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An Extended Longitudinal Model and Graphic for Benefit Risk Analysis

Kevin Gan
GlaxoSmithKline

Outline

- **Introduction**

  - Why Benefit-Risk Analysis

  - GSK BR analysis working group

  - Heat-map Graph

- **Steps in Heat-map graph Analysis Process**

  - Framing the compound's key benefits and risks

  - Quantification of benefits and Risks analysis

  - Extended methods

- **Summary and Future work**

Innovation: sharpening the statistical saw

- **Re-engineer Phase 2 will move to delivery phase in 2013**, with training provided
  – All staff will have RP2 objectives in their PDP

- **Enhance the benefit:risk (B:R) methodology, and assessment** of B:R for GSK drugs via the B:R methodology working party

- **Enhance the method for, and assessment of safety**

- **Continue to develop our methodology on missing data**

- **Make innovation in Phase 3 a key area of focus:**
  – Futility assessments in phase III trials

Background

- Increasingly, companies, regulatory agencies and other governance bodies are using structured benefit-risk (B-R) assessment approaches.

- Mentioned in various regulatory guidances (PBRER, eCTD, PDUFA V)

- Assessment of B-R is challenging

- Important to have systematic B-R assessments that incorporate a thorough understanding of different methodologies.

- Current methods typically not quantitative; can we extend beyond graphics?

PBRER: Period Benefit-Risk Evaluation REPORT

eCTD: Electronic Common Technical Document

PDUFA V: Prescription Drug User Fee Act

Lots of Activity in this Space

- EFSPI (European Federation of Statisticians in the Pharmaceutical Industry)

  http://www.efspi.org/

- QSPI (Quantitative Sciences in the Pharmaceutical Industry)

- QSPI - PhUSE Wiki

- IMI PROTECT

- PROTECT Benefit Risk

Benefit-Risk Focus has gr**OWN**

GSK's Benefit-Risk Efforts To Date

N = number of SRT consultations with BRE

PSAP: Program Safety Analysis Plan

PBRER: Period Benefit-Risk Evaluation REPORT

eCTD: Electronic Common Technical Document

GSB: Global Safety Board

2011
N=2

"try to put benefit and risk together in a graph."

Submission statements:
"the benefit risk ratio is positive."

2012
N=17
+ *vaccines*

- Industry starts to formally frame questions (e.g. BRAT)
- GSK guidance for teams
- GSB mandates BR graph at milestone reviews
- **Stats WG starts** (Susan Duke lead)

2013
N=29
+ *vaccines, others*

- BRAT framework used routinely at GSK
- BRE consultations grow
- **Stats WG delivers wave 1:** Website - a rich source of information and methods, BR in key documents (PBRER, PSAP, OneCDP). Training (basics & advanced)

July 2014
N=35
+ *vaccines, PML, & external*

- BRE member of GSB
- BR Portal GO LIVE
- **Stats WG moves to wave 2: to embed and educate, to develop guidance for quantitative methods**
- All PSAPs (+BR sections) in place by end of year
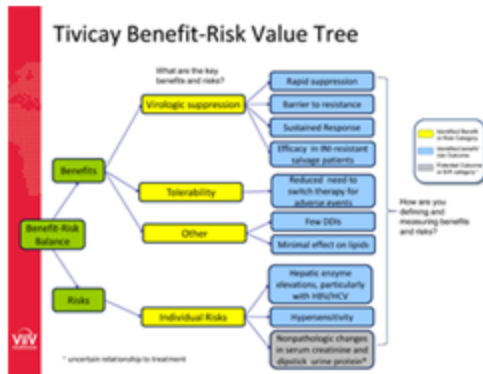- More training planned

6

Benefit Risk Working Group

- The Benefit Risk Working Group is a multi-function group consisting of colleagues in Clinical Statistics, Epidemiology, SERM (Safety Evaluation & Risk Mgmt), VEO (Value Evidence & Outcomes) and VEA (Value Evidence Analytics).

- There are 7 work-streams: 5Technical (T) and 2 Procedural (P) with the following deliverables coming in late 2014/ early 2015:

Work-stream
T1. Bayesian and clinical utility indices
T2. Multi-Criteria Decision Analysis
T3. Heatmap
T4. Develop BR Forest Plot output template
T5. Standard macro for anticipated incidence rates of a rare event
P1. Embed consistent process
P2. Share learnings

PSAP: Program Safety Analysis Plan
SSP: Safety Strategy Plan

Benefit Risk Portal

Benefit Risk Methods WG Wave 1 Deliverable
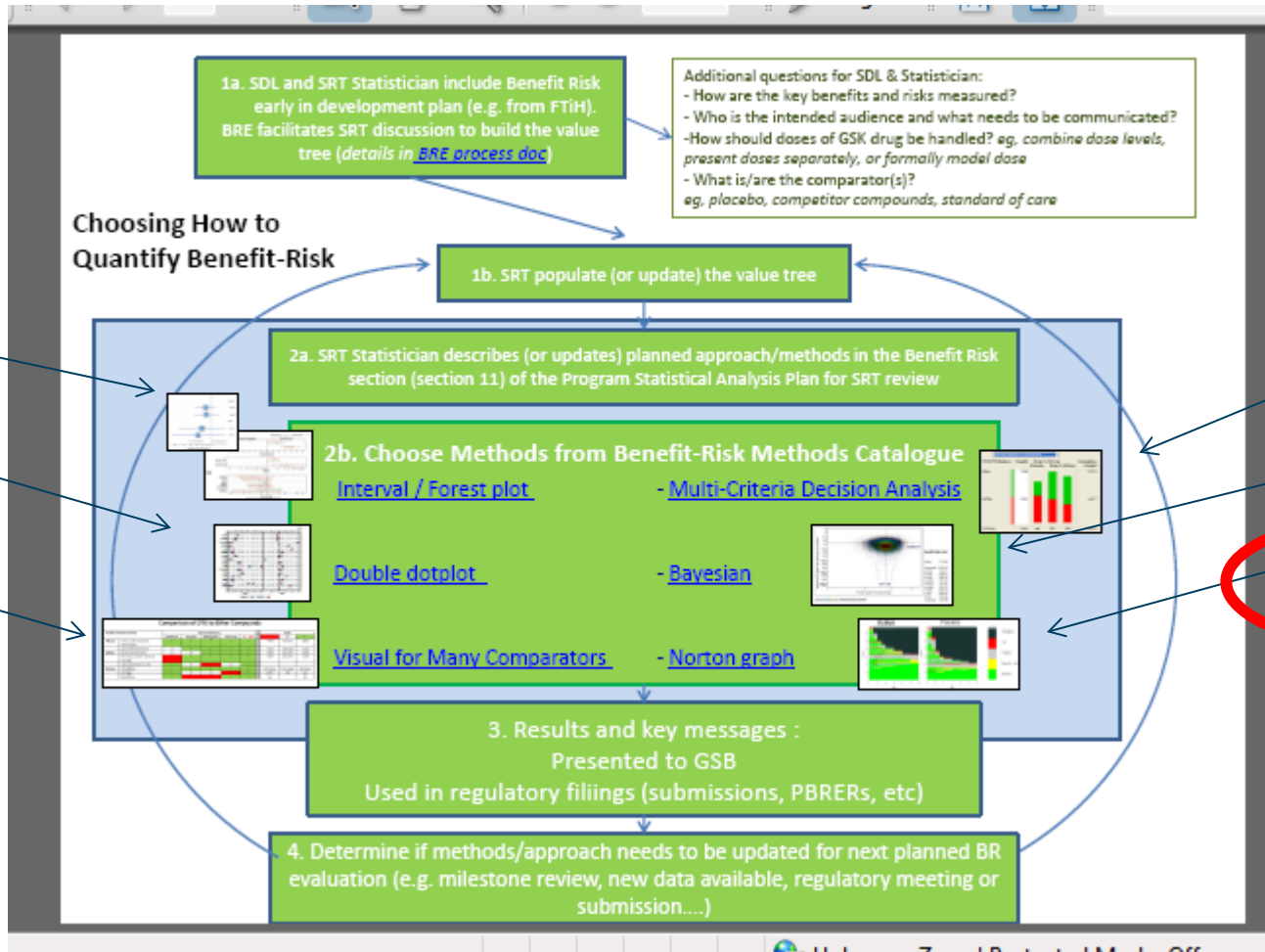
Longitudinal Model and Graphic for Benefit-Risk Assessment

- Pre-specify a multinomial outcome based on efficacy and safety data.
    -- E.g., 5 ordered categories (descending desirability)
    - Efficacy without serious side effects
    - Efficacy with serious side effects
    - No efficacy with no serious side effects
    - No efficacy with serious side effects
    - Side effects leading to drop-out

Global Benefit: Risk Setting

Category	Description	Full Color
1	**Benefit without AE**	*Green*
2	**Benefit with AE**	Yellow
3	**Neither**	*Gray*
4	**AE without Benefit**	Red
5	**Withdrew**	*Black*

Table 1: Benefit-Risk Categories, with Colors

Definition
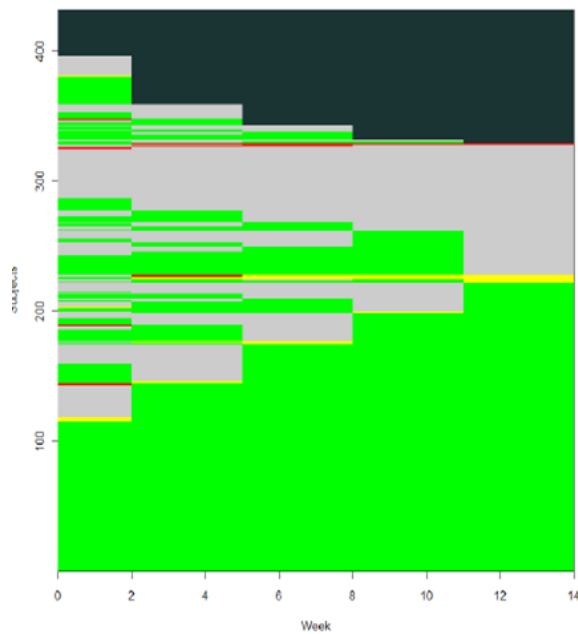
- 420 subjects, each subject has 7 visits.

- Graphic has one row for each subject
- X-axis is the time in study
- Color used to distinguish different states
- Sorting rows is critical

Advantages:

- Gives global impression of study, also shows individual responses

- Aggregate treatment effects

- Within-patient changes in states

- Temporal profile of benefits and risks

- Correlation between benefit and risks

A Picture is Worth a Thousand words
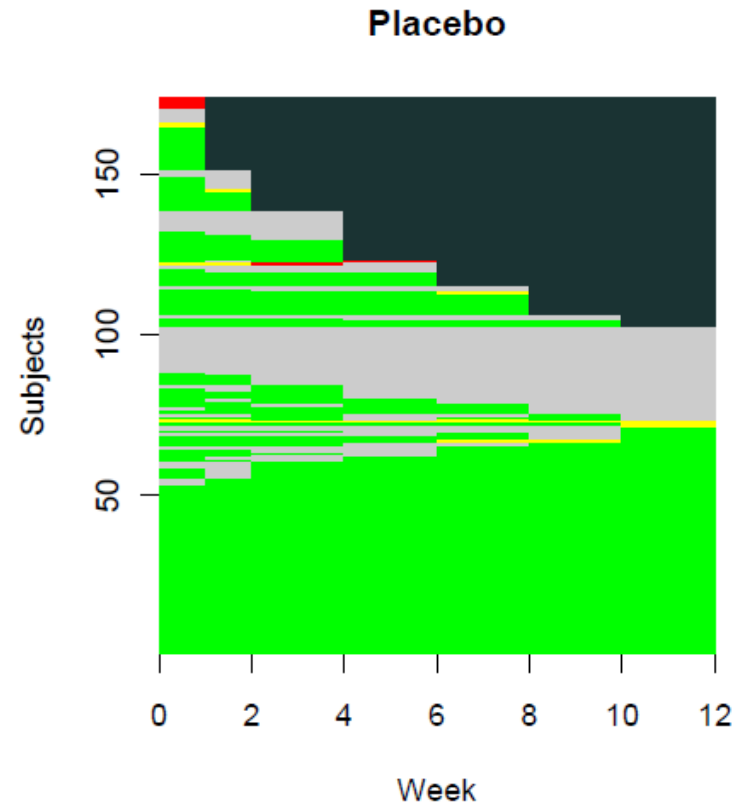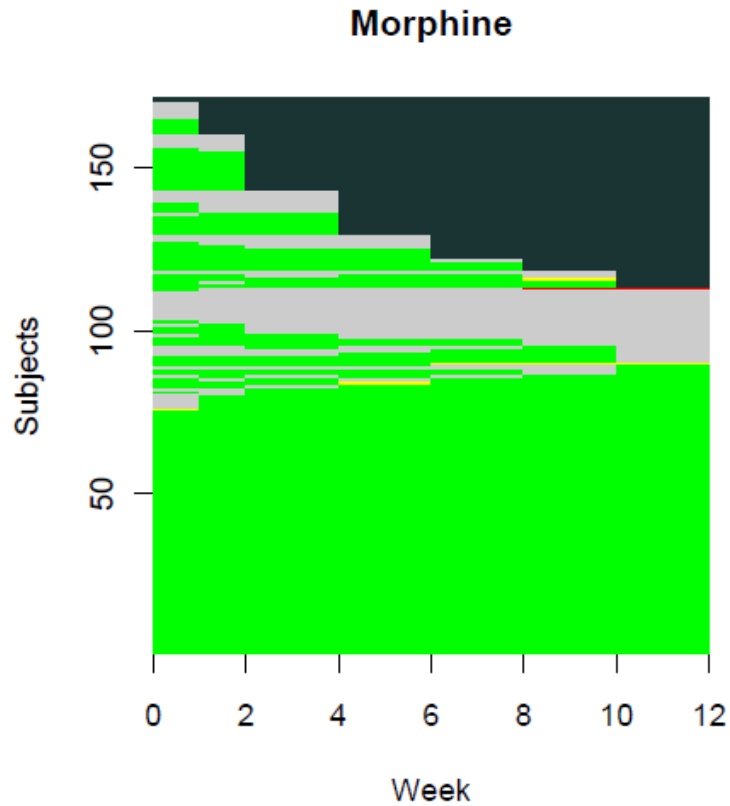
Simplicity Advantage: easy to "see" effects (even for non-technical people)

From Jonathan Norton's Presentation slides

Questions:

- How to prepare this Heatmap graph? What software?

- What kind of information need to be collected?

- Only one Benefit and one Risk?

- What question this graph can address?

- What is so different/better about this method than others?

- What process need to follow if I want to do the similar graph and analysis?

- Any statistical methods beyond the graph?

Process

- Identify important risks & benefits

- Create value tree

- Create Heat Mapping Graph

- Analyze & Evaluate
  – Assign relative weights
    1. Conduct 'Decision Conference'
    2. Increase or decrease
    3. Linear or not
  – Create groupings

- Perform sensitivity analyses

- Characterize results

Identify key Benefits and Risks

- Proactive Thinking and Planning (Program Safety Analysis Plan & Safety Strategy Plan)

- Statistician get involved with data collection

- Individual longitudinal data availability

- Key Benefit and Risk factor identification (Value Tree)

PSAP: Program Safety Analysis Plan
SSP: Safety Strategy Plan

Building the Benefit-Risk Profile: Step 1

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Value Tree

Information Location

Clinical team should be able to provide clear measurable benefit Risk context

What are the key benefits and risks?

How are you defining and measuring benefits and risks?

- Identified Benefit or Risk Category
- Identified benefit/ risk Outcome
- Potential Outcome or B/R category

Benefits

Benefit-Risk Balance

Risks
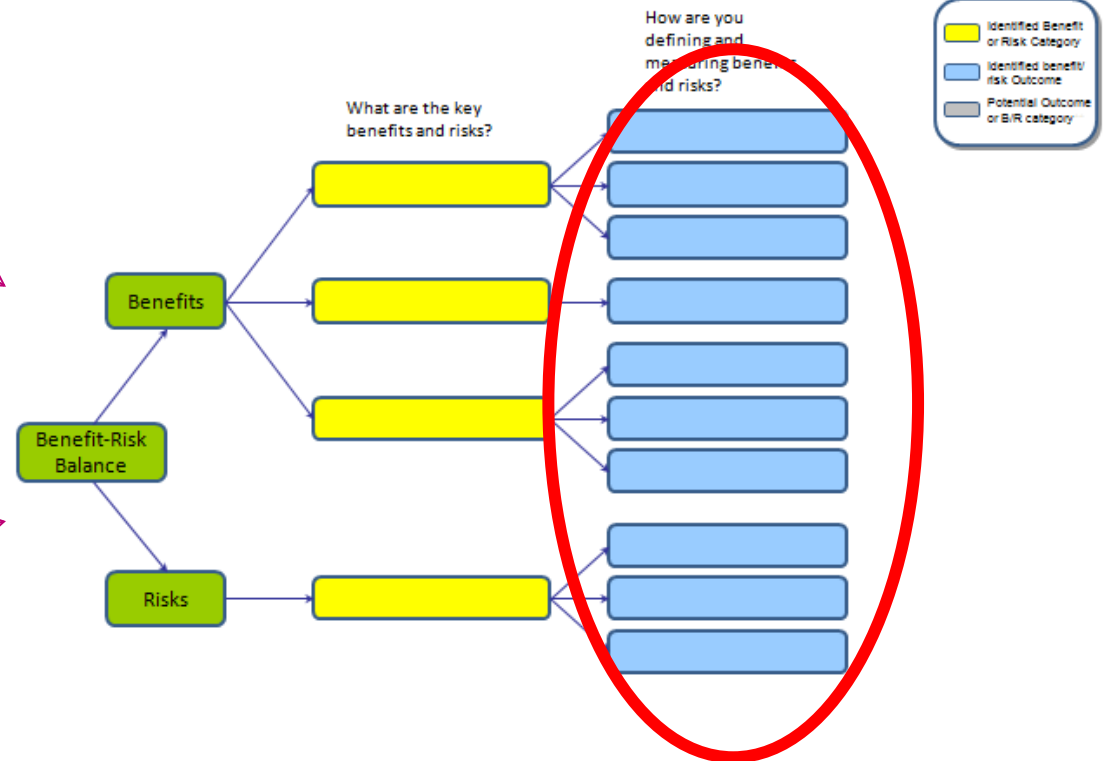
- **Study endpoints**
- **Evaluations of safety**
- **Consider future label text**

Value Tree

Benefits

How are you defining and measuring benefits and risks?

What are the key benefits and risks?

	Identified Benefit or Risk Category
	Identified benefit/risk Outcome
	Potential Outcome or B/R category

Benefits

Benefit-Risk Balance

Risks

Risks

results

(green)	1	Benefit
(yellow)	2	Benefit +AE
(grey)	3	Neither
(red)	4	AE
(black)	5	withdrawn

Graph Creation: Simulation Data

- Simulation in R: ggplot2 package needed (SAS is difficult)

- Two treatments: Active and placebo

- All subjects have the same number of time points (4), easy to extend

- 105 subjects in each treatment.

- Numbers from 1 to 5 represent the different categories.

- Sorted from withdrawal to most benefit (Assume withdrawal is worse than AE)
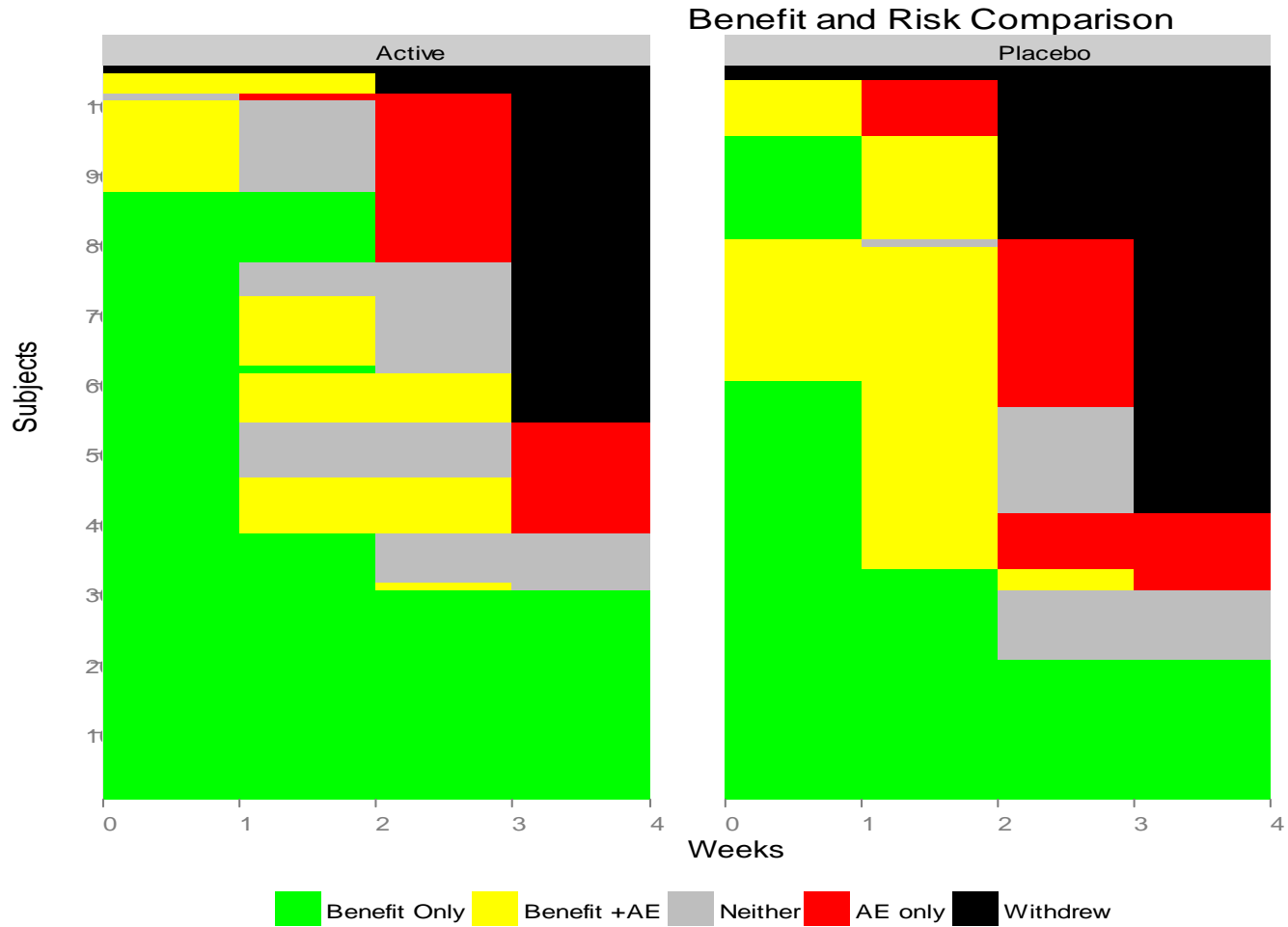
Simulated Data

Subjid	visit	group	catcd	cat
1	1	Active	1	Benefit Only
1	2	Active	1	Benefit Only
1	3	Active	1	Benefit Only
1	4	Active	2	Benefit+ AE
2	1	Placebo	1	Benefit Only
2	2	Placebo	2	Benefit+ AE
2	3	Placebo	2	Benefit+ AE
2	4	Placebo	3	Neither
…..	…	…	…	…

Heat map Graph by R

Benefit and Risk Comparison

- "A Longitudinal Model and Graphic for Benefit-Risk Analysis, with Case Study" Jonathan D. Norton, FDA, *Therapeutic Innovation & Regulatory Science*, Nov 2011 Vol.45 no.6 741-747

A Longitudinal Model and Graphic for Benefit-risk Analysis, With Case Study

Jonathan D. Norton, PhD
Division of Biometrics II,
Office of Biostatistics,
Center for Drug Evaluation
and Research, Food and
Drug Administration,
Silver Spring, Maryland

A novel method for simultaneously visualizing benefit and risk over time is presented. The underlying model represents a subject's benefit-risk state at a given time as one of five discrete clinical states, one being premature study withdrawal. The new graphic uses colors to represent each subject's changing state over the course of the clinical trial. The user can quickly grasp how a treatment affects subjects in aggregate, then further examine how individuals are affected. It is possible to tell whether the beneficial and harmful outcomes are correlated. The method is particularly appropriate for treatments that provide only symptomatic relief. An approved drug for chronic pain is presented as a worked example.

Simple Statistics Beyond Graphics

- Calculate % of areas of different colors. Treating Black < Red < Grey < Yellow < Green, the new treatment is stochastically greater than placebo.

	Black	Red	Grey	Yellow	Green
Placebo	**0.22**	**0.12**	**0.09**	**0.22**	**0.35**
Cumulative	*0.22*	*0.34*	*0.43*	*0.65*	*1.00*
New Treatment	**0.13**	**0.10**	**0.16**	**0.14**	**0.47**
Cumulative	*0.13*	*0.23*	*0.39*	*0.53*	*1.00*

Comparing two Proportions

- If we do not consider different weight. Run two proportion test

- Compare % of areas of different colors by two proportion test (two sided).

	P-value
Benefit Only	0.00097
Benefit +AE	0.00546
Neither	0.002
AE only	0.32
Withdrew	0.001

- AE is not significant different, all others are significant different.

- The results did not consider with-in and between subject variability. Any way to combine 5 comparisons into one?

Quantification Possible?

▪Assign weights to reflect the relative importance of each category or develop a distance function between categories

▪Chuang-Stein et al. defined a set of three global benefit-Risk (GBR) scores, W_i are the pre-specified weights. Pi are multinomial random variables, d ∈ {Different Treatments}

$$Linear\_Score = \sum_{i=1}^{2} w_i p_{i,d} - \sum_{i=3}^{5} w_i p_{i,d}$$

$$Ratio\_Score = \frac{(\sum_{i=1}^{2} w_i p_{i,d})^e}{\sum_{5} w_i p_{i,d}}$$

$$Cmp\_Ratio\_Score = \frac{w_1 p_{1,d}}{w_5 p_{5,d}} \left(\frac{w_2 p_{2,d}}{w_3 p_{3,d} + w_4 p_{4,d}}\right)^f$$

Reference

- Chuang-Stein C. et al. (1991) Three measures for simultaneously evaluating benefits and risks using categorical data from clinical trials.

- Chuang-Stein C. et al. (2008) Measures for Conducting Comparative Benefit Risk Assessment

- Accept for Publication:
Yueqing et al. Bayesian approach for benefit-risk assessment

Our Method (assign weight)

- Thanks for the discussion with Scott Evans from Harvard University

- Assign weight to different category for each subject level, instead of assigning weight to the category proportion in aggregate level

1. Green (Benefit Only) assign 1
2. Black and red (withdrawal and AE) assign 0
3. Yellow and grey can assign some number between 0 and 1
4. For each subject, calculate Linear BR score by adding them up

- For each treatment, have different subject-level total scores.

- Run t test or other testes for continuous variable comparisons.

Simulated data (Assign weight):

Category	Description	Full Color	Score
1	Benefit without Risk	Green	1
2	Benefit with Risk	Yellow	0.7
3	Neither Risk or Benefit	Grey	0.5
4	Risk without Benefit	Red	0
5	Withdrew	Black	0

Simulated data Illustration:

Active   **Score scale from 0 to 4**

groupcd	subjid	sum
1	28	4.0
1	29	4.0
1	30	4.0
1	31	3.0
1	32	3.0
1	33	3.0
1	34	3.0
1	35	3.0
1	36	3.0
1	37	3.0
1	38	2.0
1	39	2.0

groupcd	subjid	sum
2	158	1.7
2	159	1.7
2	160	1.7
2	161	1.7
2	162	1.7
2	163	1.4
2	164	1.4
2	165	1.4
2	166	1.4
2	167	1.4
2	168	1.4
2	169	1.4
2	170	1.4
2	171	1.4

Simulated data P-values:

Benefit Risk Score by Treatment
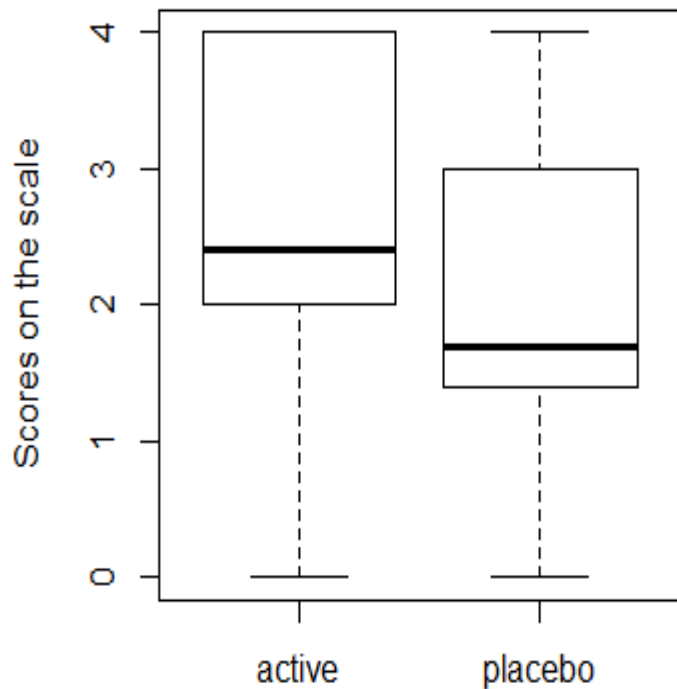
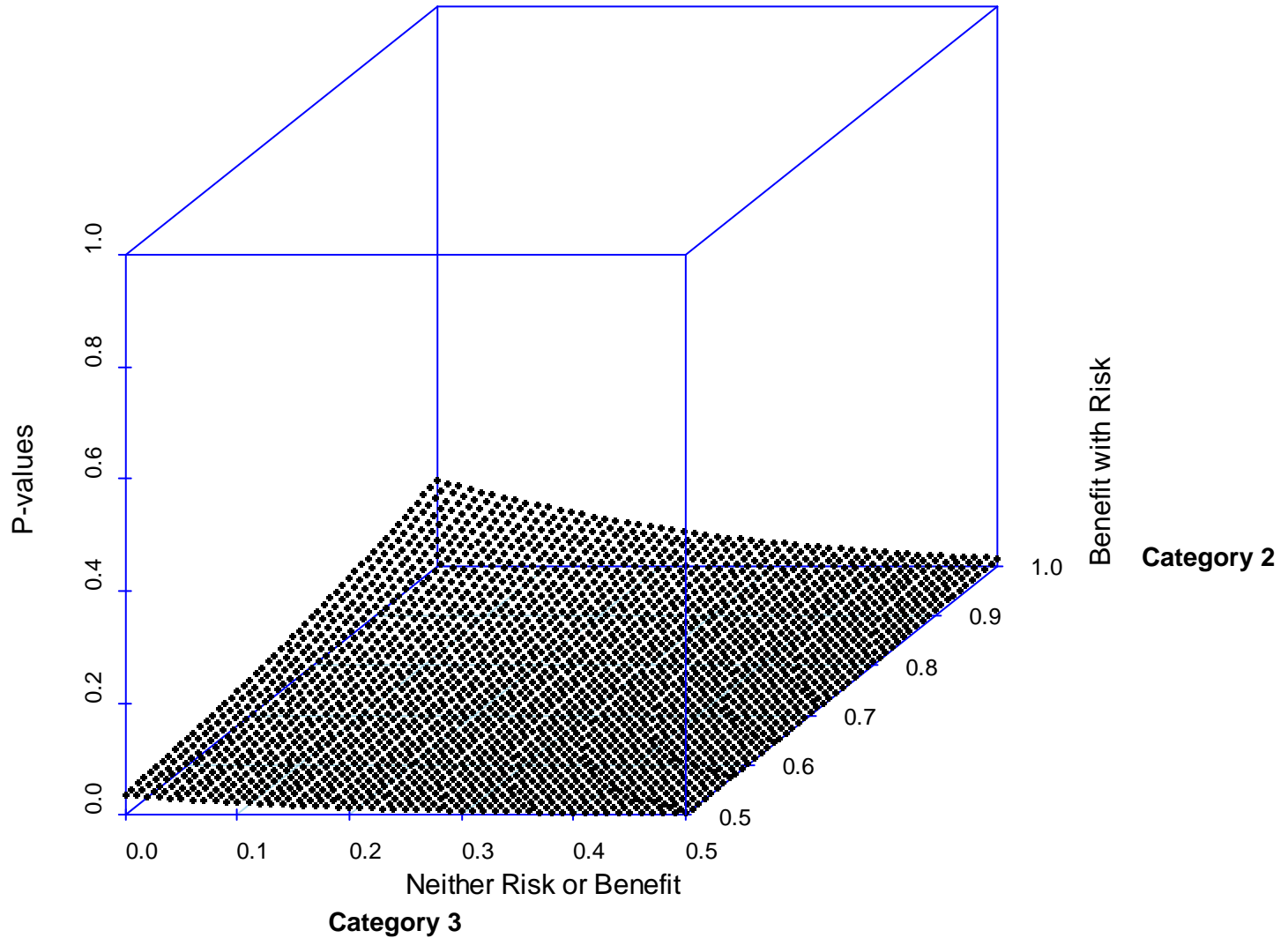- **Two sided P-value=0.0085 <0.05**

- **One sided P-value=0.0042 <0.05**

Alternative is greater

Simulated data (Sensitivity analysis):

Category	Description	Full Color	Score
1	Benefit without Risk	Green	1
2	Benefit with Risk	Yellow	0.5 to 1 by 0.01
3	Neither Risk or Benefit	Grey	0.5 to 0 by -0.01
4	Risk without Benefit	Red	0
5	Withdrew	Black	0

Simulated data P-values (One sided):

Two dimensional plots (One sided p-values)

Benefit with Risk SCORE
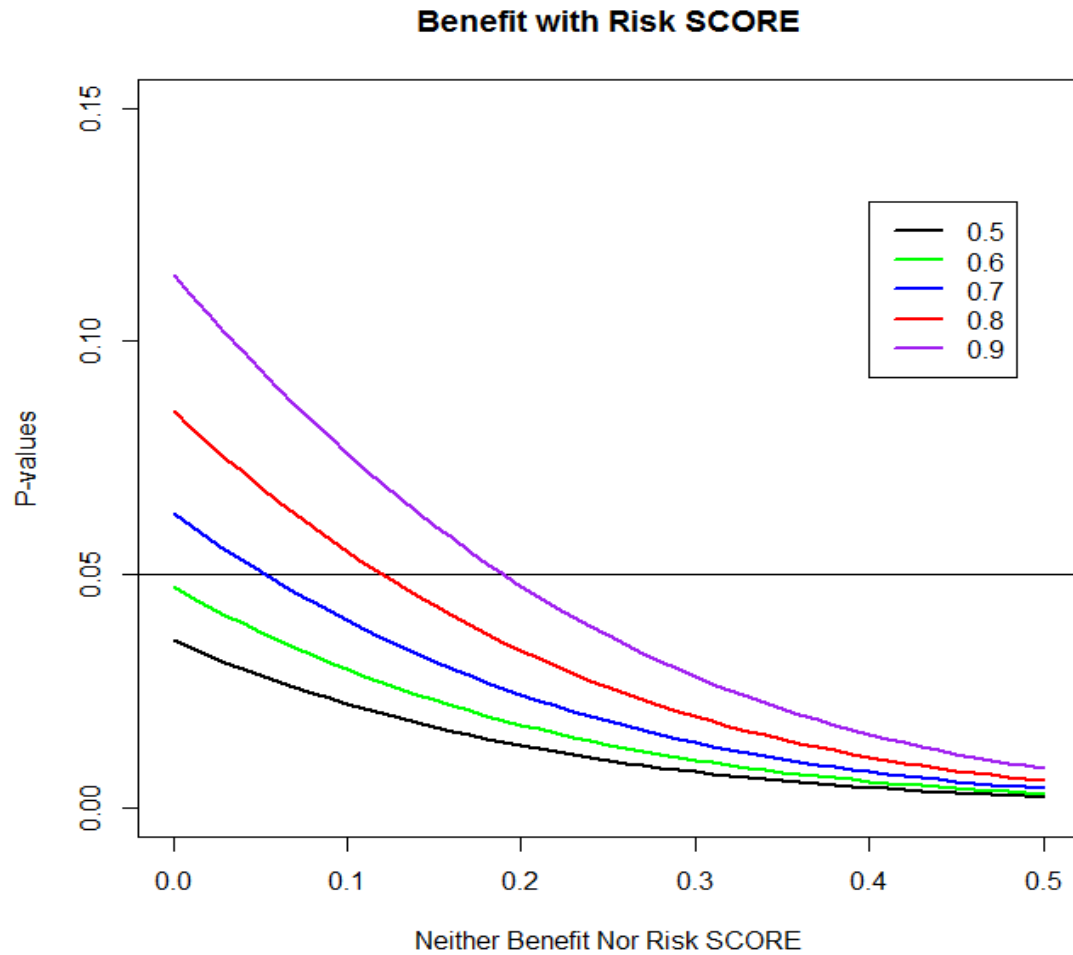
The Lines in the graph represent the different scoring assumption for **Category 2 (Benefit+ Risk)**

Category 3

Summaries of Weight assignment

- If "Neither benefit nor Risk" assignment between 0.3 to 0.5, the P-values always less than 0.05, regardless of the assignment of "Benefit with Risk"

- For the example just shown, if "Benefit with Risk" Score assignment=0.6 or 0.5, the P-values always less than 0.05, regardless of the assignment of "Neither benefit nor Risk"

- Two dimensional mutually driven

- Sensitivity analysis is critical to make consistent conclusions

- Clinical Team will provide the most informative input, getting regulatory feedback is very critical when you do the analysis.

Application: Real case (Back ground)

- Thanks for Jie Cheng and Stefanie Knoll provide real data

- Oncology compound X is currently in development

- Challenge: Extend the progression-free time but at the cost of adding side effects

- Primary outcome is "Quality of Life" score measures from baseline to post treatment visits

- Treatment (A) vs Treatment Placebo (B)

- Two additional endpoints: Time2progression and Time2discont

Categorizing Data

- Primary endpoint: Quality of Life

- Assign Category: CFB: Change from baseline

- Assumption: Missing/Withdrawal due to significant side effects

Change from baseline (CFB)	catcd	category	Color
CFB>=3	1	More Benefit	Dark Green
3>CFB>0	2	Moderate Benefit	Green
CFB=0	3	Neither	Gray
0>CFB>-3	4	Moderate Risk	Yellow
-3>=CFB	5	More Risk	Red
Missing	6	Withdrawal/Missing	Black

Heat-map graph

Benefit and Risk Comparison for all Age groups

Stats comparisons

- Calculate % of areas of different colors, and all assign the same weight (All time segments have equal weighting, all categories have equal weighting).

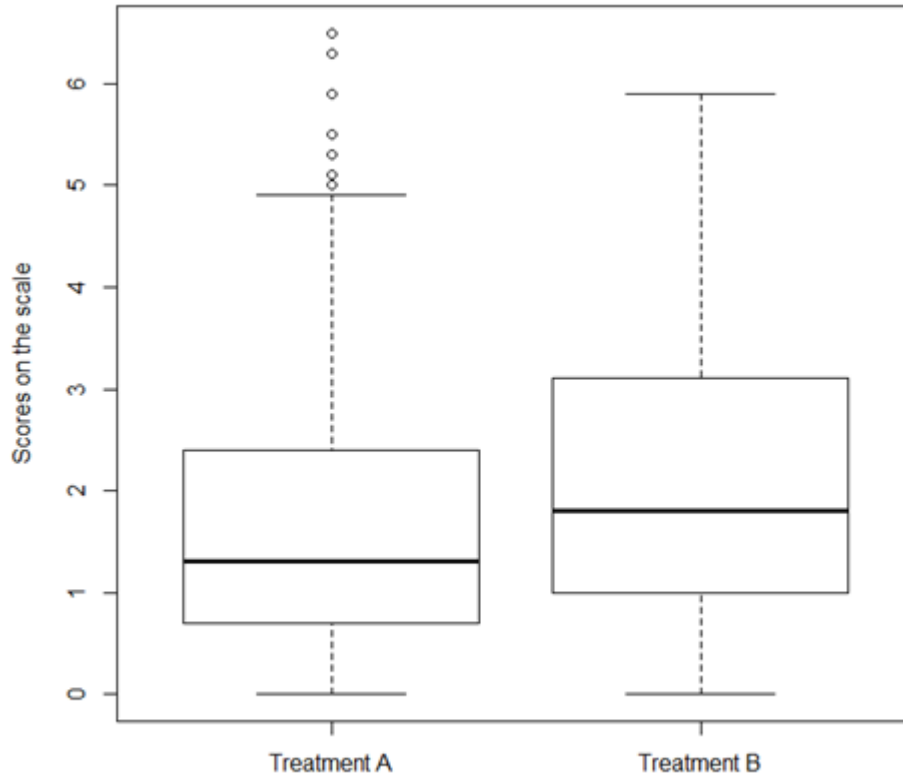|	Treatment A	Treatment B	P-value
More Benefit %	1.4	1.3	0.85
Moderate Benefit %	8.0	14.1	<0.0001
Neither %	27.7	32.5	<0.0001
Moderate Risk %	11.8	10.5	0.086
More Risk %	1.5	1.0	0.097
Missing/Withd rawal%	49.6	40.6	<0.0001

Assign the weight

- Primary endpoint: Quality of Life

- Assign Category: CFB: Change from baseline.

Change from baseline (CFB)	catcd	category	Color	Score
CFB>=3	1	More Benefit	Dark Green	1
3>CFB>0	2	Moderate Benefit	Green	0.8
CFB=0	3	Neither	Gray	0.5
0>CFB>-3	4	Moderate Risk	Yellow	0.2
-3>=CFB	5	More Risk	Red	0
Missing/Withdraw	6	Missing	Black	0

P-values (T-test)

Benefit Risk Score by Treatment

- Two sided P-value<0.001
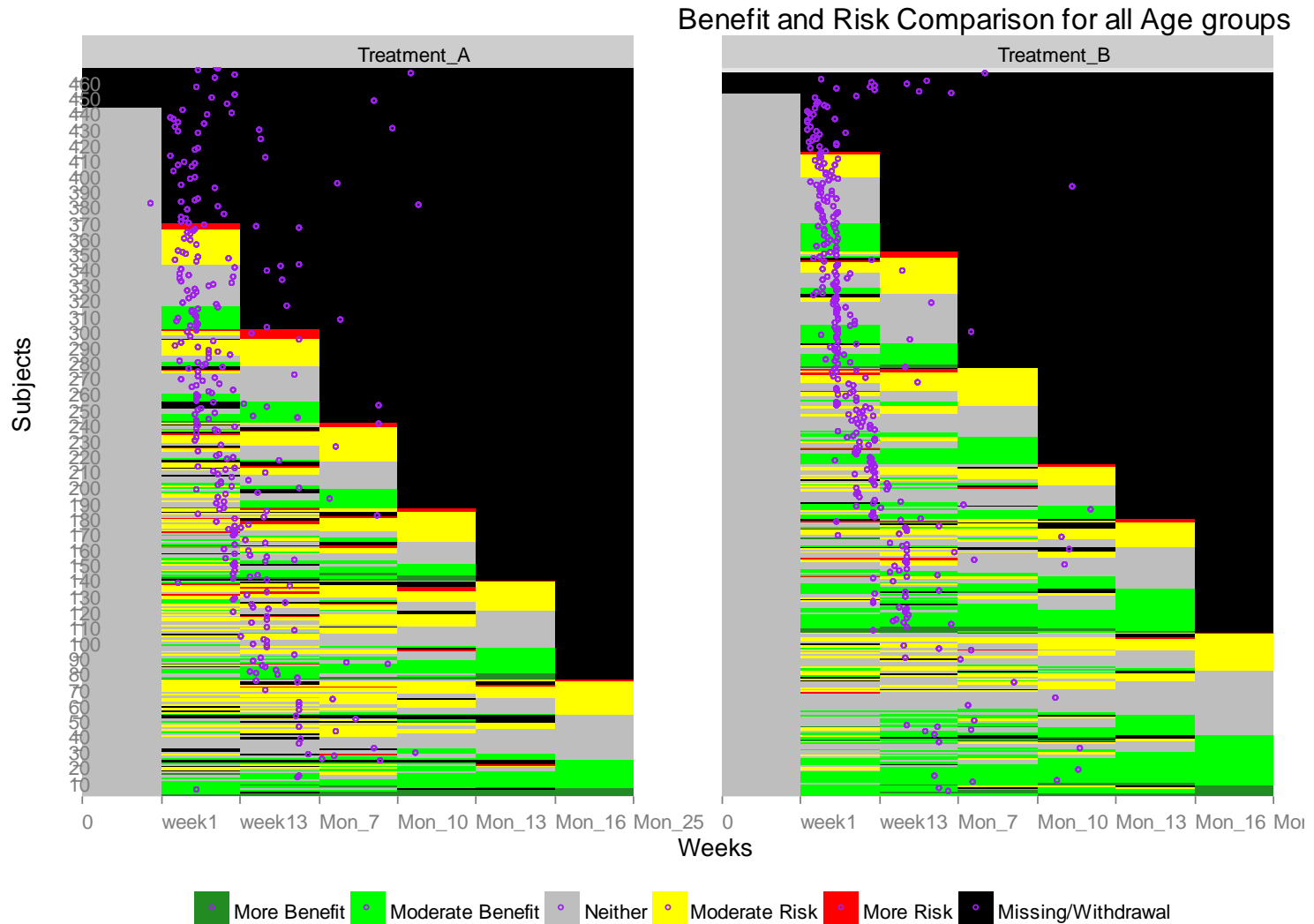- One sided P-value<0.001

Adding "Time to Discontinuation"

Benefit and Risk Comparison for all Age groups
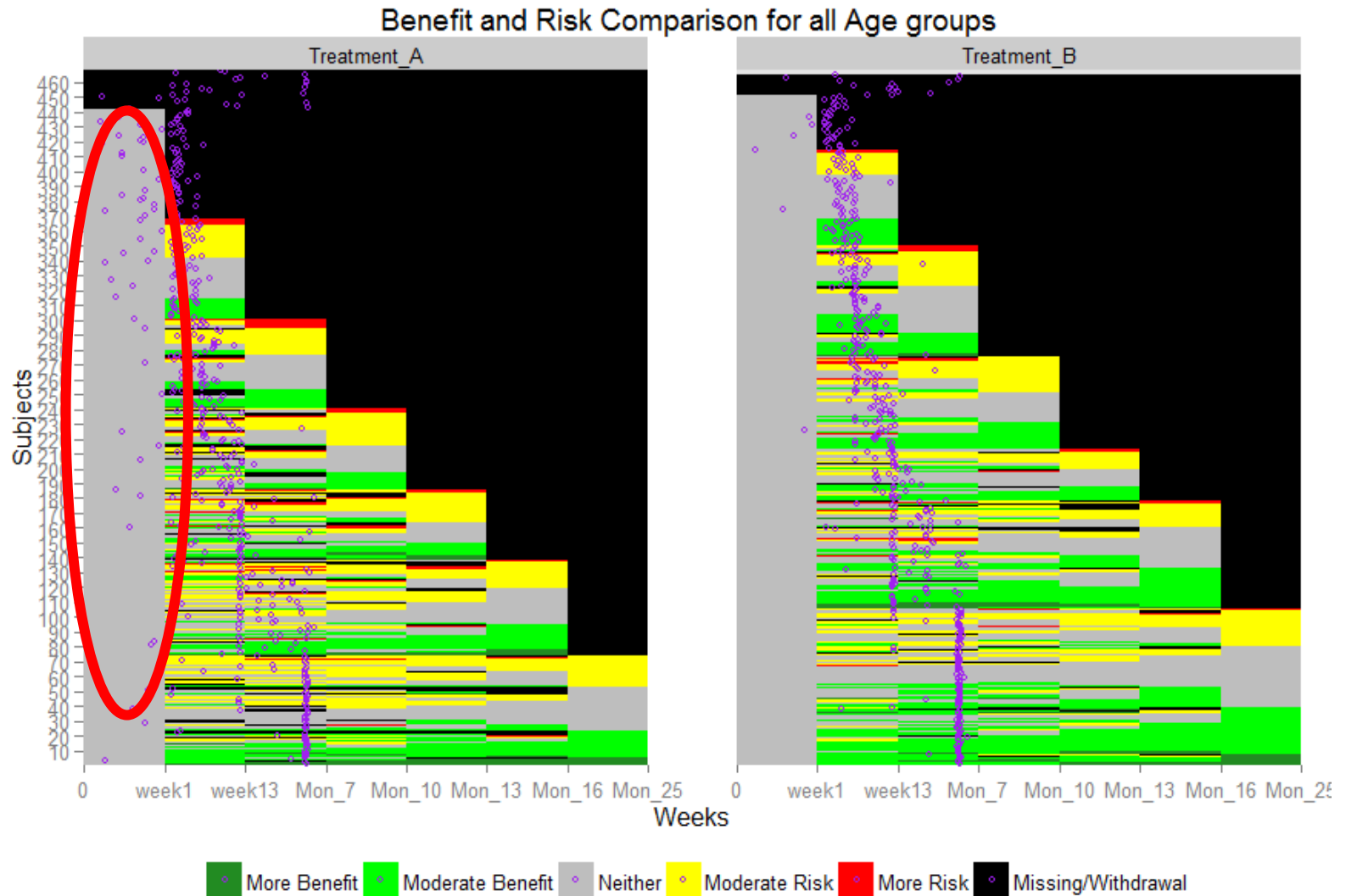
How to read "Time to discontinuation"

- Heat-map graph provide really good visualization to link Treatment discontinuation with BR data

- Subjects from Treatment A (active) tended to discontinue the drug earlier than Treatment B (Placebo)

- The duration of the treatment did not improve the overall quality of life

Adding "Time to Progression free"

Benefit and Risk Comparison for all Age groups

Legend: More Benefit · Moderate Benefit · Neither · Moderate Risk · More Risk · Missing/Withdrawal

How to read "Progression free time"

- Heat-map graph provide really good visualization to link "Progression free time" with BR data

- Subjects from Treatment A (active) had longer "progression free time" than Treatment B (placebo)

- Explore the correlation between "Progression free time" and "overall BR score"

- Placebo group did better than Active treatment on BR score

Treatment A (Active)

Treatment B (Placebo)
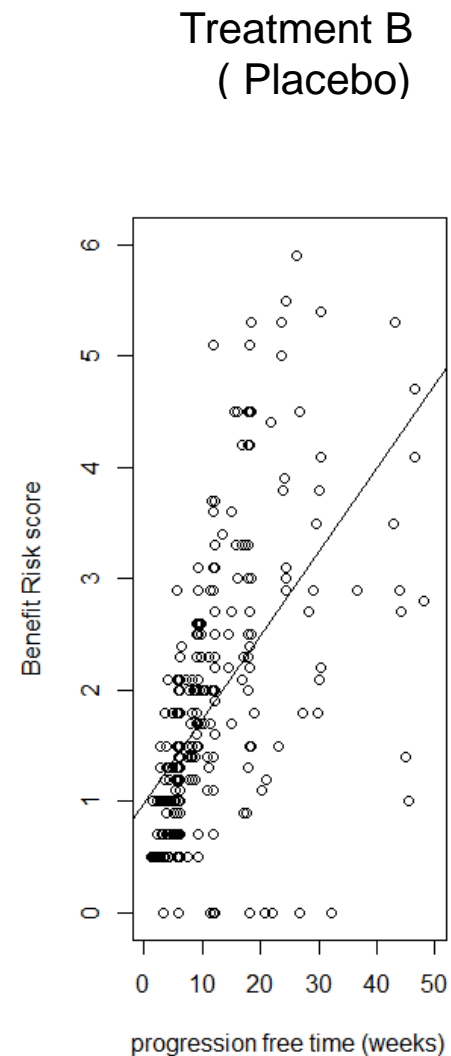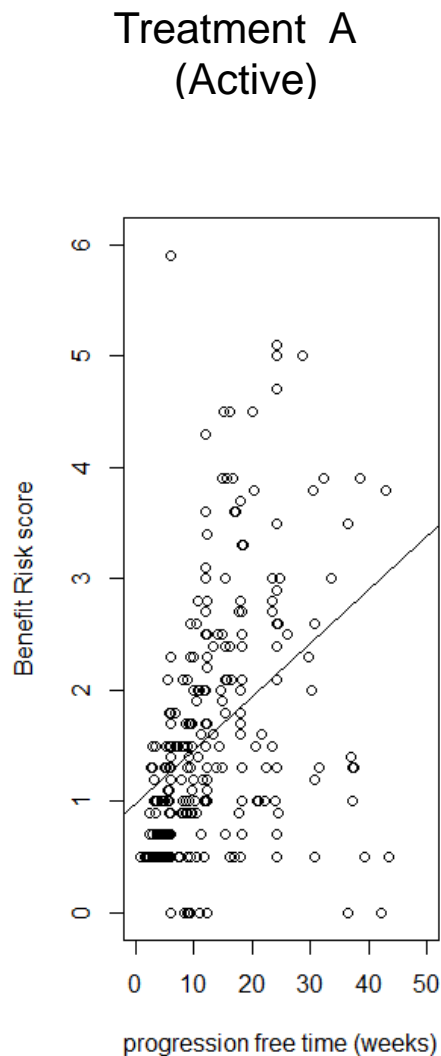
Findings

- Heat-map graph provide really good visualization and offering a different view points.

- Can do on an individual basis and then see the patterns

- Useful for exploration

- The findings of the heat-map analysis can help the clinical team to make decisions.

- The active treatment did show an improvement in progression-free survival rates over those on a placebo, but the results "do not support an overall positive benefit-risk in this indication"

- Potential to be helpful for discussion with the investigators for publications.

Re-Cap

- Heat-map graph is straightforward

- Easy to implement and interpretation

- Quickly grasp how a treatment affects subjects in aggregate

- Further examine how individuals are affected. It also can tell the correlation between benefits and harms, within-patient changes in states.

- Quantification analysis is possible

Further work:

- How many categories do we need? Not limited to 5 categories

- How to define each category, complicated situations?

- Do not have to treat all withdrawals equally

- Graphic stands by itself but sensitivity to varying weights / distance metrics needed for inference

- Different way to sort the color, how to deal with different sample size

- Statistical comparisons between two graph extension (Bayesian method)

Acknowledge

- Benefit Risk Working Group members from GSK
- Susan Duke, Colleen Russell from GSK
- Scott Evans from Harvard University

Conflict of Interest

- Kevin Gan, GlaxoSmithKline employee and Stock holder

Thank you

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live longer

Back-up slides—R code

```r
#plot data
qplot(main="Benefit and Risk Comparison ",
      x=week,
      y=counter,
      fill=cat,
      data=df,
      xlab="Weeks",
      geom="tile",
      ylab="Subjects",
      facets =  .~ group )+

  scale_y_continuous(expand=c(0,0), breaks=breaks   )+
  scale_fill_manual(  values=category_colors, #use specific colors for fill
                  name  ="")+  #supress legend title

  scale_x_continuous(expand=c(0,0),
              breaks=seq(.5,4.5,1), #control placement of x tickmarks
              labels=0:4)+ #label x labels

  theme(panel.grid.minor=element_blank()) + #supress minor grid
  theme(panel.grid.major=element_blank()) + #supress major grid
  theme(legend.position = "bottom")  +  #place legend below the plot
  theme(panel.margin = unit(2, "lines")) #increase space between plots


##dev.off()
```