

Visualizing Clinical Trial Efficacy Data from Phase 2 or 3 Randomized, Double Blind, Placebo Controlled Trials.

Munish Mehra, PhD (Biostats), M.S (C.S), M.Sc. (Math), Tigermed, USA
munish.mehra@Tigermedgrp.com
+1-240-477-3700

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OVERVIEW



- This presentation is a follow-up of a presentation at PHUSE 2020 on **summarizing a clinical trial design and results in 20 graphical displays**
https://www.lexjansen.com/phuse-us/2020/dv/DV07_ppt.pdf
- In this presentation we focus on visualizing clinical trial efficacy data only
- All examples are based on the double-blind Placebo controlled “Clinical Trial Ceftriaxone in Subjects With ALS” - ClinicalTrials.gov Identifier: NCT00349622
- Data were obtained through trial collaborator NINDS (National Institute of Neurological Disease and Stroke)
- Sponsor: Massachusetts General Hospital
<https://clinicaltrials.gov/ct2/show/NCT00349622?cond=NCT00349622&draw=2&rank=1>

Trial Design



Objective: The purpose of the study is to evaluate the safety and efficacy of ceftriaxone treatment in amyotrophic lateral sclerosis (ALS)

Number of Participants: 513

Treatment Arms & Randomization:

(2/3) Ceftriaxone vs (1/3) Placebo

Study Type: Interventional

Study Start: July 2006

Study Completion: November 2012

Schedule of Efficacy Assessments:

Week 4, 16, 32, 48, 64, 96

Stages: Stage 1 (PK), Stage 2 (Safety), Stage 3 Efficacy

Efficacy Endpoint and Baseline Prognostic Variables considered



Efficacy Endpoint: Change in function, measured by ALS functional rating scale, revised (ALSFRS-R) Total Score varies from 0 to 48 with 0 being worst score

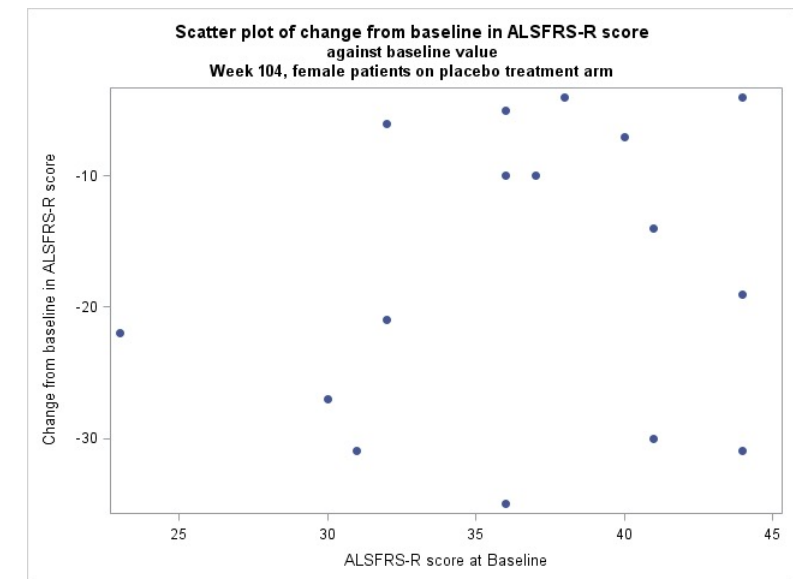
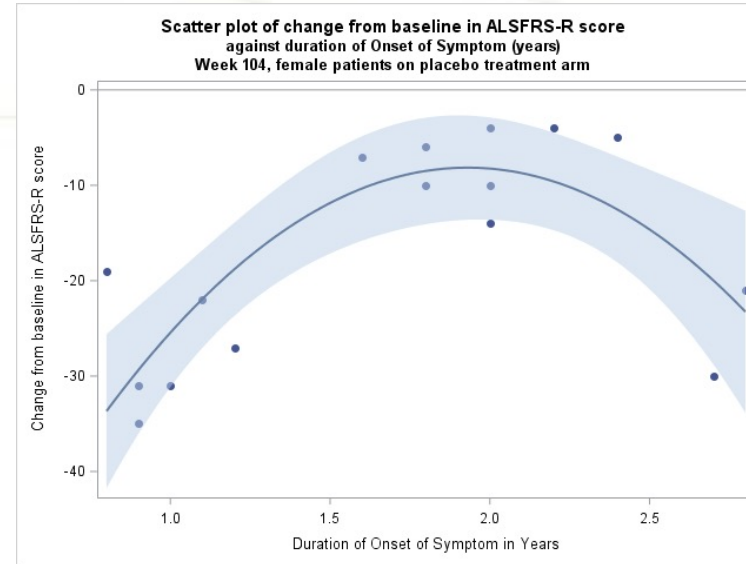
Baseline Prognostic Factors:

- ALSFRS-R
- Duration since onset of symptoms
- Vital Capacity

Two-D Scatter Plots



- Right (top) 2D plot shows possible quadratic effect with best change from baseline in efficacy for those with duration since symptom onset in range 1.5 – 2.5 years
- Bottom plot shows no clear relationship between change from baseline and the baseline value of ALSFRS-R.



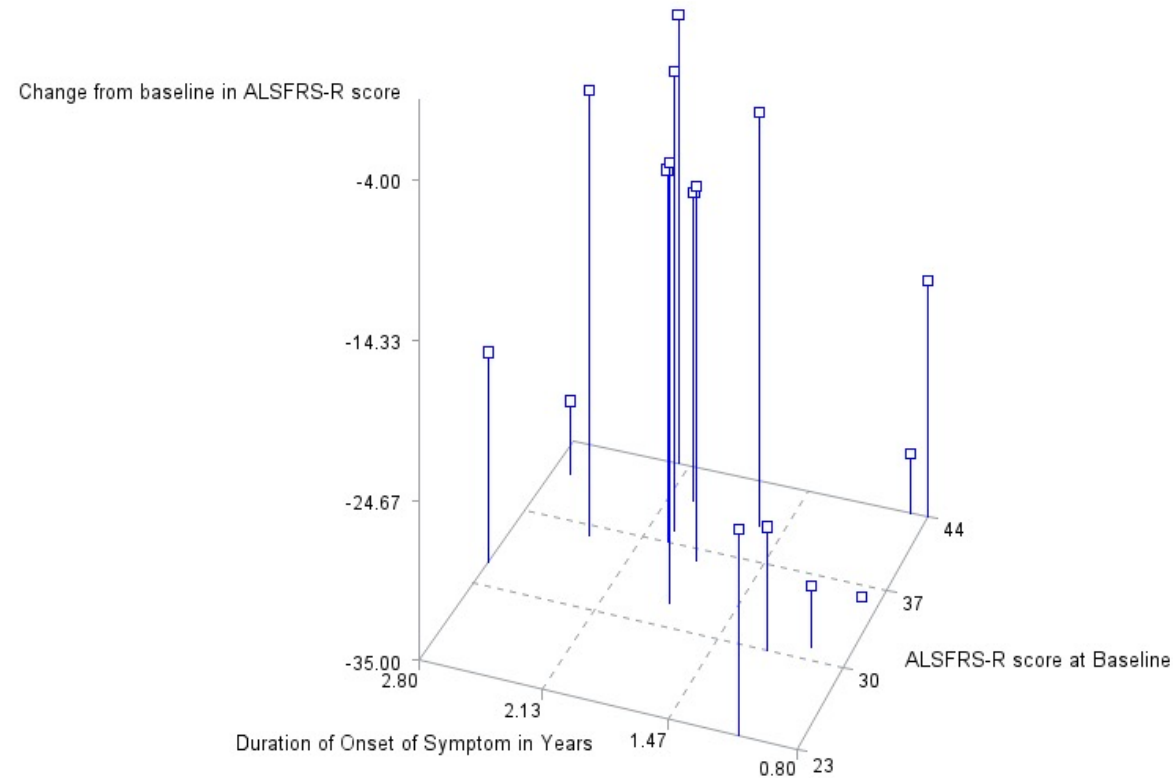
```
proc sgplot data= Adef;
  scatter x=
    &x1.y=&z./&group.markerattrs=(symbol=
    circlefilled);
  reg y = &z. x = &x1. /degree = 2 CLM
  nomarkers CLMTRANSPARENCY = .5 ;
run;
```

Three-D Scatter Plots



- 3D plot combines information from the two 2D plots
- Consider modelling a response surface

Scatter plot of change from baseline in ALSFRS-R score
against baseline value and duration of Onset of Symptom (years)
Week 104, female patients on placebo treatment arm

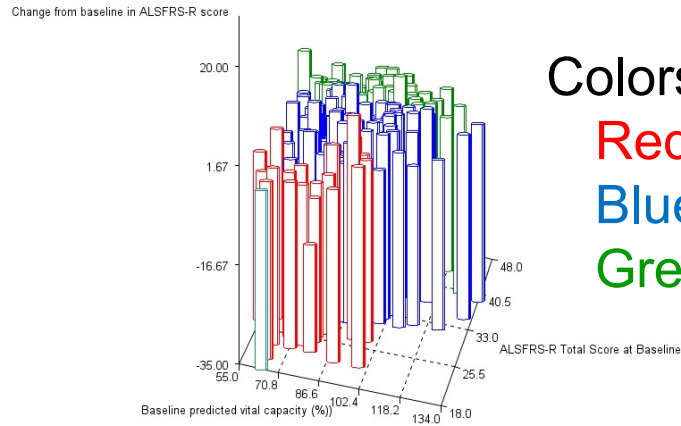


```
proc g3d data= Adeff ;  
    scatter &x1. * &x2. = &z. / color= "blue" shape= "square" size=0.5;  
run;  
quit;
```

3-D Scatter Plots - Rotated



Rotate Scatter plot matrix for ALSFRS-R change from baseline at week 32, its baseline value and baseline predicted vital capacity (%)



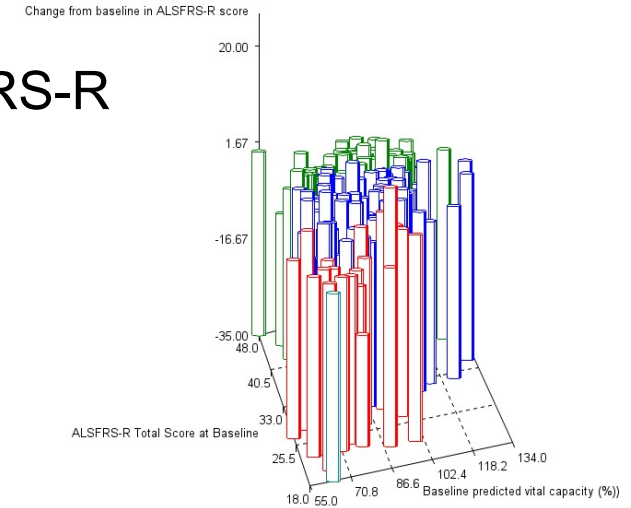
Colors of bars represent baseline ALSFRS-R

Red for ≥ 20 and < 30 (Most Severe)

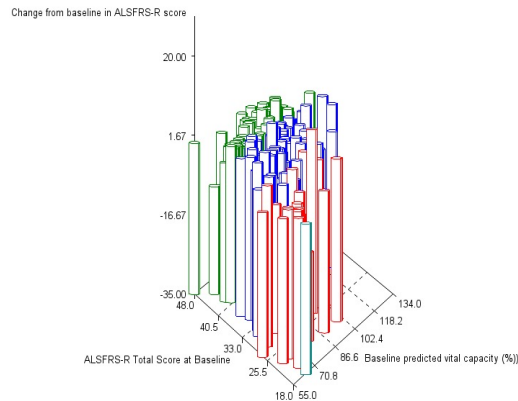
Blue for ≥ 30 and < 40

Green Red for ≥ 40 (Mildest Disease)

Rotate Scatter plot matrix for ALSFRS-R change from baseline at week 32, its baseline value and baseline predicted vital capacity (%)

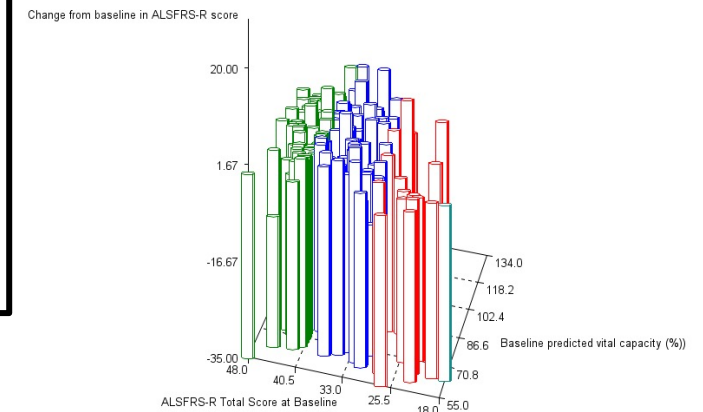


Rotate Scatter plot matrix for ALSFRS-R change from baseline at week 32, its baseline value and baseline predicted vital capacity (%)

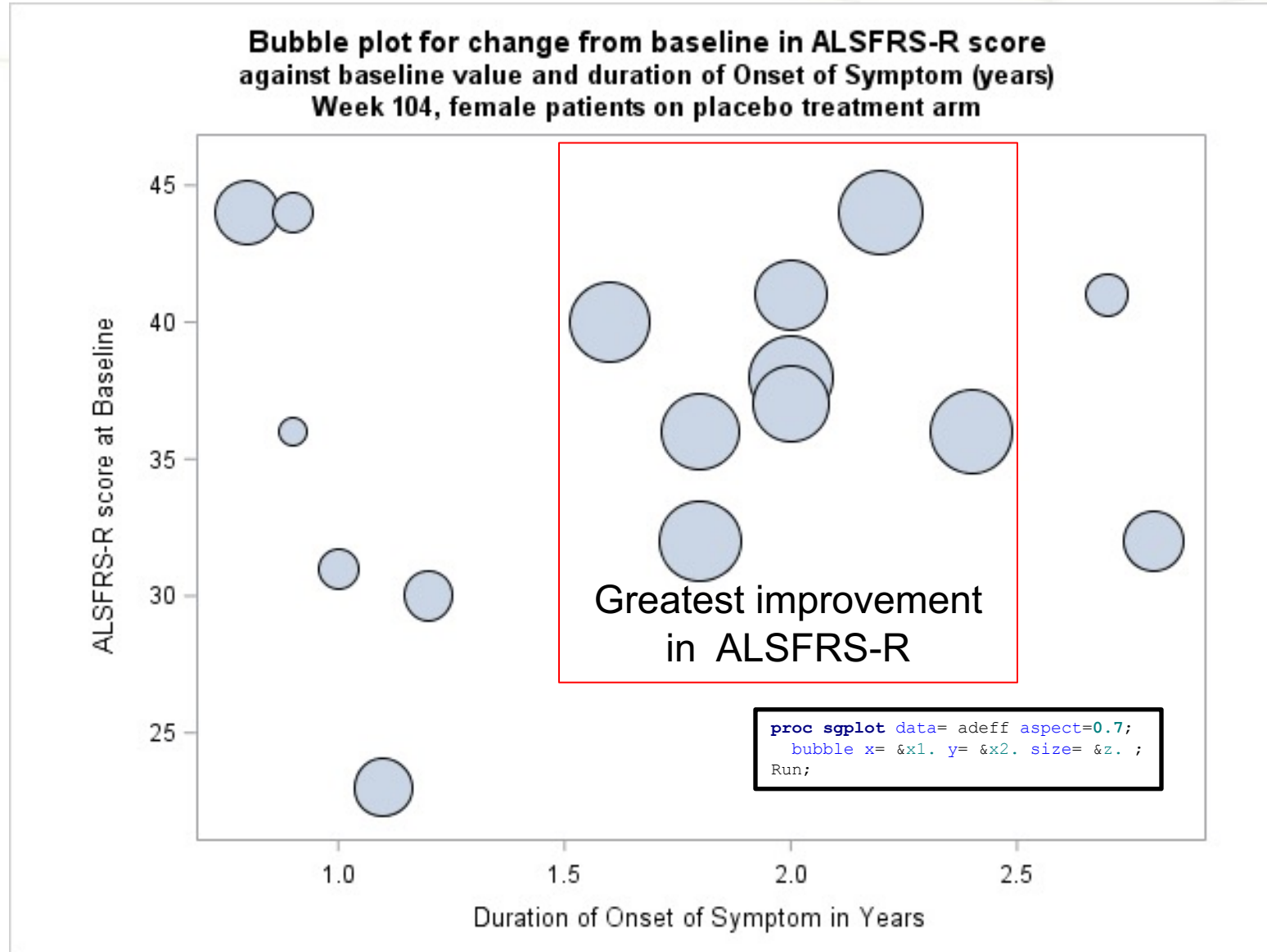


```
proc g3d data=Adeff;
scatter &x. * bsl_pred_vc = &z.
/ shape='piller' color=colorval
caxis=black
rotate=&rotate
size=0.5 yticknum=5 xticknum=6 zticknum=4
zmin=-35 zmax=20;
run;
```

Rotate Scatter plot matrix for ALSFRS-R change from baseline at week 32, its baseline value and baseline predicted vital capacity (%)

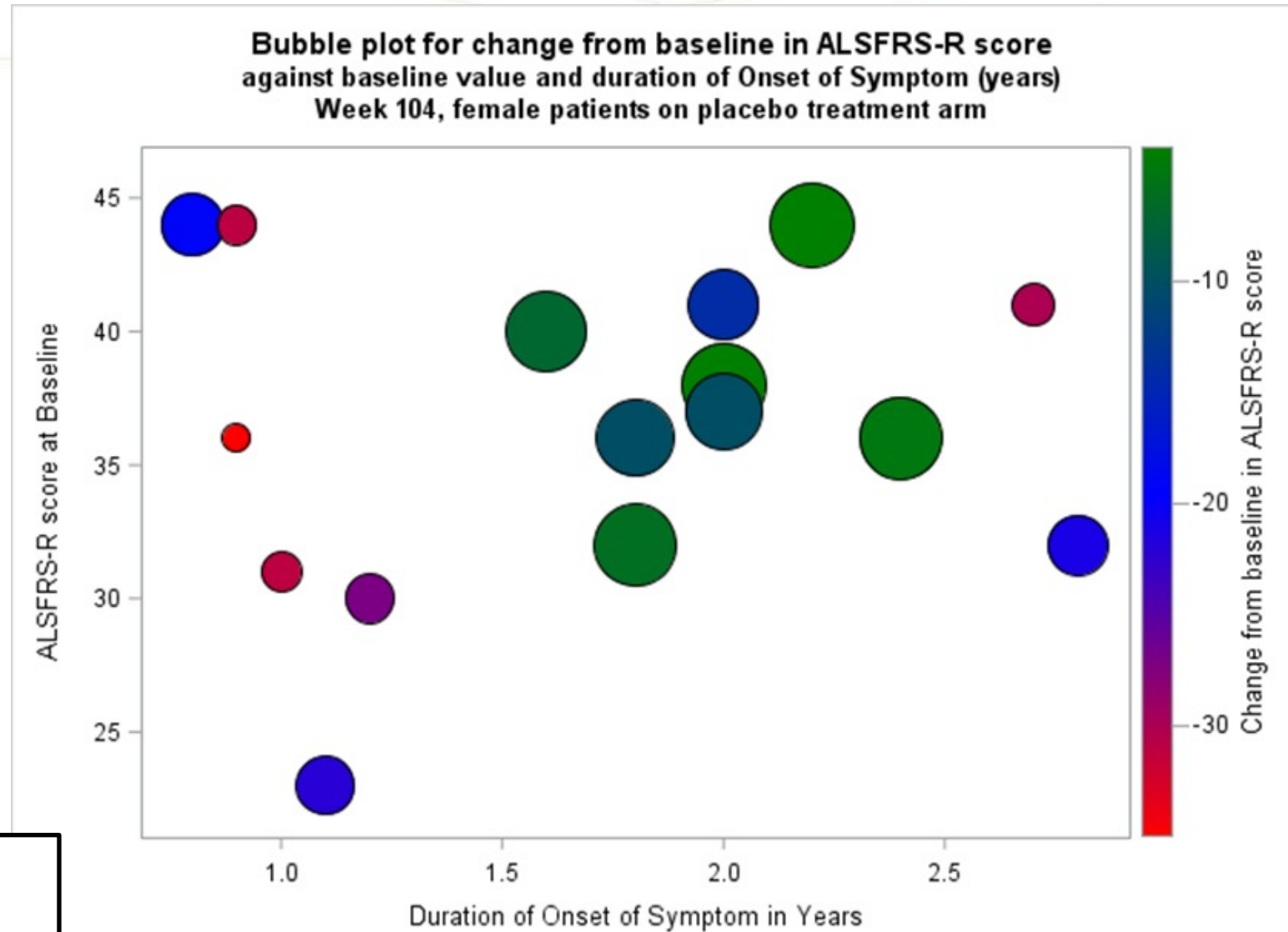


Bubble Plot – Larger size of circle indicates greater improvement



Bubble plot

- Bubble colours and size
 - colour coded (lower values, red, medium values blue, high values, green)
 - Larger for increasing values of the efficacy variable



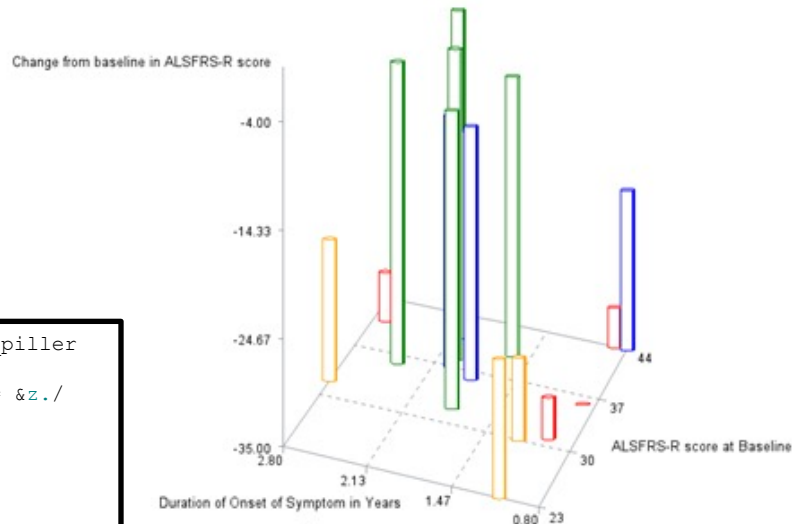
```
proc sgplot data=_3d_piller aspect=0.7 ;  
  bubble x= &x1. y= &x2. size= &z.  
  / colorresponse = &z.  
  colormodel = (red blue green);  
run;
```

Response surface shows two peaks and a valley



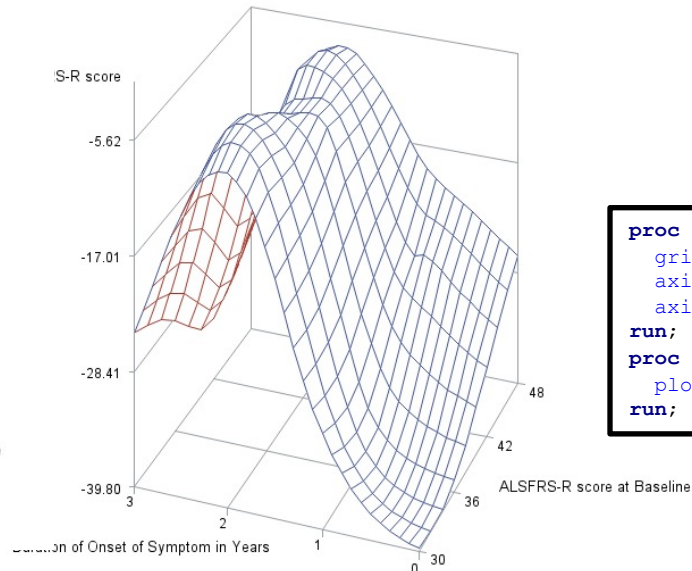
- 3d scatter plot combines the two plots and colour codes according to the value of the efficacy variable - but still a plot, need to fit model to understand efficacy
- Response surface shows
 - For 0 years of onset, change from baseline increases with baseline (right hand edge)
 - best effect (green pillars below) between 2 and 3 years for duration of onset of symptoms but may be a dip in baseline values around 40 (blue pillar within the green pillars)

Scatter plot of change from baseline in ALSFRS-R score
against baseline value and duration of Onset of Symptom (years)
Week 104, female patients on placebo treatment arm



```
proc g3d data= _3d_pillar  
;  
scatter &x1. * &x2. = &z. /  
shape='pillar'  
color = colorval  
size=0.5;  
run;  
quit;
```

Response surface for change from baseline in ALSFRS-R score
against baseline value and duration of Onset of Symptom (years)
Week 104, female patients on placebo treatment arm



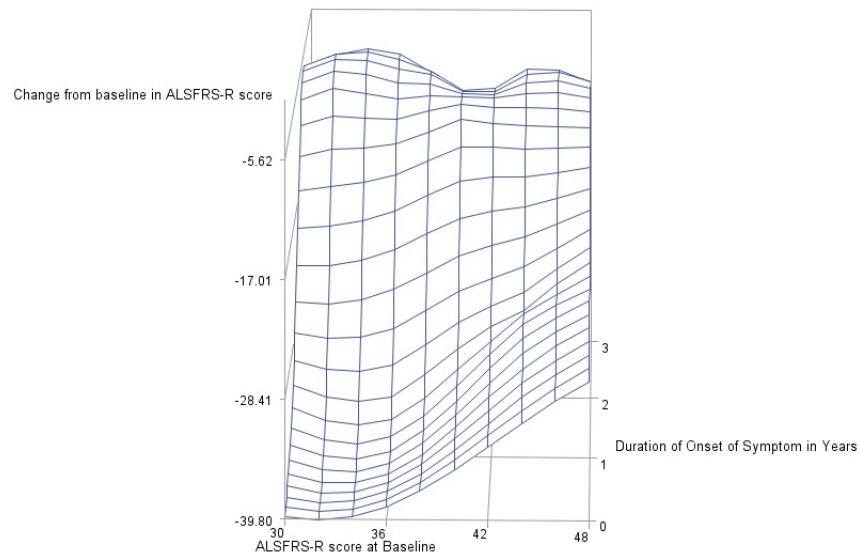
```
proc g3grid data= adeff out= smoothed;  
grid &x1. * &x2. = &z. /spline smooth=.05  
axis1= &x1_min. to &x1_max. by &x1_steps.  
axis2= &x2_min. to &x2_max. by &x2_steps. ;  
run;  
proc g3d data= smoothed;  
plot &x1. * &x2. = &z. /grid XYTYPE=3 ;  
run;
```

Other ways to Visualize the same



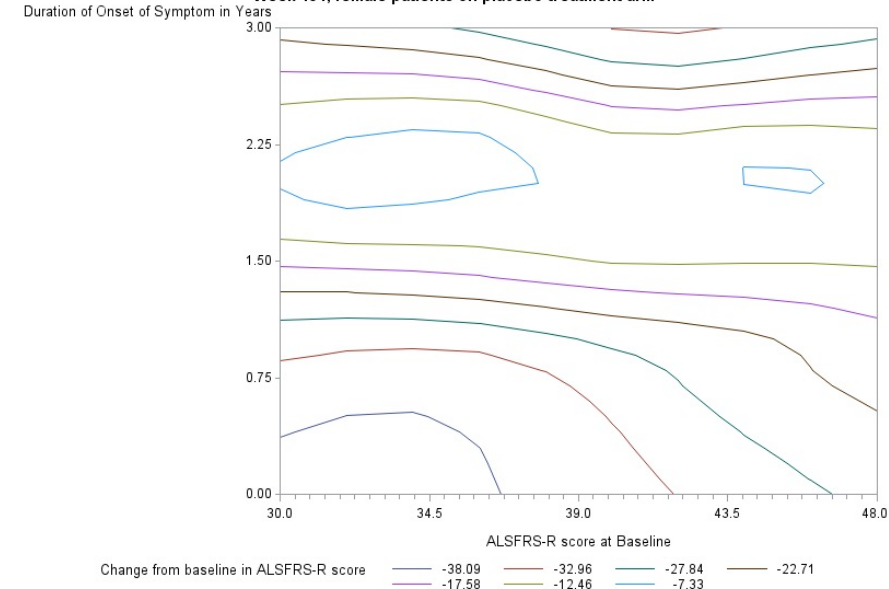
- Can explore by rotating axes
 - See “around the corner”
 - Increase in change from baseline 30 to 36, then trough around 40 then slight rise
- Contour plots show the two “peaks”
 - Both onset duration = 2 years (approx.), one at baseline approx. 32, the other around 45

Response surface for change from baseline in ALSFRS-R score
against baseline value and duration of Onset of Symptom (years)
Week 104, female patients on placebo treatment arm



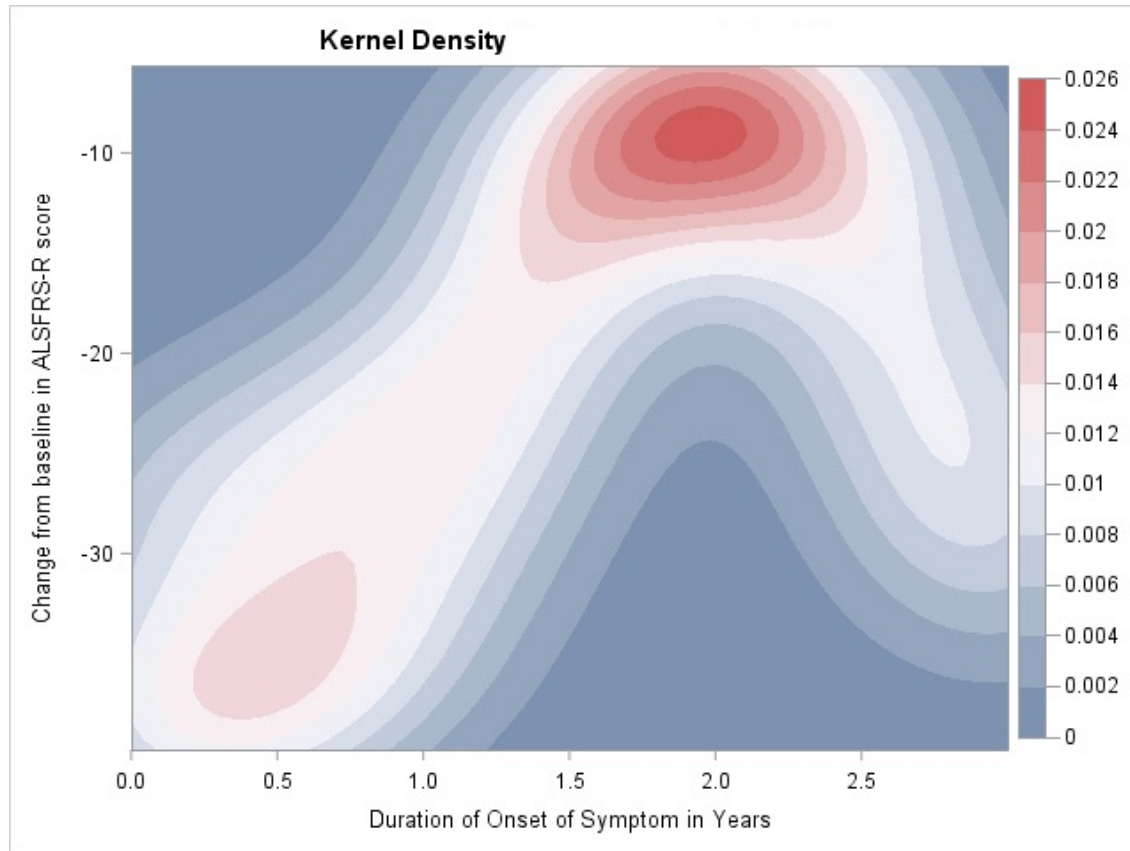
```
proc g3d data= smoothed_F_placebo_w104;  
  plot &x1. * &x2. = &z. /grid XYTYPE=3 rotate = -.5;  
run;
```

Contour lines for change from baseline in ALSFRS-R score
against baseline value and duration of Onset of Symptom (years)
Week 104, female patients on placebo treatment arm

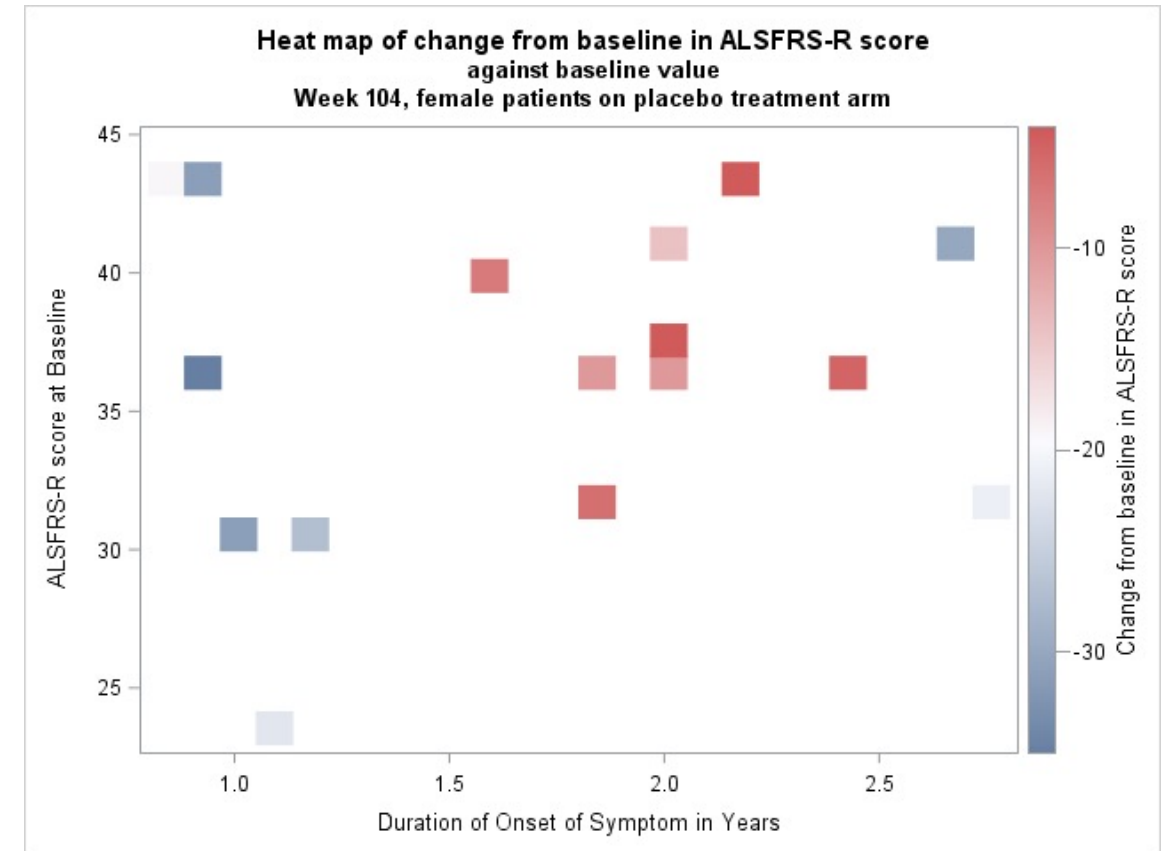


```
proc gcontour data= smoothed;  
  plot &x1. * &x2. = &z. ;  
run;  
quit;
```

Kernel Density and Heat Map

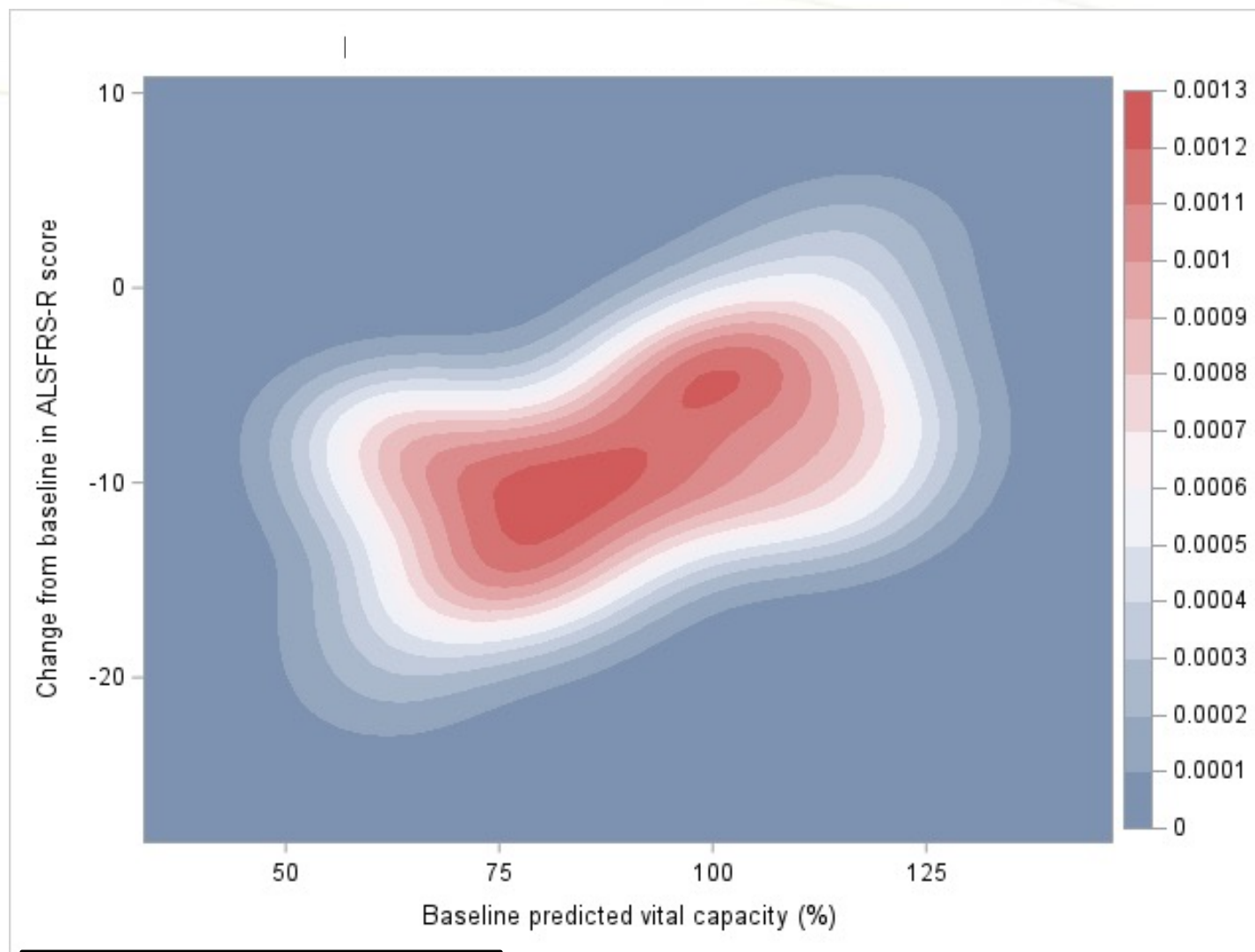


```
proc kde data= smoothed;  
  bivar &x1. &z./ plots=contour ;  
run;
```



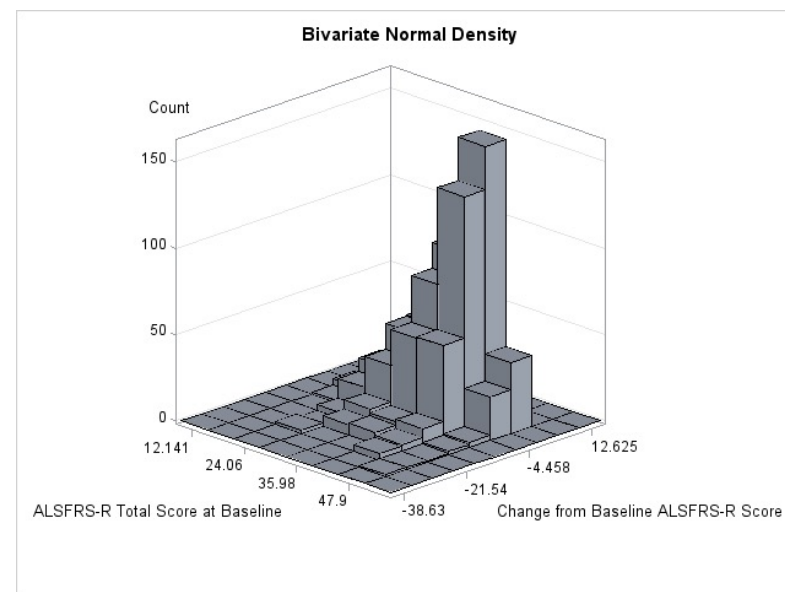
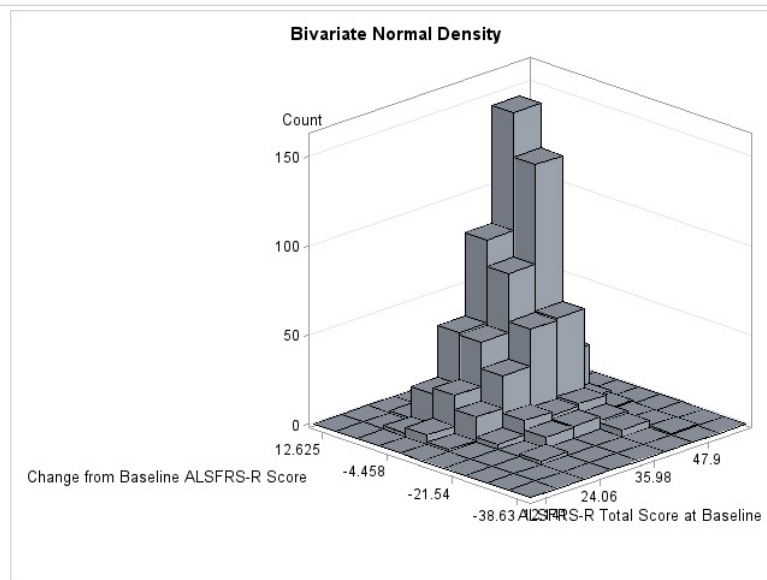
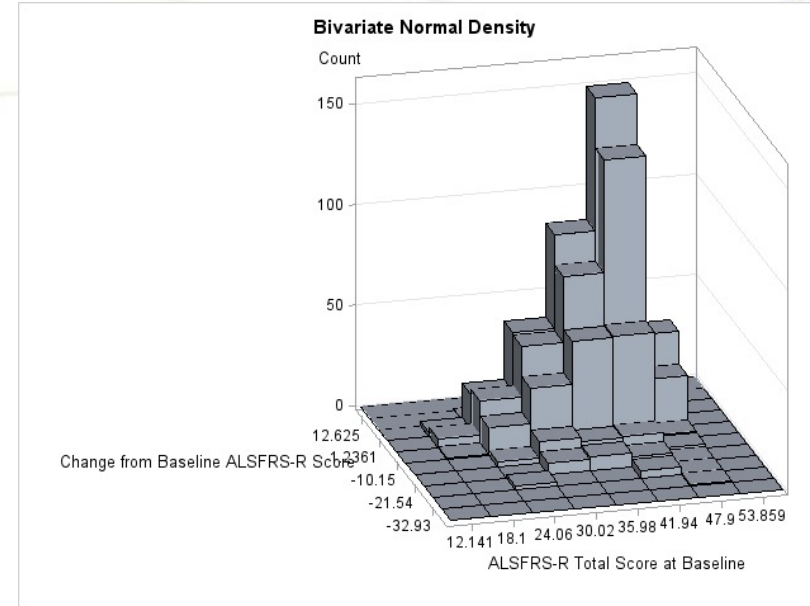
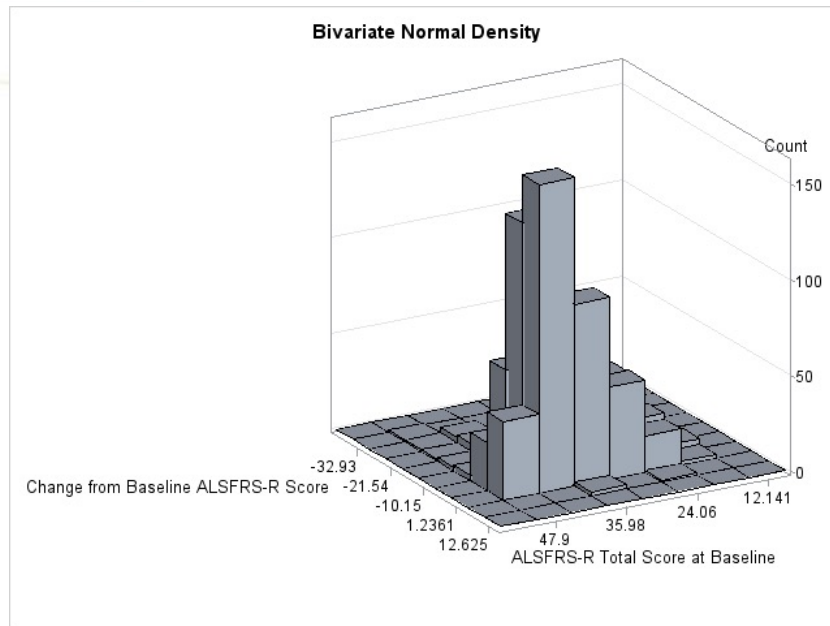
```
proc sgplot data= Adeff ;  
  heatmap x= &x1. y= &x2. /colorresponse = &z.  
run;
```

Baseline Vital Capacity also shows two-peaks



```
proc kde data= dsin;;  
  bivar bsl_pred_vc chg / plots=contour surface;  
run;
```

3-D histogram in different angles



```
proc template;

define statgraph bihistogram1a;
  begingraph;
    entrytitle "Bivariate Normal Density";
    layout overlay3d / cube=false zaxisopts=(griddisplay=on)
      xaxisopts=(linearopts=(tickvalueformat=5.))
      axisopts=(linearopts=(tickvalueformat=5.));
    bihistogram3dparm x=value1 y=value2 z=count / display=all;
  endlayout;
endgraph;

end;

proc kde data= adeff;;

bivar base(ngrid=10) chg(ngrid=10) / plots=none noprint
out=kde(keep=value1 value2 count);

run;

proc sgrender data= kde template=bihistogram1a;

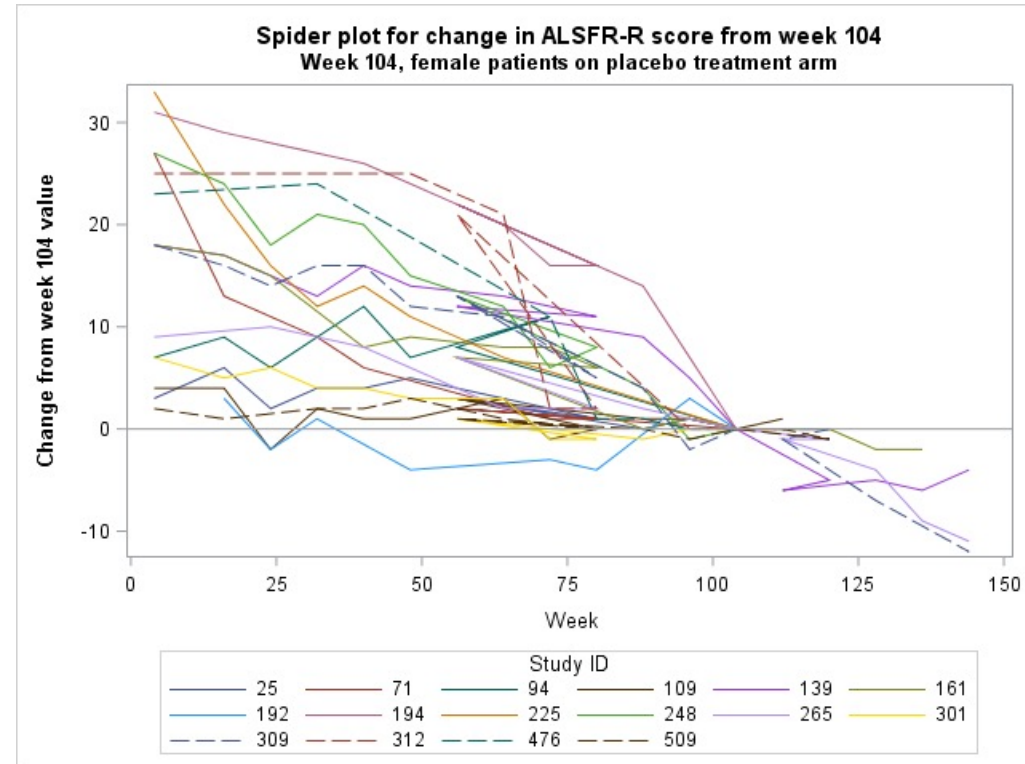
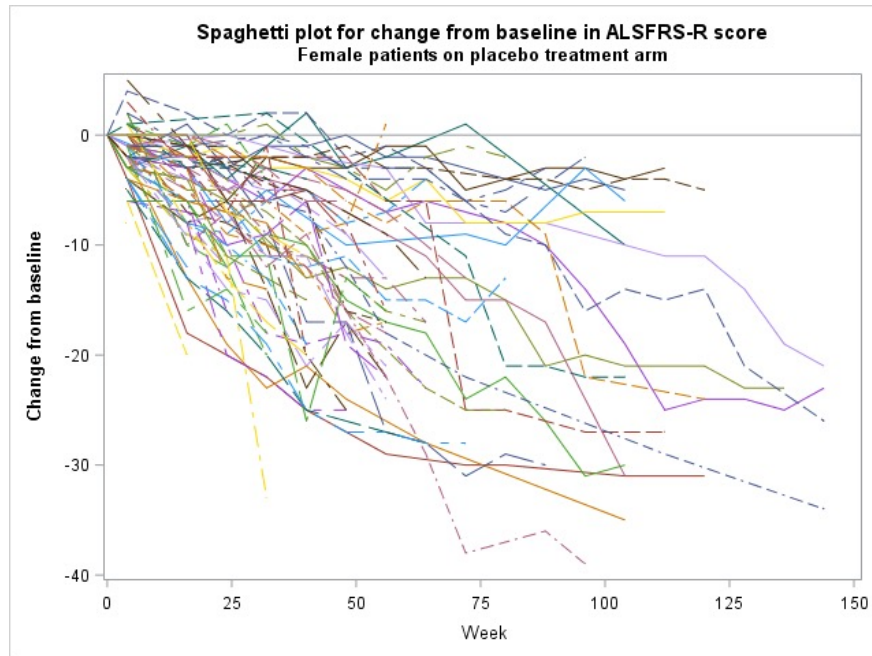
  label value1="ALSFRS-R Total Score at Baseline"
  value2="Change from Baseline ALSFRS-R Score";

run;
```

Spaghetti / Spider Plots – Understanding individual responses



Shows when patients drop out and their change at last visit (72 patients at week 0, 16 by week 104)



```
proc sgplot data = spider ;  
  series x= week_n y= cfb104/ group = Subject_id;  
  refline 0 /axis = y;  
run;
```

Acknowledgements



- Harry Staines
- Chirayu Patel

**Please do reach out to me with
suggestions on better ways to display
clinical trial data**

**Munish Mehra
munish.mehra@Tigermedgrp.com
+1-240-477-3700**