minimizing false negatives)	0	•	•	•	0
Burden on subjects	•	•	•	•	0
Burden on study team	•	•	•	•	O
Testing Costs	<b>O</b>	•	•	•	O

For	this scenario, which type of pregnancy test would you recommend using? (Choose 1)
O	Serum hCG performed in lab
O	Urine hCG performed in lab
O	Point of care urine hCG performed by study personnel
0	Home test performed by patient
For	this scenario, how do you recommend scheduling the pregnancy test(s)? (Choose 1)
O	Whenever convenient for subject
O	Timed to expected menses

A 1 month Phase II study of a new intravenous antiemetic agent for prevention of postoperative nausea and vomiting, where exposure is limited to the perioperative period, drug elimination half-life is 6 hours, and preclinical studies show no signs of reproductive toxicity. Assume subjects are using a highly effective method of contraception as specified by the protocol.

For this scenario, at which study time points do you recommend a pregnancy test be performed? (Choose 1)					
O	Before study only Before and during study Before, during, and after study exposure completed				
The	e final two questions on this page are only shown if applicable to the answer above.				
Prio	or to study drug administration, when do you recommend testing for pregnancy? (Choose 1)				
O	At screening visit Immediately before administering study drug At screening visit and immediately before administering study drug				
Ηο	w often do you recommend testing for pregnancy during the study?				
<b>O</b>	Every month  Every other month  Every three months  Other (Please Specify)				
How long after study exposure is completed do you recommend continuing to perform pregnancy testing?					
O O O	1 month 2 months 3 months 6 months 12 months				

of contraception as specified by the protocol.
Would you recommend excluding pregnant women from this study?
O Yes O No
If No Is Selected, Then Skip to End of Block
Please answer some additional questions about the previous scenario, restated below
A Phase I study of a new chemotherapeutic agent in an advanced cancer patient population. The agent is administered once weekly for 4 weeks. Assume subjects are using a highly effective method of contraception as specified by the protocol.
In your opinion, what is the acceptable risk of a false negative pregnancy test resulting in exposure to study drug to the embryo or fetus?
O Less than 1 in 100,000 (0.001%)
O Less than 1 in 10,000 (0.01%)
O Less than 1 in 1,000 (0.1%)

O Less than 1 in 100 (1.0%)

Scenario: A Phase I study of a new chemotherapeutic agent in an advanced cancer patient population. The agent is administered once weekly for 4 weeks. Assume subjects are using a highly effective method

	Not important at all	Not very important	Moderately important	Very important	Extremely important
Negative predictive value (minimizing false negatives)	0	•	•	•	0
Burden on subjects	•	•	•	•	0
Burden on study team	•	•	•	•	O
Testing Costs	<b>O</b>	•	•	•	O

For	this scenario, which type of pregnancy test would you recommend using? (Choose 1)
0	Serum hCG performed in lab Urine hCG performed in lab Point of care urine hCG performed by study personnel
	Home test performed by patient
For	this scenario, how do you recommend scheduling the pregnancy test(s)? (Choose 1)
O	Whenever convenient for subject
$\mathbf{C}$	Timed to expected menses

A Phase I study of a new chemotherapeutic agent in an advanced cancer patient population. The agent is administered once weekly for 4 weeks. Assume subjects are using a highly effective method of contraception as specified by the protocol.

For this scenario, at which study time points do you recommend a pregnancy test be performed? (Choose 1)					
O	Before study only Before and during study Before, during, and after study exposure completed				
Pri	or to study drug administration, when do you recommend testing for pregnancy? (Choose 1)				
O	At screening visit				
$\mathbf{O}$	Immediately before administering study drug				
0	At screening visit and immediately before administering study drug				
Но	w often do you recommend testing for pregnancy during the study?				
O	Every month				
O	Every other month				
	Every three months				
0	Other (Please Specify)				
	How long after study exposure is completed do you recommend continuing to perform pregnancy testing?				
O	1 month				
0	2 months				
	3 months				
	6 months				
0	12 months				

Scenario: A Phase II study of a new chemical entity, with no worrisome preclinical data on reproductive
toxicity. Study drug is administered for 6 months. Assume subjects are using a highly effective method
of contraception as specified by the protocol.

Would you recommend excluding pregnant women from this study?				
O Yes O No				
If No Is Selected, Then Skip to End of Block				
Please answer some additional questions about the previous scenario, restated below				
A Phase II study of a new chemical entity, with no worrisome preclinical data on reproductive toxicity. Study drug is administered for 6 months. Assume subjects are using a highly effective method of contraception as specified by the protocol.				
In your opinion, what is the acceptable risk of a false negative pregnancy test resulting in exposure to study drug to the embryo or fetus?				
<ul> <li>Less than 1 in 100,000 (0.001%)</li> <li>Less than 1 in 10,000 (0.01%)</li> <li>Less than 1 in 1,000 (0.1%)</li> <li>Less than 1 in 100 (1.0%)</li> </ul>				

	Not important at all	Not very important	Moderately important	Very important	Extremely important
Negative predictive value (minimizing false negatives)	0	0	0	•	0
Burden on subjects	•	•	•	•	0
Burden on study team	•	•	•	•	O
Testing Costs	<b>O</b>	•	•	•	O

For	For this scenario, which type of pregnancy test would you recommend using? (Choose 1)					
O O	Serum hCG performed in lab Urine hCG performed in lab Point of care urine hCG performed by study personnel Home test performed by patient					
For	this scenario, how do you recommend scheduling the pregnancy test(s)? (Choose 1)					
O	Whenever convenient for subject					
O	Timed to expected menses					

A Phase II study of a new chemical entity, with no worrisome preclinical data on reproductive toxicity. Study drug is administered for 6 months. Assume subjects are using a highly effective method of contraception as specified by the protocol.

	this scenario, at which study time points do you recommend a pregnancy test be formed? (Choose 1)
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O	At screening visit Immediately before administering study drug At screening visit and immediately before administering study drug
Ηο	w often do you recommend testing for pregnancy during the study?
О О	Every month  Every other month  Every three months  Other (Please Specify)
	w long after study exposure is completed do you recommend continuing to perform pregnancy ting?
O O	1 month 2 months 3 months 6 months 12 months

If there are other factors that contribute to your decision making about designing pregnancy testing protocols for clinical research that have not been included here, please describe them below. NOTE: Please do not include any identifying information in your response.

[Free text box provided]		