Duke Obstetrics & Gynecology

Avoiding Unplanned Pregnancy in Clinical Research

Balancing Science, Safety, and Ethics

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Disclosures

- Consultant
  - Merck, Inc (HPV vaccination)
  - Moderna, Inc (CMV vaccines)
  - Hologic, Inc (cervical cancer screening)

Overview

- Avoiding Pregnancy in Research: A Brief History
- Duke IRB Approach
- Common Issues with Sponsor Protocol/Consent Language
  - Pregnancy “potential”
  - Context of pregnancy and underlying condition
  - Pregnancy testing
  - Contraceptive Methods
  - What happens if pregnancy occurs
- Research/Policy Agenda

Inclusive Language

- Duke IRB currently reviewing and updating consent language and policies to be more inclusive/gender-neutral
- Reflected in this presentation except when referencing original sources

Avoiding Pregnancy in Research: A Brief History

Thalidomide

- 1957
  - Marketed in Germany as sedative/hypnotic, anxiolytic, anti-emetic.
  - Claimed to be particularly effective for morning sickness
  - OTC by late 1957
- 1956-57
  - SKF conducted clinical trials in US, declined to market (no evidence of effectiveness)
- 1958
  - WS Merrell agreed to market/distribute
- 1960
  - FDA application, rejected multiple times
- 1961-1962
  - Accumulating evidence of teratogenic effects
  - Estimated 10,00 cases of phocomelia worldwide
  - 50% mortality

Regulatory Response

- 1962: Kefauver/Harris Amendment
  - Requirement of proof of safety and *efficacy* prior to marketing
  - Post-marketing reporting of side effects
  - Evidence of efficacy based on controlled clinical studies
    - Informed consent of subjects
  - Retrospective evaluation of drugs approved between 1938 and 1962 for efficacy
  - FDA empowered to
    - Define good manufacturing practice and conduct inspections of production facilities
    - Control of prescription drug advertising, mandating accurate information about side effects
    - Control marketing of generic drugs to avoid simply re-marketing under new name

Regulatory Impact on Pregnant People: Restricted Access to Research Participation

- 1975
  - Pregnant women defined as “vulnerable research subjects”
- 1977
  - FDA “General considerations for the clinical evaluation of drugs prohibits women of childbearing potential from participating in early phase clinical research except for life-threatening conditions”

The Pendulum Swings Back: Increasing Access

- 1986
  - NIH advisory committee recommends grants should include women able to become pregnant unless explicit rationale provided
- 1993
  - FDA “Guideline for study and evaluation of gender differences in the clinical evaluation of drugs” reverses 1977 guidance
- 1998
  - FDA requires NDA to present safety/efficacy data by sex
- 2000
  - Amendment to CFR gives FDA authority to place trial for life-threatening disease or condition on clinical hold if sponsors exclude potential subjects only because of reproductive potential
- 2019
  - PRGLAC—cross-agency HHS task force recommendations to encourage enrollment of pregnant and lactating individuals into trials
  - Released December 2019—NOT considered in COVID treatment/vaccine trials

Excluding Pregnant People from Research

- Despite PRGLAC, majority of interventional studies still exclude pregnant or lactating people
- Legitimate reasons for exclusion of pregnant or lactating people from specific studies
  - Scientific: Effects of physiological changes of pregnancy/lactation on
    - Drug metabolism
    - Disease natural history
    - Study outcomes
      - All can affect study precision/validity/generalizability
  - Ethical
    - Known or unknown risks of study interventions to a developing pregnancy (or nursing infant) in setting of uncertain benefits from study intervention

Remainder of Presentation

- Assumes that exclusion of pregnant or lactating people from a particular protocol is scientifically and ethically justified
- Focuses on protocols to minimize the probability of
  - Unknown pregnancy at time of study enrollment
  - Pregnancy occurring during potential embryonic/fetal exposure to study interventions
  - In event pregnancy does occur, minimizing duration of exposure

Definition of “RISK”

- In FDA/regulatory use, “bad outcome”
- In statistics/decision science, “probability that you can estimate”

- Will be used in both senses here

- Primary argument
  - For reproductive “risks” in particular, our focus on the “bad outcome” definition leads us to ignore the “probability” definition
  - This leads to protocols and consent processes where the “benefit” of an incrementally reduced probability of a bad outcome may be outweighed by burdens or harms to research participants (and their nonconsenting partners)

Current Sponsor Approach to Minimizing Risks

- Define “Women of childbearing potential”
- Unknown pregnancy at enrollment ruled out by test
  - Ongoing testing may required
- Contraception requirement
- For many studies, male subjects with partners “of childbearing potential” also required to use contraception
- If pregnancy occurs, reported to sponsor

Implications

- Protocol requirements typically based ONLY on potential risk (“outcome”) of study drug/intervention to a developing pregnancy
- No consideration of risk (“probability”) of pregnancy in specific study population
  - Pragmatic
    - Unnecessarily increases length/complexity of consent forms
      - Inefficient use of resources
      - Cognitive burden/impact on decision making
    - Potential conflicts between sponsor and IRB
    - Unnecessary burden on research subjects
      - Barrier to enrollment
      - Potential impact on quality-of-life
  - Ethical
    - Patronizing
      - Potential violation of principle of RESPECT
    - Imposing extra risk/burden on subjects with no gain
      - Potential violation of principle of BENEFICENCE
    - May limit ability to participate in research
      - Potential violation of principle of JUSTICE

Duke IRB Process

Duke IRB Process

- Pre-2018
  - Review by primary IRB reviewer
    - "Standard language" for consents
    - Pregnancy testing policy complex (for institutional historic reasons)
      - Serum testing required for most studies
    - Any issues with appropriateness or inconsistency with reproductive biology and math usually only identified if OB/GYN representative was present at meeting
- 2018
  - Broad guidance on pregnancy testing and contraception
  - Required elements of consent
  - Review of all new protocols excluding pregnant women (or pregnancy in partners) by (n-of-1) "Pregnancy Committee"
    - Selected amendments with substantial revision of previously approved reproductive risk aspects of protocol and/or ICF
  - Modifications requested at time of review
  - If necessary, discussion/negotiation with sponsor

Review Considerations

- Potential reproductive “risks” (adverse outcomes) of study interventions
- “Risk” (probability) of “risks” (adverse pregnancy outcomes) in patient population independent of study participation
- “Risk” (probability) of becoming pregnant in patient population
- “Risks” (adverse outcomes) of specific pregnancy testing and contraceptive requirements in patient population
- Ethical implications

Theoretical pregnancy risks ("bad outcomes") from potential study-specific exposures

- Pregnancy loss/miscarriage
  - Direct effects of drug, radiation, hypoxia
  - Genetic damage to egg or sperm
  - Problem—early miscarriage common (20-30% of all conceptions), more common in older mothers, difficult to assign causation
- Teratogenic effects
  - Genetic
  - Anatomic development (limb abnormalities, neural tube defects)
  - Growth/Neurologic development—usually associated with exposures later in pregnancy, very unlikely in context of most trials
- Mechanisms of exposure
  - Female
    - Direct effects on eggs
    - Direct effects on embryo/fetus (radiation)
    - Transplacental transfer of drug
  - Male
    - Direct effect on sperm (genetic or epigenetic)
    - Excretion of drug into semen→vaginal/anal/oral absorption→drug in maternal blood→transplacental transfer of drug

“Risks”(outcome) by Type of Exposures

- Drugs
  - Animal data (not always predictive of human effects)
  - Human data (uncommon in pre-approval studies unless known class effect)
  - Duration of potential exposure related to pharmacology of drug, potential mechanism of action, biology of egg and sperm development
- Radiation
  - Only during intervention
  - Existing guidance on risks from different imaging methods
- Procedures
  - Only during intervention
  - Related to potential effect of procedure on uterine blood flow, oxygenation, perioperative drug exposures
- Implications for Consent
  - No need for extensive description of need for contraception for studies of short-acting exposures that occur entirely in the in-patient setting
    - Recent example: Full page of 15-page consent describing requirements for contraception for study of inhaled CO in intubated patients with respiratory distress syndrome

Common Issues: Defining Pregnancy “Potential”

“Woman of Childbearing Potential”

- In practice, anyone with probability of becoming pregnant > 0.0%
- Menarche to menopause
- Protocol requirements apply equally

“Woman of Childbearing Potential”

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“Woman of Childbearing Potential”

Pregnancy and Infant Outcomes in the Clinical Trials of a Human Papillomavirus Type 6/11/16/18 Vaccine: A Combined Analysis of Five Randomized Controlled Trials

Garland SM, et al, on behalf of the Quadrivalent Human Papillomavirus Vaccine Phase III Investigators

Obstet Gynecol 2009;114:1179-88

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Obstet Gynecol 2009;114:1179-88

Number of female subjects

23,369

Number of pregnancies

3,620

Pregnancy Rate

15.5% (95% CI 15.0-16.0%)

Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2–positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials

Lambertini M, et al

Cancer 2019;125:307-16

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Cancer 2019;125:307-16

Number of female participants

8,836

Number of female participants premenopausal or < 55

3,947

Number of pregnancies

12

Pregnancy Rate

0.3% (95% CI 0.2-0.5%)

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Pregnancy Rate

0.3%

Number of particpants ≤ 40

1,486

Number of pregnancies

12

Pregnancy Rate

0.81% (95% CI 0.4-1.3%)

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Pregnancy Rate

0.3%

Number of participants ≤ 40

1,486

Number of pregnancies

12

Pregnancy Rate

0.81%

Pregnancy Rate in participants 41-55

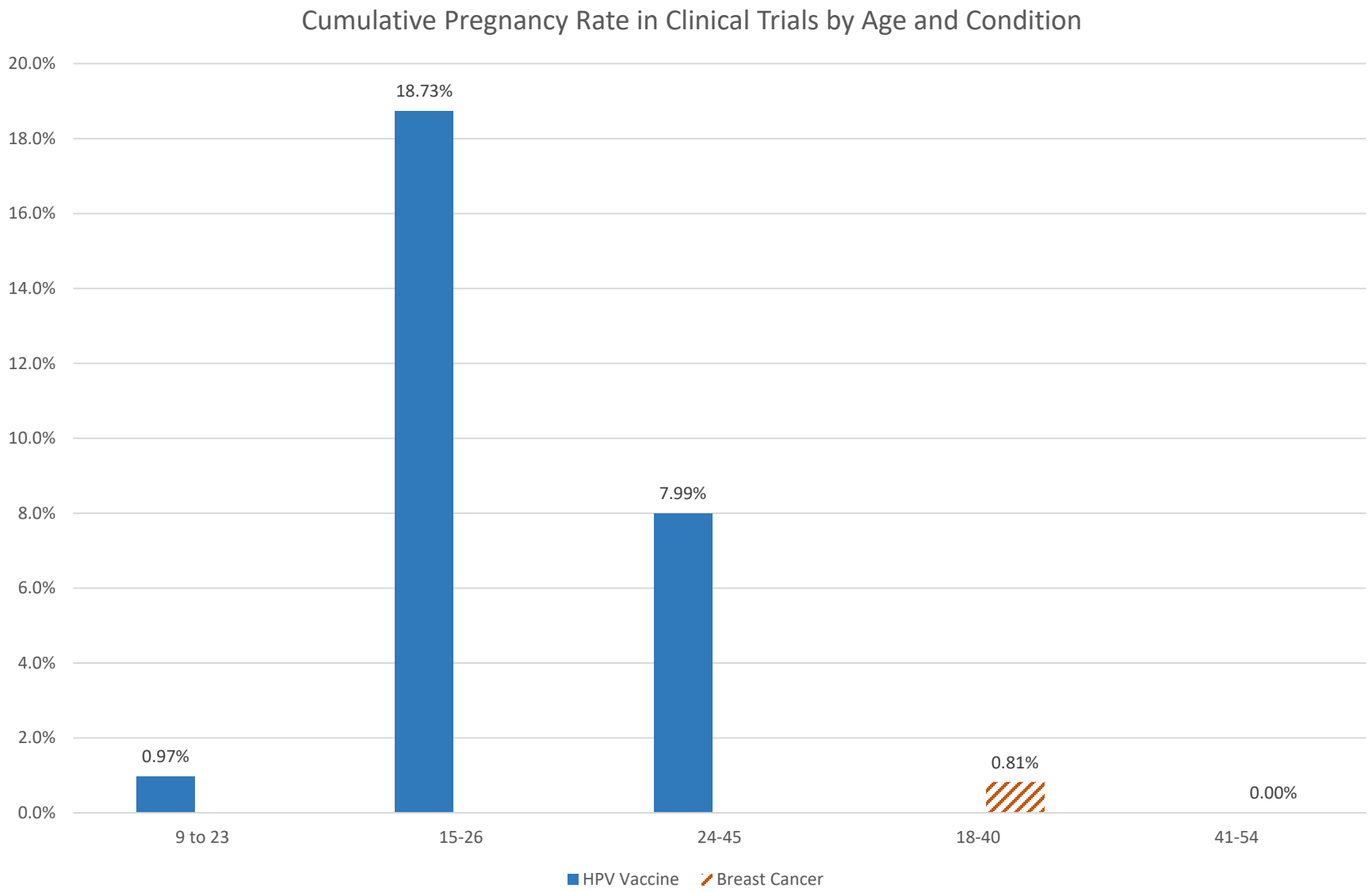
0% (95% CI 0-0.12%)

Factors Affecting Probability of Pregnancy

- **Female partner age**
  - Male partner age less important
- Coital frequency
  - Decreases with age
  - Effects of underlying disease and/or treatment (including in partners)
- Past or current treatments
  - Many chemotherapy agents affect ovarian function
- Contraceptive methods
- Duration of follow-up

Risk ("probability")of Pregnancy Varies in Different Patient Populations

- HPV vaccine trials inclusion criteria
  - Healthy
  - Most 16-26 years old
    - One smaller trial in 27-45 year olds—pregnancy rate lower
  - Sexually active
  - Mix of contraceptive methods typical of age group, only required around time of vaccine
  - 2-3 years of observation
  - 10-15% is expected!
    - Pregnancy rate within 30 days of vaccine: 1%
- Many, if not most, clinical trials have very different patient populations in terms of age, coital frequency, previous treatments, contraceptive methods


Cumulative Pregnancy Rate in Clinical Trials by Age and Condition
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
18.73%
7.99%
0.97%
0.81%
0.00%
9 to 23
15-26
24-45
18-40
41-54
HPV Vaccine
Breast Cancer

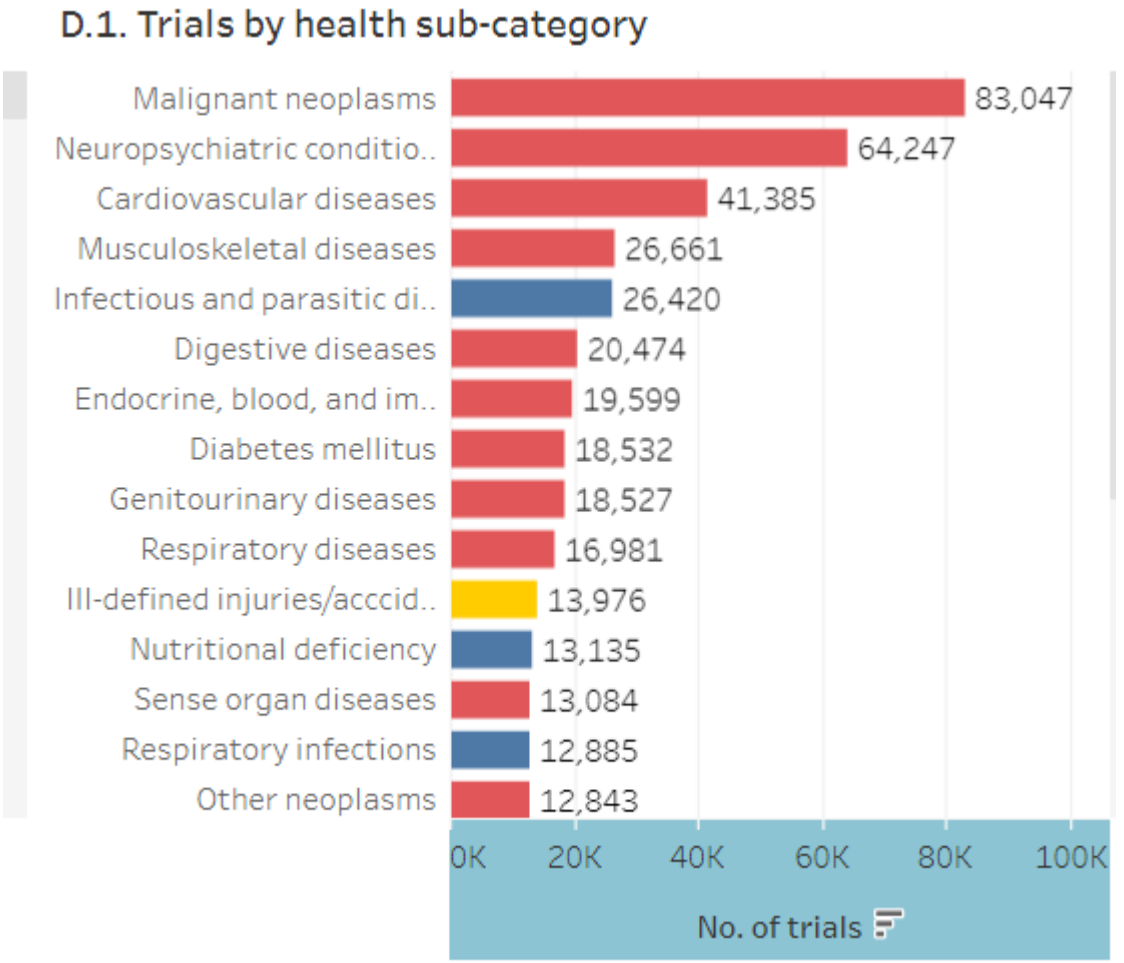
Age and Risk of Adverse Pregnancy Outcomes due to Drug Exposure

- Drugs with known teratogenic syndromes or adverse pregnancy outcomes
  - Thalidomide
  - Retinoic acid (acne treatment)
  - Hydantoin and other anti-epileptics
  - Some anti-depressants
  - Warfarin
  - Methotrexate
- All drugs that were/are used in women 15-44, often during pregnancy
  - Not the case for many other drugs
  - How many pregnancies in women 45-54?

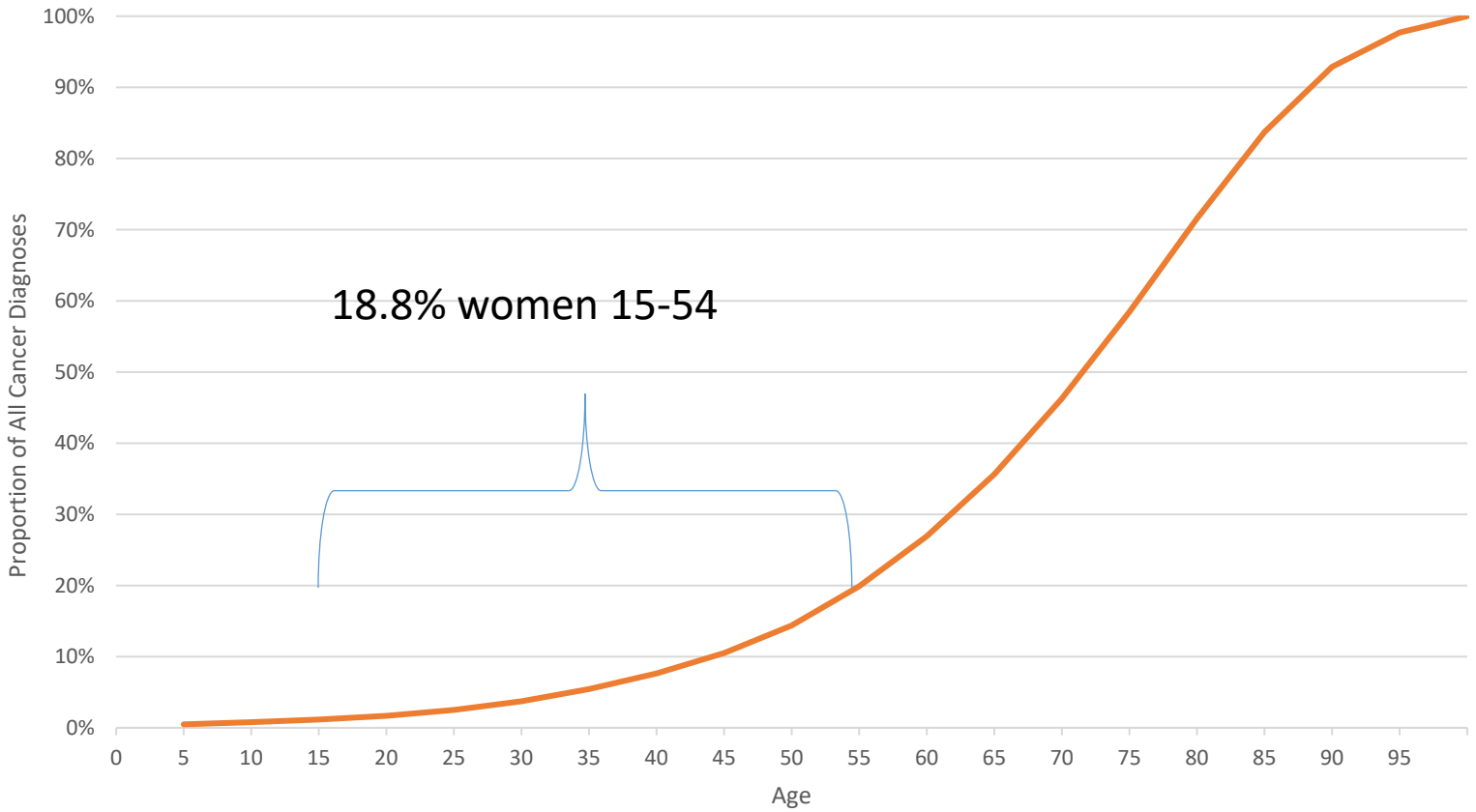
Interventional Trials by Condition

Trials registered in WHO International Clinical Trials Registry Platform

1999-2021

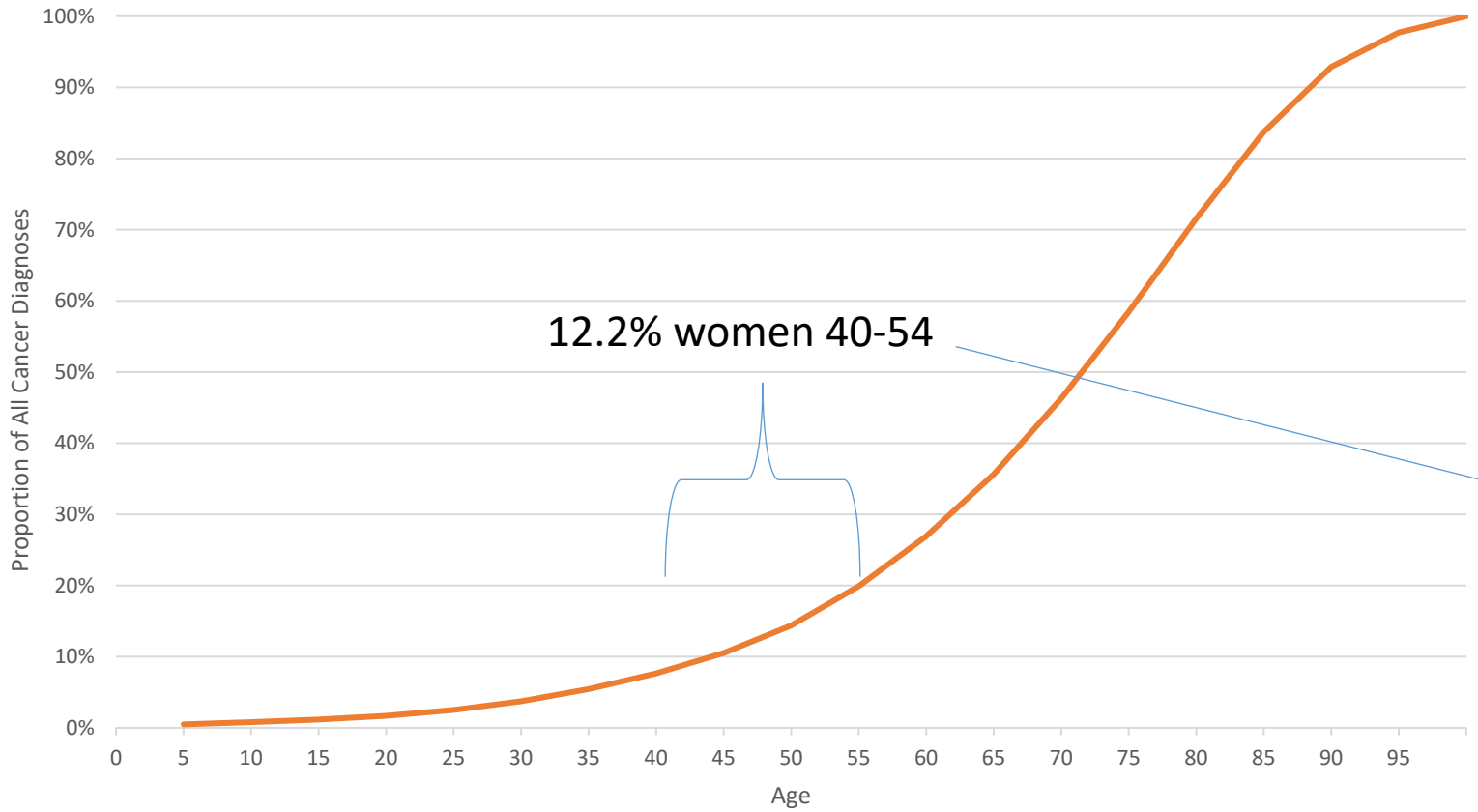


Age Distribution among Women with Malignant Cancer Diagnosis other than Breast or GYN



SEER, 2015-2017

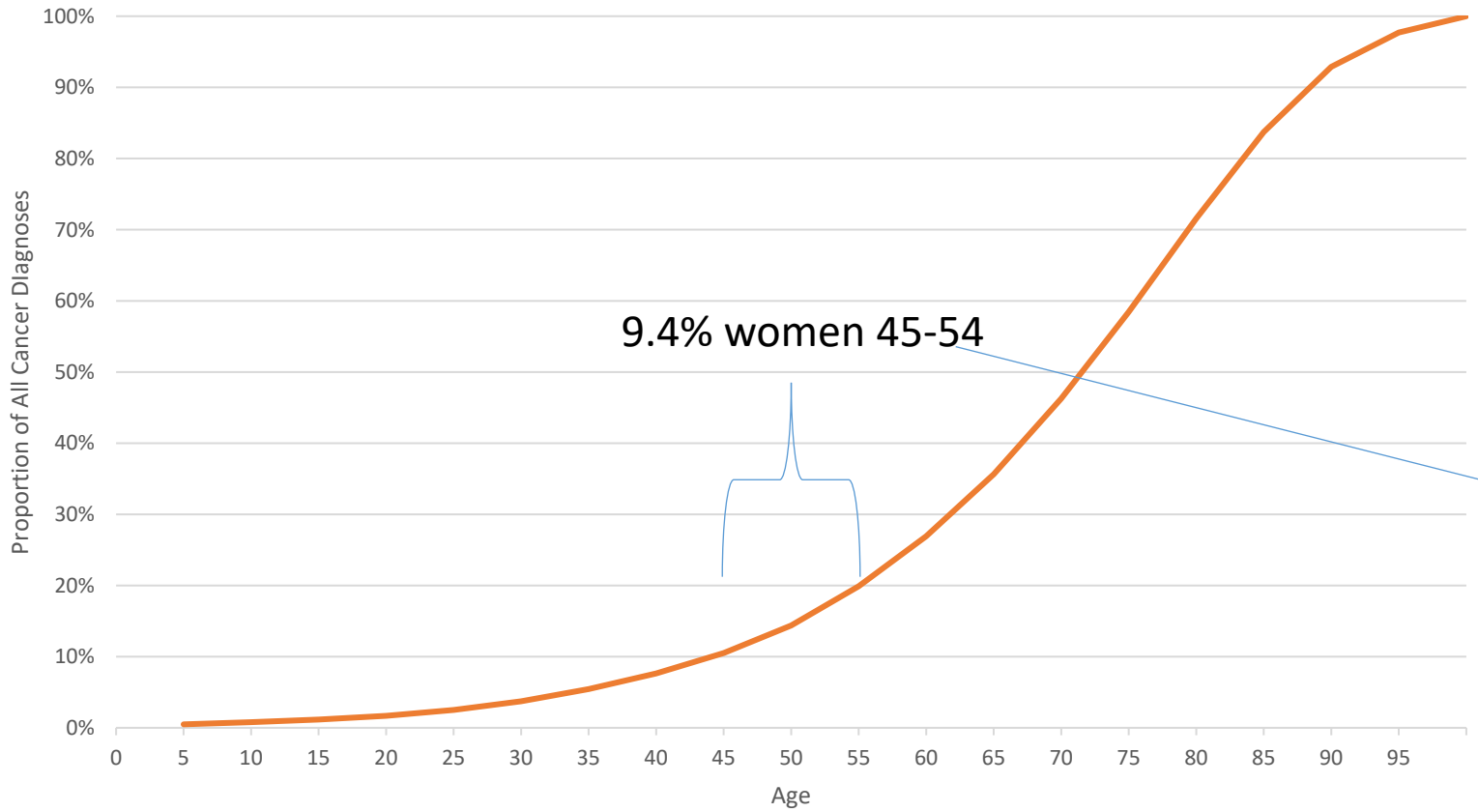
Age Distribution among Women with Malignant Cancer Diagnosis other than Breast or GYN



65% of "reproductive age" women with cancer

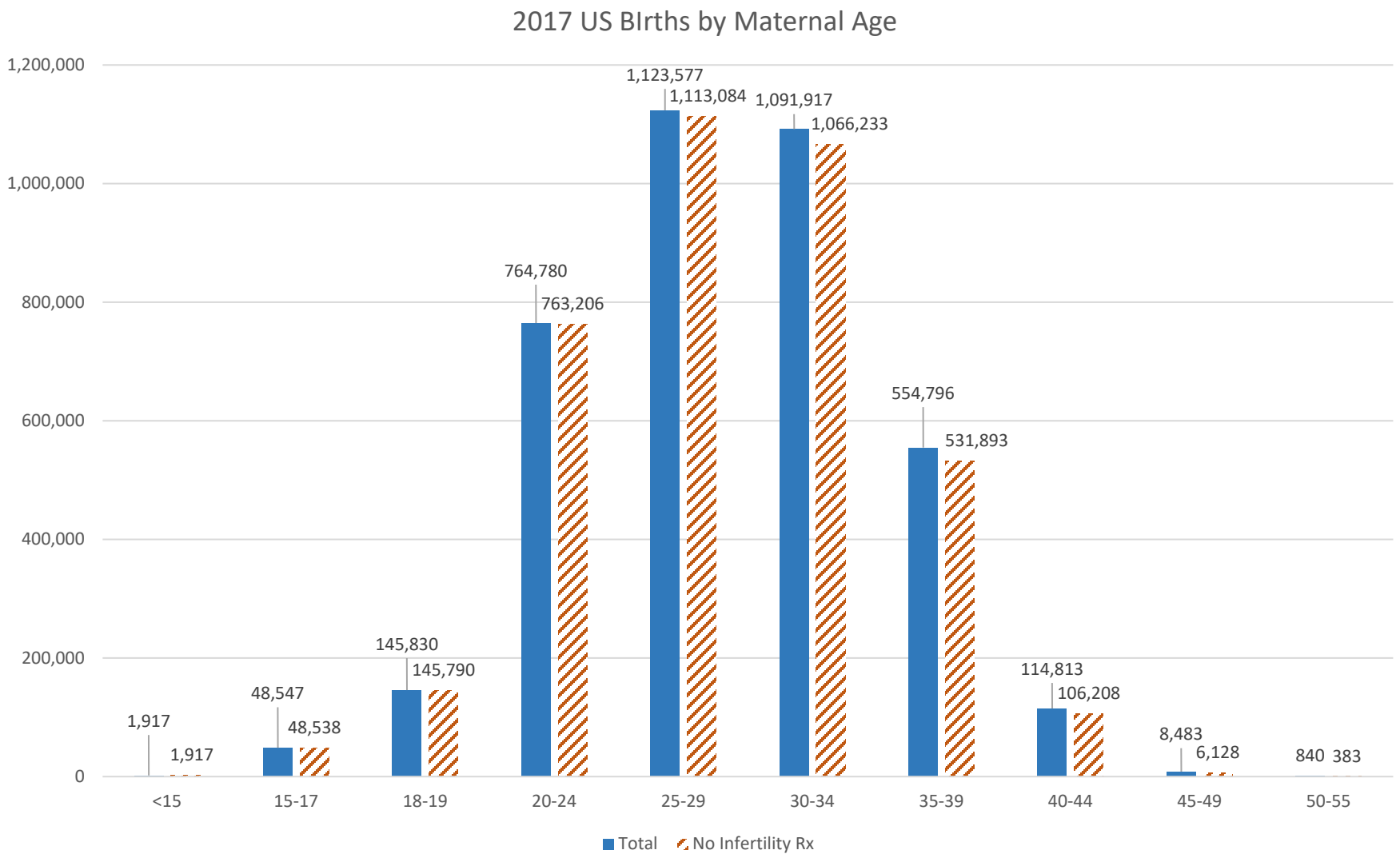
SEER, 2015-2017

Age Distribution among Women with Malignant Cancer Diagnosis other than Breast or GYN



50% of "reproductive age" women with cancer

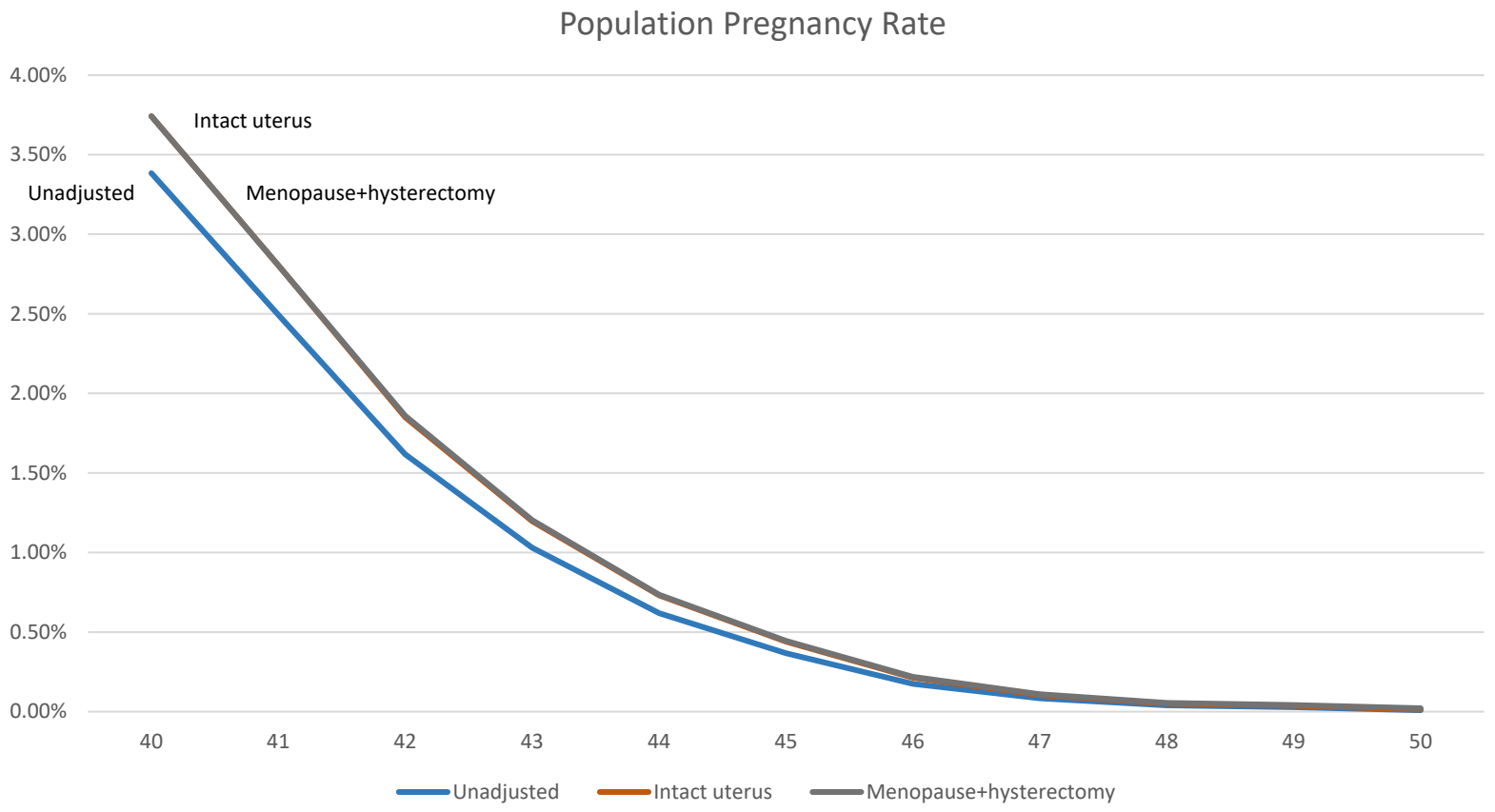
SEER, 2015-2017



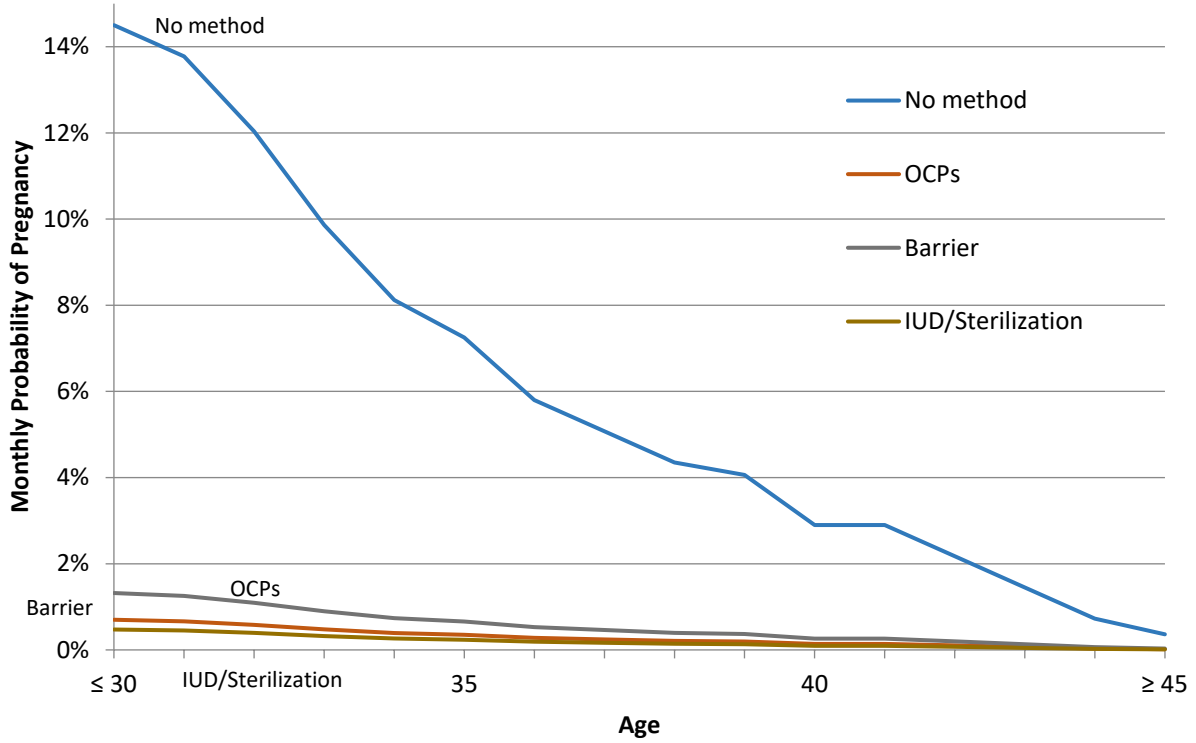
Births with no infertility treatment documentation

Ages 10-14: 1,917
Ages 50-54: 383

Annual Population Pregnancy Rate
(Livebirths + Miscarriages + Abortions)
(Total Women – Menopause – Hysterectomy)



Estimated monthly probability of pregnancy by age and contraceptive method.



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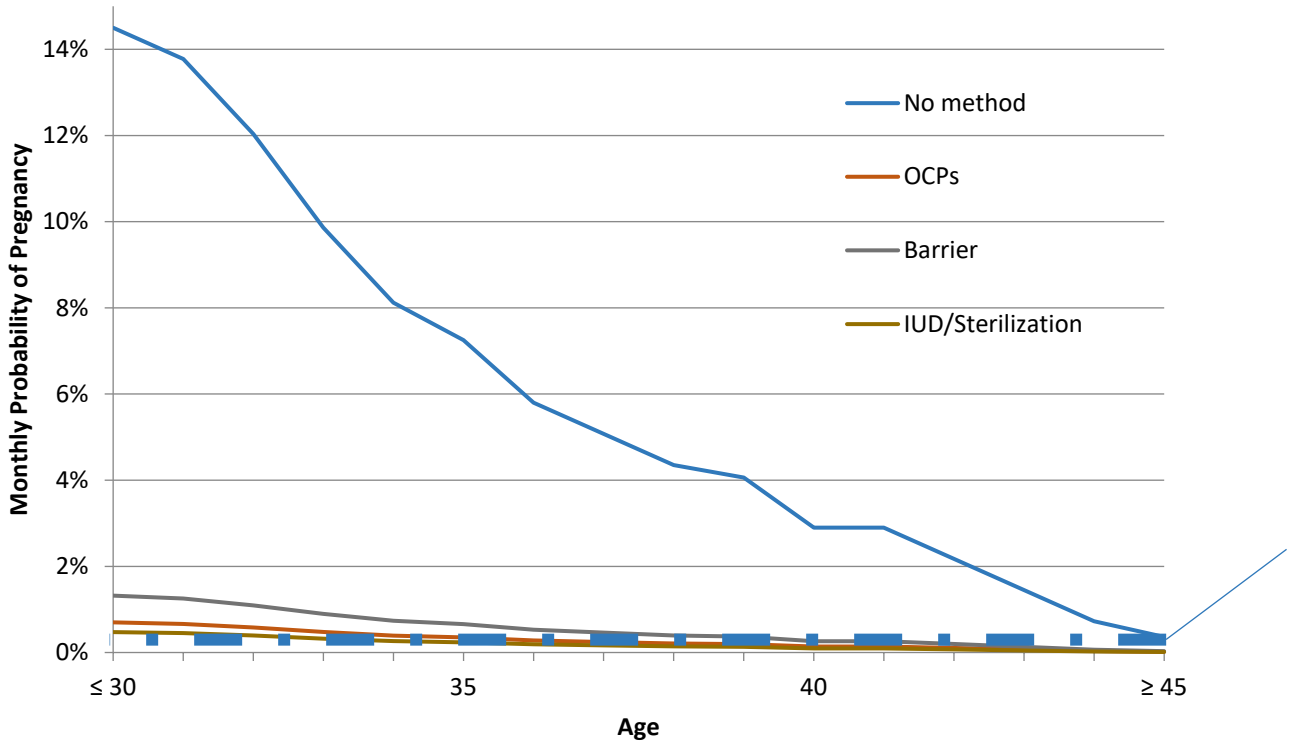
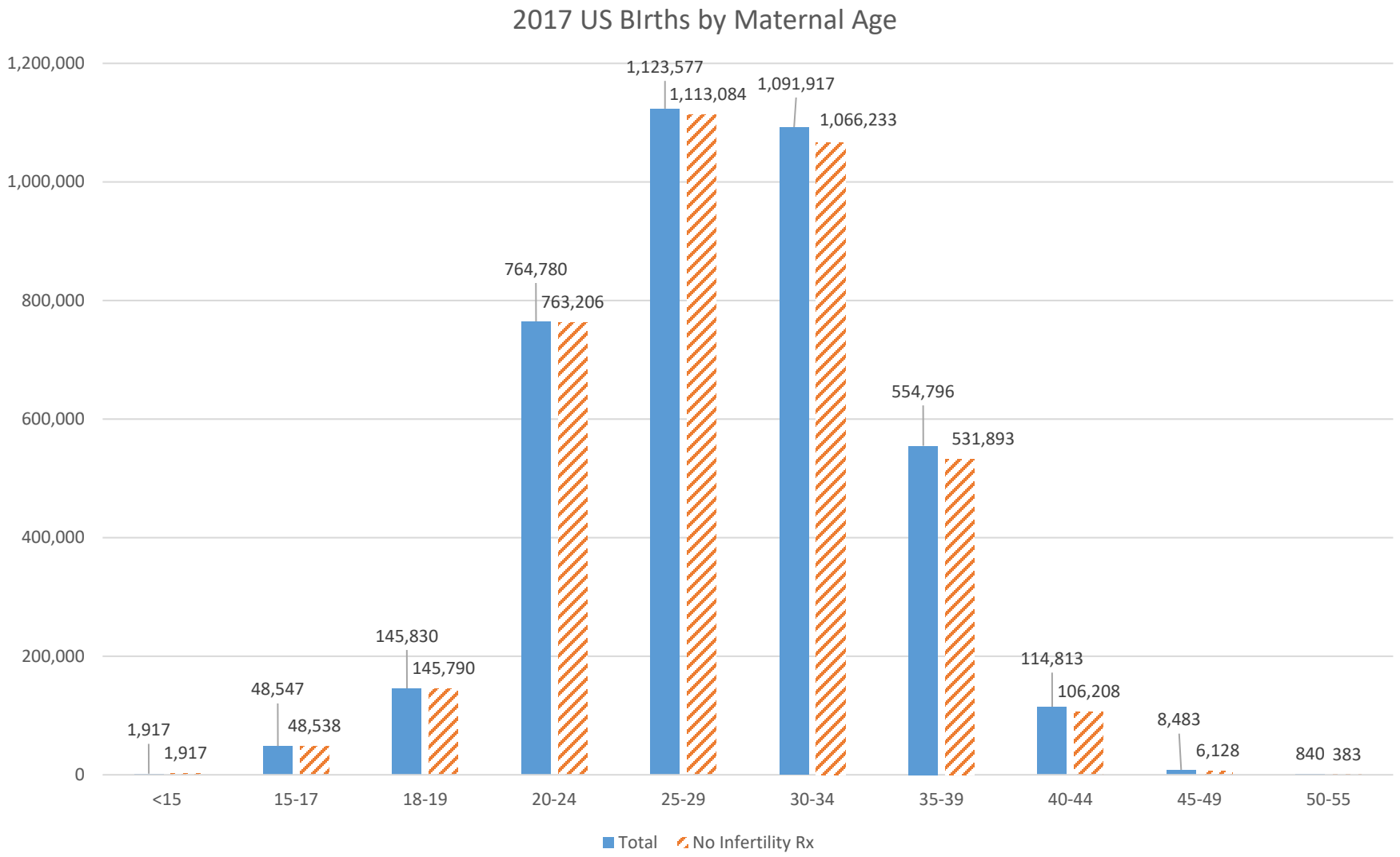


Pregnancy probability for 45-year-old with no contraception lower than probability of 30-year-old using oral contraceptives



Births with no infertility treatment documentation

Ages 10-14: 1,917
Ages 50-54: 383

“Woman of Childbearing Potential”

“Player of NBA Potential”

Duke IRB Definition: "Woman of Childbearing Potential"

- "Person who could possibly become pregnant"
- Started menarche
  - "If your child has begun to have their periods…"
- Postmenopausal
  - "You have not completed menopause"
    - Typically 12 months since last menses and/or based on FSH
    - No need to have specific criteria in ICF
  - 99% by age 55, no spontaneous pregnancies—OK to exclude based on age 55 alone
- No prior hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy
  - History of bilateral salpingectomy alone not common now, but more frequently being done to reduce risk of ovarian cancer
- Common for sponsors to equate hysterectomy and tubal ligation (BTL) as "sterilization" excluding from any pregnancy testing requirement
  - BTL has failure rate higher than vasectomy, IUD, or progestin implant
    - If pregnancy testing required for those methods, no rationale for excluding it with BTL

Definition:
“Woman of Childbearing Potential”

- “Have a partner who can produce sperm”
  - Ethical issues of respect, equity
  - Component of “Pregnancy Reasonably Excluded Guidelines”
  - Pragmatic—if participant would lie about sexual orientation in order to avoid pregnancy test, how could they be trusted to adhere to more onerous study requirements?
  - Most sponsors accept
    - One responded that we couldn’t know if subjects had been assaulted

Exclusion of People who Could Get Pregnant

- 2000 amendment to Common Rule allows clinical hold on studies under IND for drugs intended to treat life-threatening disease or condition affecting both genders
  - If men or women of reproductive potential excluded solely because of perceived risk of reproductive or developmental toxicity from drug
- Twice in past 5 years
  - Trientine (approved to treat Wilson's disease) for heart failure
    - Previous studies cited in protocol included women who could get pregnant
    - Sponsor not willing to amend (Duke prepared 10 page document, hour long discussion)
    - My recommendation—not approve, voted on by full IRB—not approved
  - Gene therapy for age-related macular degeneration, minimum age 50
    - Gene product plausibly embryotoxic
    - Alternative treatments available
    - Relatively few women affected given epidemiology of disease
    - Sponsor indicated FDA likely to include limitation if treatment approved
    - Approved

Populations where Pregnancy is Impossible

- Most gyn cancers, castration-resistant prostate cancer (CRPC)
- Treatment either removes essential reproductive organs or completely suppresses production of gametes
- Issues
  - Adds unnecessary length to already complex ICF
  - Potential confusion/distraction/emotional impact
    - "My doctor said I could never get pregnant again"
  - Burden—if patient with CRPC able to have intercourse with assistance, condom requirement has significant impact on QoL
- Preferred solution—ICF addendum for extremely rare cases where risk is not 0%
  - Standard in gyn oncology
  - Variable success with sponsors for CRPC

Gamete Donation

- Requirements that participants cannot donate ova or sperm
  - Common in advanced cancer protocols
  - Recent examples include several protocols for heritable gene disorders like sickle cell and Duchenne muscular dystrophy
- For people with ovaries
  - Most donor programs have maximum age of 25, some as high as 30
  - All have extensive health screening
  - Donation requires a cycle of ovarian hyperstimulation then transvaginal oocyte retrieval
    - No woman eligible for participation in cancer clinical trial would be eligible for egg donation—equally likely to be eligible for kidney or partial liver donation
    - No oncofertility program would start hyperstimulation on patient on active treatment
- For people with testes
  - Age limit is slightly higher
  - Technically much easier than oocyte donation, so not completely impossible
  - Donation is FDA-regulated, and highly unlikely
    - Usually leave in ICF as “concession” to sponsor when I remove oocyte donation language

Gamete Donation vs Preservation

- Should explicitly distinguish donation from preservation
- “You should not donate eggs or sperm” is typical
- “If you are considering storing eggs, ovarian tissue, or sperm to preserve future fertility, you must complete this process before starting this study” strongly preferred

Definition of “childbearing potential”

- Recent examples where this was an issue
  - Monthly home pregnancy testing for all females 10 and older, regardless of menarchal status (spinal muscular atrophy)
  - Pregnancy testing and contraception requirements for protocol and consent form with minimum age of eligibility of 60 (age-related macular degeneration)

Common Issues: Pregnancy in the Context of Underlying Disease

Pregnancy in Context of Underlying Disease

- Most people able to get pregnant meeting eligibility criteria for clinical trials should be using contraception as standard of care
  - Based on age alone, high risk of miscarriage (>50% over 40), anomalies, complications
  - Many pre-existing cardiac diseases have maternal mortality rates > 10%
    - Of 13 approved drugs with REMS secondary to reproductive toxicity, 4 are for pulmonary arterial hypertension, which has maternal mortality of 30-50%
  - Renal, liver, rhematologic diseases all associated with increased risk of pregnancy complications
  - Pregnancy can affect disease progression or symptoms
  - SOC drugs may be teratogenic (warfarin, methotrexate, anti-convulsants, chemotherapy)
- Start ICF with brief description of this context
  - Informed decision making—risk of study participation and contraceptive needs compared to non-participation
  - “Pregnancy in people with [condition] is associated with an increased risk of …”
  - Now common in FDA labels/prescribing information

Pregnancy in Context of Underlying Disease

- “Unborn child”, “unborn baby”, or similar language not appropriate
  - “Charged” terminology
  - High risk of miscarriage or indicated termination in many cases even without study participation
  - Preferred term “developing pregnancy”

Gene Therapies and Long-term Effects

- Example: gene therapy to correct enzyme deficiency, 5 year follow-up
  - Reasonable to avoid pregnancy during study for scientific reasons
  - If therapy works, pregnancy should theoretically no longer be high risk
  - ICF should include a statement about uncertainty about impact of treatment on long-term fertility and pregnancy outcomes

Common Issues: Pregnancy Testing

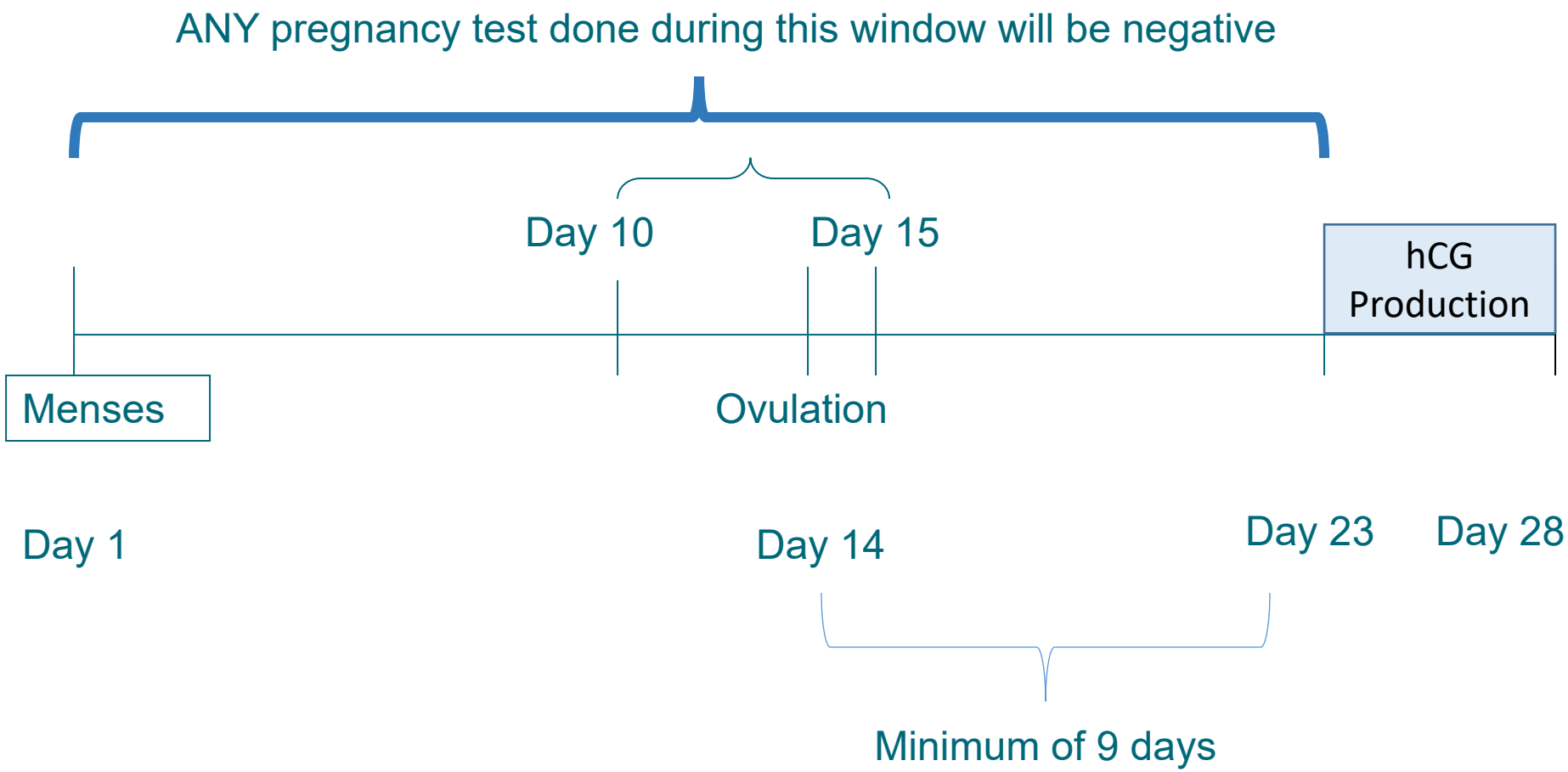
Purpose of Pregnancy Testing

- Prevent people who are pregnant at time of enrollment from exposure to potentially harmful study interventions
- Minimize duration of exposure in people who become pregnant while on study drug
- Documentation that participant did not become pregnant during study
  - Only possible rationale for testing after exposure has stopped and required window has passed—e.g., end-of-study pregnancy test)
- All prioritize negative predictive value
  - Higher test sensitivity and/or low pre-test probability of pregnancy

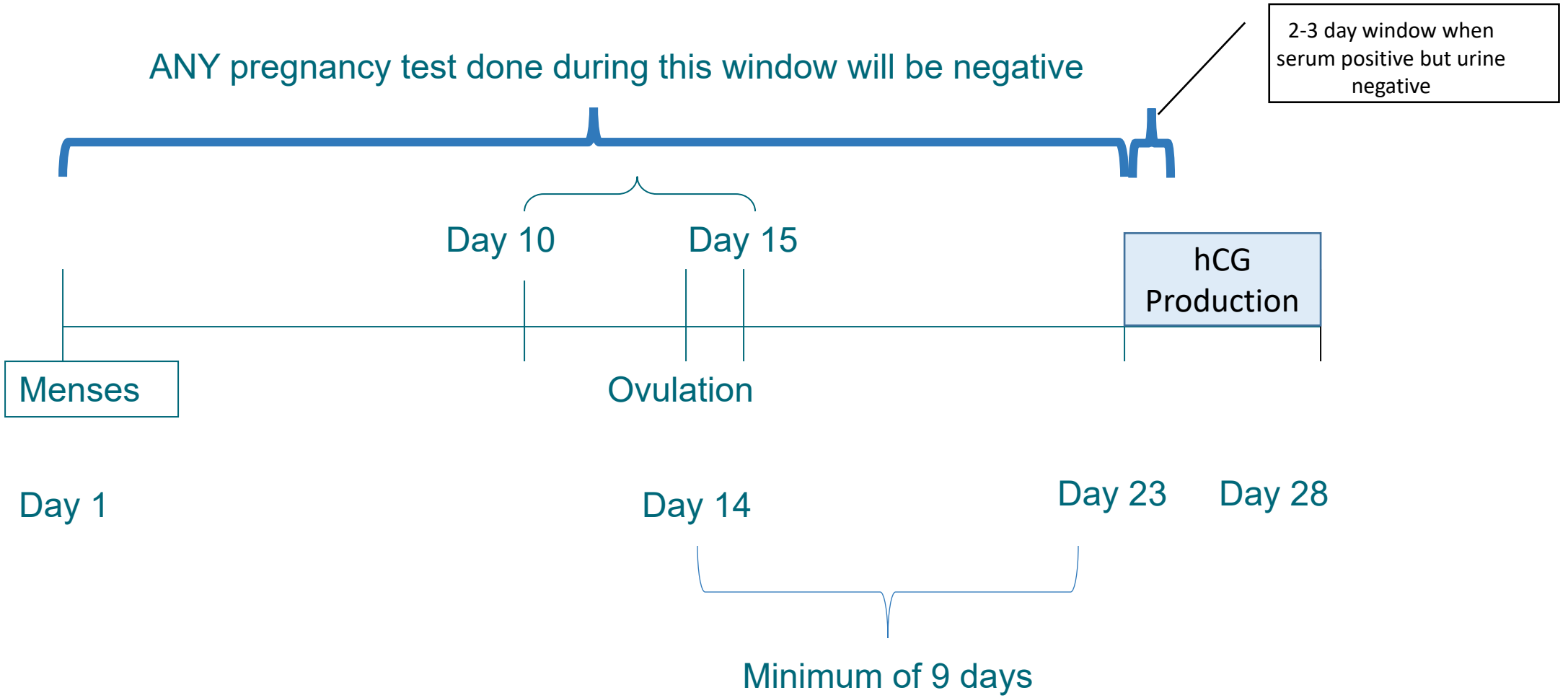
Test Sensitivity

- Sensitivity of pregnancy tests
  - Serum—5 mIU/L
  - Urine—20-25 mIU/L

Timing of Conception

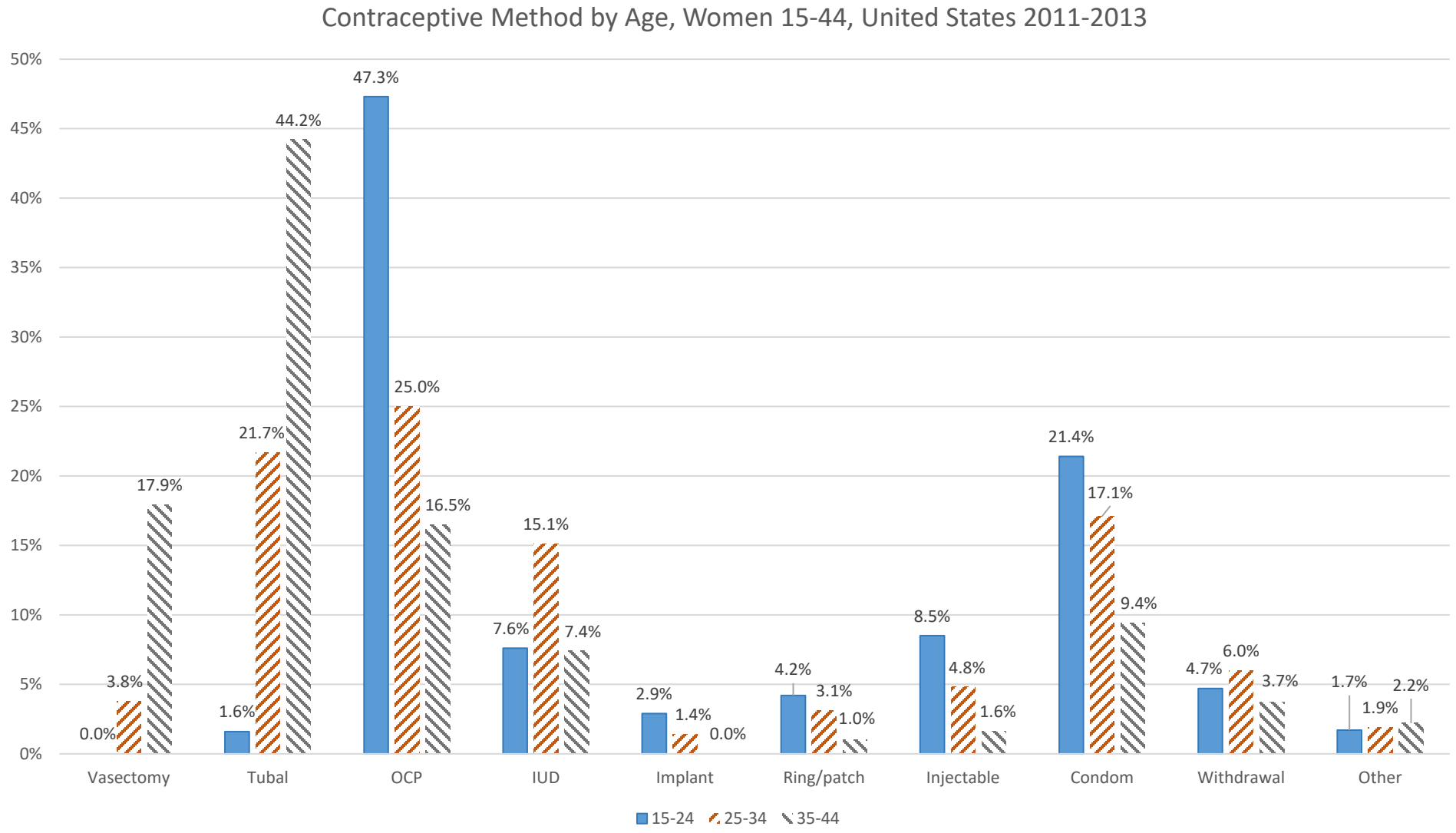


Timing of Conception



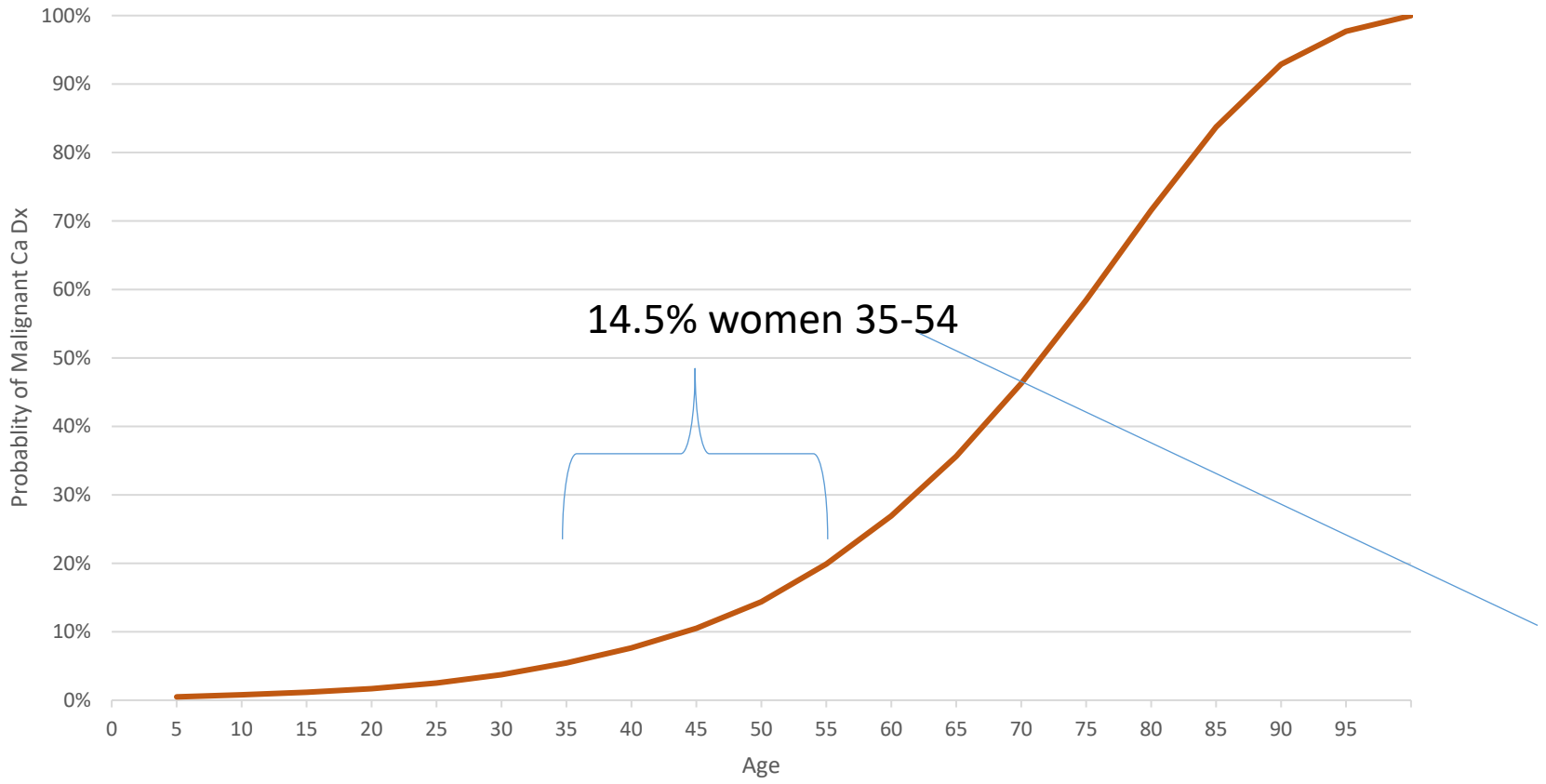
Factors Affecting Probability of Pregnancy

- Female partner age
  - Male partner age less important
- Coital frequency
  - Decreases with age
  - Effects of underlying disease and/or treatment (including in partners)
- Past or current treatments
- Contraceptive methods
- Duration of follow-up



Source: National Survey of Family Growth

Age Distribution among Women with Malignant Cancer Diagnosis other than Breast or GYN



77% of "reproductive age" women with cancer

AT LEAST 60% using vasectomy or BTL

SEER, 2015-2017

Serum vs Urine

- Very low probability of pregnancy in most patient populations
- Better sensitivity of serum test only useful if performed in the 2-3 window when hCG >5 but <20-25
  - Pregnancy testing almost always random relative to menstrual cycle
- Very small gain (well less than 1%) in NPV in most settings
  - Documentation of use of highly effective contraception has higher negative predictive value than random pregnancy test in family planning population
- False positives with serum
  - 2-3% in women 40 and older will have hCG >5, increasing with age (10% age 55)
    - Perimenopausal increase in GnRH leads to pituitary secretion of hCG
    - Pregnancy ruled out with FSH

Serum vs Urine

- Minimal gain in NPV with risk of false positive
  - Hard to justify serum if women under 40 unlikely to be in study
  - VERY hard to justify serum for follow-up tests when contraception required

- If serum testing required, consent must include
  - “In people 40 years and older, blood pregnancy tests can sometimes give a false positive or indeterminate result, and additional testing may be required”
  - Unexpected positive test has potential for significant distress→research-related risk that must be disclosed

Ongoing Testing

- Given concomitant contraception requirements, mostly performative
- Some protocols do intervals > 1 month
  - No plausible rationale
  - IF sponsor is going to require follow-up pregnancy testing, then only rational interval is monthly while on drug

Home Pregnancy Testing

- Designed for confirmation of pregnancy in women trying to get pregnant
- All available evidence suggests that patients perform worse in interpreting results than trained study staff
- False negative rate as high as 40-50%
  - Would be more cheaper and equivalent effectiveness to give participants a quarter to toss each month
- All current REMS requiring pregnancy testing explicitly rule out home tests
- Pragmatic issues
  - Not feasible for some patient populations (visual acuity, manual dexterity)
  - Also ethical (embarrassment if partner or parent have to assist)
- Ethical issues
  - Emotional burden on patient
    - Guilt if false negative
    - Stopping study drug if false positive
- Had value in context of COVID restrictions

Home Pregnancy Testing

- Duke IRB has generally not approved
  - If sponsor is concerned enough about pregnancy to require monthly testing, why use a test that has documented higher false negative rate?
  - OK to have test performed locally if travel an issue
- Exception during COVID
  - ICF explicitly states that home testing has higher false negative rate

- Recent issues
  - Monthly serum testing, Parkinson's, minimum age 50—DCRI coordinating center protocol, suggested revision to avoid
  - Monthly home testing, early Parkinson's—PI stated that most patients able to perform, allowed
  - Monthly home testing, 10-year-olds with spinal muscular atrophy
    - Sponsor unwilling to amend protocol
    - Balancing considerations of (a) rare disease with few available treatments, (b) burden of physically coming to clinic, (c) burden on parents and patients
    - Allowed, but required parents to have option to have testing done at local clinic at sponsor expense

Common Issues: Contraceptive Methods

EFFECTIVENESS OF FAMILY PLANNING METHODS*

*The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method.

MOST EFFECTIVE

Less than 1 pregnancy per 100 women in a year

6-12 pregnancies per 100 women in a year

18 or more pregnancies per 100 women in a year

LEAST EFFECTIVE

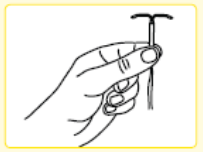
REVERSIBLE

Once in place, little or nothing to do or remember.

Implant

0.05%

Intrauterine Device (IUD)



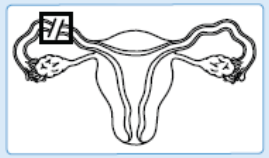
0.2% LNG

0.8% Copper T

PERMANENT STERILIZATION

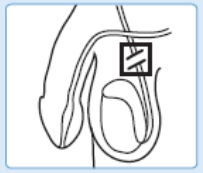
After procedure, little or nothing to do or remember.
Use another method for first 3 months (Hysteroscopic, Vasectomy).

Female (Abdominal, Laparoscopic, and Hysteroscopic)



0.5%

Male (Vasectomy)

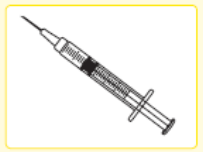


0.15%

REVERSIBLE

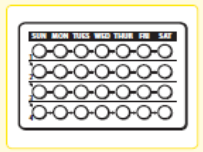
Get repeat injections on time. | *Take a pill each day.* | *Keep in place, change on time.* | *Use correctly every time you have sex.*

Injectable



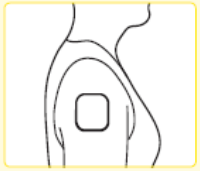
6%

Pill



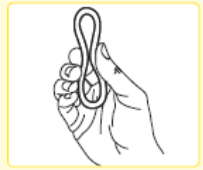
9%

Patch



9%

Ring



9%

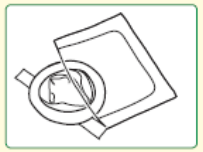
Diaphragm

12%

REVERSIBLE

Use correctly every time you have sex.

Male Condom

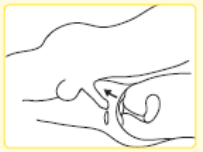


18%

Female Condom

21%

Withdrawal



22%

Sponge

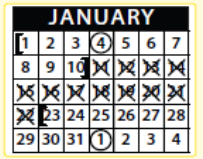
12% Nulliparous Women

24% Parous Women

Condoms should always be used to reduce the risk of sexually transmitted infections.

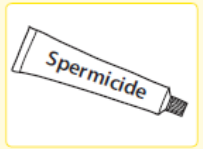
Fertility Awareness-Based Methods

Abstain or use condoms on fertile days.



24%

Spermicide



28%

Other Methods of Contraception: (1) **Lactational Amenorrhea Method (LAM):** is a highly effective, temporary method of contraception; and (2) **Emergency Contraception:** emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.

Adapted from World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD; Geneva, Switzerland: CCP and WHO; 2011; and Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Contraceptive Methods

- Effectiveness varies across methods AND patient population
  - "Typical use" vs "perfect use"
  - Prior probability of pregnancy
    - 25 year old on OCPs more likely to get pregnant than 45 year old using nothing
  - Potential drug/drug interactions for hormonal methods
- Every method has potential downsides/harms
  - Personal/cultural/religious preferences
  - Impact of different methods on sexual function
- Potential side effects in specific conditions or other treatments
  - Thrombosis with estrogen-containing methods
  - If thrombosis is an issue with underlying condition (heart disease) or listed potential risk of study drugs, estrogen-containing methods shouldn't be listed as "acceptable" in ICF

Double methods

- Some sponsors/protocols require two methods
  - Often ICF states any two from list, no matter how impractical
    - Other than barrier plus second method, only pragmatic possibility is vasectomy plus tubal if second partnership
    - No physician would start hormonal method or insert IUD in women with a tubal ligation or partner with vasectomy solely to allow participation in a trial
  - May explicitly require barrier plus second method, even for non-hormonal methods where drug/drug interaction not an issue

Double methods

- Requiring two methods in the 45-54 age population
  - Risk of pregnancy with no method lower than risk of pregnancy with many highly effective methods in younger women
  - Difficulties with use of barrier methods
    - Perimenopausal vaginal changes
    - Erectile dysfunction
    - Latex allergies
    - Issues with manual dexterity or visual acuity
    - Out-of-pocket costs
  - Forces potential participants to choose between
    - Lying about adherence to protocol
    - Potentially starting new method that may be difficult/uncomfortable/affect quality-of-life
    - Declining to participate
  - For many (?most) studies, additional reduction in probability of unplanned pregnancy does not justify the burdens placed on participants and their partners
    - Current ongoing discussions with sponsor for Parkinson's study with minimum age of 55

Double methods

- Barrier requirement is reasonable for viral vectors
  - Only condoms (male or female) effective in preventing transmission
  - Should be required for all sexual activity regardless of reproductive status of partner
  - Consents often ambiguous or inconsistent
    - Focus on male→female transmission
    - Many do not discuss other sexual partnerships

Methods for People Who Can Produce Sperm

- Potential rationales
  - Seminal transmission of drug
    - Analogous to prevention of viral STIs like HIV/hepatitis
    - Requires condom use in all cases (including post-vasectomy)
    - Most protocols only discuss partners who could possibly become pregnant, but, like HIV/hepatitis, potential exposure is highest with non-vaginal intercourse
    - If condoms required, ICF needs to include statement that condoms required for all types of intercourse in the event of pregnant or breastfeeding partner
    - Minimal post-study drug requirement for condom use: 5 terminal half-lives of drug
  - Direct DNA/sperm damage
    - Minimal post-study drug requirement: 90 days (life span of sperm)
    - No rationale for requiring condoms if female partner is using a highly effective method (analogous to allowing partner vasectomy for female participants)

- Protocols often ambiguous about rationale
  - Inconsistent durations of contraception requirement
  - Inconsistent requirements

Methods for People Who Can Produce Sperm

- Male contraception requirement for trials of drugs already approved for another indication
  - Very few approved drugs have explicit language in label or prescribing information regarding potential pregnancy outcomes from paternal use
  - Rationale for requirement in this setting is not clear
    - From sponsor's perspective, ?potential liability exposure
      - In event of pregnancy loss or anomaly in partner of patient taking drug for approved indication: "Why did you warn participants in clinical trial about potential risks but not my client?"

Partners who Could Possibly Become Pregnant

- Requirement for partners able to become pregnant to use a highly effective method of contraception
  - Pragmatic issues
    - No current REMS for reproductive toxicity have any statements about female partner use (including thalidomide)
    - Documentation (HIPAA?)
    - Minor partners
    - No gynecologist would prescribe hormonal methods/place IUD in 50+ perimenopausal patient in order to allow partner to participate in a trial
  - Ethical issues
    - Partners are not consenting to research participation and do not have therapeutic relationship with study team
    - All systemic methods have risks, and even barrier methods have potential issues
      - Requiring nonconsenting partner to take on those risks/burdens as condition of partner participation violates basic research ethics
    - Telling participant to inform their partner they “should” or “must” use specific methods
      - Sponsor, study team, participant do not have knowledge or right to judge appropriateness of specific methods for specific female partner—violates principles of both research ethics and reproductive justice
      - Creates potential conflict for couple

Partners who Could Possibly Become Pregnant

- Duke approach
  - "You should tell your partner about your participation in this research and the potential risks to a pregnancy. If you have not had a vasectomy and they are not using another method of birth control, they should discuss options with their doctor."
  - Alternative: protocol amendment to make partner use of specified methods at time of enrollment an eligibility criterion
    - Still have issues with documentation, but avoids issues arising when partner not using specified methods

Common Issues: What Happens if Pregnancy Occurs

Pregnancy Reporting

- Most protocols require reporting of pregnancy and follow-up of pregnancy outcomes
  - Almost all include language such as “health of the baby for up to one year” that implies all pregnancies will result in a live birth
  - Doesn’t
    - Account for very high miscarriage rate even in healthy women (20-30%, over 55% in women over 40)
    - Potential for termination, either elective or because of high risk of underlying condition (maternal mortality >50% for some cardiac conditions)
  - Add qualifier such as “if appropriate, information on the health of the baby”
- Reporting of partner pregnancy
  - Requires separate consent
  - In states where pregnancy does not automatically emancipate minor (NC), would require parental consent as well
    - Specified in Duke adolescent ICFs where partner reporting is mentioned
  - If pregnant partner reporting required, then need to include contraceptive language in consent
    - To ethically justify research, there has to be uncertainty
    - If sufficient uncertainty about effects of paternal exposure to justify collecting data, then participants should be informed and asked to take precautions

Impossible Scenarios

- “You should not breastfeed during the study and for 3 months after your last dose of study drug”
  - Breastfeeding excluded at screening
  - Study drug stopped in event of pregnancy
    - No scenario where breastfeeding would be possible within 3 months.

Pregnancy-related Costs

- “The sponsor has not set aside funds to pay for obstetric, newborn, or pediatric care and is not responsible for such costs” in reproductive risk/contraception section
- Pregnancy possible even if participant conscientiously follows contraceptive requirements
  - Analogous to a complication of a standard-of-care treatment/test
- By including in section on need to avoid pregnancy, sponsor is implicitly suggesting that reimbursement for pregnancy-related care is a potential incentive to not following contraception requirements
- If included, belongs in section related to compensation for research-related risks

Summary

What I See When I Read the Inclusion/Exclusion Criteria

What I See When I Read the Inclusion/Exclusion Criteria

What I See When I Read the Pregnancy Testing and Contraception Protocol

Summary

- Majority of sponsor protocols/ICFs
  - Assume all potential study participants have the fertility, libido, and judgment of a college freshman on a Saturday night
- Reality
  - Risk of unplanned pregnancy is very low for majority of trial participants
  - Study specific requirements do not meaningfully reduce this risk and often impose undue burdens that can have significant impact on quality of life
- Development of consistent, evidence-based standards would make things better for everyone, most of all participants

Research Agenda

- Quantifying pregnancy risk for specific diseases/conditions
  - Prioritizing implementation of PRGLAC recommendations
  - Prioritizing improved contraception strategies for conditions associated with teratogenic drug use and/or severe maternal morbidity and maternal mortality
  - Identifying conditions where pregnancy risk rare enough to improve comfort with alternative approaches (such as consent addendums)
  - Estimating efficiency of requirements
    - Time costs for reviewing contraception requirements/number of pregnancies prevented by the requirements

Research Agenda

- Participant Perspective
  - **Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES)**
    - NIH-funded
    - Interviews with people able to become pregnant in US and Africa with HIV about contraception requirements for studies, participation during pregnancy
    - Insight into perspectives relevant to cultural differences, impact on relationships, convenience, control
  - Similar empiric work needed for other conditions
    - Particular focus on 40-54 age group
    - Impact of specific requirements on
      - Willingness to participate
      - Quality-of-life
    - Consent language
      - Impact on overall consent process
        - E.G, impact of irrelevant material on overall understanding of participation requirements, risks, potential benefits
  - Parents and adolescents
    - Pregnancy testing and contraception requirements
    - Long-term issues with gene therapies

Policy Agenda

- Multiple stakeholder consensus process
  - Patients/participants
  - Research study teams
  - FDA (probably international regulators as well)
  - Contract research organizations
  - IRBs (including major central IRBs)
  - Sponsors
    - Industry
    - NIH/other federal
    - Non-profits (ACS, AHA, etc)

Policy Agenda

- Uniform definition of “pregnancy potential”
  - Existing guidance from Clinical Trials Facilitation and Coordination Group, but not universally used
  - Definitions of “childbearing potential” and contraceptive method effectiveness are reasonable, but no consideration of different patient populations
- Incorporation of effects of age and condition into
  - Pregnancy testing requirements
  - Contraception requirements for participants and partners
- Sample consent language templates

Resources

- Clinical Trials Transformation Initiative: Pregnancy Testing
  - https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/recommendations/pregnancytesting_recommendations_final_0.pdf
- CDC: Contraception Effectiveness and Medical Eligibility
  - https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html
- Male Contraception Considerations
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4960246/
- ICH Guidance on Contraception and Pregnancy Testing
  - https://www.uni-due.de/imperia/md/content/ethikkomission/kontrazeption.pdf
- Duke IRB Policy/Guidance
  - https://irb.duhs.duke.edu/policies-and-regulations/policies/pregnancy-testing
  - https://irb.duhs.duke.edu/policies-and-regulations/policies/contraceptive-use
- HHS Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)
  - https://www.nichd.nih.gov/about/advisory/PRGLAC
- PHASES
  - http://www.hivpregnancyethics.org/