

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

**Duke-Margolis Center for Health Policy**

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April 16, 2018

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

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 #TrialsEligibility

# **Inclusion and Exclusion in Clinical Trials**

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**CDER - FDA**

April 16, 2018

# Diversity in Clinical Trials



## Historical Perspective

- Typically, researchers try to limit variability in study population to avoid altering the outcome of interest and to maximize the chances of showing effect.
- This could lead to excluding older patients and patients with multiple chronic conditions.
- Although narrowing the study population may help demonstrate the effect of interest, it also reduces the chances of understanding how a specific drug will work in real world (limiting generalizability).



# Diversity in Clinical Trials

## Historical Perspective



- FDA had long warned against the exclusion of particular subgroups from clinical trials without scientific basis.
- One of the earliest attempt to broaden inclusion was back in 1983 - FDA published draft guidance: "Guideline for the Study of Drugs Likely to be Used in the Elderly" which was finalized in 1989 (elderly was defined as over 65).
- 1993 ICH E7 - Studies in Support of Special Populations: Geriatrics  
*"It is important, however, to seek patients in the older age range, 75 and above, to the extent possible."*
- In 1993, the FDA published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs.

# Diversity in Clinical Trials

## Historical Perspective



- Although there are no regulatory requirement for broad patient participation, there is a long standing interest in the content of an NDA – FDA called for integrated summaries of effectiveness and safety including analysis by subgroups (gender, age, racial, patients with renal failure and different level of disease severity).
- In 2013 CDER released a revised Good Review Practices (MAPP) which encouraged all IND reviewers to be concerned about and to discourage needless exclusions from clinical trials.
- Recently (April 2018) FDA issues a draft guidance on the inclusion of pregnant women in clinical trials.

## Good Review Practice - Clinical Review of Investigational New Drug Applications

- “Reviewers should consider the distribution of subjects and ensure
  - That there are no unjustified subject exclusions (e.g., subjects over 75 years of age)
  - that PK differences among different subpopulations (including age, gender, race and organ dysfunction) are examined in specific trials or by population PK to determine the need for dosage adjustment in these subpopulations”
- “Reviewers should closely examine exclusions in phase 3 trials to consider whether they are really needed. It has been common, for example, to exclude patients older than 75, but there is no good reason to do this. Similarly, exclusions of patients with a history of psychiatric or cardiovascular illness, unless dictated by the drug’s pharmacology, decrease the opportunity to detect important drug-drug interactions and should be discouraged.”

# Analysis of Subgroup



- Inclusion is only a start.
- FDA has long encouraged analysis of effectiveness and safety data in demographic and other subgroups.
- Since 1985, guidances have more fully emphasized the need to consider population subgroups.
- 1988 guidance on Format and Content of the Clinical and Statistical Sections of an Application
  - Urges analysis of pooled data for effectiveness and safety as well as dose response in subgroups including those with concomitant illnesses, smokers, patients with varying disease severity, etc.



# Labeling



- Labeling Requirements listed in 21CFR201.57 refer to the need to address and describe subgroup differences with respect to:
  - Indications and usage (age, severity)
  - Dosage and administration (Pediatric, geriatric, renal or hepatic disease, genetic characteristics)
  - Contraindications (age, severity, concomitant therapy, etc.)
  - Adverse reactions (dose, demographic, etc.)
- Guidances elaborate on best practices on how to present such data (i.e., forest plots).

# Inclusion / Exclusion are **NOT** Everything



- There are multiple other reasons that may discourage or prevent enrollment of subpopulations in clinical trials, for example:
  - Difficulties getting to the clinic (e.g., cannot drive or leave a job)
    - Potential remedy – Home-based studies, mHealth, TeleHealth, etc.
  - Historical lack of trust
    - Potential remedy – Community communication and involvement (e.g., barber shops)

# Why are We Interested in Subgroups?



- Some population characteristics have predictable results.
- For example, people with the following conditions have reasonably predictable differences in response:
  - Other drugs that block metabolism (DDIs)
  - Poor renal function
  - Genetic deficiency in metabolic enzymes such as CYP450 2D6, or 2C19
  - Hepatic dysfunction
  - Genetic abnormalities
- **BUT** – at times, identified differences in response could not have been anticipated and would not be detected unless they are specifically investigated.

# Real Life Lessons...



- What is of interest is subset differences not expected from known PK interactions or renal/hepatic dysfunction – there are not many of these, but could it be that they are not sought enough?
  - BiDiI
  - LIFE - Losartan vs. Atenolol
  - PLATO - Ticagrelor
  - iib/iiia inhibitor



Losartan vs. atenolol  
(n=9193) in  
hypertensives with  
LVH. Endpoint: time  
to CV death, non-fatal  
stroke, NFMI

Treatments	
Losartan 50 +12.5 mg HCTZ	Atenolol 50 +12.5 mg HCTZ
Losartan 100 +25 mg HCTZ +other (not BB, ACEI, AIIB)	Atenolol 100 +25 mg HCTZ +other (not BB, ACEI, AIIB)
BP 144.1/81.3	145.4/80.9

# Results - LIFE



	Losartan N (%)	Atenolol N (%)	Risk Reduction	95% CI	P
Composite	508 (11)	588 (13)	13%	2-23	0.021
CV Mortality	125 (3)	134 (3)			
NF Stroke	209 (5)	286 (6)			
NF MI	174 (4)	168 (4)			
Individual Endpoint					
Stroke (F/NF)	232 (5)	309 (7)	25%	11 to 37	0.001
AMI (F/NF)	198 (4)	188 (4)	-7%	-13 to 12	0.491
CV Mortality	204 (4)	234 (5)	11%	-7 to 27	0.206
CHD	125 (3)	124 (3)	-3%	-32 to 20	0.839
Stroke	40 (0.9)	62 (1)	35%	4 to 67	0.032
Other	39 (0.8)	48 (1)	10%	-28 to 45	0.411

Results in Blacks			
	Losartan	Atenolol	HR (95% CI)
Composite	46/270 (17%)	29/263 (11%)	1.67 (1.004-2.56) p=0.03
Stroke	24/270 (9%)	12/263 (4.5%)	2.2 (1.079-4.401) p=0.03
Composite: black vs. non-black interaction p=0.005			

# Amlodipine

## ADRs by Gender

ADR	Amlodipine		Placebo	
	M(%)	F(%)	M(%)	F(%)
	n=1218	n=512	n=914	n=336
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

Pooled placebo controlled trials, all doses

# Ticagrelor - PLATO

18,624 patient study in ACS within 24 hours of event randomized to ticagrelor, 180 mg, 90 mg bid or clopidogrel 600 mg, with 25 mg daily maintenance.

	Ticagrelor N = 9333	Clopidogrel N – 9271	HR
Composite (CV death, MI, stroke)	9.8	11.7	0.84
First Event			p = 0.0003
CV death	2.9	4.0	0.74
NFMI	5.8	6.9	0.84
NF Stroke	1.4	1.1	1.24
Total Events			
CV death	4.0	5.1	0.79 p = 0.0013
MI	5.8	6.9	0.84 p = 0.0045
Stroke	1.5	1.3	1.17 p = 0.22 <sup>14</sup>

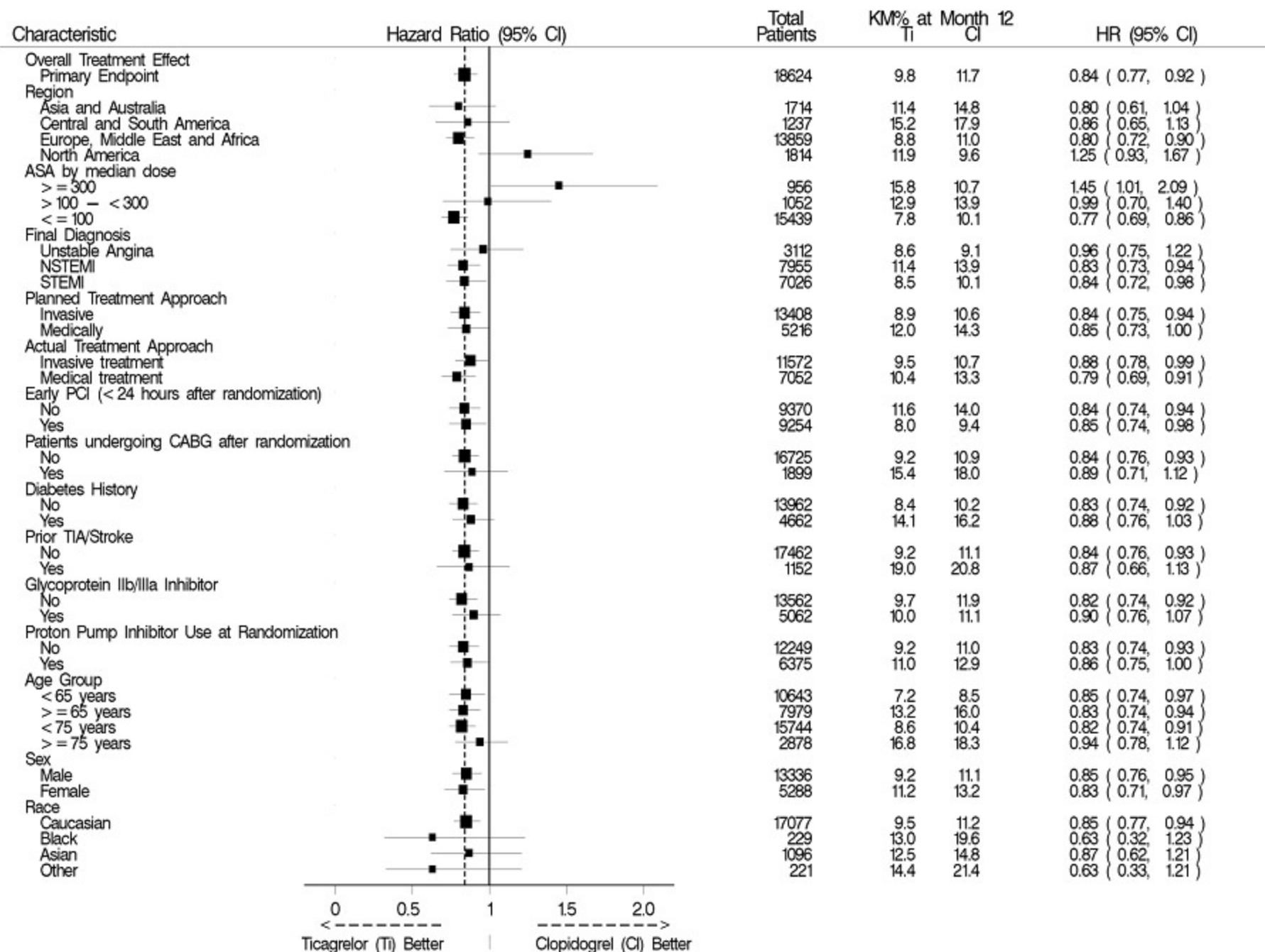
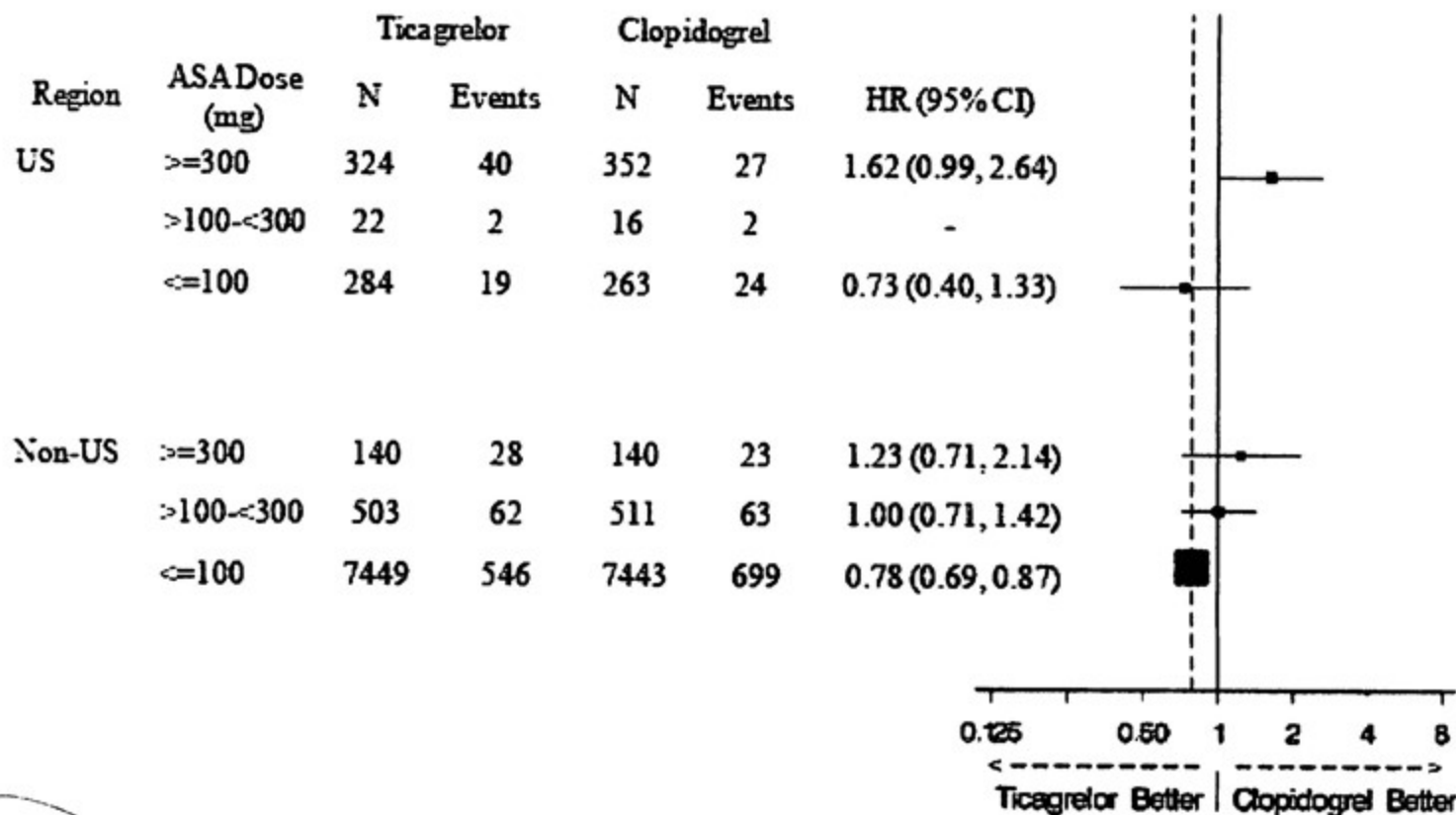


Table 5 - PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US



Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.



# FINAL COMMENT



- FDA thus has a long-standing interest in factors that can alter results (effectiveness or safety) in subsets of the population, including subsets defined by demography, renal or hepatic function, concomitant illness or treatment, or genetic or pathophysiologic differences.
- Understanding these differences enhances treatment effects and reduces risk.







# Rationale for Inclusion and Exclusion Criteria

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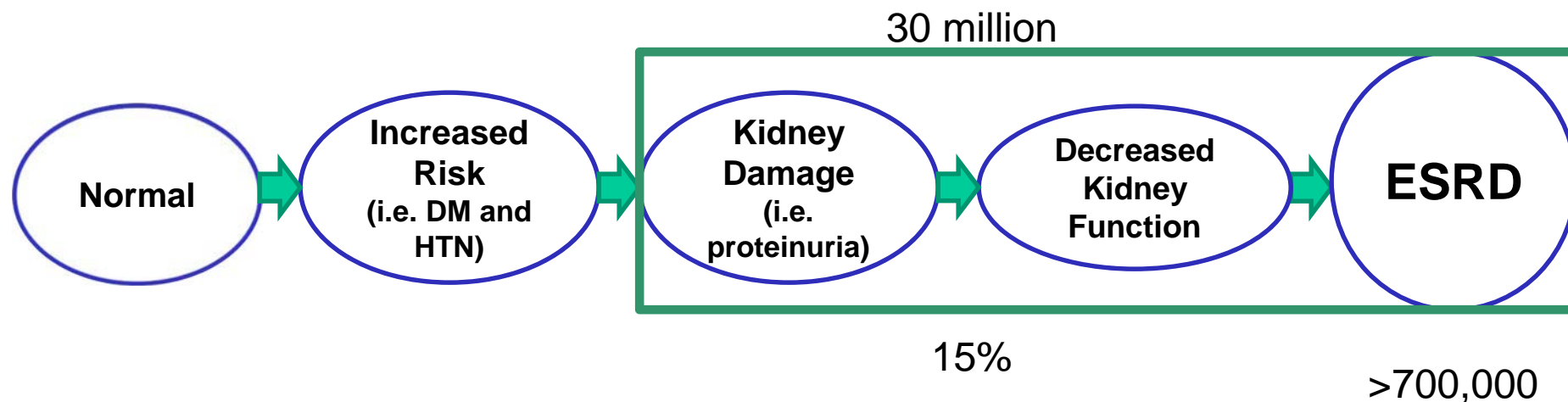


@DrDeidraCrews





# Chronic Kidney Disease Conceptualized



**Race/ethnicity**  
**Socioeconomic status**  
**Dietary pattern**  
**Family history/genetic factors**

# Kidney Disease Research Underfunded Relative to Costs of Kidney Care

- Government Accountability Office (GAO)
  - More spent on kidney failure in Medicare than the *entire* NIH budget

## Key Takeaways from GAO report data:

- ✓ NIH investments equal  
**<1% of the cost of care<sup>1</sup>**
- ✓ **\$103 billion**  
All Medicare kidney patient costs<sup>2</sup>
- ✓ **\$32.8 billion**  
Medicare kidney failure patient costs<sup>1</sup>
- ✓ **\$564 million**  
NIH investments in kidney research<sup>1</sup>

Government Accountability Office, January 18, 2017. Kidney Disease Research and Priority Setting.

# Clinical Trials in Kidney Disease

- Number of RCTs conducted in patients with kidney disease is among smallest compared with other medical subspecialties
- Nephrology RCTs have often examined intermediate outcomes that are of unclear significance to patients, providers, and families
- Complex nature of kidney disease has often led to **restrictive enrollment criteria** in clinical trials, limiting external validity

De Boer I., Kovesdy, C., Navaneethan S., Peralta C., Tuot D., Vazquez M., Crews D. for the ASN Chronic Kidney Disease Advisory Group. Pragmatic Clinical Trials in Chronic Kidney Disease – Opportunities and Challenges. J Am Soc Neph. 2016 Oct;27(10):2948-2954.



# The Trust 'Gap' Likely Influences Minority Participation in RCTs



- Compared to whites, African Americans & Hispanics experience:
  - Lower levels of trust in physicians and hospitals
  - Less participatory communication
  - More technical and biomedical conversation
  - Less rapport-building and psychosocial conversation

**Implicit Bias**

Hooper EM, Med Care (1982); Roter DL, JAMA (1997); Cooper-Patrick L, JAMA (1999); Oliver MN, J Nat Med Assoc (2001); Boulware LE, Pub Health Rep (2002); Cooper LA, Ann Intern Med (2003); Johnson RL, Am J Public Health (2004); Ghods B, J Gen Intern Med (2008); Cene C, J Gen Intern Med (2010); Beach MC, J Gen Intern Med (2010)

# Five, Plus Nuts and Beans *for Kidneys* Trial



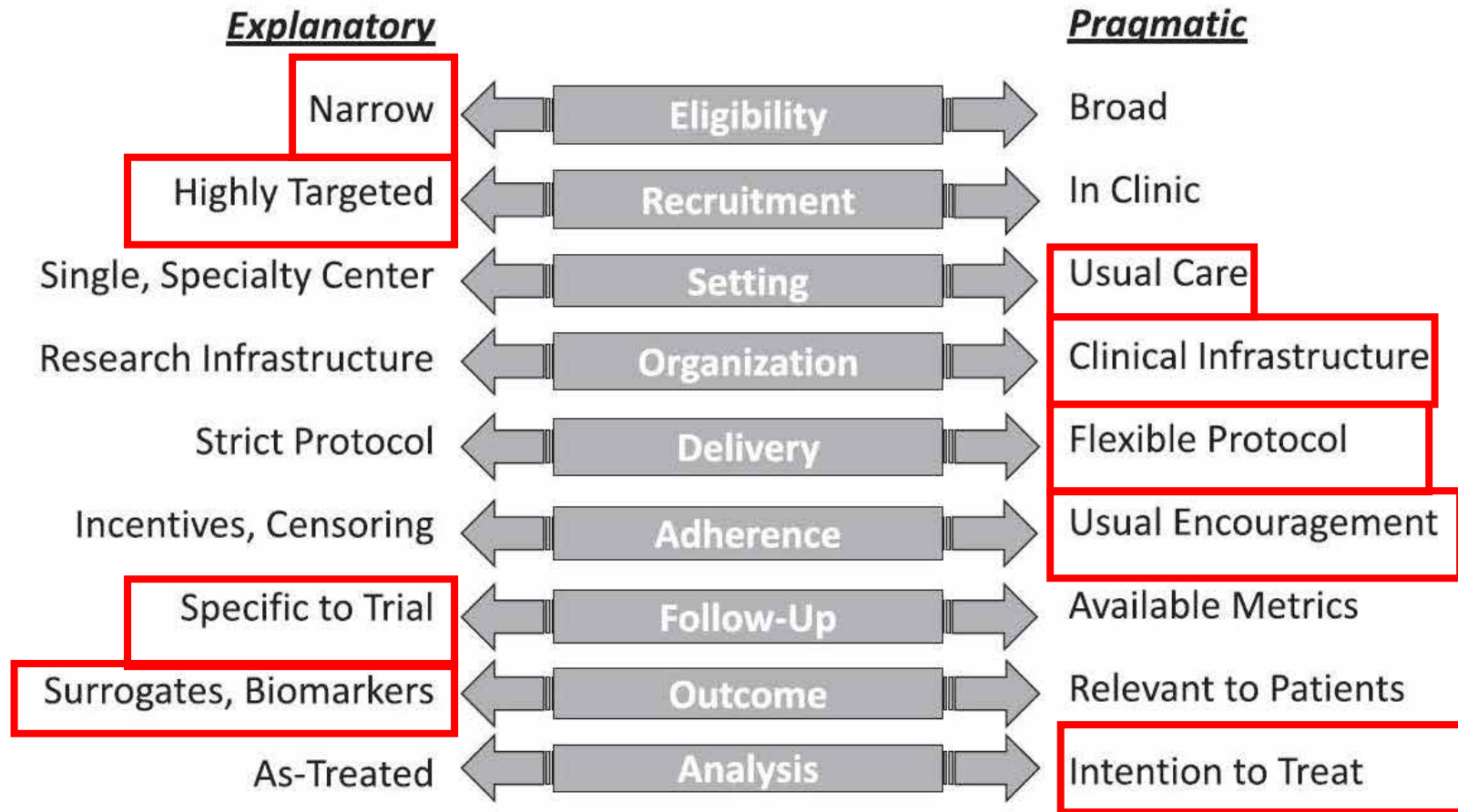
- Building upon the Five Plus Nuts and Beans pilot study (Miller ER, et al. *Am J Prev Med.* 2016)
- 12 month, community-based dietary RCT in **150 low income African Americans with hypertension and early kidney disease**
- Hypothesis: coaching to adopt the DASH diet and \$30 per week worth of potassium-rich foods (fruits, vegetables, nuts and beans) from a local grocer, **will reduce urinary albumin excretion**
- BP reduction is secondary outcome

Community-Based Dietary Approach for Hypertensive African Americans with Chronic Kidney Disease. National Institute for Minority Health and Health Disparities.

NCT03299816 <http://fiveplus4kidneys.weebly.com/>

PIs: Deidra Crews and Edgar 'Pete' Miller.

# Explanatory versus Pragmatic Trials



**Figure 1.** Domains of the explanatory-pragmatic clinical trial design spectrum.

De Boer I., Kovesdy, C., Navaneethan S., Peralta C., Tuot D., Vazquez M., Crews D. for the ASN Chronic Kidney Disease Advisory Group. Pragmatic Clinical Trials in Chronic Kidney Disease – Opportunities and Challenges. J Am Soc Neph. 2016 Oct;27(10):2948-2954.

# Inclusion Criteria



- Self-identified African American race
- Age 21 years or older
- Clinical diagnosis of hypertension and have a urine ACR of  $\geq 30$  mg/g with or estimated glomerular filtration of at least 30 ml/min/1.73m<sup>2</sup>.
- Must be under regular care with their Johns Hopkins Community Physicians provider (seen within the past 12 months).
- Must have a systolic blood pressure of  $\leq 160$  mmHg and a diastolic blood pressure of  $\leq 100$  mmHg (average of two visits)
- Be on stable doses of antihypertensive medications for a minimum of two months prior to randomization



# Exclusion Criteria



- Cardiovascular (CV) event within prior 6 months
- Chronic disease that might interfere with trial participation (e.g. eGFR  $<30$  ml/min/1.73m<sup>2</sup>)
- Unwillingness or inability to adopt a DASH-like diet
- Consumes over 14 alcoholic drinks per week
- Poorly controlled diabetes (Hemoglobin A1c  $>9\%$ ), or use of insulin
- Serum potassium  $>4.6$  mEq/L
- Urine albumin-to-creatinine  $\geq 1,000$  mg/g
- Pregnant or trying to become pregnant

# Final Thoughts on Inclusion/Exclusion Criteria

- Selected criteria can exist on the spectrum of explanatory to pragmatic trials
- Socially disadvantaged groups may have mistrust of RCTs, influencing their participation
- Medically complex patient populations may require tailored criteria
- Selected criteria dictate the external validity of the study findings



Thank you

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 #TrialsEligibility



# Review of Eligibility Criteria From a Sample of Approved Drugs and Biologics

Kaveeta Vasisht M.D., Pharm.D.

Office of Medical Policy

CDER/FDA

April 16, 2018

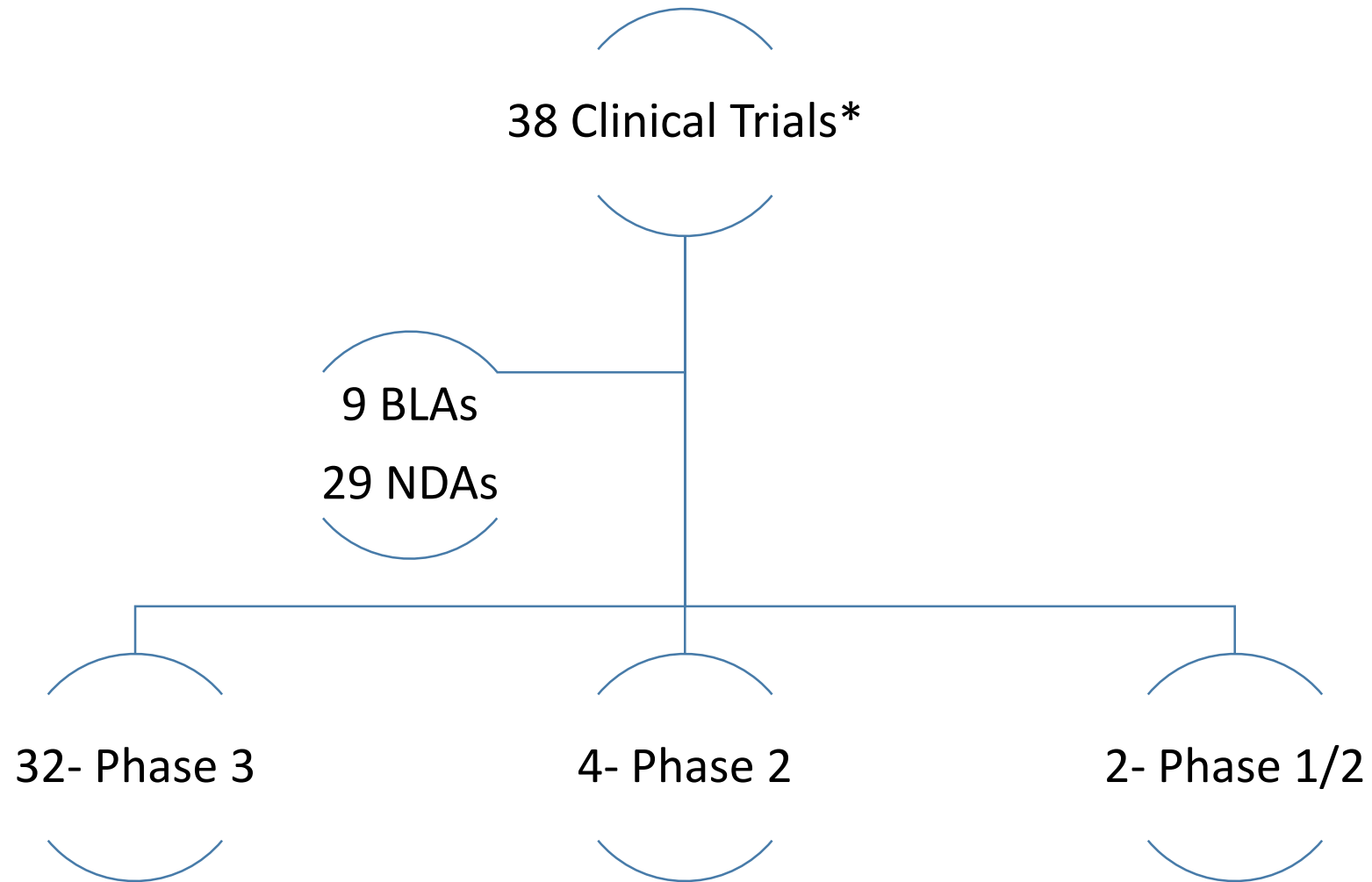
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

# Study Details

A retrospective pilot study that reviewed eligibility criteria from a sample of pivotal trials supporting drug/biologic approvals.

## Objectives:

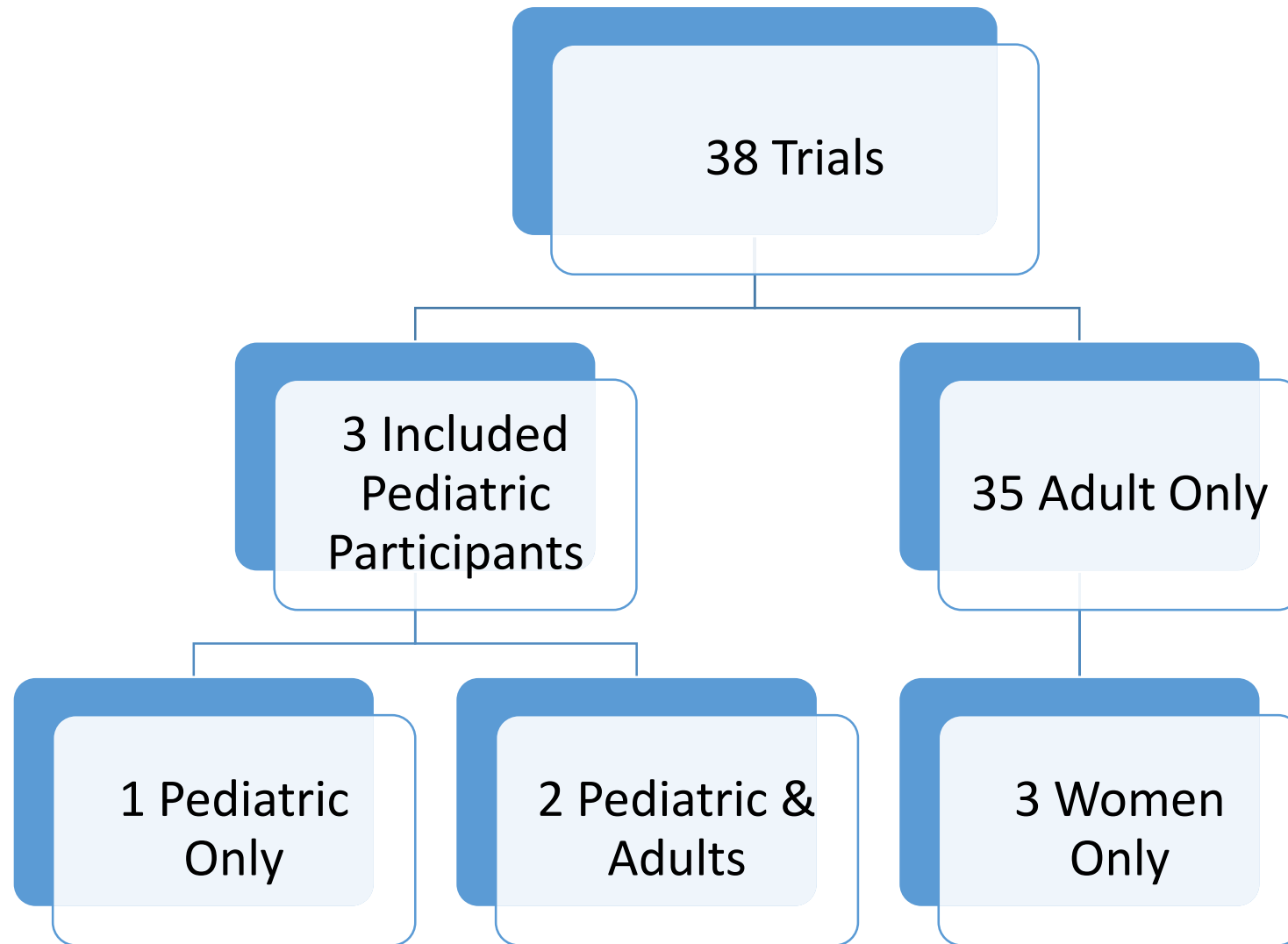
- Identify general patterns in exclusion criteria.
- Describe the demographic characteristics of enrolled participants.



\* 37 of the trials were from 37 different novel drug approvals (new molecular entities or original biologic products) between 2014-2017. 1 trial was not from a novel drug approval.

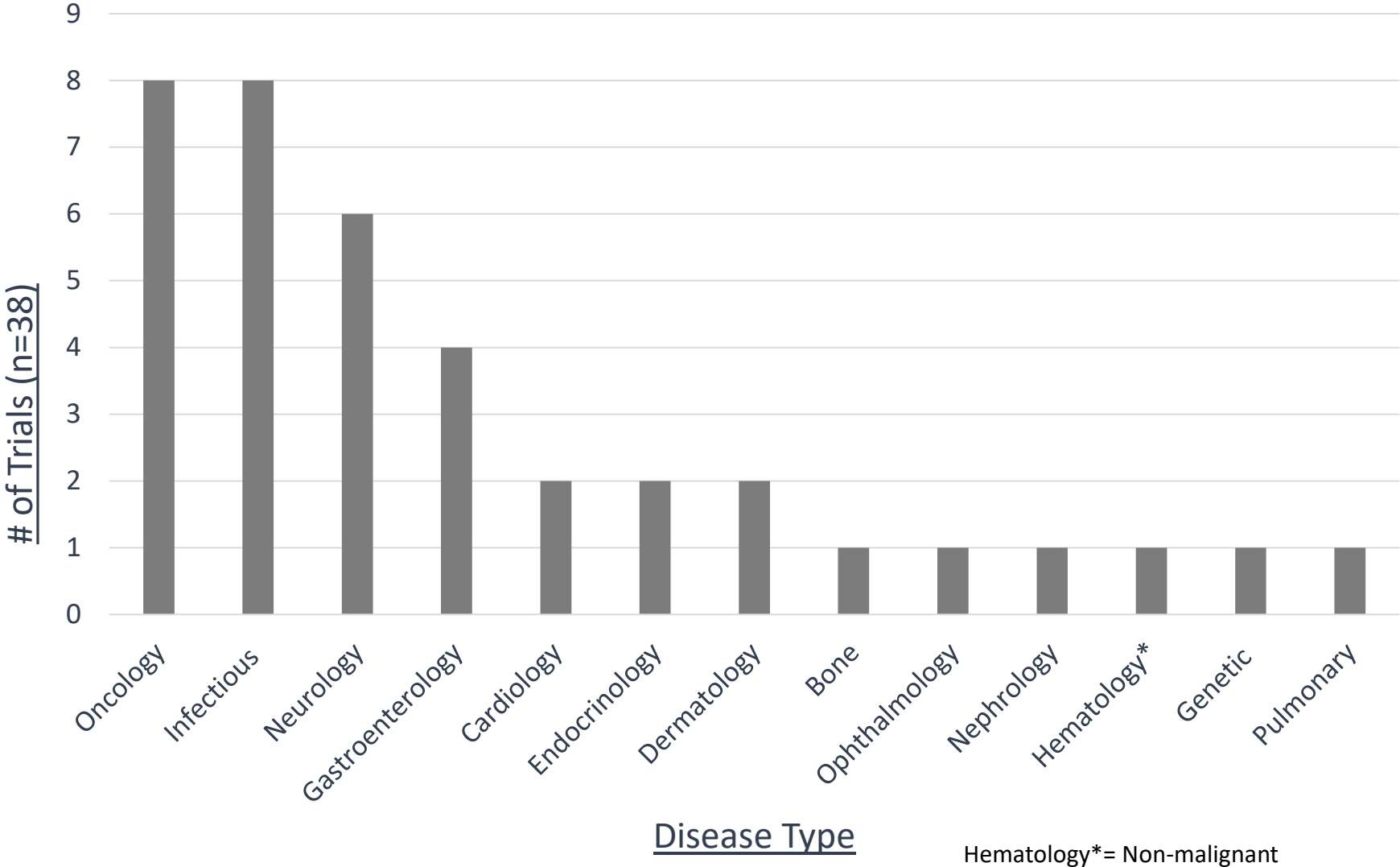
NDA= New Drug Application, BLA= Biologics Licensing Application





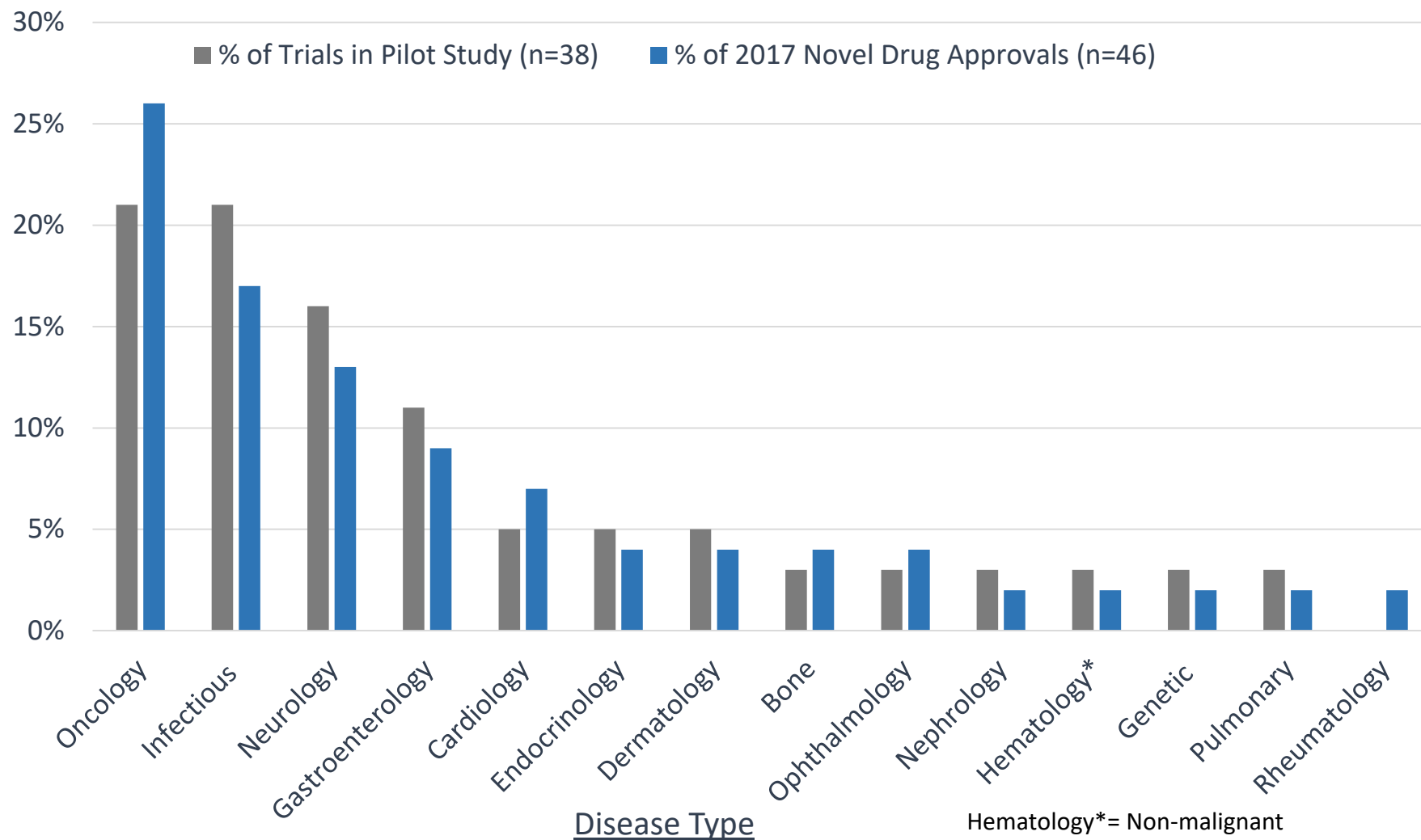


# Distribution of Trials by Disease Type





# Distribution of Trials Compared to 2017 Novel Drug Approvals



# Criteria Commonly Not Excluded

Demographic Criteria	% of Trials (n=38)
Females	100
Males*	100
Race/Ethnicity	100
Age >65 yrs.**	95
Age >75 yrs.**^	86

\*n=35 (excludes studies for indications limited to females),

\*\*n=37 (adult only trials), 1 trial excluded participants > 70 yrs.,

^ 5 trials excluded participants > 80 yrs.

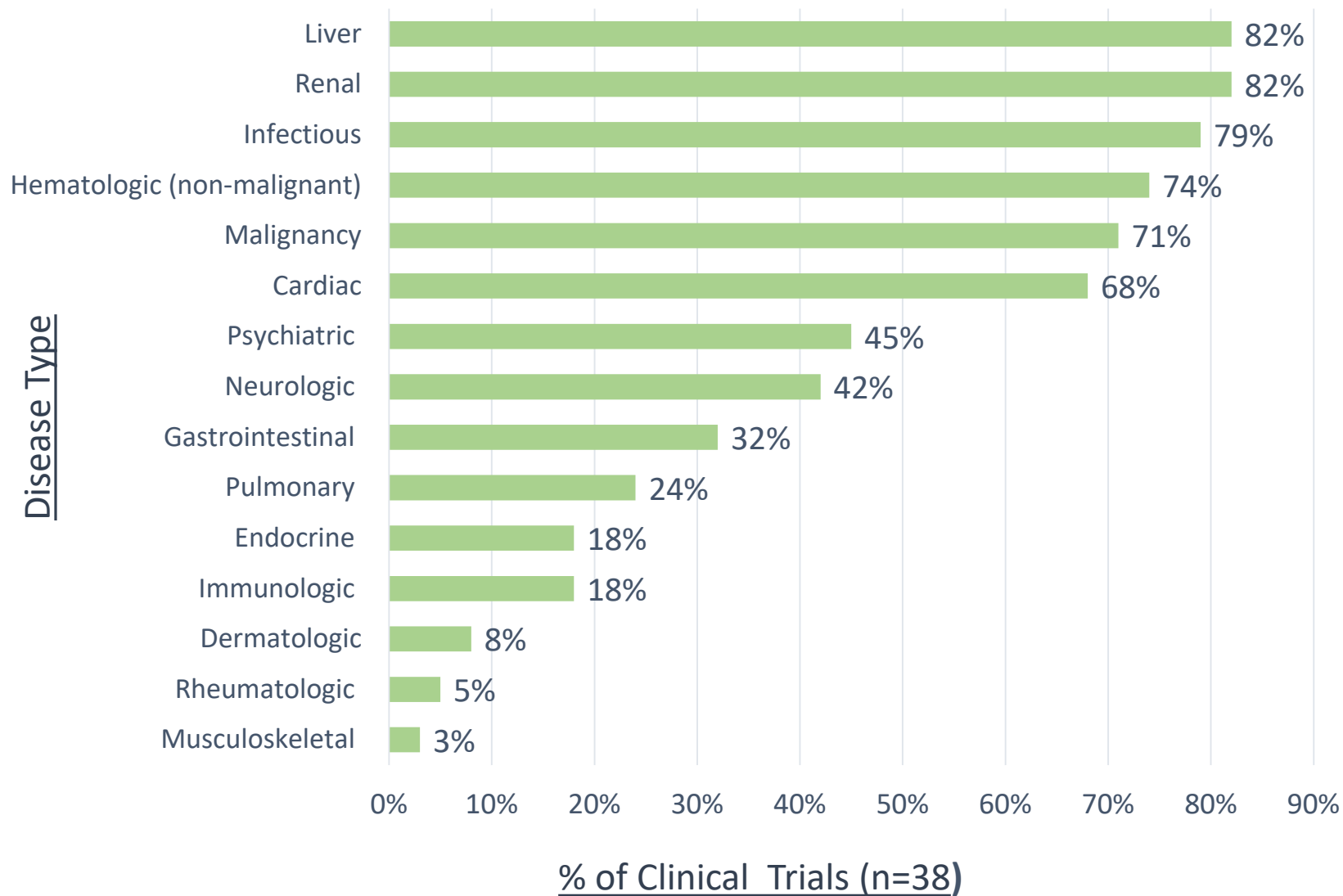


# Common Exclusions

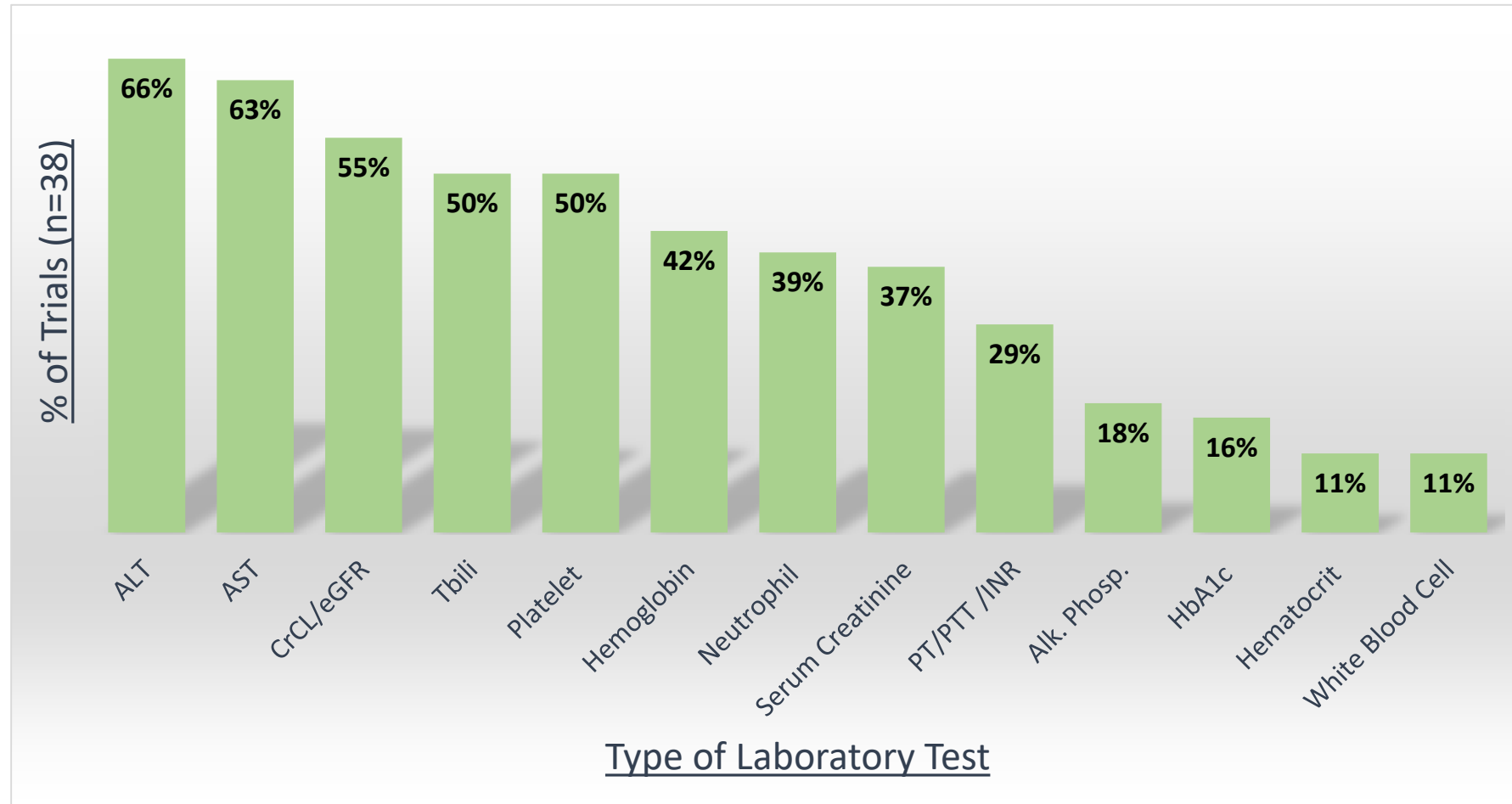
Criteria	% of Trials (n=38)
Age <18 yrs.	95
Pregnant women	95
Lactating/Breastfeeding*	92
Women of reproductive potential <b>NOT</b> on adequate contraception	82
Investigator's discretion	79

\* Majority of trials excluded lactating women (34% excluded for breastfeeding)

# Exclusions by Disease Type



# Exclusions by Laboratory Test



ALT= Alanine Aminotransferase, AST= Aspartate Aminotransferase, CrCl= Creatinine Clearance, eGFR= estimated Glomerular Filtration Rate, PT= Prothrombin Time, PTT= Partial Thromboplastin Time, INR= International Normalized Ratio, Alk. Phosp.= Alkaline Phosphatase.



## Renal Related Exclusions

Criteria	% of Trials (n=38)
Any renal related criteria	82
CrCl or eGFR*	58
Serum Creatinine**	37
Other Renal	24

\* CrCl/eGFR: 47% of trials had a exclusion based on CrCl, 13% excluded based on eGFR. Majority used a cutoff of < 60 ml/min.

\*\* Serum Creatinine: > 1.5 – 2.0 mg/dL or 1.5x upper limit of normal.



# Liver Related Exclusions

Criteria	% of Trials (n=38)	% of Trials *(adjusted, n=33)
Any liver related criteria	82	79
ALT	66	67
AST	63	67
T.bili	50	45
Other Liver	47	39

\*(adjusted, n=33) excludes trials conducted for a liver related condition.  
AST and ALT exclusion range: 2-10x upper limit of normal. Equal number of studies excluded participants for 2, 2.5 or 3x upper limit of normal.

# Infection Related Exclusions

Criteria	% of Trials (n=38)
Any infection related criteria	79
HIV or AIDS*	59
Positive Hep B	47
Positive Hep C **	40

\*n=37 trials (excludes HIV study), \*\*n=35 trials (excludes Hepatitis C studies)



# Cardiac Related Exclusions

Criteria	% of Trials (n=38)	% of Trials *(adjusted, n=36)
Any cardiac related criteria	68	67
Heart Failure	34	33
Other Cardiac	34	42
Myocardial Infarction	29	28
EKG abnormality	29	31
QTc	26	28
Cerebrovascular Accident	24	22
Blood Pressure	24	19

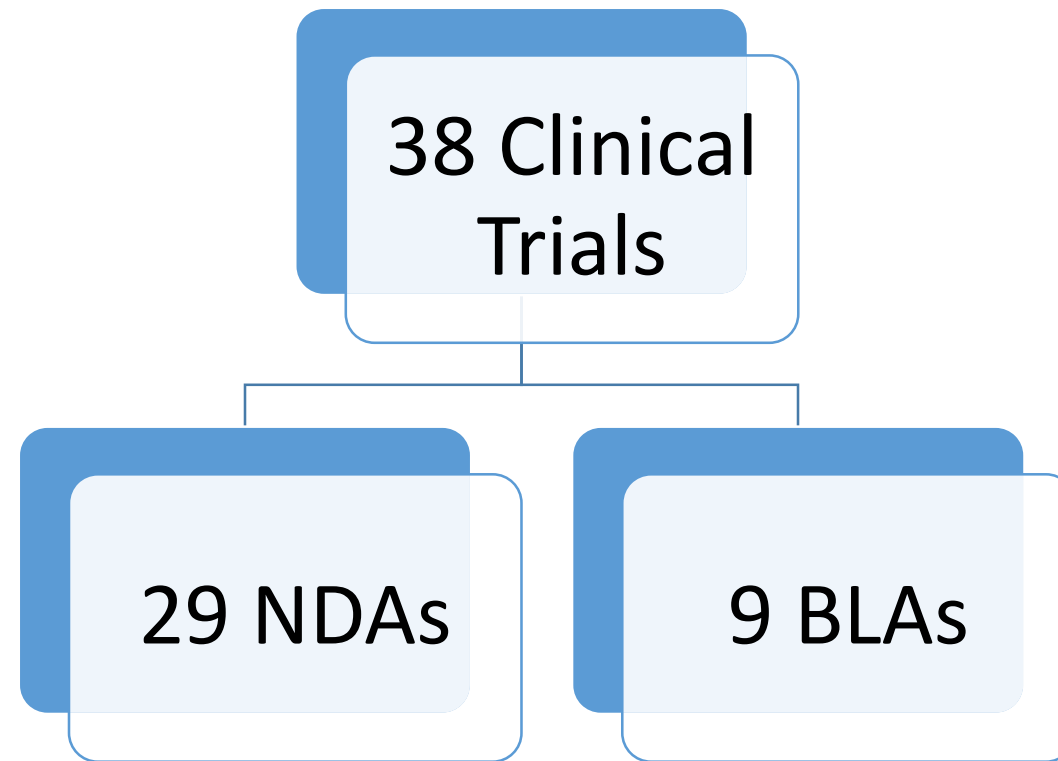
\*(adjusted, n=36) excludes trials conducted for a cardiac related condition.

# Malignancy and Substance Abuse Exclusions

Criteria	% of Trials (n=38)	% of Trials *(adjusted, n=30)
Malignancy	71	63
<ul style="list-style-type: none"><li>Exclusions ranged from active malignancies to within the past 2 to 5 years.</li></ul>		
Criteria	% of Trials (n=38)	
Substance Abuse	50	
<ul style="list-style-type: none"><li>Exclusions ranged from active use to within the past 3 months to 2 years.</li></ul>		

\* (adjusted, n=30) excludes trials conducted for a malignancy.

# NDA's vs. BLA's



NDA= New Drug Application, BLA= Biologics Licensing Application



# Exclusions: NDAs and BLAs

Criteria	% of NDAs (n=29)	% of BLAs (n=9)
Age <18 yrs.	97	89*
Pregnant women	93	100
Lactating/Breastfeeding	93	89
Women of reproductive potential <b>NOT</b> on adequate contraception	83	78
Investigator's discretion	83	67

\*1 pediatric only study.

## Exclusions: NDAs and BLAs

Disease Criteria	% of NDAs (n=29)	% of BLAs (n=9)
Renal	90	56
Liver	83	78
Infectious	79	78

# Eligibility Criteria Conclusions

- 82% of clinical trials in our pilot study had a renal or liver based exclusion.
  - The majority were based on a laboratory threshold.
- $\approx$  80% of clinical trials allowed investigators to use their discretion in excluding subjects.
  - No evidence if, or how often, used
- NDAs had a higher percentage of renal exclusions compared to BLAs.

# Demographics

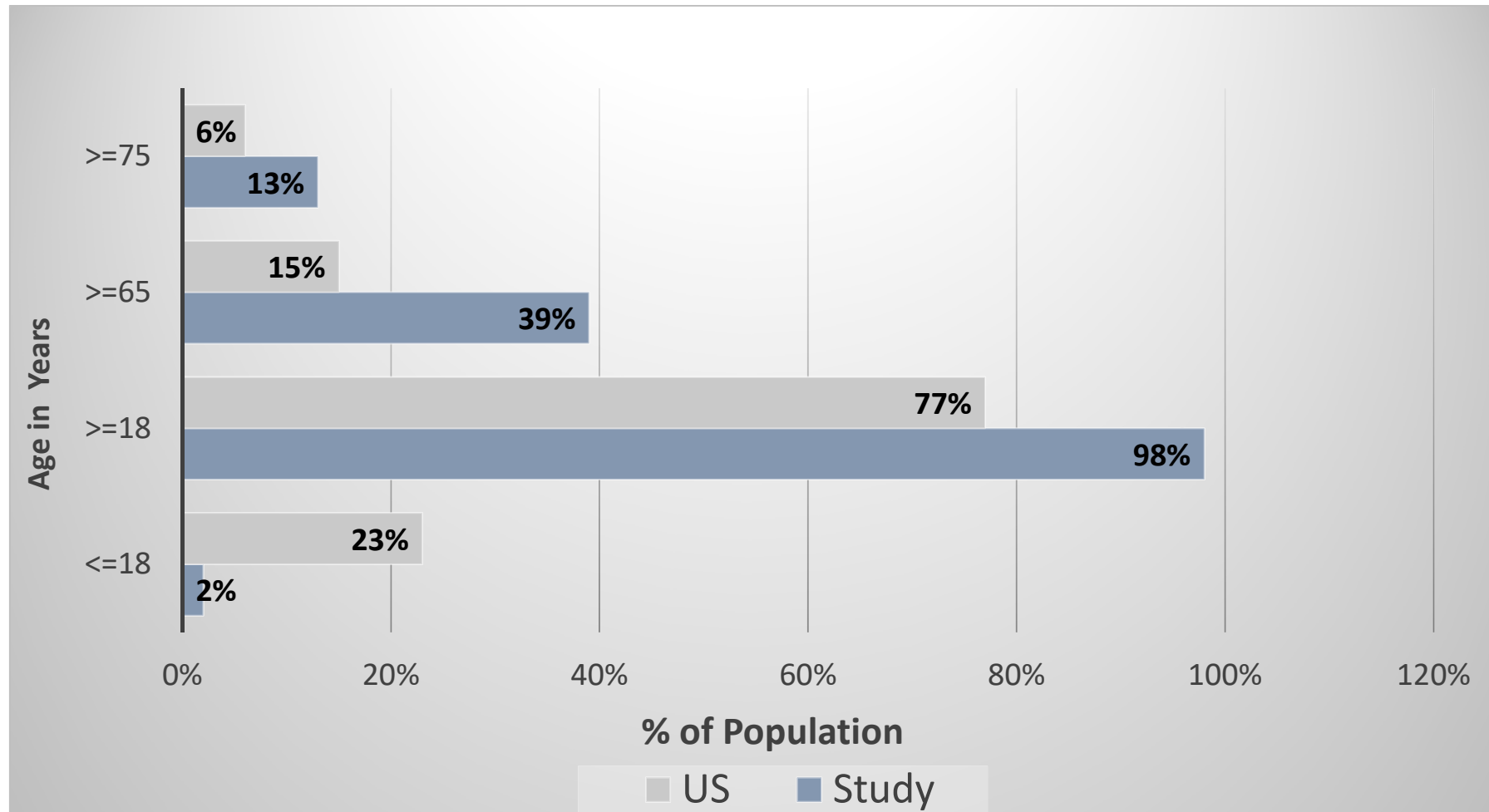
## Baseline Demographics of Study Population by Age

Total Population 40,892 (n=38)

Mean age	50.56	
Min, Max (n=33)	<1, 100	

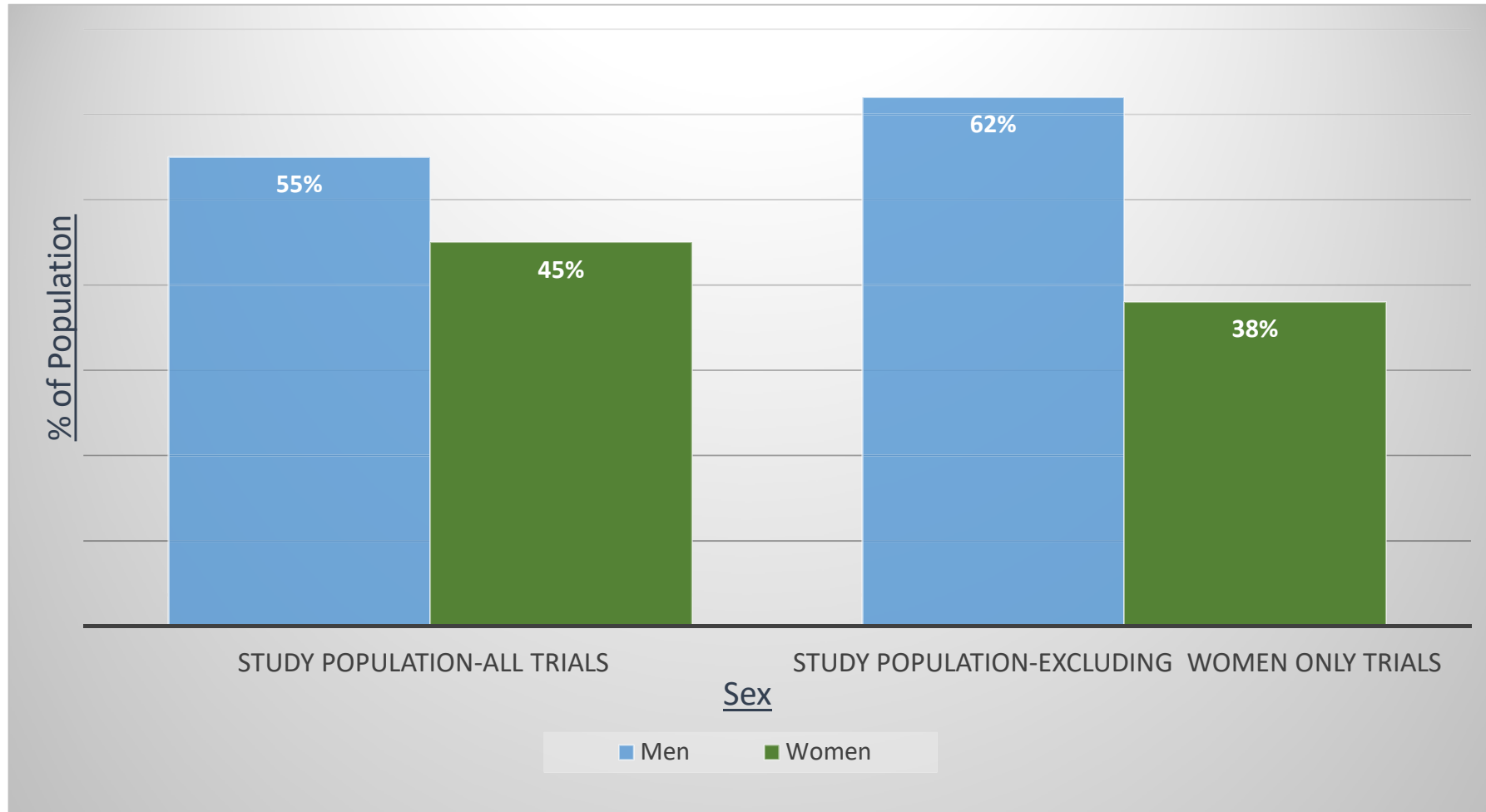
Age in years (# of trials)	Population	% of Population
$\geq 18$ (n=37)	40,073 /40,758	98
$\geq 65$ (n=33)	14,467 /37,458	39
$\geq 75$ (n=19)	2,751 /20,684	13

# Age Demographics of Study Population Compared to U.S. Population\*



\* July 1, 2016 US Census Bureau (V2016)(a)

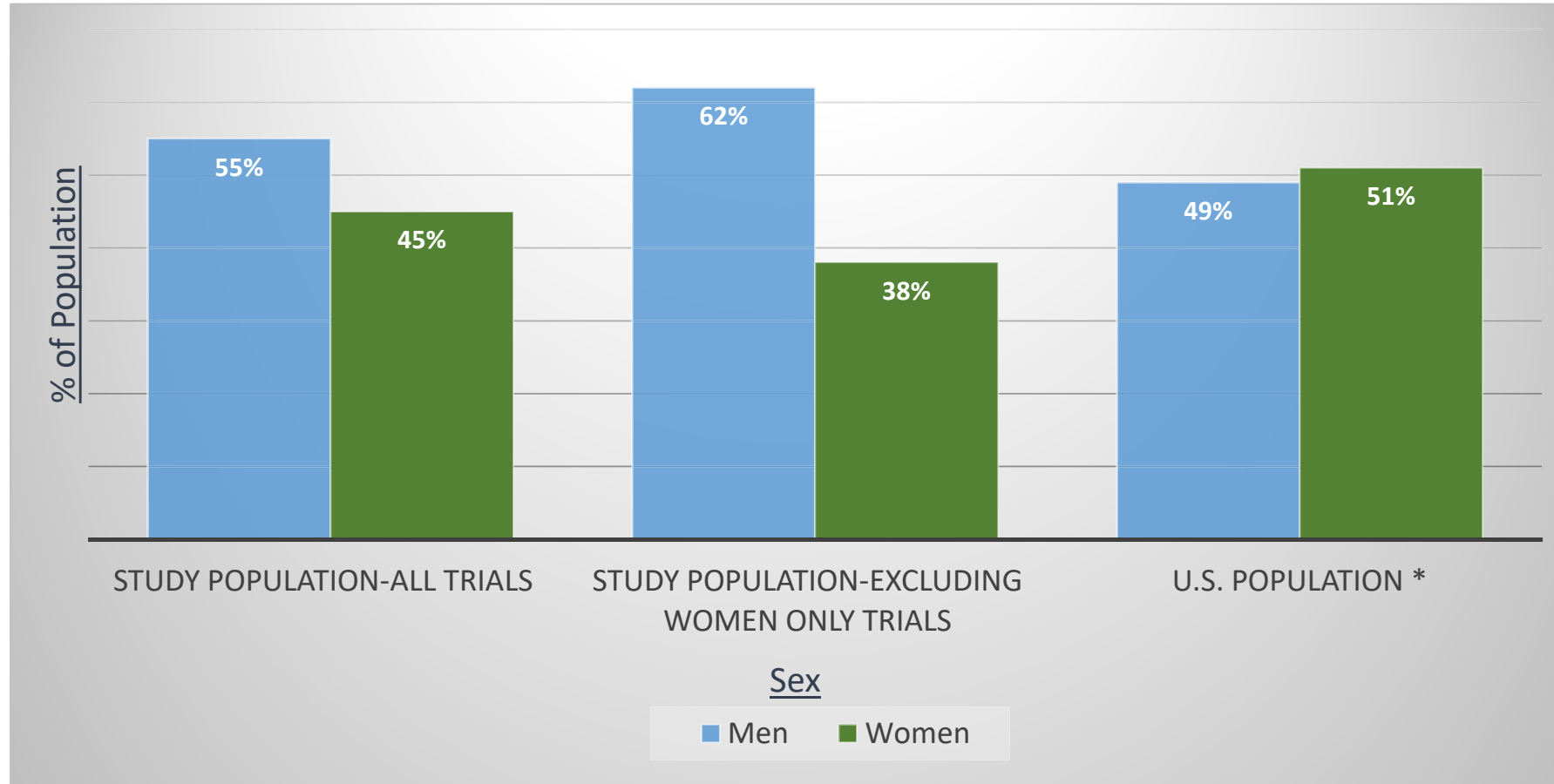
# Sex Demographics of Study Population



Study Population: All Trials (N= 40,892); Excluding Women Only Trials (N=36,644)

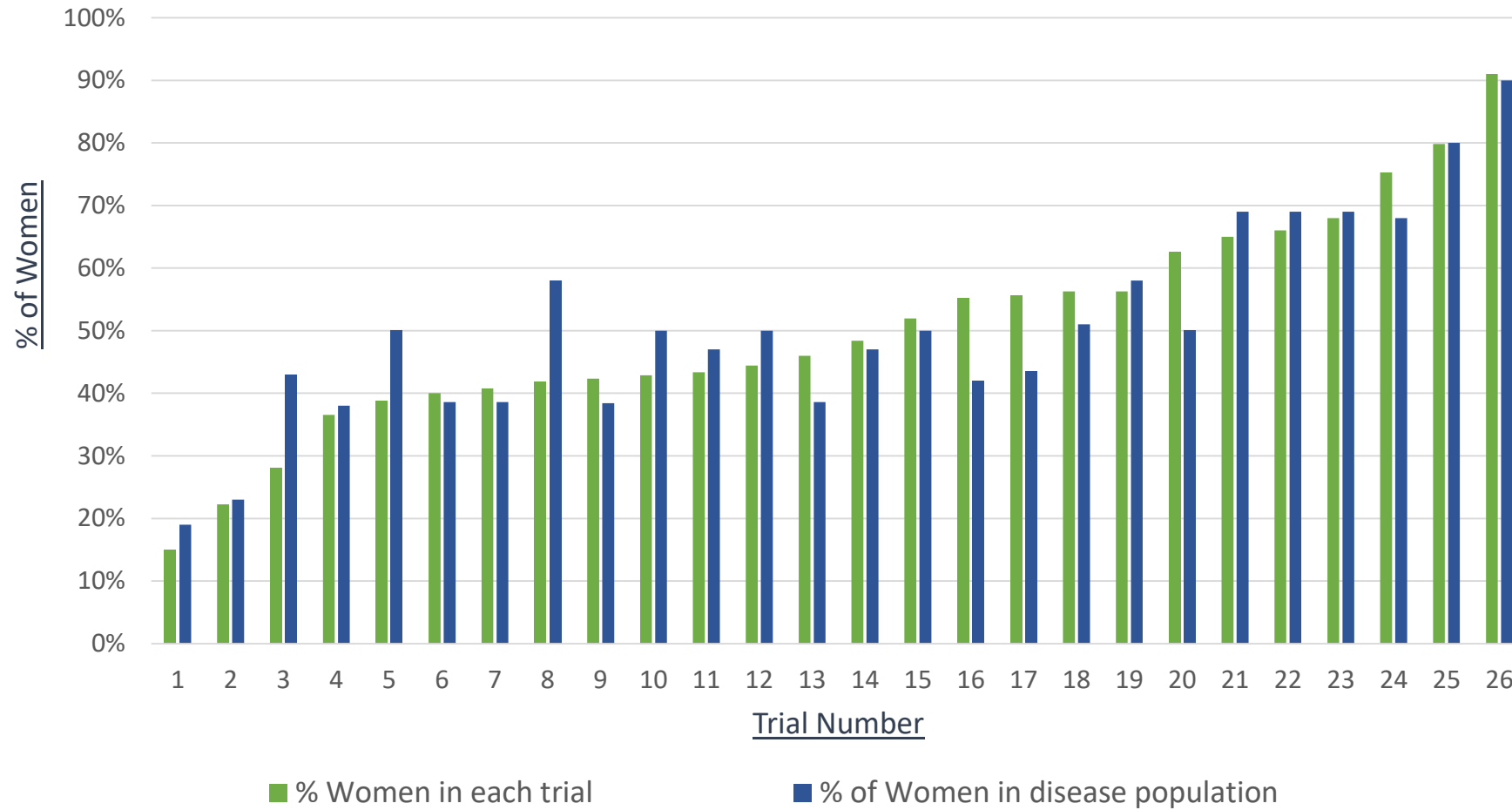


# Sex Demographics of Study Population Compared to U.S. Population\*

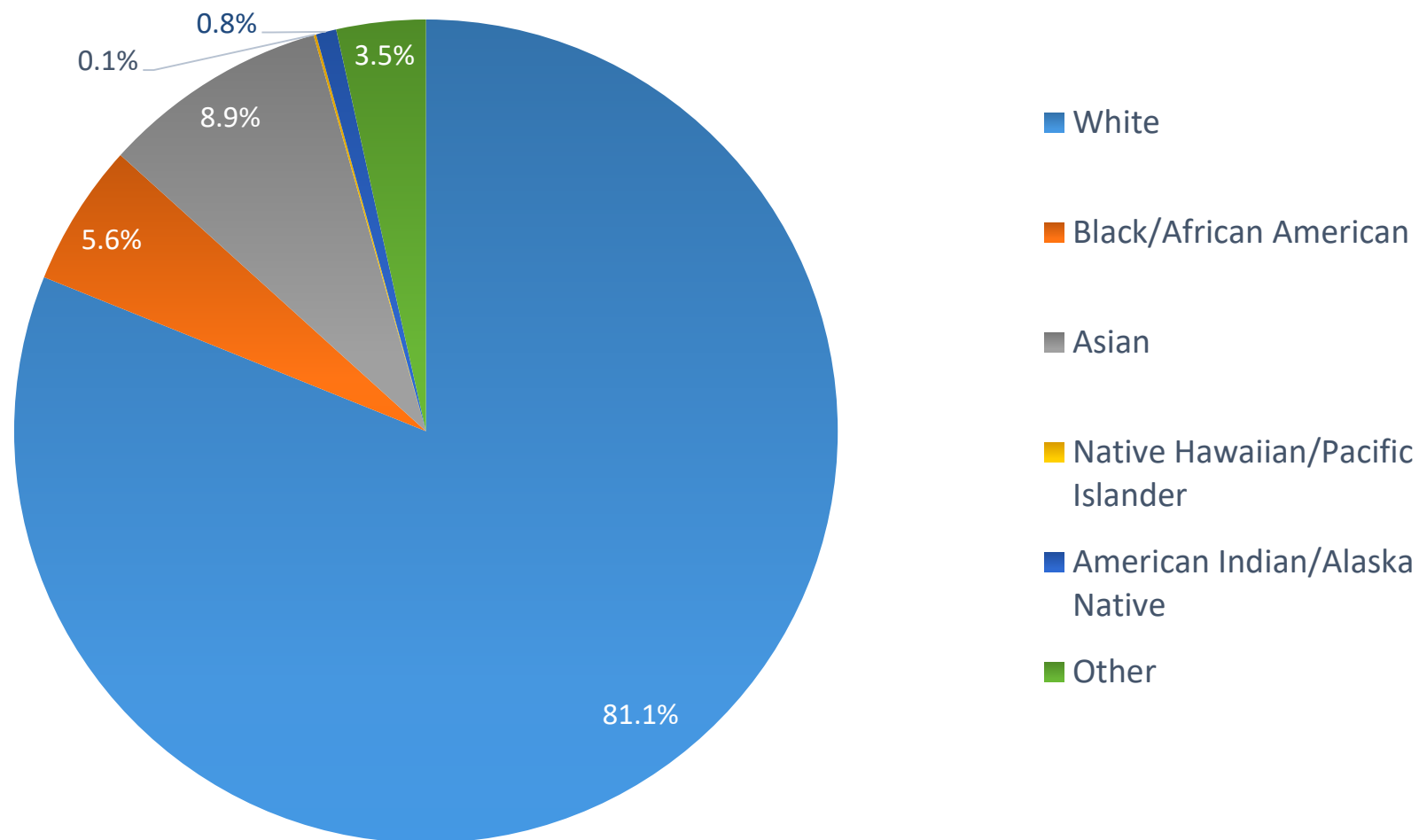


\* July 1, 2016 US Census Bureau (V2016)(a)

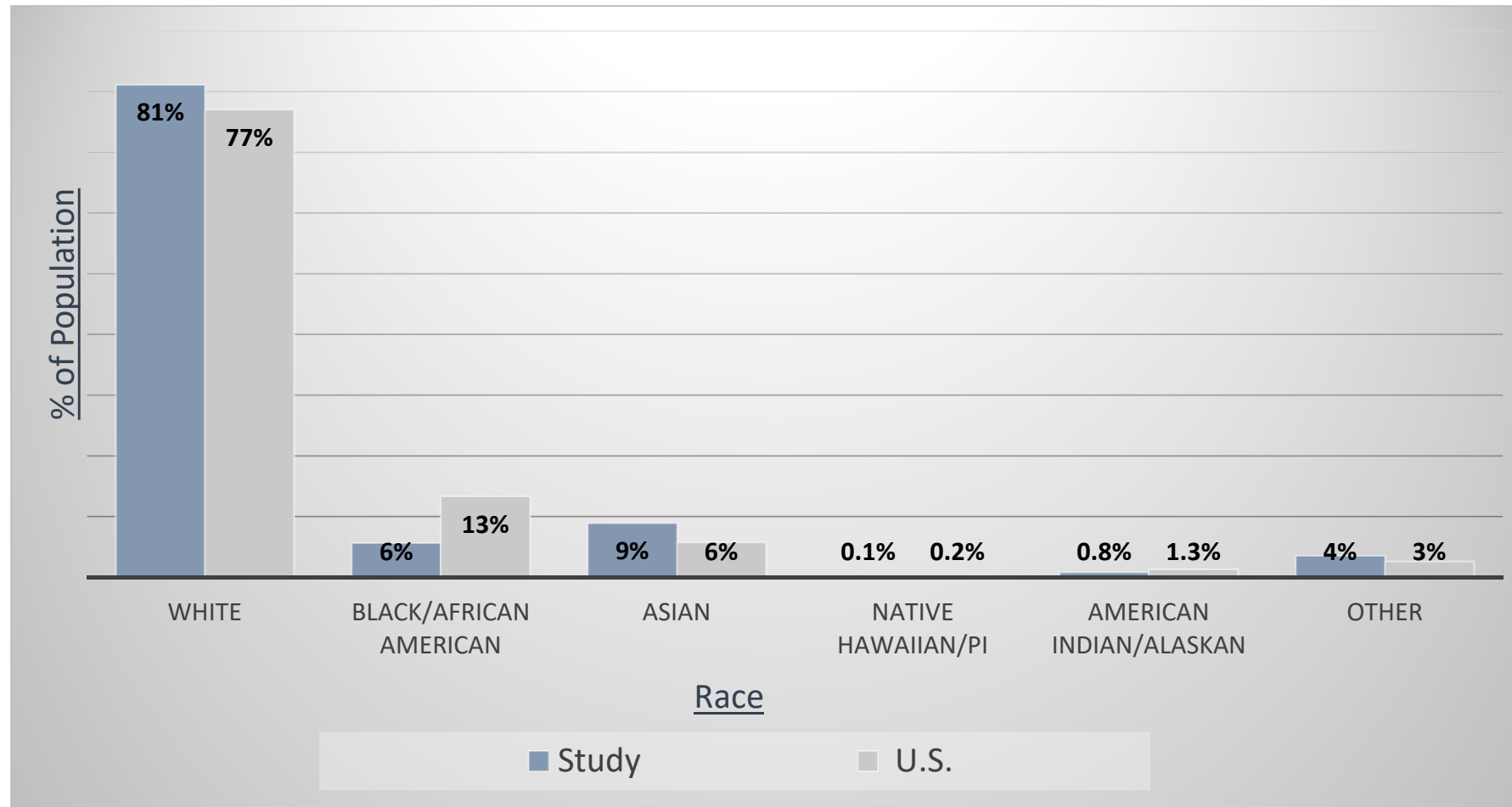
# Women in Each Trial Compared to Women in the Disease Population (n=26)



# Race Demographics of Study Population (N=40,619)



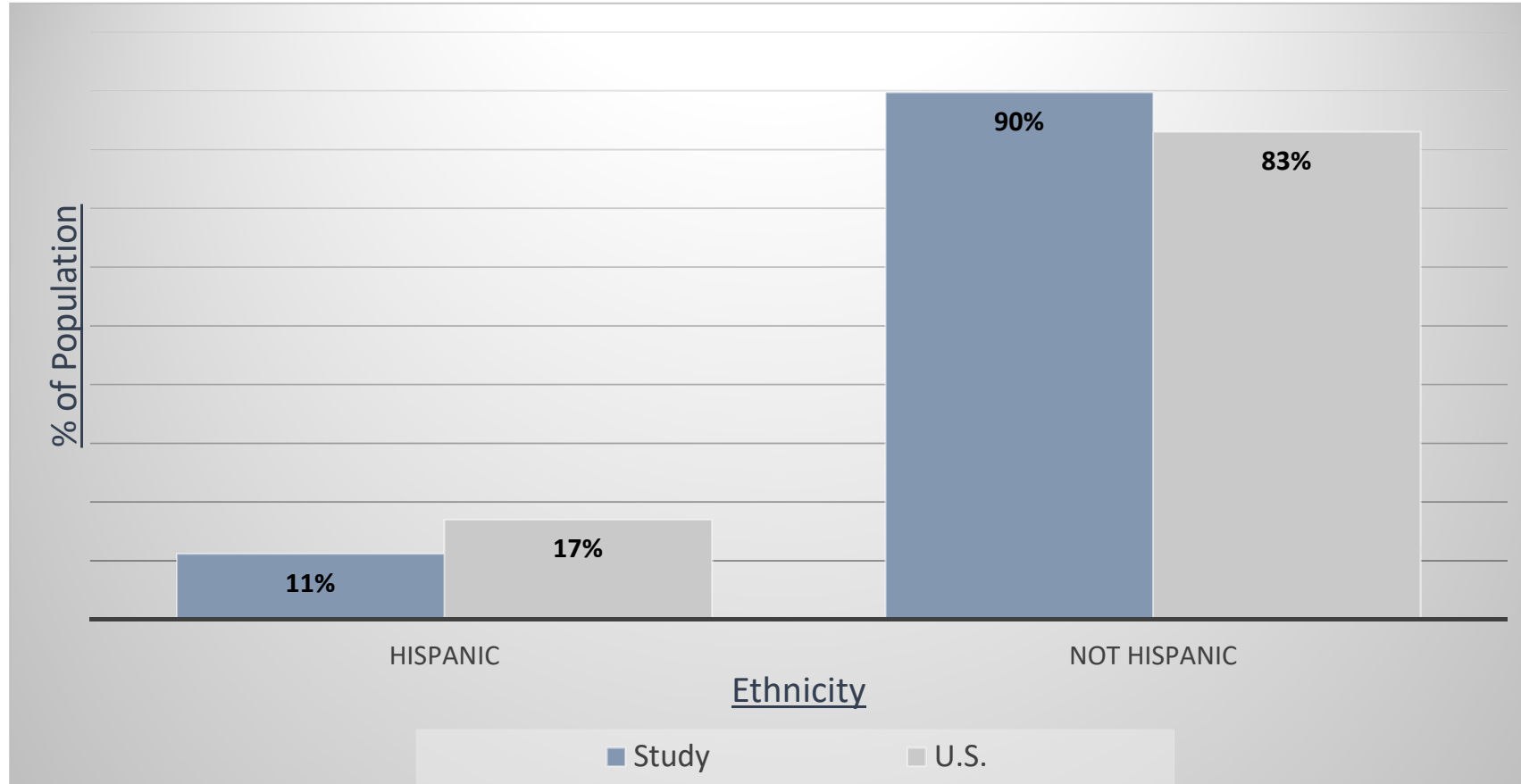
# Race Demographics of Study Population Compared to U.S. Population\*



PI= Pacific Islander, Alaskan= Alaska Native

\* July 1, 2016 US Census Bureau (V2016)(a)

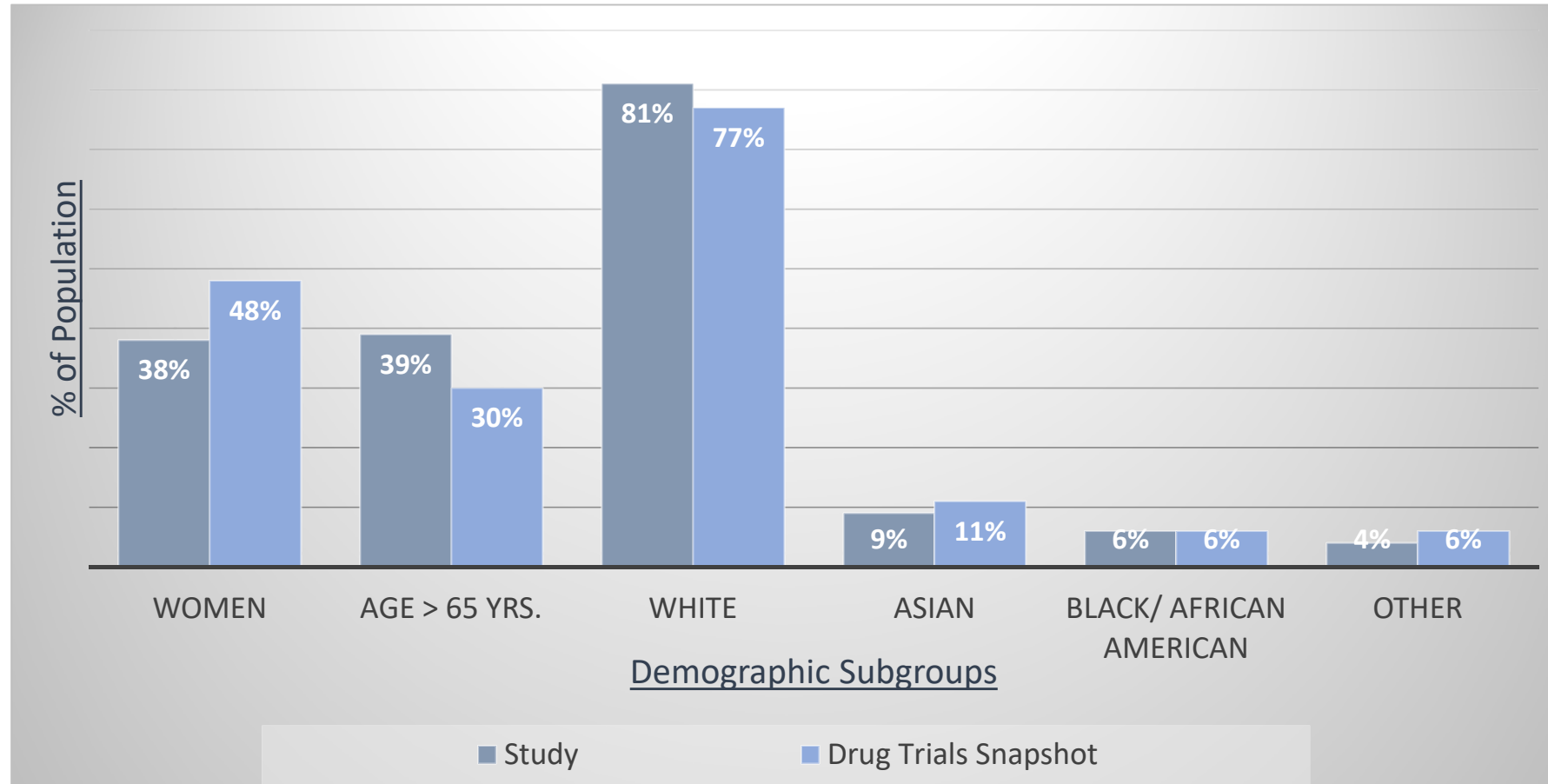
# Ethnicity Demographics of Study Population\* Compared to U.S. Population\*\*



\* (N=27,362)

\*\* US Population Source: 2012-2016 American Community Survey 5-Year Estimates

# Study Demographics Compared to Data from Drug Trials Snapshots\*



\*Data from Drug Trial SnapShots Summary Reports from 2015-2017 (n= 113 approvals)  
Courtesy of Professional Affairs and Stakeholder Engagement (PASE), FDA/CDER

# Limitations

- Small number of clinical trials in our study (n=38, 41,000 subjects).
- Trials not representative of all disease areas.
- Did not evaluate the rationale for specific exclusions.
- Did not evaluate the impact of exclusions on actual enrollment.
- Did not compare the distribution of age and race in the trials to the distribution in the disease population.



# Conclusions – Demographics

- Overall gender representation of women appeared comparable to the disease population.
  - Disparities in a small number of trials.
- Elderly subjects were not under represented compared to the census data.
- Black/African American subjects were under represented compared to the census data.
- These disparities were not the result of eligibility criteria exclusions.

# Acknowledgements

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Ison Gwynn

Rosanna Setse

FDA – PASE Team

Thank you!

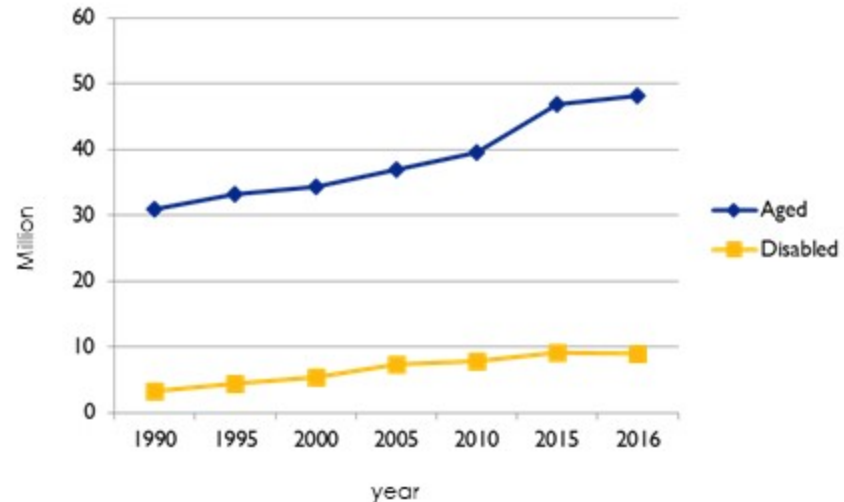


# MEDICARE COVERAGE & EVIDENCE DEVELOPMENT

KATE GOODRICH, M.D., MHS  
CHIEF MEDICAL OFFICER  
DIRECTOR, CENTER FOR CLINICAL STANDARDS & QUALITY

# Medicare Construct

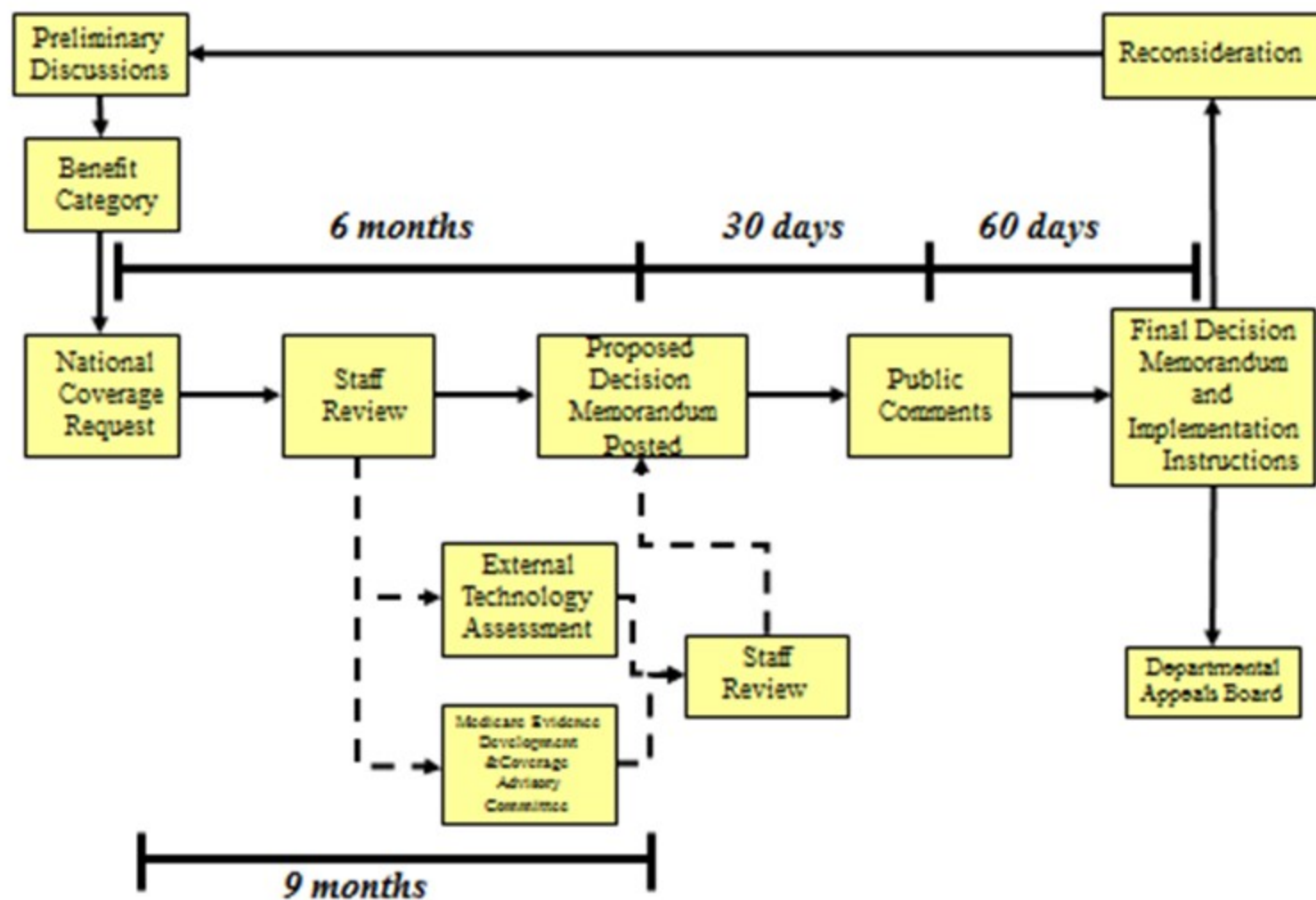
- Established by the Social Security Act of 1965, Title XVIII
  - § 1862(a)(1)(A) reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member
  - (E) in the case of research conducted pursuant to § 1142, which is not reasonable and necessary
- Defined benefit program
  - Beneficiaries
    - Age  $\geq 65$  years
    - Disabled individuals
    - End stage renal disease (557 million)
  - Providers
  - Settings



## Evidence-based Medicare Coverage

- Coverage determinations address whether the evidence is sufficient to conclude that the item (drug or device) or service improves clinically meaningful health outcomes for the Medicare population
- Considers the quality, strength and totality of evidence
- Focuses on important patient centered outcomes

## MEDICARE NATIONAL COVERAGE PROCESS



# Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

- Reviews and evaluates evidence and examines benefits, harms, and appropriateness of items and services.
- Recent meetings have discussed health outcomes for chronic heart failure and obesity/bariatric surgery.



# Medicare Beneficiaries in Clinical Studies

- Initial studies on new technologies may not include many older adults  $\geq 65$  years of age for several reasons including:
  - Heterogeneity – may have multiple comorbidities and/or be taking multiple medications
  - Non-adherence - may have difficulty following protocols and/or making all study follow-up visits
  - Other considerations – measurement issues, cognitive function

## Study Endpoints and Eligibility Criteria

- Important to determine the strength and generalizability of published evidence to the Medicare population
- May assist in establishing parameters of coverage with evidence development (CED)

# Inclusion Criteria in National Coverage Determinations

- Patients eligibility criteria in national coverage determinations (NCDs) may reflect inclusion criteria of the studies forming the evidence base for the item or services, for example:
  - Implantable cardioverter defibrillators

Trial	Covered Indication
Multicenter Automatic Defibrillator Trial (Moss, 1996)	Documented prior myocardial infarction, left ventricular ejection fraction $\leq 0.35$ , and inducible, sustained ventricular tachycardia or fibrillation at electrophysiology study.
Multicenter Automatic Defibrillator Trial II (Moss, 2002)	Documented prior myocardial infarction and a measured left ventricular ejection fraction $\leq 0.30$ .
Sudden Cardiac Death in Heart Failure Trial (Bardy, 2005)	Nonischemic dilated cardiomyopathy $> 3$ months, NYHA Class II or III heart failure, and measured LVEF $\leq 35\%$ .

## Study Exclusion Criteria

- Older adults may be excluded from initial studies assessing efficacy.
- Patients with end stage renal disease (ESRD) are often excluded.

## Coverage with Evidence Development (CED)

- Coverage in the context of approved clinical studies or with the collection of additional clinical data
- Allows for positive coverage when evidence is insufficient for a more favorable decision.
  - Evidence gaps may be due to low number of beneficiaries in clinical studies, lack of meaningful health outcomes, limited generalizability, inconsistency of study findings.
- May involve randomized controlled trials, observational studies and/or registries
  - Specific interventions,
  - benefits and harms,
  - health outcomes

## Other Clinical Studies under Medicare

1. Investigational Device Exemptions (IDE) Studies
  - Regulation at 42 CFR 405.201
  - New centralized process in 2015
2. Clinical Trial Policy
  - Routine costs in clinical trials funded by certain federal agencies
  - National Coverage Determination (NCD)  
Pub 100-3, Section 310.1



# FDA-CMS Parallel Review Program

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Centers for Medicare & Medicaid Services

[CMS-3180-N4]

### Food and Drug Administration

[Docket No. FDA-2010-N-0308]

### Program for Parallel Review of Medical Devices

**AGENCY:** Food and Drug Administration;  
Centers for Medicare & Medicaid  
Services, HHS.

**ACTION:** Notice.

---

**SUMMARY:** The Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) (the Agencies) are informing the public that the Parallel Review of medical devices pilot program will be fully implemented and extended indefinitely. The Agencies are soliciting nominations from manufacturers of innovative medical devices to participate in the "Program for Parallel Review of Medical Devices." The Parallel Review program is a collaborative effort that is intended to reduce the time between FDA marketing approval or FDA's granting of a de novo request and Medicare coverage decisions through CMS's National Coverage Determination (NCD)

process. This program is intended to ensure prompt and efficient patient access to safe and effective and appropriate medical devices for the Medicare population.

**DATES:** The program described in this document for parallel review for medical devices is effective October 24, 2016. The program will be fully implemented as of the date of the publication of this document in the **Federal Register**.



***INNOVATORS’  
GUIDE TO  
NAVIGATING  
MEDICARE***

**Version 3  
2015**



# Contact Information

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*Centers for Medicare and Medicaid Services*

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# Inclusion Across the Lifespan

**Marie A. Bernard, M.D.**  
**Deputy Director**  
**National Institute on Aging**  
**Co-Chair, NIH Inclusion Governance**  
**Committee (IGC)**



# Objectives of Presentation

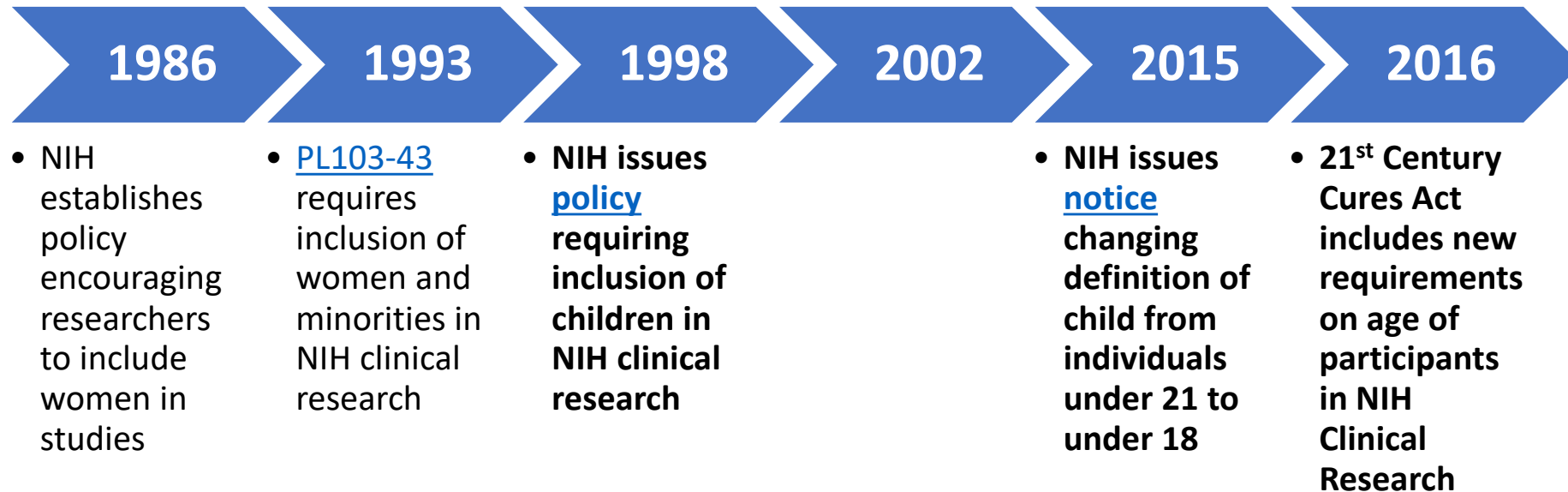
- Review steps taken to implement requirements of 21<sup>st</sup> Century Cures regarding age of participants in clinical research
- Present resultant changes to policy and procedures



# Background



# Timeline of NIH Inclusion Policies and Participant Data Collection



## H.R.34 - 21st Century Cures Act

114th Congress (2015-2016) | [Get alerts](#)

### Requires NIH to:

1. Convene a workshop on age groupings and age exclusions in clinical research within 180 days of enactment
  - Post workshop findings on NIH website
2. Publish data on age of participants in NIH clinical research, including pediatric subgroups
3. NIH Director must determine whether the inclusion guidelines on age need revision within 180 days of the workshop



# Actions Taken



# Inclusion Across the Lifespan Workshop

## June 1-2, 2017 Bethesda, MD

**Purpose:** To discuss the challenges and barriers to including children and older adults in clinical research and to identify strategies that would produce more age-inclusive clinical studies.





# Baseline NIH Analysis

## Older Adults

- Examined the top 10 diseases/disorders that caused hospitalizations &/or affected DALYs in older adults
- Analyzed information on
  - Inclusion/Exclusion Criteria
  - Age Requirement
  - Mean Age/Age Range

## Children

- NIH funded grants and associated pubs were reviewed for inclusion of children
- Age was coded according to age at enrollment and for longitudinal and follow up studies



# Summary of Key Findings in Pediatric Inclusion

- Inclusion: ~65% of all NIH grants plan to include children <21; about half of those plan to include children <18.
- Analysis: In 60% of NIH phase III clinical trial grants that planned to include children, researchers did not plan to analyze results by age.
- Inclusion: ~25% of grants stated they intended to include subjects <18, but did not include children <18 in published results.
- Analysis: 36% of grantees differed from their original analysis plan in their published results.



# Summary of Key Findings in Older Adult Inclusion

- For diseases highly prevalent among older people, clinical trials often excluded subjects based on age
  - 27% of studies had arbitrary upper age caps
- Indirect exclusion factors may apply
  - Co-morbid conditions (hypertension, diabetes, cancer, etc.)
  - Polypharmacy
- Participants in trials may not represent real-world populations with the disease



# Inclusion Across the Lifespan Working Groups

- Four working groups discussed the following topics:
  - Study Populations
  - Ethical Issues
  - Study Design
  - Data Collection and Reporting
- Workshop identified a number of themes applicable to NIH, government research entities, and the scientific community as a whole.



# Inclusion Across the Lifespan RFI

## Request for Information (RFI): Invitation to Comment on Inclusion in Clinical Research Across the Lifespan

---

Notice Number: NOT-OD-17-059

### Key Dates

**Release Date:** April 26, 2017

**Response Date:** June 30, 2017

### Related Announcements

None

### Issued by

National Institutes of Health ([NIH](#))

### Purpose

In response to scientific need and a congressional mandate in the 21st Century Cures Act (P.L. 114-255), the National Institutes of Health (NIH) is convening a workshop of experts on the appropriate inclusion of pediatric and older populations in research studies involving human subjects. A workshop will be held on June 1-2, 2017, to bring together experts in clinical research to discuss augmenting participation of these populations in NIH-funded clinical studies. In addition, the NIH is publishing this Notice to solicit input from the wider scientific community and welcomes comments from the public concerning inclusion in research.

### Background

The 21st Century Cures Act states in part:

*Appropriate Age Groupings in Clinical Research*

1) Input from Experts – Not later than 180 days after the date of enactment of this Act, the Director of the National Institutes of Health shall convene a workshop of experts on pediatric and older populations to provide input on –



# Inclusion Across the Lifespan Workshop

- Videocast available  
at <https://videocast.nih.gov/launch.asp?23334>
- Workshop summary available at [www.report.nih.gov](http://www.report.nih.gov). –  
Reports/Other Special Reports
- or  
[https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20 FINAL 508.pdf](https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20FINAL%20508.pdf)





# [www.report.nih.gov](http://www.report.nih.gov)

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# Notice of Intent to Revise the Policy

## Notice of Intent to Revise the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects

---

**Notice Number:** NOT-OD-18-008

### Key Dates

**Release Date:** December 1, 2017

### Related Announcements

[NOT-OD-16-010](#)

[NOT-98-024](#)

### Issued by

National Institutes of Health ([NIH](#))

### Purpose

The purpose of this Notice is to inform the research community that NIH intends to revise the NIH Policy and Guidelines on the Inclusion of Children. On November 9, in consultation with NIH Institute and Center Directors and in follow-up to the June 1-2, 2017 NIH workshop on Inclusion Across the Lifespan, the NIH Director determined that NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects will be revised. A discussion of this issue is scheduled as a formal agenda item for the upcoming December 14-15 meeting of the Advisory Committee to the NIH Director.

### Background

Section 2038 of the 21st Century Cures Act, enacted December 13, 2016, includes new provisions requiring NIH to address the consideration of age as an inclusion variable in research involving human subjects, to identify the criteria for justification for any age-related exclusions in NIH research, and to provide data on the age of participants in clinical research studies. Furthermore, the Act requires NIH to convene a workshop of experts on pediatric and older populations to provide input on these issues, and taking account input received through the workshop, the NIH Director is charged with deciding whether any changes to NIH inclusion policies are needed.





# NIH Inclusion Across the Lifespan Policy Revision

Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects

---

Notice Number: NOT-OD-18-116

## Key Dates

**Release Date:** December 19, 2017

## Related Announcements

[NOT-OD-16-010](#)

[NOT-98-024](#)

## Issued by

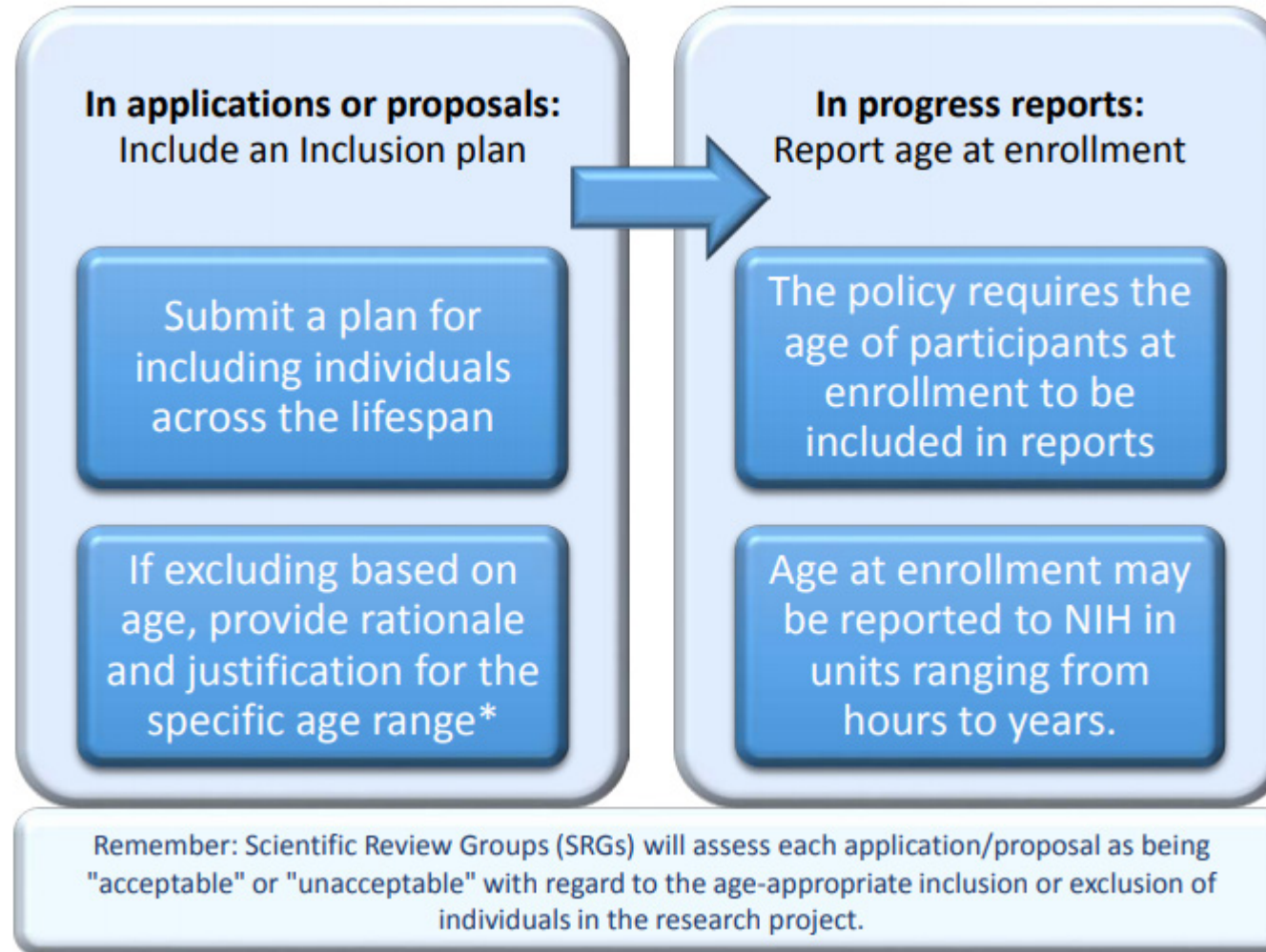
National Institutes of Health ([NIH](#))

## Purpose

This revised Notice replaces [NOT-98-024](#). The purpose of this Notice is to inform the research community that NIH is revising its NIH Policy and Guidelines on the Inclusion of Children. Changes to the policy include (1) the applicability of the policy to individuals of all ages, including children and older adults; (2) clarification of potentially acceptable reasons for excluding participants based on age; and (3) a requirement to provide data on participant age at enrollment in progress reports.



# Inclusion Across the Lifespan: Guidance for Applying the Policy



# Acknowledgements



# Inclusion Across the Lifespan Workshop Planning Committee

Jane Atkinson, NIDCR (Co-Chair)

Samir Sauma, NIA (Co-Chair)

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Monica Basco, ORWH

Marie Bernard, NIA

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Cliff Lane, NIAID

Jaron Lockett, NIA



# Inclusion Across the Lifespan Workshop Planning Committee, cont.

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# Questions?





# Task Force on Research Specific to Pregnant and Lactating Women

Catherine Y. Spong, M.D.  
Deputy Director, NICHD



## Presentation Overview

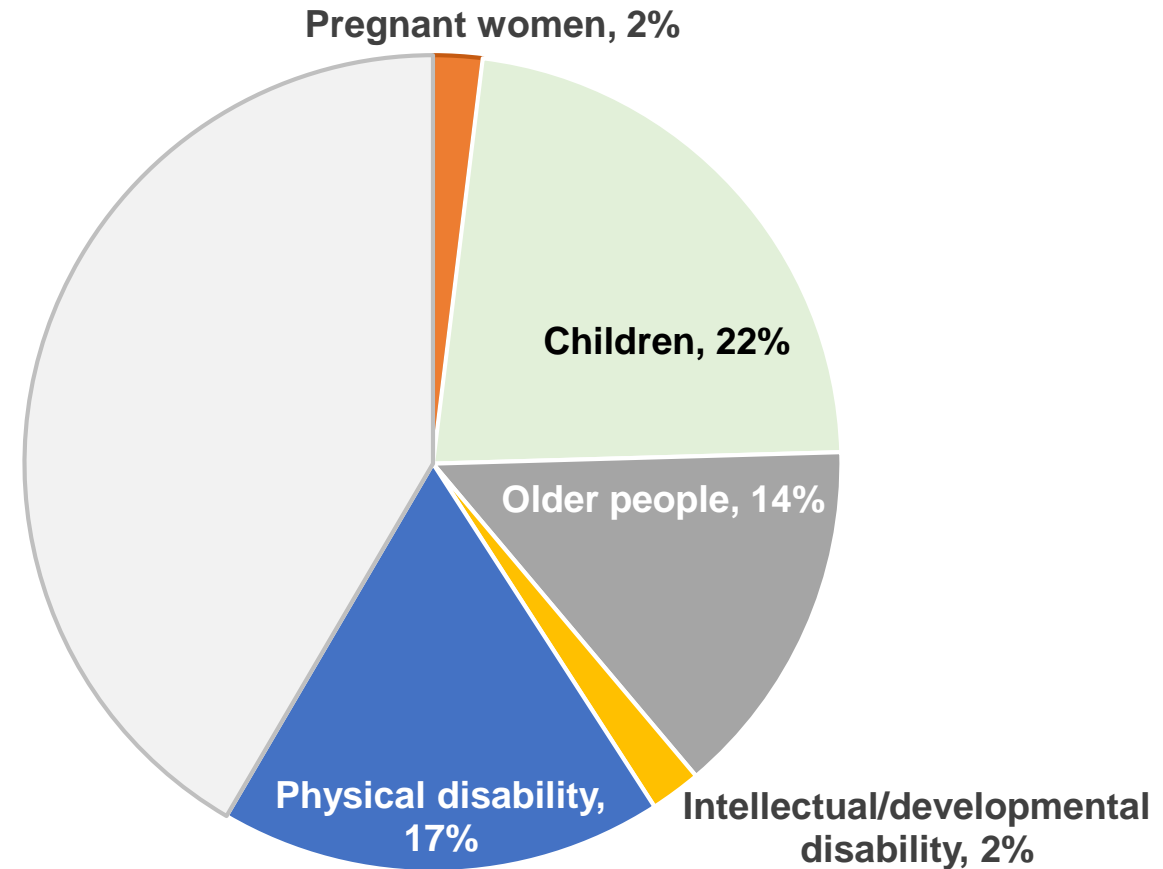
- Description
- Scope
- Current status of data
- Task Force on Research Specific to Pregnant Women and Lactating Women





# Importance of Inclusion in Research

## Underrepresented Groups in Research



Up to 59% of the U.S. population is comprised of people who typically are not included in research studies (pregnant women, children, older people, those with intellectual and physical disabilities).

These numbers are approximate to provide a general impact, the numbers do not account for overlap between categories.

**VIEWPOINT** Improving Public Health Requires Inclusion of Underrepresented Populations in Research

**Catherine Y. Spong, MD**  
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

**Diana W. Bianchi, MD**  
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

**Advances in genomics** have ushered in promising therapies tailored to the individual. Personalized medicine is promoted and has begun to positively influence care. For example, medications such as trastuzumab for the 30% of breast cancers that overexpress ERBB2 and vemurafenib for patients with late-stage melanoma who carry the V600E variant have been beneficial.<sup>1</sup> Despite these advances, for many sectors of the population—children, older adults, pregnant and lactating women, and individuals with physical and intellectual disabilities—limited evidence-based therapies optimized to their specific medical needs exist. Combined, these groups comprise as much as 58% of the US population (Table in the Supplement).<sup>2</sup> Research focusing on or at the very least includes members of these groups is critically needed.

Until the initial passage of the Best Pharmaceuticals for Children Act in 2002, pediatric drug doses were based on extrapolation from adults. Importantly, body composition and metabolic processes change as children develop, resulting in different safety and efficacy profiles.<sup>2</sup> Similarly, medication needs change with age

and are often prescribed with minimal evidence to support their use, especially psychotropic drugs with significant adverse effects.

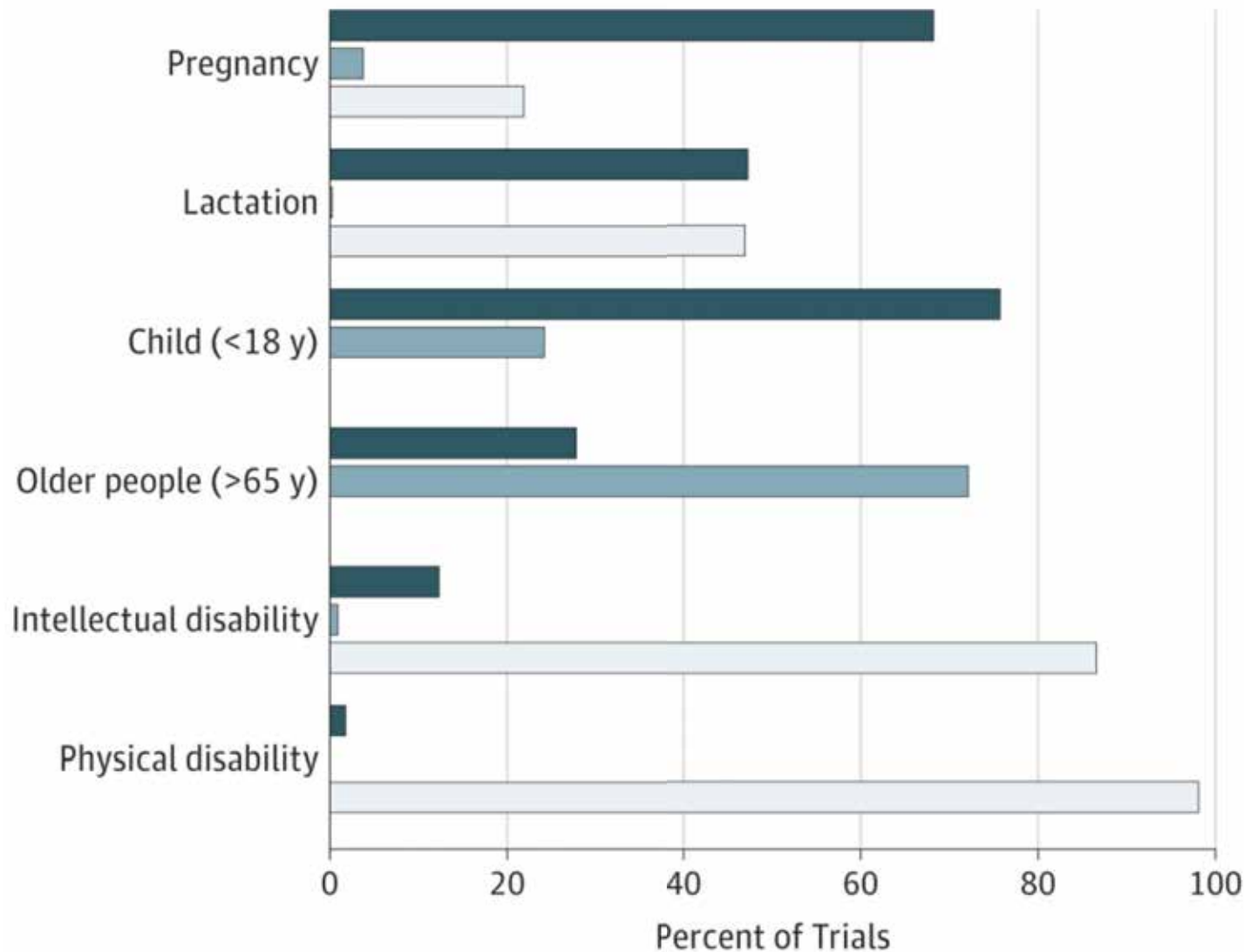
Recently, discussions have arisen about the need for inclusion in research and elimination these gaps. In 2017, the National Institutes of Health (NIH) held a workshop, “Inclusion Across the Lifespan,” that highlighted current federal regulations that include protections for “vulnerable populations” (pregnant women, fetuses, neonates, prisoners, and children). Although these regulations were originally designed to protect these individuals, many investigators have called for reconsideration, opting to protect them through research, rather than from research. Inclusion will likely yield data that will benefit more people.

Many underrepresented populations encounter barriers to participation in research. In a review of 338 phase 3 and 4 NIH-funded actively recruiting studies in ClinicalTrials.gov, explicit exclusion was found in 68% for pregnant women, 47.3% for lactating women, 75.7% for children, 27.8% for older people, 12.4% for those with

**Supplemental content**

## Underrepresented Groups Eligibility in Open NIH-Funded Phase 3 and 4 Studies

Exclude Include Not stated



### Explicit exclusion

- 68% pregnant women
- 47.3% lactating women
- 75.7% children
- 27.8% older people
- 12.4% intellectual/developmental disabilities
- 1.8% physical disabilities

### Figure Legend:

Open NIH-Funded Phase 3 and 4 Studies as of October 19, 2017

Clinicaltrials.gov records (N=338) were reviewed.

Exclusion for intellectual disabilities was based on IQ and defined intellectual disability or cognitive impairment; physical disabilities: exclusions for physical disabilities were inability to ambulate, extreme immobility, and paraplegia.



## Striking US Statistics



- 6.3 M women become pregnant
  - >90% of women take medications
  - 70% are prescribed medications
- 500,000 woman annually have difficulty making milk





# State of Research on Pregnancy and Lactation

- Literature
  - Limited in pregnancy
  - Extremely limited literature on lactating women
- Complexity of pregnancy
  - Fetus and placenta change over gestation, timing of exposure
  - Physiologic changes of pregnancy
  - Impact of external factors, such as obesity, environment...
  - Co-existing chronic or acute conditions
- Lactation
  - Benefits of breastfeeding vs. medications in woman
  - Limited assays for assessment of medications in breastmilk
- Limited pipeline



# Pregnancy and Lactation Publications on Medicinal Therapies for Asthma, by Publication Type, 2006-2017

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Editorial/Comment	Other
Asthma (Pregnancy)	21	0	60	4	58	29	184	29	26
Asthma (Lactation)	3	0	0	0	1	1	11	0	0

Almost all the pregnancy- and lactation-related research focused on pregnancy only, and not lactation.

\*Of note, prevalence of asthma in pregnant women is ~8.5%, with 4% of pregnant women experiencing an asthma attack in the prior year



# Publications on Medicinal Therapies for Nausea and Vomiting in Pregnant Women, by Research Type, 2006-2017

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Editorial/Comment	Other
Nausea and vomiting	5	6	4	22	30	62	106	17	12

Hyperemesis Gravidarum occurs in 3% of pregnancies and is a pregnancy-specific condition.

Of the publications, 78 (30%) addressed non-drug medicinal therapies, with 33 (42%) original research articles. 5 RCTs were on herbal or other "natural" therapies.



## Publications on Medicinal Therapies for Low Milk Supply in Lactating Women, 2006-2017

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/ Comment	Other
Low milk supply	1	0	0	8	8	3	18	6	4

Insufficient milk supply is one of the most commonly cited reasons for early cessation or decreased exclusivity in women who have initiated breastfeeding.

48 articles, published between January 2006 and July 2017, that related to medicinal therapies for low breast milk supply; four trials were concerned with herbal therapies or alternative Chinese medicine.





# NICHD Pregnancy and Lactation Literature Analysis 2006-2017: Results for Pregnancy

- RCTs rare in almost all areas
- Exceptions:
  - Gestational diabetes
  - Hypertension
  - Preterm labor
  - Labor pain medication
  - Opioids and tobacco

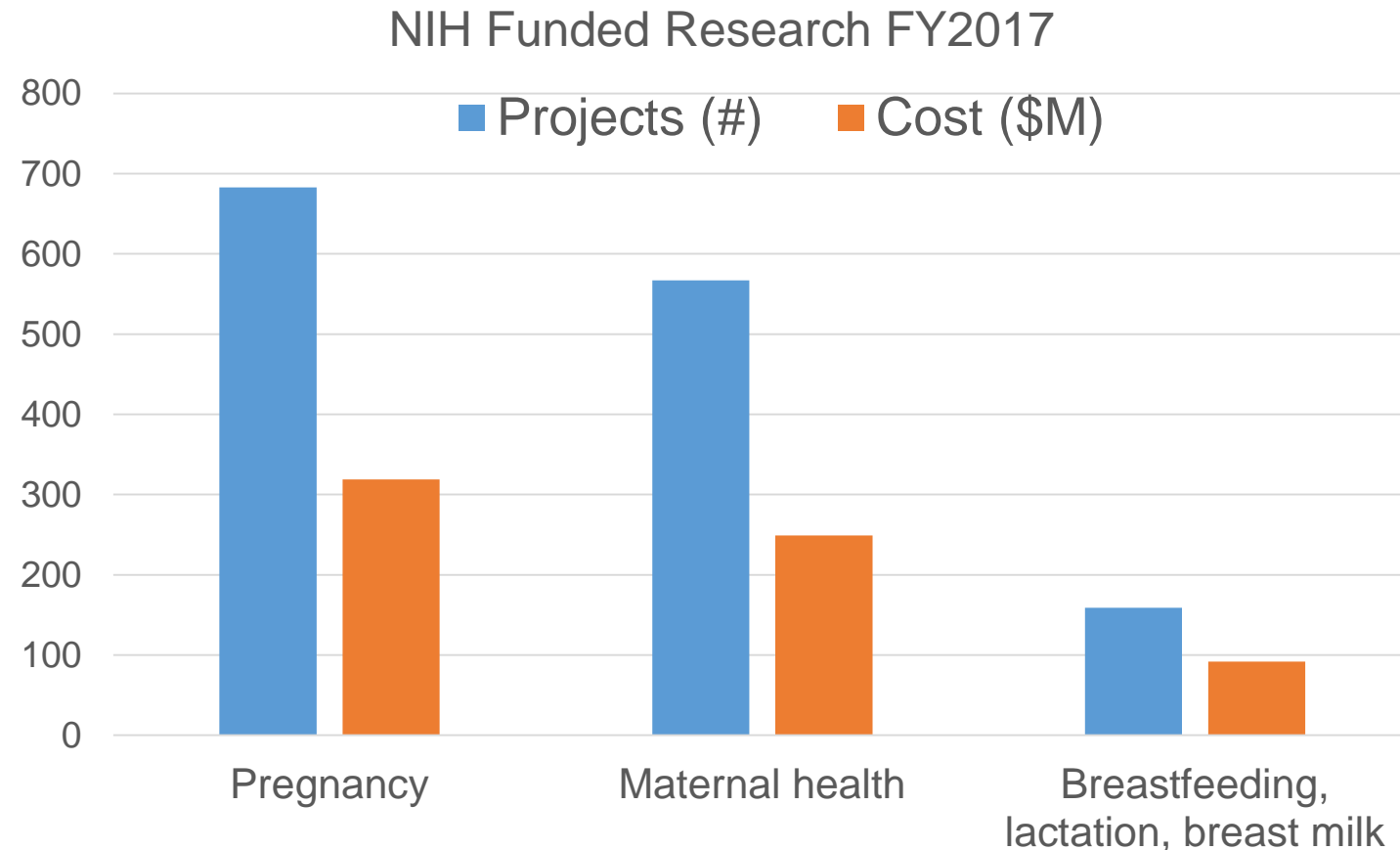
	Condition	Basic	PK/PD	Pop/DB	RCT
<b>Hypertension</b>	Hypertension	127	9	18	40
<b>Mental Health</b>	Anxiety	16	0	3	2
	Bipolar	1	0	1	0
	Depression	21	4	21	4
	Schizophrenia	11	0	1	0
<b>Pain</b>	Labor Pain	5	0	7	49
	Headache/migraine	0	0	5	1
<b>Preterm labor</b>	Preterm labor	152	21	35	169
<b>Substance Abuse</b>	Alcohol	26	0	0	0
	Cocaine	6	0	1	0
	Meth/amph	10	3	1	0
	Opioids	22	3	9	25
	Tobacco	22	3	16	27





# NIH Data FY 2017: Research on Pregnancy, Maternal Health, Breastfeeding, Lactation, and Breast Milk

- Pregnancy
  - 683 projects, \$319M total
  - 21 ICs + NIH OD
- Maternal Health
  - 567 projects, \$249M total
  - 19 ICs + NIH OD
- Breastfeeding, Lactation, and Breast Milk
  - 159 projects, \$91.7M total
  - 20 ICs + NIH OD





# Historical Recommendations for Pregnant and/or Lactating Women



# Timeline

- 1985: HHS Report of PHS Task Force on Women's Health Issues
- 1991: Institute of Medicine meeting: Women and Health Research
- 1992: IOM Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies (Pub 1994)
- 1993: NIH Revitalization Act: Inclusion of women in clinical studies
- 2005: FDA draft Guidance for Industry: Clinical Lactation Study
- 2007: ACOG Committee Opinion: Research Involving Women
- 2009: The Second Wave Initiative: Toward Responsible Inclusion of pregnant women in research
- 2010: NIH ORWH workshop: Enrolling Pregnant Women: Issues in Clinical Research
- 2011-2013 NIAID meetings regarding study design of clinical trials of vaccines in pregnant women
- 2012: National Vaccine Advisory Committee established Maternal Immunization working group (Pub 2017)
- 2015: ACOG Committee Opinion: Ethical considerations of including women as research subjects
- 2015: NICHD/SMFM/ACOG/AAP workshop: Medications in Pregnancy and Lactation
- 2016: FDA meeting Evaluation of the Safety of Drugs and Biological Products used During Lactation
- 2016: Am. Society for Clinical Pharmacology and Therapeutics Inclusion of pregnant and breastfeeding women in research
- 2017: Cures Act establishing Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- 2017-2018: PRGLAC meetings
- 2018: FDA Risk Communication Advisory Committee meeting Requirements for Pregnancy and Lactation Labeling

1985

*Women's Health*

**Report of the  
Public Health Service  
Task Force on  
Women's Health Issues**

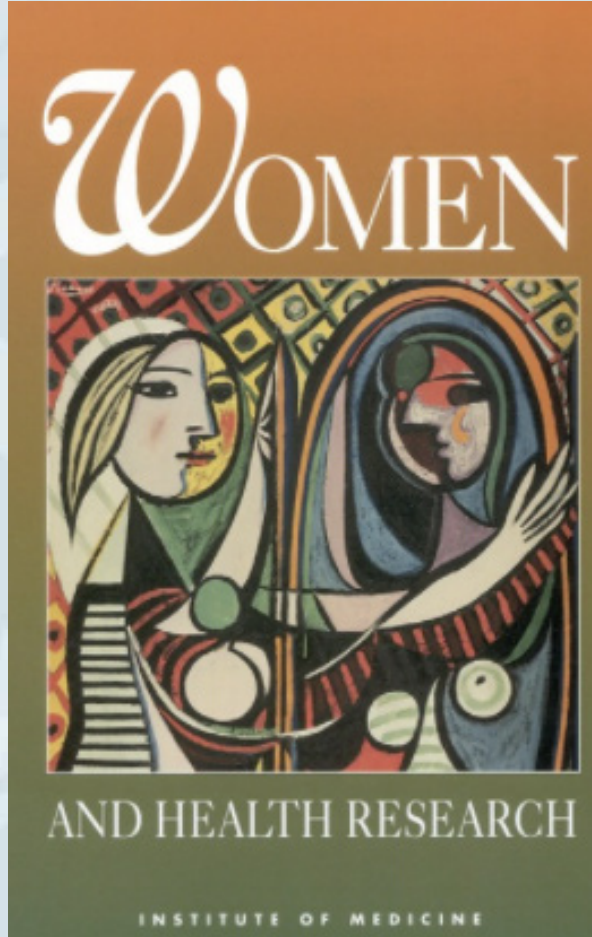
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- the issuance of a Public Health Service-wide policy directing all operating units to review their research guidelines to ensure that sex differences are routinely studied, wherever feasible. Such instructions should be included in grant application kits.
- the requirement that postmarketing surveillance of all prescription drugs should include reporting of the adverse effects in women of drug interactions with alcohol, commonly used psychotherapeutic drugs, and drugs commonly used in relation to hormonal changes in women.
- the requirement that adequate numbers of women be included in clinical trials of drugs that will be used by women, and of all new drugs that are to be recommended for use by women.
- the commissioning of an interdisciplinary panel of senior scientists, including women, to review existing research and research protocols or methodologies and to develop a comprehensive plan for addressing any gender bias identified in research in general, but in particular in alcohol, drug abuse, and mental health research.
- the establishment of a task force to review mental health issues related to women and to make recommendations for changes in the Fourth Revision of the Diagnostic and Statistical Manual (DSM IV) of the American



1994



The committee also struggled with how to accommodate within its support for the shift of the presumption to *inclusion* of pregnant women (from that of exclusion) a role for conscience and an individual investigator's moral commitments. It was agreed that, at a minimum, such a mechanism would require that the investigator provide the IRB with a written explanation of his or her concerns of conscience and that the IRB review any such requests in light of a presumption that favors the inclusion of pregnant women in clinical studies. It is because of the potential for abuse of a "conscience" exemption that the committee could not resolve whether or under what conditions such an exemption should be constructed.

At least a technical amendment to Subpart A, sec. 46.111(a)(3), eliminating the reference to pregnant women as a "vulnerable population" will be required by the recommended revision to Subpart B.

**The committee recommends that OPRR revise and reissue subpart B of the DHHS regulations for the Protection of Human Subjects, titled "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human**

2015



The American College of Obstetricians and Gynecologists supports a woman's autonomy in making decisions during her pregnancy. Recognition of the rights of the nongestational intended parent during pregnancy may infringe upon and weaken maternal autonomy. As in other clinical situations, the pregnant woman's consent should be sufficient for research interventions that affect her or her fetus.

All women, regardless of race, ethnicity, sexual orientation, or socioeconomic status, should be presumed eligible for participation in research studies. The potential for pregnancy should not automatically exclude a woman from participating in a study, although the use of contraception may be required for participation. Inclusion of women in research studies is necessary for valid inferences about health and disease in women. The generalization of results from trials conducted in men may



## Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)





# 21st Century Cures Act

- Passed the House on November 30, 2016, by vote of 392-26
- Passed the Senate on December 5 by a vote of 94-5
- President signed the bill on December 13, 2016







## **SEC. 2041. TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.**

ESTABLISHMENT.—Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the “Secretary”) shall establish a task force, in accordance with the Federal Advisory Committee Act...

(2) DUTIES.—The Task Force shall provide advice and guidance to the Secretary regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.



# Task Force Implementation

- January 19, 2017
  - Authority delegated from HHS Secretary to NIH Director
  - NIH Director asks NICHD to lead
- February 2017
  - Task Force Plan submitted by NICHD
- March 13, 2017
  - Charter establishing Task Force filed
- May 2017
  - Slate of nominees prepared for Secretary's approval
  - Federal members designated
- February 2018
  - All non-federal members approved






# Meetings

- Announced in Federal Register
- Open to the public
  - August 21-22, 2017
  - November 6-7, 2017
  - February 26-27, 2018
  - May 14-15, 2018 – **Registration open**
- Proceedings archived on the NIH videocast website
  - <https://videocast.nih.gov/default.asp>

# Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)

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> Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

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### Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary.

Federal members include the directors of NIH, NICHD, the Centers for Disease Control and Prevention, the HHS Office on Women's Health, and the HHS National Vaccine Program Office, as well as the Commissioner of Food and Drugs. Non-federal members include representatives from relevant medical societies, non-profit organizations, and industry.

We need your suggestions! See [Request for Information \(RFI\): Research Specific to Pregnant Women and Lactating Women – Responses due April 2, 2018](#)

**Please note:** No recommendations have been finalized; the topics listed in the RFI have been raised during Task Force discussions, and we thought that further input would be beneficial.

#### Meetings

- August 21-22, 2017
- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

#### More Information

- Roster (PDF 72 KB)
- Federal Register Notice - January 23, 2018
- Federal Register Notice - October 2, 2017
- Federal Register Notice - July 13, 2017
- PRGLAC Charter (PDF - 73 KB)
- Federal Register Notice - April 18, 2017
- Federal Register Notice - March 21, 2017
- U.S. Code Authorizing PRGLAC (42 USC 289a-2)

#### Contact

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Executive Secretary  
[kaeserl@mail.nih.gov](mailto:kaeserl@mail.nih.gov)

#### Advisory Groups

- [Board of Scientific Counselors \(BSC\)](#)
- [National Advisory Child Health and Human Development \(NACHHD\) Council](#)
- [National Advisory Board on Medical Rehabilitation Research \(NABMRR\)](#)

#### Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

#### Learn More

- [NICHD News Releases & Features](#)
- [Division of Extramural Research \(DER\)](#)
- [Division of Intramural Population Health Research \(DIPHR\)](#)
- [Division of Intramural Research \(DIR\)](#)
- [Office of Committee Management \(OCM\)](#)

<https://www.nichd.nih.gov/About/Advisory/PRGLAC>



# Important Deadlines

- September 2018 – Send report to HHS Secretary and Congress
- December 2018 – Secretary required to act on Task Force recommendations
- March 2019 – Task Force will sunset after two years, unless extended





## Report will include

- (1) Plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies
- (2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research
- (3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women



## Report will include (continued)

- (4) Identification of federal activities, including:
  - (a) State of research on pregnancy and lactation
  - (b) Recommendations for the coordination of and collaboration on research related to pregnant women and lactating women
  - (c) Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public
  - (d) Existing federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including research on pharmacokinetics, pharmacodynamics, and toxicities
- (5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women





# Report Components and Strategy

TF 3	(1) Plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies
TF 2	(2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research
TF 3	(3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women
TF 1	(4) Identification of federal activities, including: <ul style="list-style-type: none"><li>(a) State of research on pregnancy and lactation</li><li>(b) Recommendations for the coordination of and collaboration on research related to pregnant women and lactating women</li><li>(c) Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public</li><li>(d) Existing federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including research on pharmacokinetics, pharmacodynamics, and toxicities</li></ul>
TF 4	(5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women





# Request for Information

## Request for Information (RFI): Research Specific to Pregnant Women and Lactating Women (PRGLAC)

**Notice Number:** NOT-HD-18-003

### Key Dates

**Release Date:** February 15, 2018

**Response Date:** April 2, 2018

### Related Announcements

None

### Issued by

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

## Purpose

The 21st Century Cures Act established a [Task Force on Research Specific to Pregnant Women and Lactating Women \(PRGLAC\)](#), to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary. A series of workshops, open to the public, are being held to develop this report. In addition, the NIH is publishing this Notice to solicit input from the wider scientific community and welcomes comments from the public.

## Background

The 21st Century Cures Act states in part that the report will include:

- A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies;
- Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research;
- Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women;
- Identification of Federal activities, including:
  - The state of research on pregnancy and lactation;
  - Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;
  - Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public; and
  - Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and
- Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Details of the workshops, archived videocasts, materials and information on upcoming workshops can be found on the [PRGLAC](#) website.

Under the Common Rule (<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html>), pregnant women are listed as an example of a vulnerable population. The revised common rule would no longer include pregnant women as an example of a vulnerable population, although the provisions of Subpart D (45 CFR 171.101-171.117) regarding the protection of research subjects who are pregnant, breastfeeding, or nursing remain in effect.



# PRGLAC Meeting May 14-15, 2018

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

May 14-15, 2018

## Sponsor/Co-Sponsor(s)

NICHHD, NIH

## Location

National Institutes of Health  
6710B Rockledge Drive  
Bethesda, MD 20892

- Review report from prior meetings
- Review comments from RFI
- Public comment
- Discussion of incentives and liability mitigation
- Recommendations for the report

Meeting is free, open to the public, register to attend in-person or via videocast

<https://www.nichd.nih.gov/about/meetings/2018/051418>

## Presentation Summary

- Description
  - 68% of pregnant women explicitly excluded
- Scope
  - 6 million women are pregnant yearly
- Current status of data
  - Extremely limited
- Task Force on Research Specific to Pregnant Women and Lactating Women





I welcome your interest in this topic and all questions



# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
[ClinicalTrials.Margolis@Duke.edu](mailto:ClinicalTrials.Margolis@Duke.edu)

 #TrialsEligibility

# What Leads to Underrepresentation: Addressing the Exclusion of Children from Clinical Research

Robert “Skip” Nelson, MD PhD FAAP  
Senior Director, Pediatric Drug Development  
Child Health Innovative Leadership Department (CHILD)

April 16, 2018

At the heart of it all



# Disclosure

- The presentation is intended for educational purposes only. Statements of fact and opinions expressed are those of the participant individually and, unless expressly stated to the contrary, are not the opinion or position of any company, institution or third party entity.
- Robert Nelson is a full-time employee of Johnson & Johnson.





# History of US Pharmaceutical Regulations

## Children as “Canaries in the Mine”

- **Biologics Control Act of 1902**
  - Catalyzed by the deaths of 22 children from contaminated diphtheria antitoxin and smallpox vaccine
- **The Food and Drugs Act of 1906**
  - Mrs. Winslow's Soothing Syrup contained enough morphine sulfate to kill the average child (nicknamed “the baby killer”)
- **Federal Food, Drug, and Cosmetic Act of 1938**
  - Antibiotic sulfanilamide (formulated in diethylene glycol) killed 107 persons, many of whom were children
- **Kefauver-Harris Drug Amendments of 1962**
  - Thalidomide, a new sleeping pill, causes birth defects in thousands of babies born in Europe



# Unintended Consequences

## Violation of distributional justice (i.e., “fairness”)

- As FDA was given a greater role to ensure drug purity, safety, and efficacy, the pediatric community was expressing concern about the shift toward overprotection and thus exclusion from research.
  - “Therapeutic orphan” (1968) - children denied the use of many new drugs because of language discouraging pediatric use
  - Lack of drug testing in children was leading to reduced access in the clinical setting to safe and effective medications.
- Harms to children led to the societal benefit of established standards for demonstrating the safety and efficacy of drugs, **yet legislation had the unintended consequence of unjustly excluding children from reaping the benefits of those same standards**

Shirkey H. Editorial comment: therapeutic orphans. Journal of Pediatrics. 1968;72(1):119– 120.



# Developing Human Subjects Protection

## The National Commission (1974 – 1979)

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (“the National Commission”) formed in 1974 to identify ethical principles and develop guidelines on the conduct of research involving human subjects
  - In response to human research abuses (e.g., U.S. Public Health Service study of untreated syphilis at Tuskegee: 1932-1972)
- Pediatric example: intentional administration of live hepatitis virus to intellectually disabled children housed at the overcrowded Willowbrook State School, where conditions and questionable medical practices and experiments prompted Senator Robert Kennedy to call it a “snake pit.”



# Additional Safeguards for Children

## 21 CFR 50 Subpart D

### Appropriate Balance of Risk and Benefit

- Research involving children either
  - must<sup>†</sup> be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child (emphasis added), or
    - 21 CFR 50.51/53; 45 CFR 46.404/406
  - must<sup>†</sup> present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    - 21 CFR 50.52; 45 CFR 46.405

<sup>†</sup> Approval following an FDA determination under 21 CFR 50.54 may be an option.

43 Fed. Reg. 2085 (1978)



# The Belmont Report

Three ethical principles are woven into rationale for recommendations on research involving children.

- **Respect for Persons**
  - “individuals should be treated as autonomous agents, and... persons with diminished autonomy are entitled to protection.”
- **Beneficence**
  - (1) do not harm and (2) maximize possible benefits and minimize possible harms.”
- **Justice**
  - Equitable selection – “a matter a social justice that there is **an order of preference** in the selection of... subjects (e.g., adults before children).” (emphasis added)

44 Fed. Reg. 23191 (1979)



# Pediatric Research Incentive

## Addressing the Exclusion of Children

### Required Pediatric Studies (PREA)

- Established 2003 (permanent in 2012), PREA requires all applications (or supplements) to contain a pediatric assessment unless waived or deferred
- A pediatric assessment must contain data to assess the drug's dosing, safety and efficacy for the claimed indication in all relevant pediatric subpopulations

### Added Marketing Exclusivity (BPCA)

- Established 1997 (permanent in 2012), sponsor may receive 6 mos. marketing exclusivity added to existing patents on all forms and uses of active moiety
- Requires pediatric studies for all indications where there may be a “meaningful therapeutic benefit” in children

Since 1998 -- 728 pediatric labeling changes as a result BPCA and/or PREA incentives.



# Extending the Reach of PREA

## There is much more work to be done!

- **Molecular Targeting in Pediatric Cancers**

- Children’s cancers often occur in different organs than adult cancers, thus manufacturers are able to obtain a waiver from PREA requirements.
- FDA Reauthorization Act of 2017 requires an original application for a new active ingredient (1) intended to treat an adult cancer and (2) directed at a molecular target that is “substantially relevant to the growth or progression of a pediatric cancer” to include the required pediatric assessment(s) under PREA (absent waiver or deferral).

- **Eliminating the Pediatric “Carve Out” for Orphan Designation**

- “FDA *no longer intends to grant orphan drug designation to drugs for pediatric subpopulations of common diseases*” (emphasis added)

Draft Guidance for Industry: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases (December 2017)

# Ethical Principle of Scientific Necessity

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children
  - Derives from justice of equitable selection and minimizing risks [21 CFR 56.111(a)(1) and (b); 45 CFR 46.111(a)(1) and (b)]
  - Practical application (using **extrapolation**): determine type (and timing) of clinical studies required to establish "safe and effective" pediatric use
  - Claim: effective and efficient use of extrapolation is a **moral obligation**.
- “A more targeted generation of evidence should help to ensure that children **only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children** and address the requirements for regulatory decision-making.” (emphasis added)
  - EMA Reflection Paper on Use of Extrapolation (9 October 2017)

# Setting Up Pediatric Extrapolation

Building a Foundation with Appropriately-Designed Adult Studies

## Some examples:

- Using a pediatric PK study alone requires understanding exposure-response relationships in adults (which may require testing more than one dose level).
- Depending on the degree of uncertainty, validating a “PK only” extrapolation concept may require exploring exposure-response in pediatrics.
- Exploring exposure-response in pediatrics may require a PD endpoint that correlates with clinical response, or using a pediatric clinical endpoint that can be correlated with the adult clinical endpoint.
- Lacking such endpoints, it may be necessary to use adult clinical trial(s) to establish an endpoint that could be used for extrapolation of the adult clinical results to pediatrics. Otherwise a full pediatric clinical trial may be necessary.
- With “proof of concept” for sufficient prospect of direct benefit to justify risks, adolescents (e.g.,  $\geq 12$  to  $< 18$  yrs.) could be included in “adult” clinical trial as “source” population for extrapolating to younger children (e.g.,  $< 12$  yrs.).





# Closing Remarks

- In spite of pediatric tragedies being a major impetus for the reform of US pharmaceutical regulations and human subjects protections, children were (and continue to be) systematically (and unjustly) excluded from appropriate clinical trials.
- This exclusion has been partially addressed by the incentives put into place over the past two decades to conduct pediatric clinical trials in support of adequate labeling for use in children.
- Children remain vulnerable – a situation partially addressed by the additional ethical safeguards for children. However, we have a moral obligation to give children a “fair deal” by providing safe and effective pediatric drugs.
- Children are exposed to unnecessary or overly burdensome clinical trials by failing to design adult clinical trials (e.g., evaluating exposure-response, incorporating endpoints that are applicable to all ages) to support extrapolation of adult results to adolescents and/or younger children.



# Thank you



# Session IIa Discussion Questions

- What are the considerations for excluding children, infants and adolescents?
- What are barriers to enrollment when there are not specific exclusions?
- What strategies can be used to enhance inclusion and increase enrollment?

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
[ClinicalTrials.Margolis@Duke.edu](mailto:ClinicalTrials.Margolis@Duke.edu)

 #TrialsEligibility

# Inclusion of Older Adults and Patients with Multiple Chronic Conditions

For Duke-Robert J. Margolis, MD, Center for Health Policy Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials

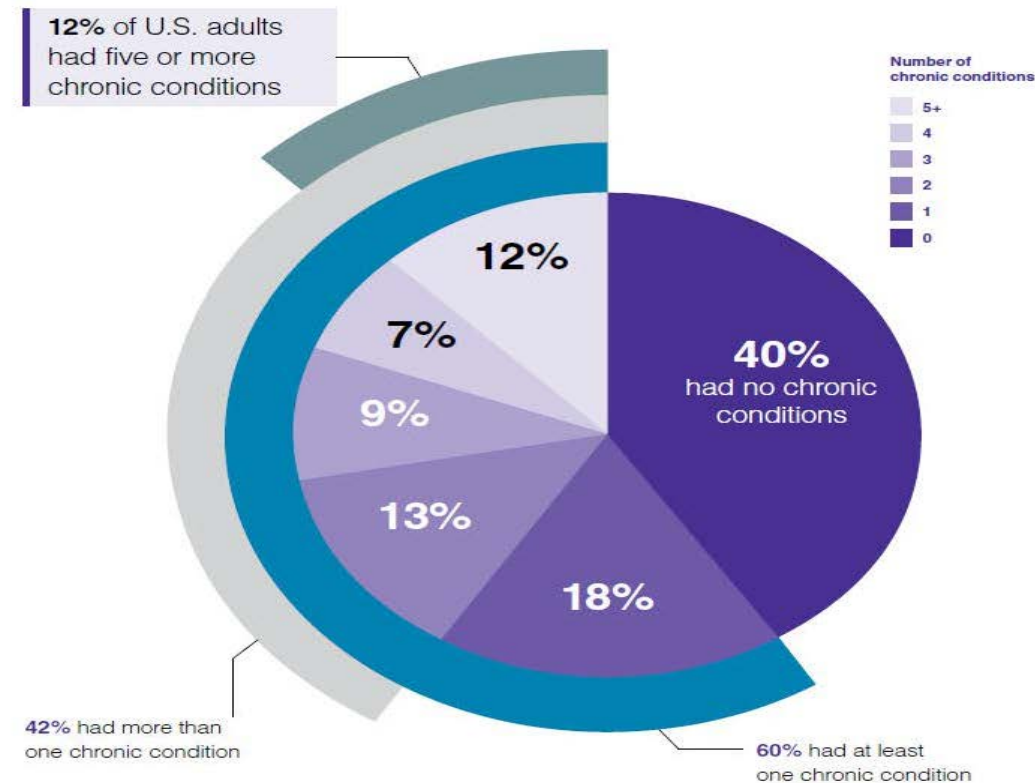
Anand K. Parekh, MD MPH  
Chief Medical Advisor  
Bipartisan Policy Center

April 16, 2018

# Prevalence of Multiple Chronic Conditions

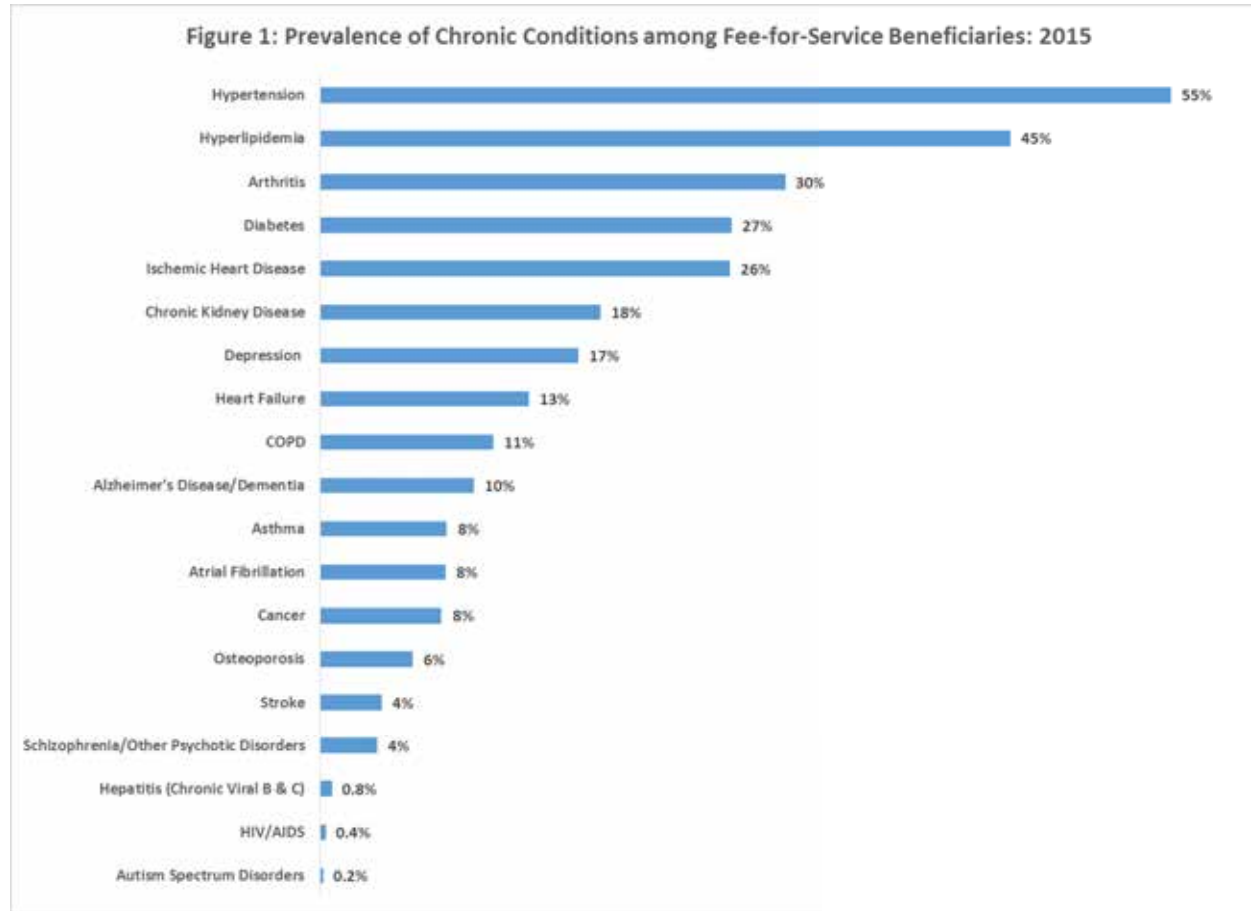
As of 2014, 60 percent of American adults had at least one chronic condition, and 42 percent had more than one chronic condition.

Figure 1.1. Percentage of U.S. Adults with Chronic Conditions, by Number of Chronic Conditions (2014)

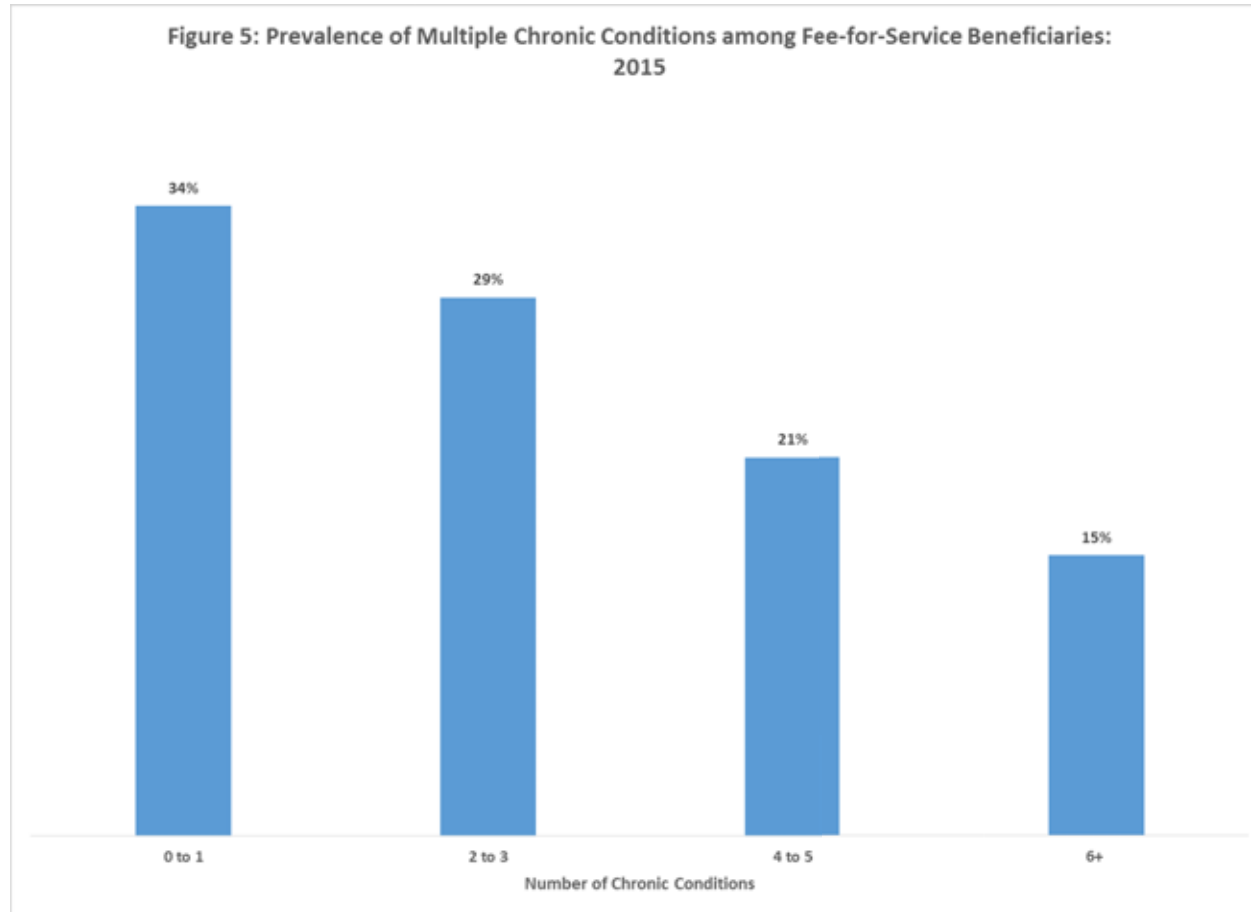


NOTE: Percentages may not total 100 because of rounding.

# Medicare & Chronic Conditions

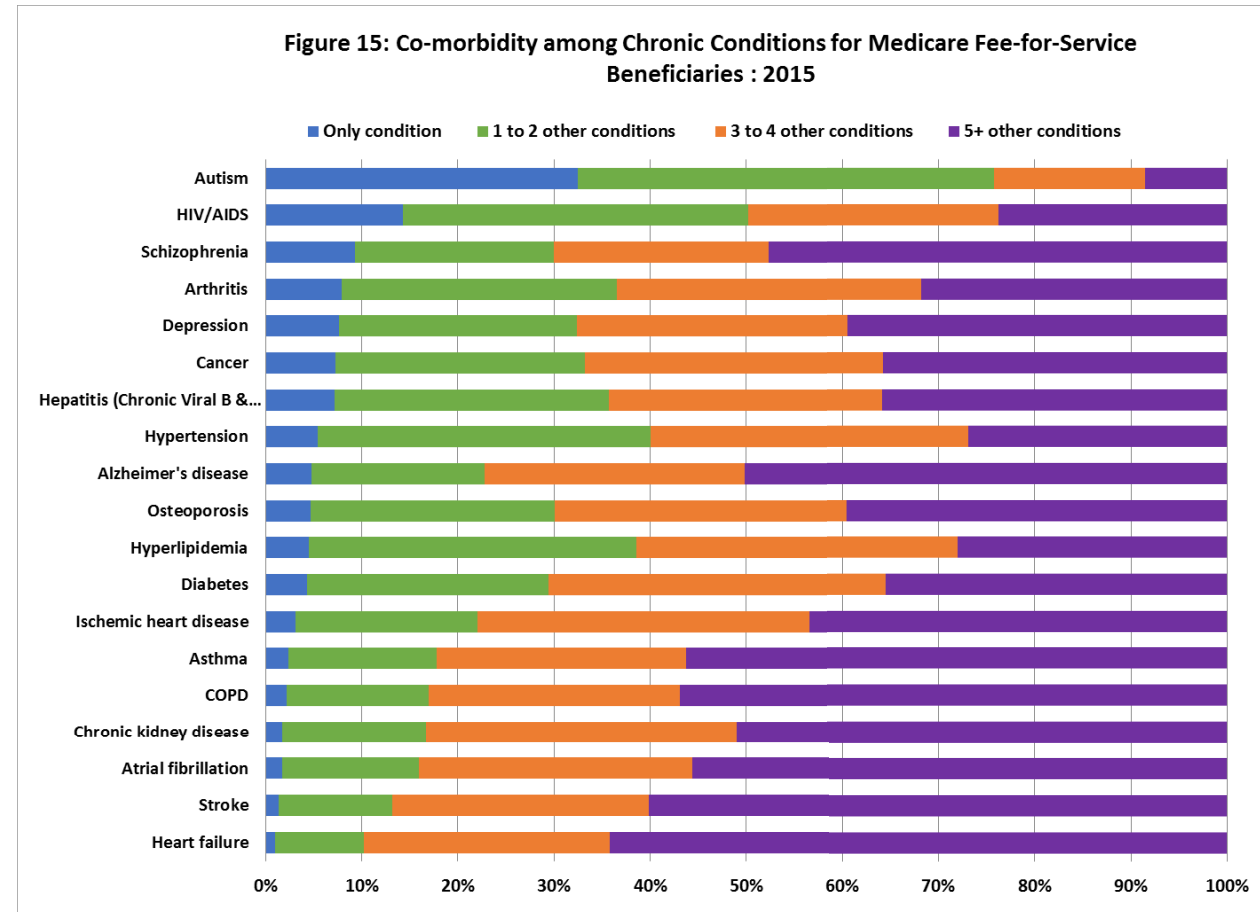


# Medicare & Multiple Chronic Conditions





# Medicare & Multimorbidity



# Age, Chronic Disease Burden & Willingness to Participate

838-5

## Enrollment Disparities on the Basis of Age and Chronic Disease Burden in Cardiovascular Clinical Trials: Are Patients' Decisions the Reason?

Anand Parekh, Neil R. Powe, Joel B. Braunstein, Johns Hopkins Medical Institutions, Baltimore, MD

**Background:** Randomized controlled trials have been criticized for enrolling select groups of patients, while excluding those most representative of the population under study. In cardiovascular disease, this concern implies inadequate representation of patients who are older and have multiple comorbidities. We determined willingness to participate (WTP) in a cardiovascular clinical trial among a community-based sample of patients with these characteristics.

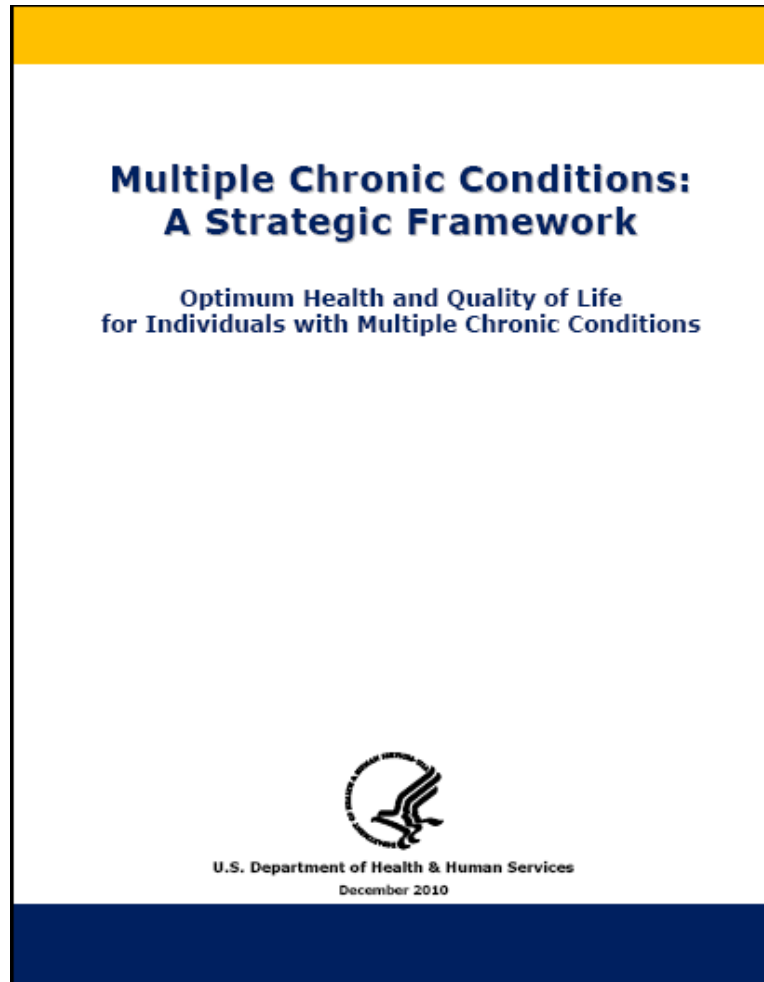
**Methods:** We approached 1440 randomly selected individuals from 13 Maryland-based outpatient cardiology and internal medicine clinics to complete a brief self-administered survey, which contained a 1-page description of an efficacy trial of a new drug for prevention of myocardial infarction. We measured WTP on a 5-point Likert response scale (+ response = Very likely/ likely). Patients provided demographic and socioeconomic information, along with a report of their comorbidity burden, measured by presence of conditions included in the Deyo-Charlson case-mix severity index.

**Results:** Of 1132 patients eligible, 789 (70%) patients responded. Patients were mean aged  $54 \pm 16$  (range 18-89) years, 51% female, and 35% black, with a median of 2 comorbidities (range 0-11). Older-aged patients ( $\geq 75$  years)(n=79) were less WTP than younger patients (19% vs. 36%,  $p < 0.01$ ). Patients with more extensive comorbidity, however, were no less WTP than those with less extensive comorbidity (WTP = 29% if no comorbidity, 34% if 1 comorbidity, 35% if 2-4 comorbidities, 39% if  $\geq 5$  comorbidities,  $p = 0.43$ ). In multivariable logistic regression, after adjusting for race, gender, income, and education, older age was associated with a 65% lower likelihood of WTP (OR, 95% CI = 0.35, 0.19-0.64;  $p = 0.001$ ), while each categorical increase in comorbidity was associated with a 19% higher likelihood of WTP (1.19, 1.00-1.42;  $p < 0.05$ ).

**Conclusion:** While older age is independently associated with lower WTP in cardiovascular clinical trials, more extensive comorbidity is not. These findings warrant consideration in the design of future trials, which seek to adequately enroll cardiac patients who are most representative of those encountered in routine clinical practice.

# HHS Multiple Chronic Conditions Initiative

Opinion



## VIEWPOINT

**Anand K. Parekh, MD, MPH**  
Office of the Assistant Secretary for Health, US Department of Health and Human Services, Washington, DC.

**Richard Kronick, PhD**  
Agency for Healthcare Research & Quality, US Department of Health and Human Services, Washington, DC.

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Centers for Medicare & Medicaid Services, US Department of Health and Human Services, Washington, DC.

**Corresponding Author:** Anand K. Parekh, MD, MPH, Office of the Assistant Secretary for Health, US Department of Health and Human Services, 200 Independence Ave SW, Washington, DC 20201 (anand.parekh@hhs.gov).

## Optimizing Health for Persons With Multiple Chronic Conditions

**The challenges** for the US health care system of high health care costs and poor health outcomes in individuals with multiple (2 or more) concurrent, chronic conditions have been well documented.<sup>1,2</sup> Estimates are that more than one-quarter of all adults have multiple chronic conditions<sup>3</sup>; in addition, more than two-thirds of Medicare fee-for-service beneficiaries have multiple chronic conditions, with 14% having 6 or more common conditions.<sup>4</sup> Recently, the Centers for Medicare & Medicaid Services (CMS) released new data resources on chronic conditions among Medicare fee-for-service beneficiaries to better define the burden of chronic conditions among beneficiaries and the implications for the US health care system.

In response to this public health challenge, the US Department of Health and Human Services (HHS) released its report "Strategic Framework on Multiple Chronic Conditions" in 2010. The strategic framework, developed with private sector input, provides HHS and its partners with a roadmap for improving the health status of persons with multiple chronic conditions across 4 overarching goals<sup>5</sup> (Box). Within the first few years of implementation, the strategic framework has led to the following selected actions and continues to offer additional opportunities for further collaboration.

### Goal 1: Foster Health Systems Change

#### New Models of Care

The Affordable Care Act has accelerated efforts to coordinate and manage care for individuals with multiple chronic conditions through broad-based models such as accountable care organizations and patient-centered medical homes. In addition, specific models focused on the multiple chronic conditions population are also being tested by CMS, such as the Independence at Home demonstration, which is providing home-based primary care to 8000 frail Medicare beneficiaries with multiple chronic conditions and functional limitations. In addition, the Medicaid Health Home state plan option to coordinate the primary, acute, behavioral, and long-term care of individuals primarily with multiple chronic conditions, many of whom have a serious mental illness, has been adopted by 15 states and serves more than 1 million Medicaid beneficiaries at the time of this publication. Approximately 40 000 Medicare-Medicaid enrollees, a group traditionally with high prevalence rates of multiple chronic conditions, are currently enrolled in new integrated care models in 6 states.

#### Payment for Non-Face-to-Face Care Management Services

In its 2014 physician fee schedule final rule, CMS finalized regulations to start in 2015 to establish separate payments for managing the care of patients with multiple chronic

conditions outside of a face-to-face visit. This decision recognizes the importance of care-management services for patients with multiple chronic conditions, particularly those most vulnerable to poor outcomes and high costs.

### Goal 2: Empower Individuals

#### Evidence-Based Self-management Programs

In 2010, the Administration on Aging awarded approximately \$30 million in grants from American Recovery and Reinvestment Act funds to expand participation in Stanford University's Chronic Disease Self-Management Program. To date, 185 000 older US residents, the vast majority with multiple chronic conditions, have participated in a chronic disease self-management program. These programs have been shown to improve symptoms, prevent exacerbations of illness, and decrease emergency department visits. In 2013, CMS issued a report to Congress mandated by the Affordable Care Act on evaluating community-based wellness and prevention programs such as chronic disease self-management programs for their effects on Medicare beneficiaries. Retrospective analyses suggest potential cost savings for certain physical activity, falls prevention, and self-management programs.

### Goal 3: Equip Clinicians

#### Clinical Practice Guidelines and Quality Measures

In 2012, the Institute of Medicine and HHS convened expert stakeholders to discuss integrating information on comorbidities in clinical practice guidelines for specific conditions. Since that time, a number of professional societies, including the American College of Cardiology, American Heart Association, and the American Society of Clinical Oncology, have published guidelines with comorbidity-specific information to assist physicians and other frontline clinicians in better understanding the complexity of their patient populations. In addition, in 2012, the National Quality Forum, with funding from HHS, released a multiple chronic conditions measurement framework to provide guidance to measure developers as they generate appropriate measures for clinicians treating individuals with multiple chronic conditions.

#### Education and Training

In 2013, the Office of the Assistant Secretary for Health, in conjunction with the Health Resources Services Administration, launched an interprofessional health care education and training initiative to inform undergraduate, graduate, and continuing education curricula on core competencies essential to caring for the multiple chronic conditions population. The resources developed are slated to be released by the end of 2014 and then disseminated to training programs by the Health Resources Services Administration.

# Increasing the External Validity of Clinical Trials

**Objective A: Increase the external validity of trials**—As the number of individuals with MCC grows, ensuring that treatment interventions (e.g., drugs, devices, lifestyle modifications, alternative medicine) for these conditions are safe and effective becomes more important. To achieve this end, efforts to improve understanding of interactions between comorbidities and to limit exclusions of this increasingly large population in clinical trials may assist in preventing adverse events and poor outcomes that otherwise might have occurred if this population were not included in the study design.

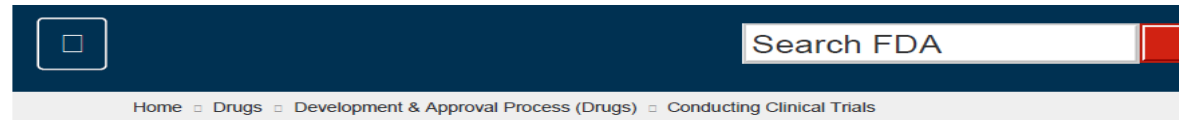
- Strategy 4.A.1. Develop methods to assess the inclusion of individuals with MCC in clinical trials. Such methods should include determining 1) optimal trial designs for including MCC patients; 2) optimal approaches for recruiting MCC patients; 3) the potential risks of exposing some MCC patients to new interventions; and 4) the appropriate analysis of outcomes data from clinical trials that include individuals with MCC.
- Strategy 4.A.2. Improve the external validity of HHS-funded community and clinical intervention trials by ensuring that individuals with MCC are not unnecessarily excluded (as determined by scientific experts and external stakeholders).
- Strategy 4.A.3. Ensure, through guidance or regulation, that individuals with MCC are not unnecessarily excluded from clinical trials for the approval of prospective drugs and devices.

- FDA/ASPE supported study by Digital Infusion assessing exclusions from clinical trials submitted to support drug applications in 2010.
- Key study findings:
  - 71% of studies excluded patients with a psychiatric disorder
  - 66% excluded patients with a heart disorder
  - 38% excluded diabetics



# FDA Good Review Practice: Clinical Review of Investigational New Drug Applications

U.S. Department of Health and Human Services' Initiative on Multiple Chronic Conditions



## U.S. Department of Health and Human Services' Initiative on Multiple Chronic Conditions

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The U.S. Department of Health and Human Services' [Initiative on Multiple Chronic Conditions \(MCC\)](#) is an effort to improve the health and quality of life of Americans living with two or more chronic diseases. Part of FDA's role in this initiative is to encourage drug developers to include a diverse, "real world" patient population in the clinical trials used to study the effects of a drug in development.

Drug developers sometimes exclude older patients and patients with chronic illnesses in their studies because of concerns that these individuals might eventually drop out of the study, use other medicines that could alter the effects of the drug being studied, or have complications related to their other disease. This approach, however, does not show how a drug affects those people who have other diseases or who are using other medications who may one day take the drug in question.

FDA [internal policy \(PDF - 46KB\)](#) now instructs that a closer examination of the populations to be included in clinical trials should be a regular part of FDA's assessment of clinical trials and FDA expects the development plans proposed by drug developers to include patients with multiple chronic conditions. FDA's goal is to ensure that products coming to market will be as safe and effective as possible for all members of the public, and clinical trials that closely mirror the current patient population are an important part of achieving this goal.

### Related Information

- [Multiple Chronic Conditions: A Strategic Framework](#)

[More in Conducting Clinical Trials](#)

# HHS MCC Initiative Impact on NIH Programs

- New Funding Opportunities focused on the multiple chronic conditions population
  - Health care systems research collaboratory to fund demonstration projects for pragmatic clinical trials focused on management of multiple chronic conditions
- Internal Assessment of Inclusion/Exclusion Criteria in NIH-funded studies

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
[ClinicalTrials.Margolis@Duke.edu](mailto:ClinicalTrials.Margolis@Duke.edu)

 #TrialsEligibility

# Duke

**Robert J. Margolis, MD**  
**Center *for* Health Policy**

**Session IIb:**

## **What Leads to Underrepresentation?**

**Public Workshop:**

**Evaluating Inclusion and Exclusion Criteria in Clinical Trials**

**The National Press Club • Washington, DC April 16, 2018**

Meryl Comer, President & CEO, Geoffrey Beene Foundation Alzheimer's Initiative;  
Co-PI, AD-PCPRN (Alzheimer's, Dementia, Patient & Caregiver Powered Research Network)





## Alzheimer's Clinical Trial Recruitment

Currently in the United States:

- 85-90% of Alzheimer's clinical trials have DELAYS in RECRUITMENT
- 30% DO NOT meet their enrollment GOAL
- ONLY 7% of trial sites recruit their projected # of PARTICIPANTS



## Common Inclusion Criteria for an MCI/AD Trial

- A DIAGNOSIS of mild cognitive impairment or Alzheimer's disease
- Able & willing to undergo BRAIN SCANS, including MRI's & PET SCANS
- If no diagnosis, subjective MEMORY COMPLAINTS for six+ months
- Between the AGES of 55-99
- Able to come in for REGULAR STUDYVISITS, usually monthly
- A reliable STUDY PARTNER (someone who spends at least 10 hours with the participant a week) who could join for all or most study visits



## Common Exclusion Criteria for an MCI/AD Trial

- Any uncontrolled HEALTH PROBLEMS or a history of cancer within the last 5 years
- A NEUROLOGICAL DISEASE that may affect cognition or ability to complete a study, such as a different dementia (i.e. Parkinson's, vascular, etc.) or epilepsy
- Current participation in any OTHER CLINICAL TRIALS involving an investigational therapy
- Recent or current chronic ALCOHOL or DRUG ABUSE



## Alzheimer's Prevention Trials

- Make recruitment process as CONSUMER-CENTRIC as Amazon
- Inclusion/Exclusion screens on both PATIENTS & CARE PARTNERS
- Mobile technology - let people PRE-SCREEN themselves
- Care partners as DATA COLLECTORS between Clinical Visits
- Care partner as asymptomatic or "POTENTIAL 2<sup>nd</sup> PATIENTS"
- Replace subjective with PASSIVE DATA COLLECTION

**Rethink Engagement: Change the Conversation**

# Session IIb Discussion Questions

- What are the considerations for excluding elderly patients and patients with concomitant illness?
- What are barriers to enrollment when there are not specific exclusions?
- What strategies can be used to enhance inclusion and increase enrollment?

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
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 #TrialsEligibility



# Session III Discussion Questions

- What are the factors that ensure representative enrollment?
- How can we balance enrichment strategies with providing more generalizable trial results?
- How does the variability in designing and applying inclusion and exclusion criteria effect generalizability of trial results?
- What can we learn from the design of in rare disease trials regarding inclusiveness?
- How can subjects with different degrees of disease severity be appropriately included into clinical trials?

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
[ClinicalTrials.Margolis@Duke.edu](mailto:ClinicalTrials.Margolis@Duke.edu)

 #TrialsEligibility



# Inclusion of Patients with Organ Dysfunction: Utility and Challenges of Clinical Pharmacology Approaches

Raj Madabushi, PhD  
Team Lead, Guidance and Policy Team  
Office of Clinical Pharmacology  
OTS/CDER

# Outline

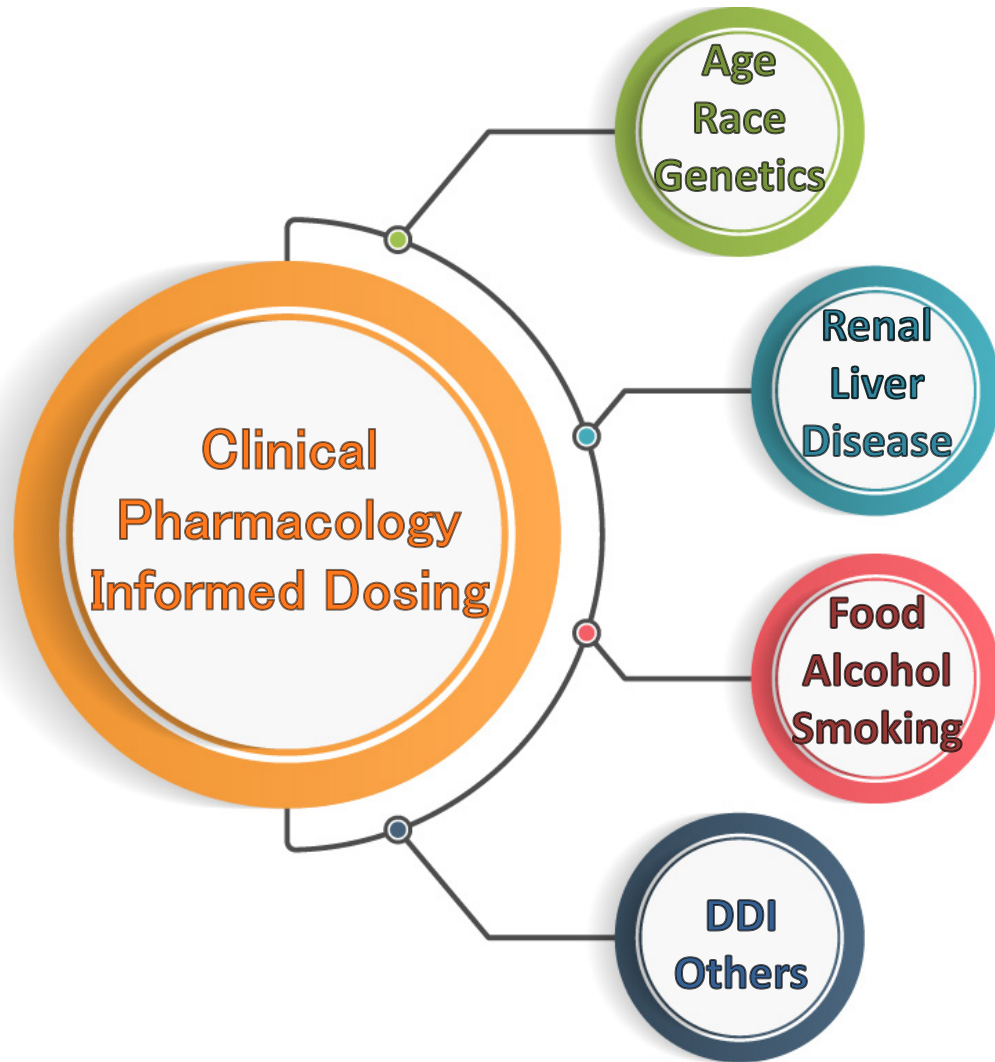
- Problem
- Current Paradigm
- Alternative Approach
- Summary

# Problem

- Patients with organ dysfunction, generally with renal or hepatic disease, are often excluded from clinical efficacy trials
  - ~80% of the trials had exclusion by renal or liver disease\*
  - At least half of the exclusions are based on markers of organ function/injury\*
- Patients with renal or liver disease are also a subgroup at higher risk for morbidity and mortality
- Gap in adequate prescribing recommendations for patient subgroups with greatest need



# Current Paradigm: Bridging the Gap with Clinical Pharmacology

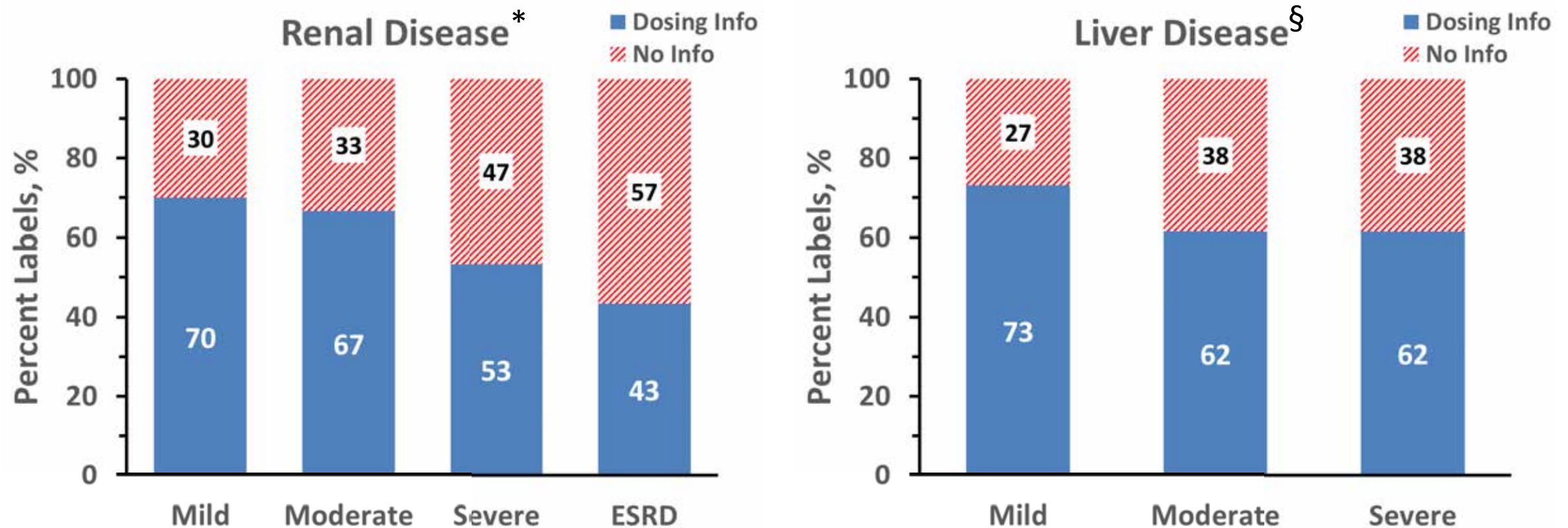


- Most drugs are cleared by liver and/or kidneys
- Any factor that affects their function can result in altered blood levels and may lead to altered benefit-risk
- Stand-alone clinical pharmacology studies can characterize the magnitude of alteration
- Dosing can be derived by “exposure-matching”
  - E.g., if a dedicated study shows a 2-fold increase in blood levels for patients with severe renal impairment, the dose for these patients should be halved



# Clinical Pharmacology Informed Dosing

*Only includes drugs with efficacy trials that had renal or liver disease exclusion*



Dosing Information: No Dose Adjustment; Dose Reduction; Not Recommended; Contraindication

\*Mild, Moderate, and Severe renal disease based on eGFR or CrCL ranges of 89 - 60, 59 – 30, and 29 – 15 mL/min respectively

§Mild, Moderate, and Severe hepatic disease correspond to Child-Pugh categories of A, B and C respectively

Data Source: Pilot retrospective review of 38 approvals over 2014 - 2017



# Alternative Approach

Broaden the enrollment of patients with organ dysfunction into efficacy trials

- Include patient subgroups with no prospective dose adjustment based on expected benefit-risk
- Can require prospective dose adjustment based on “exposure-matching” for inclusion of such patient subgroups
- When the uncertainty is high, the patient subgroup could be included as an exploratory subgroup to obtain clinical experience

# Summary

- Patients with renal or liver dysfunction are generally excluded from efficacy trials
- This exclusion can create a knowledge gap that is often filled by “dedicated” stand-alone clinical pharmacology studies in specific populations
- The current paradigm based on “exposure-matching” addresses some of the gaps in deriving adequate dosing recommendations, sometimes (but not always) translating into labeling recommendations
- Broader clinical trial enrollment of these patients has been accomplished for efficacy trials, raising nuanced clinical trial design, interpretation, and labeling issues

# Acknowledgements

- Issam Zineh, PharmD, MPH
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- Sudharshan Hariharan, PhD
- Yaning Wang, PhD



# Questions for Panelists

- What are the advantages and limitations of the current paradigm of using stand-alone clinical pharmacology studies in lieu of broadening enrollment criteria for efficacy trials?
- How should clinical efficacy trials be designed a priori to account for potential different dosing needs in patients with varying degrees of organ function?
- What are pros and cons of the alternative paradigms that broaden enrollment of patients with organ dysfunction in efficacy trials?

Thank You!

# Session IV Discussion Questions

- What are the advantages and limitations of the current paradigm of using stand-alone clinical pharmacology studies in lieu of broadening enrollment criteria for efficacy trials?
- How should clinical efficacy trials be designed a priori to account for potential different dosing needs in patients varying degrees of organ function?
- What are pros and cons of the alternative paradigms that broaden enrollment of patients with organ dysfunction in efficacy trials?

# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

E-Mail Questions to  
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 #TrialsEligibility

# **Design, Analyses and Inference with Expanded Eligibility Criteria**

**Rajeshwari Sridhara, Ph.D.**  
**Director, Division of Biometrics V**

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

# Clinical Trials

- Controlled Experiment
- Control noise/variability → Homogeneous Population
- Control known confounding factors so that observed outcome is attributable to the treatment → Patients with few or no comorbidities that may influence outcome
- Enrich population to see results quickly
- Generally not representative of the population at large

# Example: Oncology/Hematology Protocols Submitted in 2015



- Total # of INDs submitted  $\approx$  1031; 68% Research INDs, 32% Commercial INDs

Of the commercial INDs:

- 3.7% included pediatric patients
- 60% required ECOG/WHO PS of 0-1; 35% required PS 0-2
- 77% excluded known, active, or symptomatic CNS or brain metastases; 47% allowed treated or stable brain metastases
- 84.2% excluded known or active HIV patients; 1.7% allowed stable disease and patents with adequate CD4 counts

JCO 2017, 35:3745 - 3752

## Expansion of Eligibility Criteria

- Increases variability
- Observed effect may be confounded due to underlying characteristics in the expanded population – perceived as high risk population
- Potential change in balance of benefit vs risk
- How can we prospectively design, analyze and interpret results with a more heterogeneous study population?



# Trial Design Options

## 1. Randomized Clinical Trial

- Population: defined by restricted eligibility criteria ('lowriskpop') + expanded population ('highriskpop')
- Stratification factor: lowriskpop vs. highriskpop
- ITT population = lowriskpop + highriskpop; Modified ITT (MITT) population = lowriskpop
- Primary analysis based on MITT (the primary indicated population)
- Hierarchical testing: ITT after MITT; if sample size is adequate and hypothesis driven then highriskpop tested separately

## Trial Design Options

2. Simultaneous RCT in lowriskpop and single arm cohort in the highriskpop
  - ITT population = lowriskpop in the RCT; analyzed separately
  - Single arm highriskpop – descriptive statistics
    - Limited safety evaluation – attribution of toxicity challenging

# Trial Design Options

3. Phase I Study in highriskpop after tolerable dose is determined in lowriskpop.
  - If no safety concerns, then enroll in Phase III trials without stratification
  - Timeline for the Phase I with respect to Phase III?
4. Highriskpop trial as a post-marketing study
  - Feasibility – drug is marketed and available
  - Possibly comparisons of approved dose vs. a lower dose?

# Trial Design Options

5. Basket trials or Master protocols for the highriskpop with each risk group as a cohort
  - Borrowing from lowriskpop outcomes?
  - Compare to historical control? – registry data?
6. Pragmatic real world randomized trial in highriskpop possibly comparing doses
  - Different specialist services involved – pediatric patients unlikely to be treated by adult patient physicians
  - Standardization of outcome assessments

# Things to Consider – Some examples



- Who should be in the highriskpop cohort?
- Trial Option 1
  - Proportion of patients in lowriskpop > highriskpop (example, 80:20)
  - Primary hypothesis, Type I and Type II errors, number of events for the final analysis, all based on lowriskpop
  - Hierarchical testing feasible? – what if more events in the highriskpop cohort
  - Limit number of patients in highriskpop cohort?
- Trial Option 2
  - Highriskpop may be enrolled only in certain sites
  - Difficult to interpret toxic events, in particular deaths without a control arm in the highriskpop cohort



## Panel Discussion Points

- Pros and Cons for each of the trial designs including feasibility issues
- Adjustments in type I error allocation for multiple testing
- Types of Analyses
- Inferences that are possible and not misleading
- Suggestions on any other innovative trial designs

# Questions ?

# Session V Discussion Questions

- How might the following innovative trial designs and methods that maximize external validity affect study eligibility for appropriate patient populations?
  - Expanded size to allow subgroup analysis
  - Smaller trials in targeted populations
  - Pragmatic trials
  - Adaptive designs
  - Other trial designs and methods (basket based on population)
- Are there use-case examples of how a particular trial design improved external validity?



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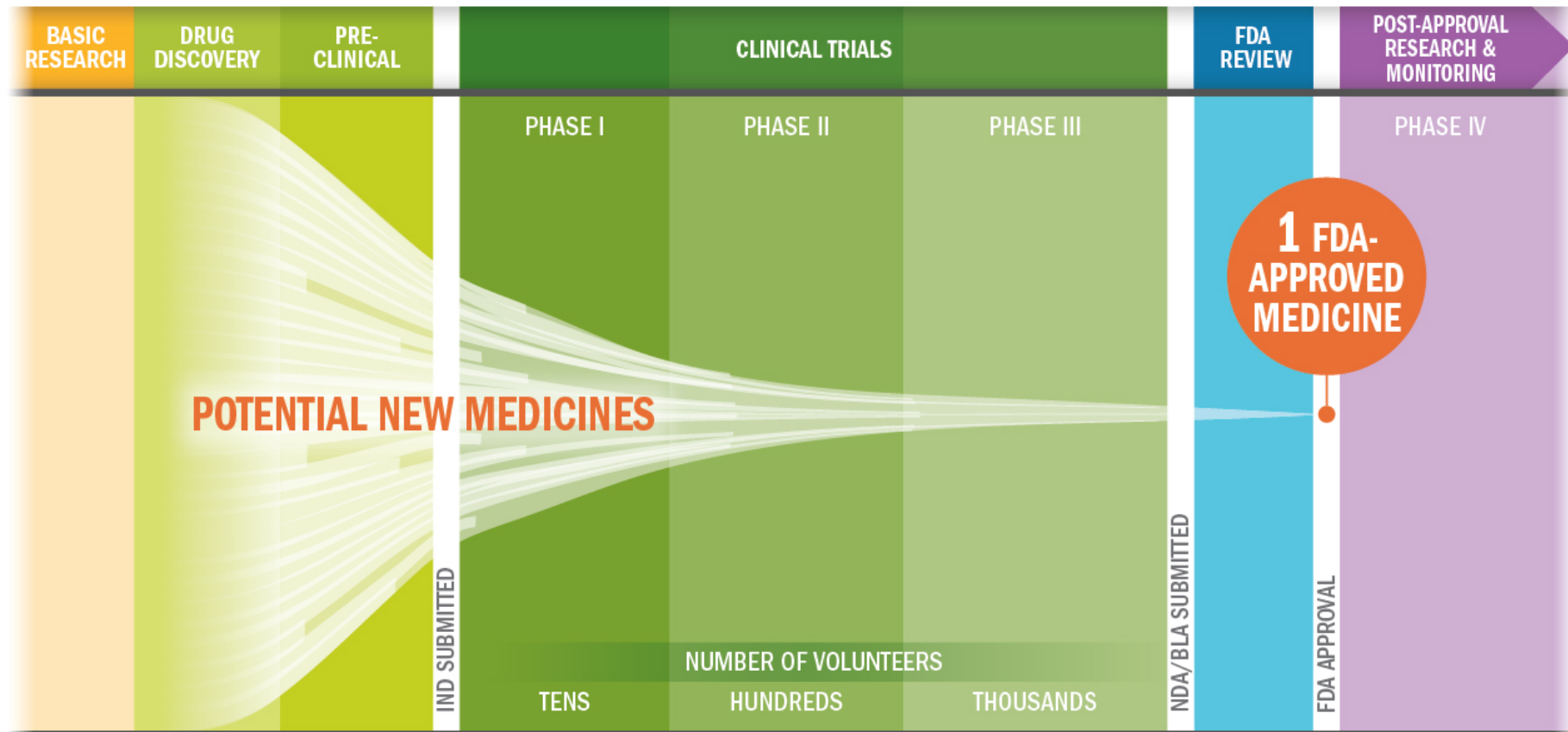


# Session VI: Utilizing Data from Expanded Access

April 16, 2018

**P7RMA**  
RESEARCH • PROGRESS • HOPE

# The Biopharmaceutical Research and Development Process



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

\*The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

# Clinical Trials are Critical for Approval

- **FDA approval remains the best way** to ensure that new safe and effective medicines are **broadly available to patients**
- **Successful completion of the clinical trial process is required to demonstrate** to the FDA that an investigational **drug is safe and effective** so that it can be made available to a broader patient population
- Sponsors need to be able to conduct clinical trials that can **best demonstrate whether efficacy exists**, this may involve studying a **select group of patients that can best differentiate an effect**
- Similarly, the trials should **reduce risk to patients before evidence of benefit exists** and not confuse safety signals, due to comorbidities
- Inclusion and exclusion criteria **should not be overly broad** and **dilute the ability to discern whether benefit exists** nor add to time to completion
- Selection of inclusion and exclusion criteria should be **science based** and carefully considered rather than derived from habit or common practice

# Expanded Access vs. Clinical Trials

**For patients with a serious or life-threatening disease who do not fit the entry criteria, use of an unapproved investigational drug via an expanded access program may be the appropriate vehicle for access**

**“Expanded access, sometimes called compassionate use, is the use outside of a clinical trial of an investigational medical product.”**

*“Wherever possible, use of an investigational medical product by a patient as part of a clinical trial is preferable because clinical trials can generate data that may lead to the approval of products and, consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible, patients may be able to receive the product, when appropriate, through expanded access.”*

**– FDA, “Expanded Access (Compassionate Use)”**

# Using Data from Expanded Access

- **Treatment vs. Research:** The primary purpose of Expanded Access is to treat a patient rather than to obtain data about the drug as in a clinical trial
  - Need to **balance** scientifically-driven considerations and the humanitarian need
  - Individual IND Expanded access does not usually yield substantial data
    - (>97% of EA requests)
- Appropriately-designed, **protocol-driven** Expanded Access programs can contribute to the overall evaluation of a drug's benefit-risk profile
  - “In a very small number of cases, adverse event information from expanded access has contributed to safety information reflected in the FDA-approved labeling for a drug product. FDA is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug.”\*
- Mechanism for more structured data collection: Expanded Access protocols under an existing IND facilitate FDA review and may facilitate identification of safety concerns
  - Intermediate-size patient population expanded access IND and protocols
  - Treatment IND or Treatment Protocol (expanded access for widespread use)
- *\*FDA Guidance, “Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers”, updated Oct. 2017*



# Assessment of Data from Expanded Access

- Expanded Access treatment generally occurs outside a controlled clinical trial setting
- Patients who do not meet the eligibility criteria for clinical trials but are treated under Expanded Access might be at increased risk for serious adverse events because of their advanced disease, concomitant medications, and/or comorbidities
- FDA needs to understand the context in which the Expanded Access use was permitted and evaluate any adverse event data obtained from an Expanded Access submission within that context
- Sponsors continue to have concerns that adverse events from expanded access may impact product development and approval
- Guidance from FDA regarding the interpretation of adverse events from expanded access would be helpful

# Opportunities for Using Efficacy Data

- Current FDA Thinking on **Use of Efficacy Data**:

“Expanded access INDs and protocols are generally not designed to determine the efficacy of a drug; however, the expanded access regulations do not prohibit the collection of such data. Because expanded access INDs or protocols typically involve **uncontrolled exposures (with limited data collection)**, **it is unlikely** that an expanded access IND or protocol would **yield efficacy information that would be useful to FDA in considering a drug’s effectiveness.**”

– FDA Guidance, “Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers”, updated Oct. 2017

- However, we must find better ways to analyze protocol driven data collection
  - Methods from observational data analysis should be explored
  - Comparisons to pivotal trial data and or historical data may also be useful in understanding potential efficacy in these alternate patient populations
- FDA has approved a small number of medications based primarily on expanded access data, all were for rare diseases



# Adjacent Trials

- **Open-label safety studies** offer another way to gain experience in patient populations which do not fit the pivotal trial
  - May be able to compare to data from the pivotal trial or prior historical data
- Other strategies may be to assess alternative dosing regimens or different endpoints in other populations outside of the pivotal trial
- Use of real world data in such trials may allow expeditious study of these populations

# Addressing Patients' Unmet Medical Needs

- The development of new safe and effective medicines for serious or life-threatening diseases represents **an urgent and unique challenge that deserves special attention from all stakeholders**
- **Need clear FDA guidance** on the use of safety and efficacy data derived from Expanded Access cases
- Advance the use of complex novel clinical trial designs, model-informed drug development, real world evidence, and other innovative drug-development tools to further expedite evaluation and approval of important medications

# Session VI Discussion Questions

- What are the benefits and challenges to utilizing data from the expanded access program?
  - What are the limitations to using the data?
  - What considerations should be taken if the data will be used to support or expand an indication?
- How would expansion of data obtained via expanded access protocols potentially impact enrollment in registration trials?

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# Evaluating Inclusion and Exclusion Criteria in Clinical Trials

**Duke-Margolis Center for Health Policy**

Closing Remarks