Comment on FDA Proposed Subgroup Regulations
(May 16, 2014)

The following comment was posted on regulations.gov on May 16, 2014 in response to the March 4, 2014 Federal Register announcement titled "Action Plan for the Collection, Analysis, and Availability of Demographic Subgroup Data in Applications for Approval of Food and Drug Administration-Regulated Medical Products; Notice of Public Hearing; Request for Comments"

Regulations on subgroup analyses should address the premises of such analyses.

1. Standard subgroup analyses are fundamentally unsound because they rely on the expectation that absent a subgroup effect an intervention will cause the same proportionate change in all baseline rates for experiencing an outcome. As explained in ref. 1 to 14, a factor that that affects the outcome rates of two groups with different baseline rates will tend to cause a larger proportionate change for the group with the lower baseline rate while causing a larger proportionate change in the opposite outcome rate for the other group. As explained in references 4 and 9, the soundest expectation as to how, absent a subgroup effect, a factor will affect the outcome rates of groups with different baseline rates is that the factor will cause the means of the risk distributions of the groups to move equal distances along the x-axis. That is, if a factor causes a baseline rate of 12.8% to change to 7.7%, the most reasonable expectation is that, absent a true subgroup effect, it will cause a baseline rate of 22.8% to change to 11.8%. See Tables 3 and 4 of reference 9. It is a departure such a pattern that should be deemed a true subgroup effect. And it is on the basis of such pattern that information from a clinical trial should be used to make decisions regarding subgroups with different baseline rates from those in the trial.

2. As explained in references 14 to 18, even apart from the point of item 1 above, the belief that, absent a subgroup effect, a factor will cause equal proportionate changes in two different baseline rates is illogical given that a factor cannot cause equal proportionate changes in two different baseline rates of experiencing an outcome while at the same time causing equal proportionate changes in the corresponding rates of experiencing the opposite outcome. That is, if Group A has a baseline rate of 5% and Group B has a baseline rate of 10%, a factor that reduces the two rates by equal proportionate amounts, say 20% (from 5% to 4% and from 10% to 8%) would necessarily increase the opposite outcome by two different proportionate amounts (95% increased to 96%, a 1.05% increase; 90% to 92%, a 2.2% increase). And since there is no more reason to expect two groups to experience equal proportionate changes in one outcome than there is to expect them to experience equal proportionate changes in the opposite outcome, there is no reason to regard it as somehow normal that the groups will experience equal proportionate changes in either outcome.

3. For reasons explained in item 2 above and references 17 and 18, according to the standard approach to indentifying a subgroup effect, anytime two groups have different baseline rates for experiencing an outcome, a factor that affects that rate will necessarily show a subgroup effect either as to the outcome or its opposite. The failure to find interaction as to either one outcome or the other in particular cases is simply a function of an insufficient number of observations for

the subgroup effect to be reflected in statistically significant terms. Given that there is no rational basis to expect a factor to cause equal proportionate changes in two different baseline rates for an outcome or for the corresponding opposite outcome, the more common situation when there are great numbers of observations would be that one would observe subgroup effects as to both outcomes, and typically the effects would be of an opposite nature. That is, for example, as shown in references 10 and 11, a factor that affects mortality will tend to show a larger proportionate change in the mortality rate of younger age groups, while showing a larger proportionate change in survival rates for older age groups than younger age groups. See also references 9, 12, 13.

References:

Due to limitations on the length of a comment, references are made available here:
http://jpscanlan.com/images/FDA_Comment_References.pdf

As indicated above, due to space limitations, references were made available by a link to a document posted on jpscanlan.com. For convenience the references are also listed below:

1. Scanlan JP. Race and mortality revisited. Society 2014;51 (July/Aug) (forthcoming)

2. Scanlan JP. Race and mortality. *Society* 2000;37(2):19-35 (reprinted in *Current* 2000 (Feb)):
http://www.jpscanlan.com/images/Race_and_Mortality.pdf

3. Scanlan JP. Divining difference. *Chance* 1994;7(4):38-9,48:
http://jpscanlan.com/images/Divining_Difference.pdf

4. Scanlan JP. Interpreting Differential Effects in Light of Fundamental Statistical Tendencies, presented at 2009 Joint Statistical Meetings of the American Statistical Association, International Biometric Society, Institute for Mathematical Statistics, and Canadian Statistical Society, Washington, DC, Aug. 1-6, 2009.
PowerPoint Presentation : http://www.jpscanlan.com/images/Scanlan_JSM_2009.ppt
Oral Presentation: http://www.jpscanlan.com/images/JSM_2009_ORAL.pdf

5. Scanlan JP. Systematizing the analysis of effect heterogeneity requires rethinking some fundamentals. Trials June 1, 2011 (responding to Gabler NB, Naihua D, Liao D, et al. Dealing with heterogeneity of treatments effects: is the literature up to the challenge. Trials 2009,10:43):
http://www.trialsjournal.com/content/10/1/43/comments#512684
6. Scanlan JP. Assessing heterogeneity of treatment effects in light of fundamental statistical tendencies. Trials May 26, 2011(responding to Kent DM, Rothwell PM, Ioannidis JPA, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010,11:85):
http://www.trialsjournal.com/content/11/1/85/comments#498686

7. Problems in identifying interaction where groups have different base rates. *BMJ* Sept. 21, 2010 (responding to Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219): Altman DG, Bland JM. Interaction revisited: the difference

between two estimates. BMJ 2003;326:219):
http://www.BMJ.com/content/326/7382/219/reply#BMJ_el_241943

8. Scanlan JP. Rethinking the premises of subgroup analyses. *BMJ* June 7, 2010 (responding to Sun X, Briel M. Walter SD, and Guyatt GH. Is as subgroup effect believable? Updating criteria to evaluated the credibility of subgroup analyses. BMJ 2010;340:850-854):
http://www.BMJ.com/cgi/eletters/340/mar30_3/c117

9. Subgroup Effects subpage of the Scanlan's Rule page of jpscanlan.com
http://www.jpscanlan.com/scanlansrule/subgroupeffects.html

10. Interactions by Age subpage of the Scanlan's Rule page of jpscanlan.com
http://jpscanlan.com/scanlansrule/interactionsbyage.html

11. Life Tables Illustrations subpage of Scanlan's Rule page of jpscanlan.com:
http://jpscanlan.com/scanlansrule/lifetableillustrations.html

12. Framingham Illustrations subpage of Scanlan's Rule page of jpscanlan.com
http://jpscanlan.com/scanlansrule/framinghamillustrations.html

13. Reporting Heterogeneity subpage of the Measuring Health Disparities page of jpscanlan.com
http://jpscanlan.com/measuringhealthdisp/reportingheterogeneity.html

14. Illogical Premises subpage of Scanlan's Rule page of jpscanlan.com
http://jpscanlan.com/scanlansrule/illogicalpremises.html

15. Ratio measures are not transportable. BMJ Nov. 11, 2011 (responding to
Schwartz LS, Woloshin S, Dvorin EL, Welch HG. Ratio measures in leading medical journals: structured review of underlying absolute risks. BMJ 2006;333:1248-1252):
http://www.BMJ.com/content/333/7581/1248?tab=responses

16. Scanlan JP. Goodbye to the rate ratio. BMJ Feb. 25, 2013 (responding to Hingorani AD, van der Windt DA, Riley RD, et al. Prognosis research strategy (PROGRESS) 4: Stratified medicine research. BMJ2013;346:e5793): http://www.BMJ.com/content/346/BMJ.e5793/rr/632884

17. Inevitability of Interaction subpage of Scanlan's Rule page of jpscanlan.com
http://jpscanlan.com/scanlansrule/inevitableinteraction.html

18. Scanlan JP. The inevitability of interaction. BMJ Dec. 19, 2011 (responding to Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219):
Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219): http://www.BMJ.com/content/326/7382/219?tab=responses