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FDA/CDRH Webinar

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Evaluation of Sex-Specific Data in Medical Device Clinical Studies - Final Guidance for Industry and FDA Staff

Jismi Johnson, M.S.
Kathryn O'Callaghan, B.S.
Lilly Yue, Ph.D.
Danica Marinac-Dabic, M.D., Ph.D.

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Overview

- Guidance Objectives, Scope and Background
- Major Comments Received on Draft Guidance
- Major Revisions Made to Final Guidance
- Content of Guidance
- Decision Framework
- Question & Answer

Introduction

- **Intended to improve quality and consistency of available data regarding device performance in both sexes**
- **Objectives**
  - Encourage consideration of sex and associated covariates during study design stage
  - Provide recommendations for study design and conduct to encourage enrollment of each sex
  - Outline recommended sex-specific statistical analyses of study data with framework for considering sex-specific data when interpreting overall study outcomes
  - Specify expectations for reporting sex-specific information in summaries and labeling for approved or cleared devices
- **2 public workshops helped to develop policy**
  - June 2, 2008
  - December 9, 2008

Scope

- Focus on sex but can also be applicable for other demographic variables(e.g., age, race, ethnicity)
- Recommendations may not applicable in all cases (e.g., OB/GYN and urology devices intended for single-sex, de-identified IVD devices)

Comments Received on Draft Guidance

- **Statistical Comments**
  - Clarification on statistical concepts
  - When should studies be powered for sex difference?
  - When would additional data be needed?
  - Primary effectiveness analyses followed by subgroup analyses
  - Poolability questions
- **Statistical Section updated -"Considering Sex in Study Design and Data Interpretation"**
  - Discussion of statistical concepts for sex-specific differences
  - Considerations when designing clinical study
  - Considerations for analyzing data from one-arm and comparative studies
  - Considerations for diagnostic devices
  - Recommendations for interpreting sex-specific data

Background

- **Sex/Gender Definitions**
  - *Sex* refers to classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement.
  - *Gender* refers to person's self representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology, and shaped by environment and experience.

Why Consider Sex Differences?

- **Certain medical products elicit different responses in women compared to men**
- **Ventricular Assist Devices (VADs)**
  - Women observed to have higher incidence of strokes [18% vs. 6%], but strokes did not have significant effect on their overall survival compared with men
  - Trends toward higher incidence of bleeding and infection events observed in women than men
- **Cardiac Resynchronization Therapy Defibrillators (CRT-D)**
  - Both men and women experienced a CRT-D benefit; however, women received a greater benefit than men [77% vs. 42%]
- **Metal-on-Metal Hips**
  - Higher revision rates in females when compared to males [e.g. 0-27.6% vs. 1.4-8.97%]

Participation of Women in Clinical Studies

- **Lack of available data for women**
  - 1970s: Women "of child-bearing potential" be excluded from drug studies
  - 1992: GAO report concluded that women were significantly underrepresented; sex-specific data analysis was performed in <50% of drug studies
  - 1994: CDRH discusses addressing possibility of "gender bias" in submissions and review documentation for new medical devices
  - 2013: FDA Report shows participation rates for women varied widely by device product area

Participation of Women in Clinical Studies

- **Barriers to Enrollment of Women in Clinical Studies**
  - *Lack of understanding about main obstacles to participation of women in clinical research*
  - *Inclusion/exclusion criteria potentially not needed to define study population may unintentionally exclude women*
  - *Lack of understanding about differences in disease etiology and pathophysiology may lead to under-diagnosis and under-referral of women*
  - *Device manufacturing limitations to accommodate anatomical differences between women and men*
  - Fear of fetal consequences if female participant becomes pregnant
  - Investigators and sponsor avoidance of female patients due to perception that it takes more time and money to recruit them
  - Family responsibilities limiting women's ability to commit time for study follow-up

Achieving Appropriate Enrollment

- **Intent is to provide context based on disease science**
  - Sponsors should investigate and report whether sex differences may or may not exist for disease or condition which device is intended to treat or diagnose
- **Methods to increase enrollment, for example:**
  - Target sites where recruitment of women is easier
  - Consider revising enrollment criteria, when appropriate, or consider parallel cohorts for collecting data on device use in women
  - Investigate reasons for under-enrollment or non-enrollment of women or other key demographic groups
- **Sponsor and Investigator responsibilities to avoid or minimize loss-to-follow up**

Considering Sex in Study Design and Data Interpretation

- **Important to consider variation in data across sex in both study design and interpretation of study data**
- **Statistical concepts for assessing heterogeneity across sex groups**
  - Identifies and define statistical terms and tests
  - Includes recommendations for new or ongoing studies, completed studies, and for postmarketing studies
- **Recommendations for Study Design:**
  - When sex group differences are anticipated
  - Prespecifying assessment of heterogeneity across sex groups in study design
  - One-arm studies and comparative studies
  - Diagnostic devices

Considering Sex in Study Design and Data Interpretation (cont'd)

- **Recommendations for Analysis and Interpretation**
  - Analysis for clinically meaningful sex differences
  - Specific considerations for one-arm studies and comparative studies
- **Interpretation of Sex-Specific Data**
  - Discuss with FDA to determine if additional data are needed
    - Insufficient data → additional data pre-market or post-market may be needed to address potential sex-specific questions
  - Clinically meaningful differences between sexes observed may lead to (rare cases):
    - Additional confirmatory studies in one or both sexes
    - Implementation of specific pre- or post-approval study conditions
    - Modification of the design of subsequent studies
  - Limitations in interpreting clinically meaningful differences in small data sets

Reporting Sex-Specific Information in Applications and Public Documents

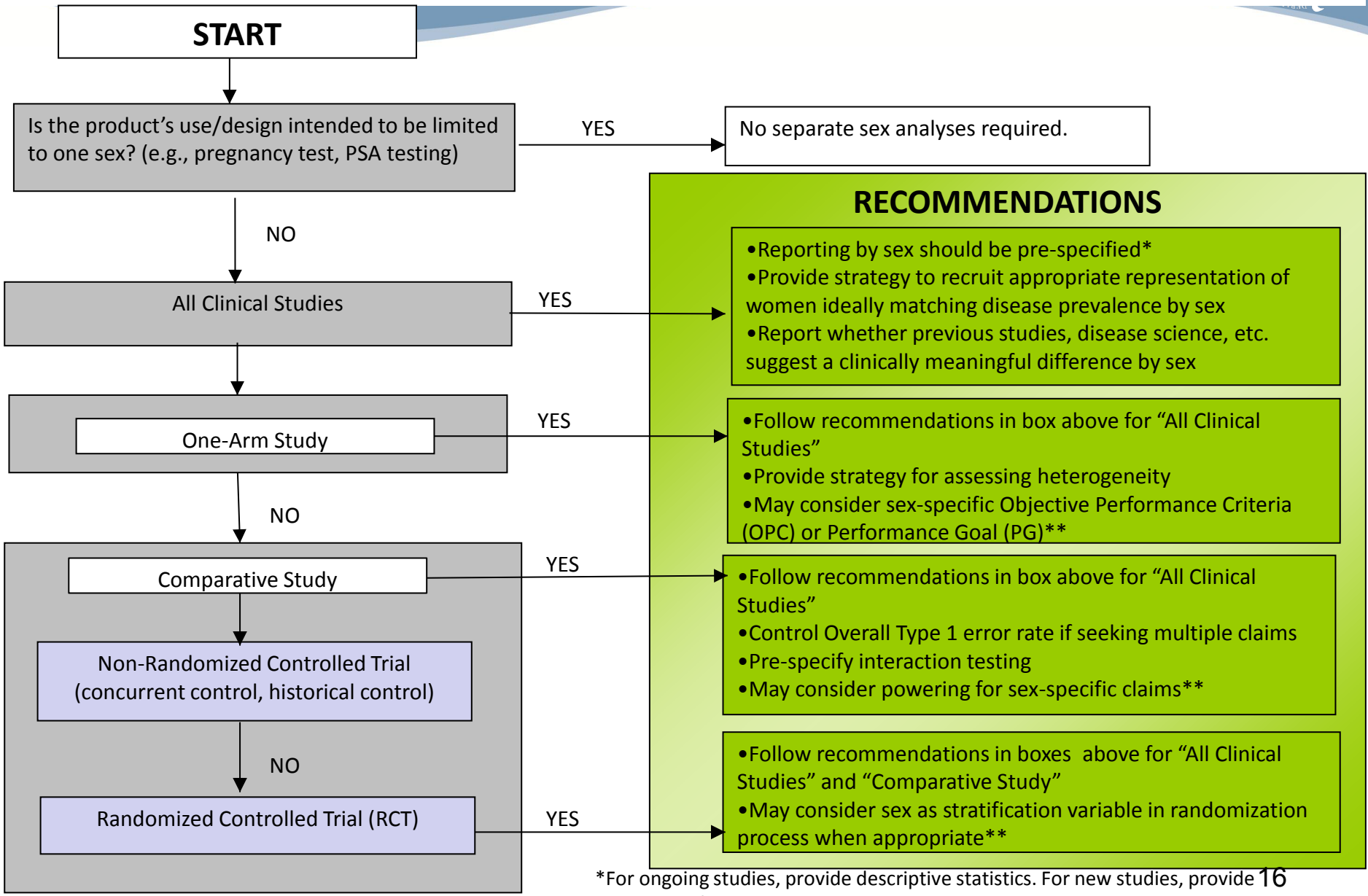
- **Report enrollment demographics, baseline characteristics, and co-morbidities**
  - Refer to guidance for example language
- **Report sex-specific outcomes (safety or effectiveness) in labeling and review summaries**
  - If results are statistically significant and clinically meaningful, report results of outcome analyses
  - If results suggest a sex difference in endpoint or event that is clinically meaningful, but statistical significance is not reached, report findings descriptively
  - If results suggest no sex differences in outcomes, report which analyses were conducted and that no differences were found

Decision Framework

- Concern that recommendations applied to every clinical study
- Uncertainty on when additional data would be needed
- Decision trees created to illustrate and assist in determining when recommendations apply

Recommendations for Sex-Specific Statistical Design

Follow recommendations associated with study design

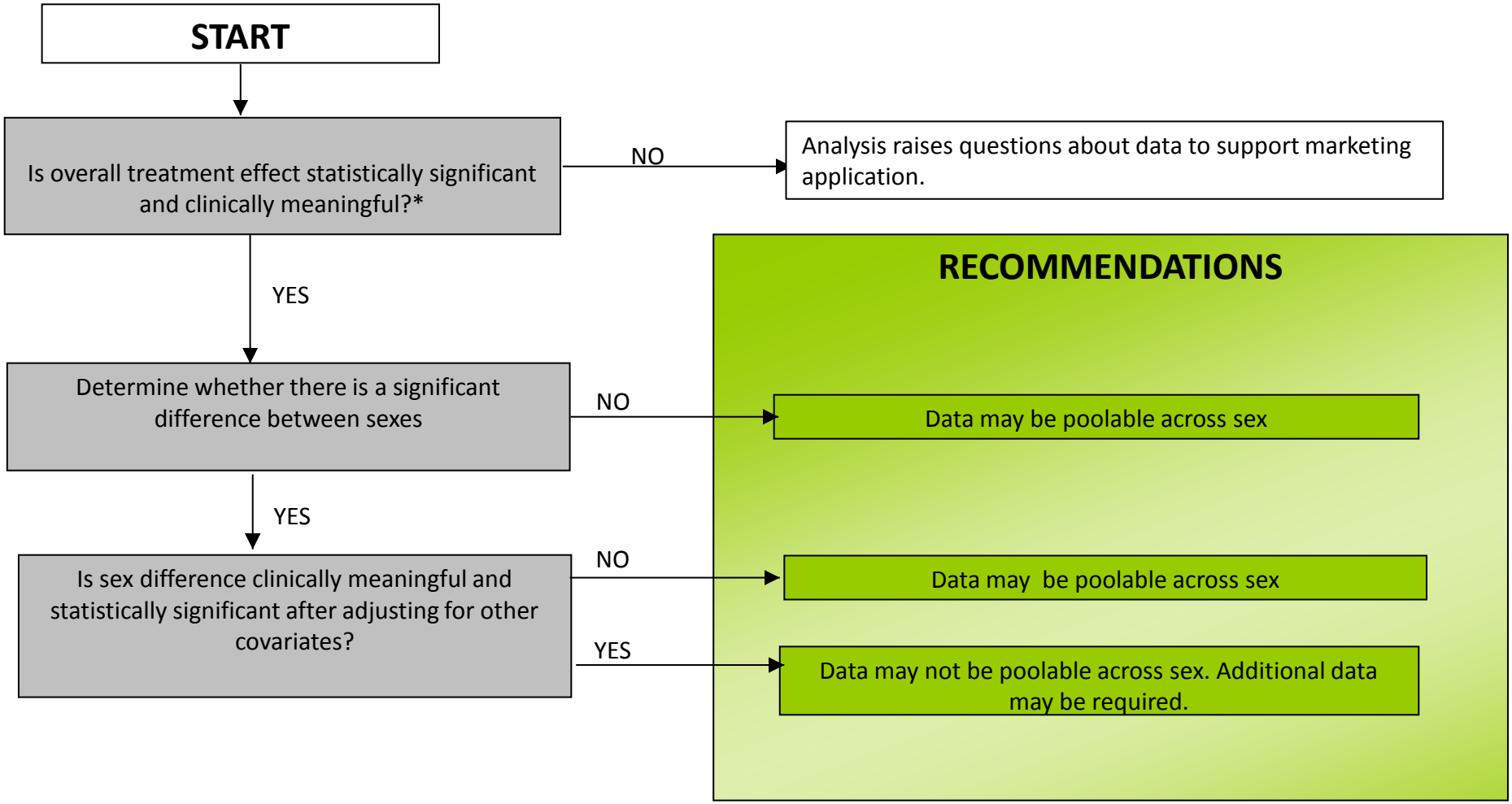


*For ongoing studies, provide descriptive statistics. For new studies, provide statistical inferences

**Applicable when sex-subgroup differences are anticipated

Recommendations for Sex-Specific Statistical Analyses for Completed Studies

One-Arm Studies (Objective Performance Criterion, Performance Goal, Observational Study)

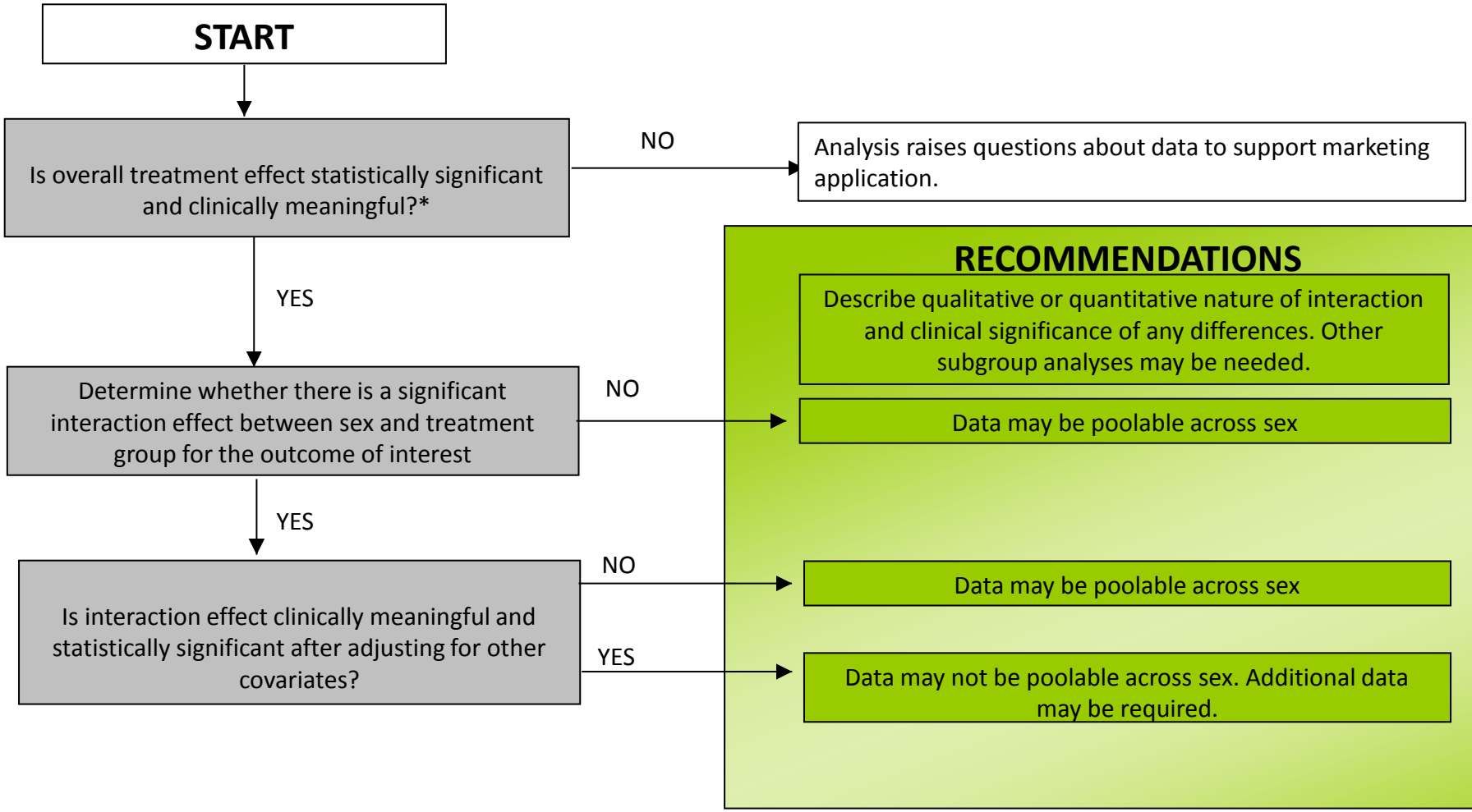


*Subgroup analyses are not recommended if overall treatment effect is not statistically significant and clinically meaningful.

Note: In some cases, the sex difference could be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

Recommendations for Sex-Specific Statistical Analyses for Completed Studies

Comparative Studies



*Subgroup analyses are not recommended if overall treatment effect is not statistically significant and clinically meaningful.

Note: In some cases, the interaction effect could be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

Questions?

CDRH/Office of the Center Director: Kathryn O'Callaghan (kathryn.ocallaghan@fda.hhs.gov)

CDRH/Office of Device Evaluation: Jismi Johnson (jismi.johnson@fda.hhs.gov)

CDRH/Office of In Vitro Diagnostics and Radiological Health: Robert Becker (robertl.becker@fda.hhs.gov)

CDRH/Division of Biostatistics: Lilly Yue (lilly.yue@fda.hhs.gov)

CDRH/Division of Epidemiology: Nilsa Loyo-Berrios (nilsa.loyo-berrios@fda.hhs.gov)

CBER/Office of Communication, Outreach and Development:

1-800-835-4709 or240-402-7800

CDRH/Division of Industry and Consumer Education: DICE@fda.hhs.gov

CDRHQuestions@fda.hhs.gov