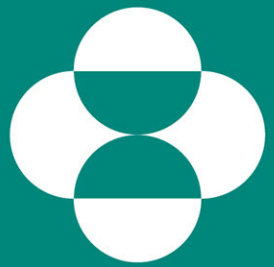
NISS – MERCK MEET-UPS

Your audio line has been placed on mute. There is no background noise. We will conduct an audio test to confirm audio a few minutes prior to our start time at 11:00 AM ET.



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September 12, 2017

AUDIO TEST

Our panel will now briefly give their name and location for an audio test.

Please use the Chat Box if you CANNOT hear any of our panelists introduce themselves.

Please DO NOT chat if you can hear them – only use the Chat Box if you hear silence.

<u>Today's Panelists</u>

Ray Bain

Alex Dmitrienko

Frank Bretz

Walt Offen

Lisa LaVange

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Dan Holder, Executive Director, BARDS, Merck

September 12, 2017

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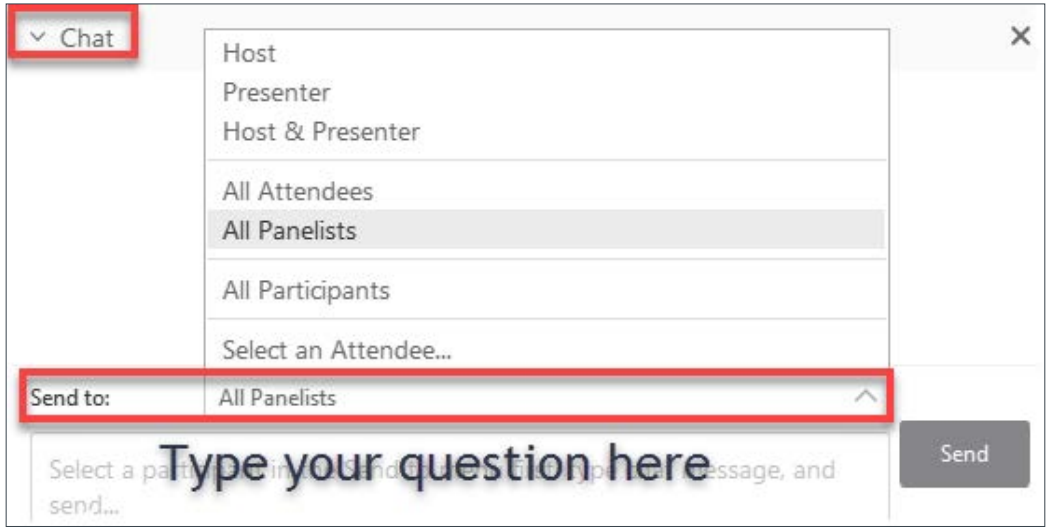
Attendee Participation



- Your audio line has been placed on **mute**
- **If you have a question for the panel**, using the **Chat** panel located to the right-hand side of the screen:
  1. Select "**All Panelists**" from the drop-down
  2. Type your question into the text box
  3. Click the **Send** button
- **If you have a question or comment to share** with other attendees, select "All Participants"

  Please no rude or disrespectful comments

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NISS-Merck Meet-Ups

NISS and Merck will be hosting a series of free virtual meetups, quarterly over the web, on emerging issues of interest to the pharma/biostatistics community.

Today's Topic: FDA draft guidance on "Multiple Endpoints in Clinical Trials"

Recorded version on NISS website

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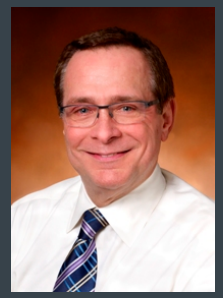
Today's Agenda & Panelists

What is NISS?

Multiplicity Guidelines

Comments on the Implementation of the FDA Guidance

Discussion



Ray Bain

SVP, Biostatistics and Research Decision Sciences, Merck

Alex Dmitrienko

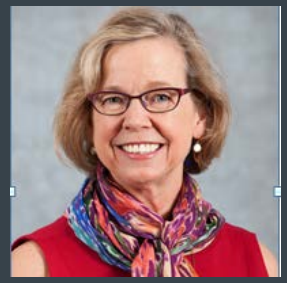
Founder and President of Mediana Inc.

Frank Bretz

Global Head of the Statistical Methodology and Consulting, Novartis

Walt Offen

Distinguished Research Fellow, Global Head of Statistical Sciences, Abbvie



Lisa LaVange

Director of the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER), FDA

WHAT IS NISS?

September 12, 2017

Ray Bain SVP, BARDS

Multiplicity Guidelines

Alex Dmitrienko (Mediana Inc)

NISS-Merck Meet-Up
September 2017

Switch to Alex's pdf file

Comments on the implementation of the FDA guideline

Frank Bretz (Novartis)

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FDA guideline offers a rationale clinical endpoint classification

Endpoint	Characterization	Implication on Approval and Product Labeling	Type I Error Rate Control
Primary	Necessary and/or sufficient to establish efficacy (trial success)	Mandatory for approval	Yes
Secondary	Additional meaningful outcomes that represent alternative facets of the disease (not just minor variations on other endpoints)	Not sufficient for approval; could lead to additional labeling claims	Yes
Exploratory	Hypothesis generating and variations on primary/secondary endpoints	Descriptive extensions (not considered new claims)	No

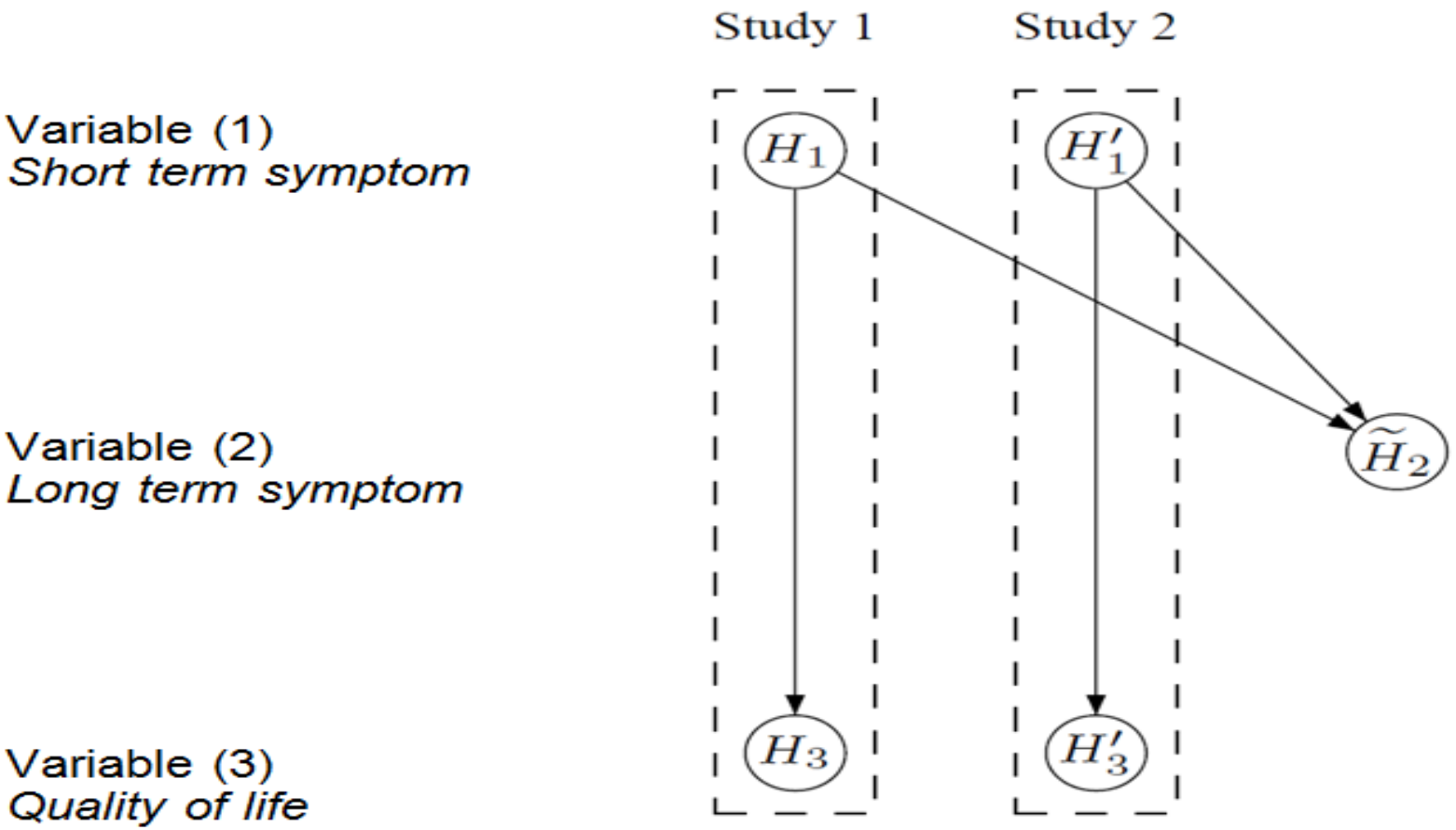
FDA guideline offers room for future research (1)

- Example: Two identical studies planned with the same three clinical outcomes.
  1. Reduction of a short-term symptom used conventionally for regulatory purposes to decide whether the new drug is effective.
  2. Reduction of a long-term clinical endpoint that is typically underpowered when planning for a single study.
  3. A variable measuring improvement of patients' quality of life.

  Question: How to come up with a suitable multiple test procedure that meets the practical constraints (e.g. sample size limitations)?

FDA guideline offers room for future research (2)

- Example strategy proposed by Bretz, Maurer and Xi (2017) using a hierarchical test strategy with separate testing of Variable (2) using the pooled data across both studies:



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Key points (1)

- Need to get agreement within clinical teams (statisticians, clinicians, marketing, ...) on which endpoints are critically important (clinically relevant) to gain approval and are to be included in the label, and on those which are not as important and should be considered more exploratory.
- Secondary endpoints are now those that were previously often labeled as key secondary endpoints. Other “secondary” endpoints are now considered exploratory.
- Avoid clinical trials with a rather large number of hypotheses and avoid trying to salvage a study with “convincing“ secondary endpoints.

Key points (2)

- Graphical and gatekeeping approaches for Type I error rate control facilitate the discussion with clinical teams and are accepted by regulatory agencies.
- Need to compare the operating characteristics of competing decision strategies via tailored clinical scenario evaluations.
- Even the best methodology cannot make up for a bad choice of endpoints, if they are not aligned with business decisions related to market approval and product labeling.

Discussion

Walt Offen

Distinguished Research Fellow, Global Head of Statistical Sciences, Abbvie

Lisa LaVange

Director of the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER), FDA

Alex Dmitrienko

Founder and President of Mediana Inc.

Frank Bretz

Global Head of the Statistical Methodology and Consulting, Novartis

THANK YOU

Special Thanks

Christy Chuang-Stein (organization)

Kara Hackman (technical)