



# **All Is Not Well in the World of Translational Research**

Ellis F. Unger, M.D.

Office of Drug Evaluation-I

Office of New Drugs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

June 21, 2012

# All Is Not Well in the World of Translational Research

Disclaimer:

The views expressed herein are mine, and do not necessarily represent the views/position of the U.S. Food and Drug Administration.

## My Interest in the Topic:

1985 – 1997:

- Translational research, Cardiology Branch, NHLBI, NIH

1988 – 1997:

- Member (chair), Animal Care and Use Committee, NHLBI, NIH

1995 – 1997:

- Clinical Investigator (IND Sponsor), NHLBI, NIH

1997 – present:

- Medical Officer (CBER) → (acting) Office Director (CDER), FDA

# What's the Problem with Translational Research?

- Bias
- Lack of knowledge
- Lack of oversight
- Lack of rigor
- Lack of standards
  - Standards for investigators
  - Standards for journal editors

# Bias – always present:

- Positive results:
  - Publications
  - Research grants
  - Speaking engagements
  - Consulting arrangements
  - Patents; licensing arrangements
  - **Career advancement**

# Bias – always present:

- Positive results:
  - Publications
  - Research grants
  - Speaking engagements
  - Consulting arrangements
  - Patents; licensing arrangements
  - **Career advancement**
- Negative results:
  - Mostly wasted time

## **Remediable Limitations of Pre-clinical POF Studies**

- Protocol may not exist; may exist but be amended without any record or chain of accountability
- Studies not universally randomized
- Studies not universally blinded
- Randomization code and/or blocking strategy may be known (or available) to investigator
- Primary endpoint often not identified; most endpoints are exploratory
- Just because an endpoint measure is objective, doesn't mean it isn't susceptible to bias!

# Remediable Limitations of Pre-clinical POF Studies

- No statistical plan; or
- Rudimentary and/or flawed statistical plan:
  - Statistical test not fit for purpose
  - Typically no plan to deal with multiplicity (multiple end points, multiple time points, or both)
  - Typically no plan to control Type-I error
- Missing data are common; prospective plan to deal with missing data is not common
- Exclusion of “outliers” is common; prospective plan to define and exclude “outliers” is not common

# Example 1

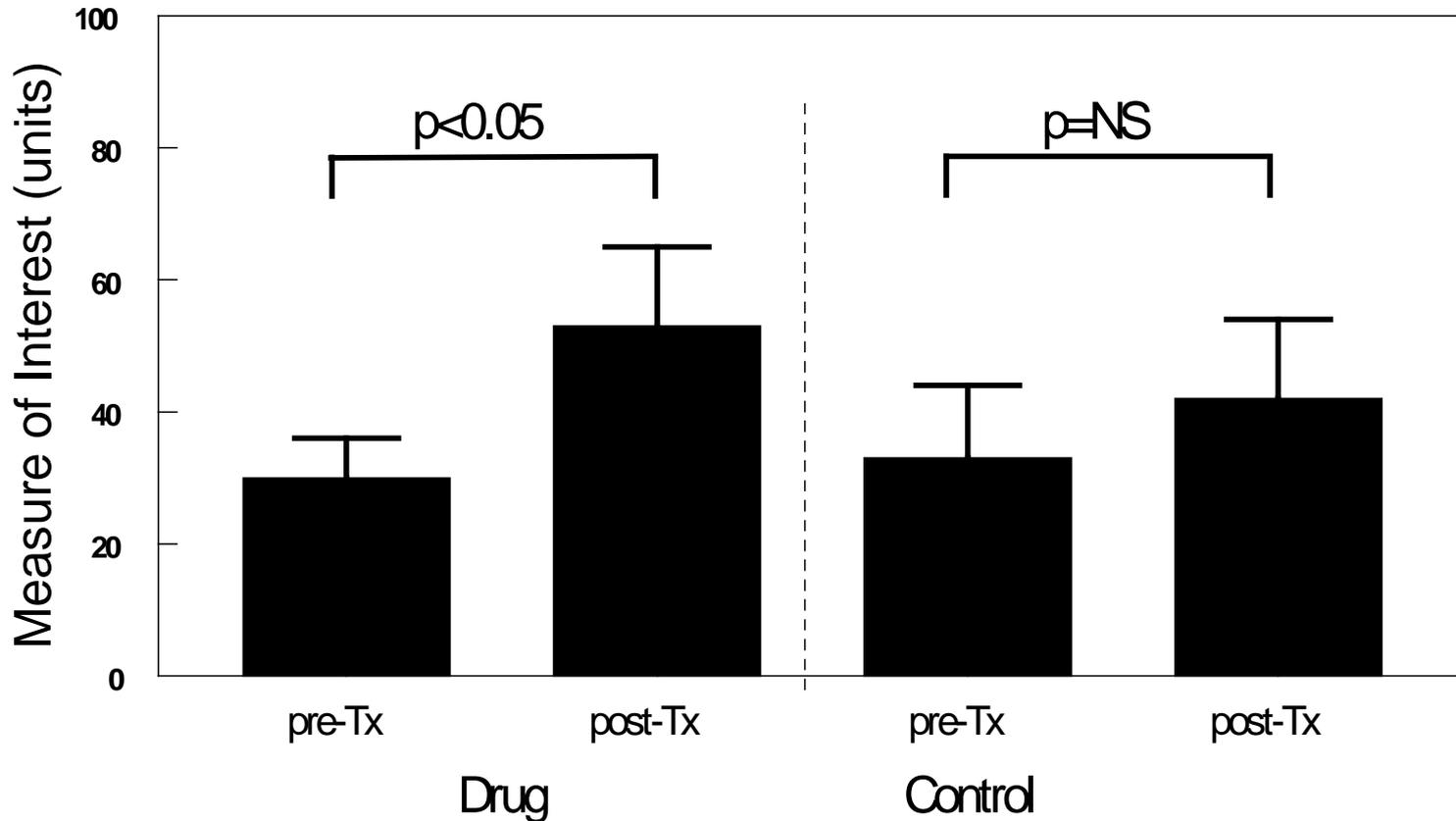
Drug	animal #	WEEK 4			WEEK 8		
		myocardial perfusion (microspheres)	myocardial perfusion ratio (microspheres)	coronary flow velocity (Doppler)	regional myocardial function (echo)	myocardial perfusion (microspheres)	myocardial perfusion ratio (microspheres)
	101	1.71	0.45	4.8	0.8		
	104	1.64	0.56	6.2	0.4		
	107	1.32	0.53	5.2	0.5		
	108	1.11	0.46	4.7	0.6		
	110	0.92	0.32	3.1	0.2		
	111	1.47	0.67	5.6	0.4		
	113	1.60	0.51	6.1	0.8		
	116	1.50	0.48	6.8	1.0		
	117	1.53	0.51	5.9	0.9		
	119	1.68	0.29	6.3	0.5		
Placebo	102	1.27	0.45	6.7	0.1		
	103	1.52	0.32	5.3	0.2		
	105	1.19	0.41	4.4	0.9		
	106	1.31	0.32	4.7	0.1		
	109	1.54	0.54	5.4	0.6		
	112	1.12	0.54	4.3	0.2		
	114	1.32	0.36	5.2	0.9		
	115	1.21	0.42				
	118	1.01	0.23	5.8	1.0		
	121	1.20	0.17	4.4	0.2		
<b>p-value</b>		<b>0.08</b>	<b>0.06</b>	<b>0.45</b>	<b>0.30</b>		

# Example 1

Drug	animal #	WEEK 4			WEEK 8		
		myocardial perfusion (microspheres)	myocardial perfusion ratio (microspheres)	coronary flow velocity (Doppler)	regional myocardial function (echo)	myocardial perfusion (microspheres)	myocardial perfusion ratio (microspheres)
	101	1.71	0.45	4.8	0.8		
	104	1.64	0.56	6.2	0.4		
	107	1.32	0.53	5.2	0.5		
	108	1.11	0.46	4.7	0.6		
	111	1.47	0.67	5.6	0.4		
	113	1.60	0.51	6.1	0.8		
	116	1.50	0.48	6.8	1.0		
	117	1.53	0.51	5.9	0.9		
	119	1.68	0.29	6.3	0.5		
Placebo	102	1.27	0.45	6.7	0.1		
	103	1.52	0.32	5.3	0.2		
	105	1.19	0.41	4.4	0.9		
	106	1.31	0.32	4.7	0.1		
	109	1.54	0.54	5.4	0.6		
	112	1.12	0.54	4.3	0.2		
	114	1.32	0.36	5.2	0.9		
	115	1.21	0.42				
	118	1.01	0.23	5.8	1.0		
	121	1.20	0.17	4.4	0.2		
<b>p-value</b>		<b>0.01</b>	<b>0.03</b>	<b>0.11</b>	<b>0.18</b>		

# Example 2

No statistical comparison between treatment groups:



# Do Editors of Journals Play a Role?

- Editors/referees often do not demand an accounting of the details of the study – the study plan or the results
- Limitations section is disingenuous: writers typically ignore the REAL limitations; write about limitations of the model to predict human disease (dah!), or point out a limitation they are already addressing in a new study, “setting the table” for the subsequent study



# **What Should be Done?**



# Fix these problems!



# Questions?