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The Clinical Data Cinema

The many roles of data visualization in clinical development Jürgen Löffler, Novartis Pharma AG, Basel London, 9th October 2015



Motivation

Data tables: what does it all mean?

| Subject $^{\diamond}$ | Visit 🍦 | AVAL | † ID † | TRTO | LPN ÷ | sex 🔅 | age 🔅 | BASE | ÷ | ratio | pchg | ÷ | chg | ÷ | | | | | | | | |
|-----------------------|---------|----------|-------------|------|-------------|-----------|----------|---------|------|-----------|--------|-----|--------|--------|---|-----|------|-------------------|----------------------|---------------------|-----------|------------|
| 1001 | 0 | 10.50547 | 9 1 | | 1 | 2 | 61 | 10.505 | 479 | 1.000000 | 0.000 | 000 | 0.0000 | 000 | | | | | | | | |
| 1001 | 3 | 19.01652 | 4 1 | | 1 | 2 | 61 | 10.505 | 479 | 1.8101529 | 81.015 | 286 | 8.5110 | 443 | | | | | | | | |
| 1001 | 778 | 9.44337 | 5 1 | | 1 | 2 | 6 | Visit 🔅 | AVA | L ÷ | ID ‡ | TRI | 01PN 🗧 | sex | ÷ | age | ÷ | BASE [‡] | PASI100 [‡] | PASI90 [‡] | PASI75 | ÷ PASI50 ÷ |
| 1001 | 1 | 19.90248 | 7 1 | | 1 | 2 | e | 0 | 20.2 | 28729856 | 1 | | 1 | | 1 | | 25 | 20.287299 | N | N | N | N |
| 1001 | 2 | 19.47185 | 0 1 | | 1 | 2 | e | 16 | 5.2 | 22783246 | 1 | | 1 | | 1 | | 25 | 20.287299 | N | N | N | Y |
| 1001 | 6 | 19.60768 | 2 1 | | 1 | 2 | e | 8 | -1.4 | 2217679 | 1 | | 1 | | 1 | | 25 | 20.287299 | Y | Y | Y | Y |
| 1002 | 1 | 21.04831 | .3 2 | | 1 | 2 | 6 | 1 | 19.7 | 73067642 | 1 | | 1 | | 1 | | 25 | 20.287299 | N | N | N | N |
| 1002 | 778 | 9.50144 | 0 2 | | 1 | 2 | 6 | | | 52338986 | 1 | | 1 | | 1 | | | 20.287299 | | Y | Y | Y |
| 1002 | 0 | study 🌣 | subgroup 🗧 | nl ‡ | n2 ‡ | parms | | 4 | | 52258949 | 1 | | 1 | | 1 | | | 20.287299 | | Y | Y | Y Y |
| 1002 | 3 | X2301 | >= 65 years | 26 | 25 | Adverse | event | 12 | | 34085618 | - 1 | | 1 | | 1 | | | 20.287299 | | N | Y | Y |
| 1002 | 6 | X2301 | < 65 years | 89 | 85 | Adverse | event | | | 36523212 | 1 | | 1 | | 1 | | | 20.287299 | | N | N | N |
| 1002 | 2 | X2301 | >= 65 years | 26 | 25 | Complet | e respo | | | | | | | | | | | | | | | |
| 1003 | 778 | X2301 | < 65 years | 89 | 85 | Complet | e respo | | | 86711571 | 2 | | 1 | | 2 | | | 25.967181 | | N | N | N |
| 1003 | 6 | X2301 | >= 65 years | 26 | 25 | Partial r | esponse | 8 | | 79213767 | 2 | | 1 | | 2 | | | 25.967181 | | Y | Y | Y |
| | | X2301 | < 65 years | 89 | 85 | Partial r | esponse | 0.55 | 0.4 | Yrrona 8 | 3 32 | NA | 3.5 | 23692 | Î | 174 | 532/ | 85 (37.7%)" | 48/89 (53.9% |) 1.9 (1.05 | 5, 3.52) | 0.48 |
| | | X2302 | >= 65 years | 58 | 57 | Adverse | event | 0.20 | 0.1 | 0 18 | 3 5 | NA | 12.7 | 751994 | | 115 | 5/ ! | 57 (8.8%) | 18/ 58 (31.0% |) 4.4 (1.49 | 9, 12.75) | 0.18 |
| | | X2302 | < 65 years | 121 | 123 | Adverse | event | 0.15 | 0.0 | 5 19 | 9 8 | NA | 6.1 | 158143 | | 244 | 8/1 | 23 (6.5%) | 19/121 (15.7% | 6) 2.6 (1.09 | 9, 6.16) | 0.12 |
| | | | >= 65 years | 58 | | Complet | | | | | | NA | | 529105 | | | | | 25/ 58 (43.1% | | | 0.35 |
| | | | < 65 years | 121 | | Complet | | se 0.40 | | | | NA | | 18399 | | | | | 37/121 (30.6% | | | 0.36 |
| | | | >= 65 years | 58 | | Partial r | | 0.50 | | | | NA | | 848937 | | | | | 34/58 (58.6% | | | 0.53 |
| | | | < 65 years | 121 | | Partial r | | 0.55 | | | | NA | | 54996 | | | | | 61/121 (50.4% | | | 0.49 |
| | | | >= 65 years | 20 | | Adverse | | 0.20 | | | | 25 | | 00000 | | | | | 9/20 (45.0%) | 6.8 (1.24 | | |
| | | | < 65 years | 45 | | Adverse | | 0.15 | | | | 25 | | 00000 | | | | | 4/45 (8.9%) | 9.2 (0.00 | | 30.0 |
| | | X2303 | >= 65 years | 20 | 22 | Complet | e respon | se 0.36 | 0.2 | 5 7 | 7 7 | NA | 4.1 | 46928 | | 42 | 7/3 | 22 (31.8%) | 7/20 (35.0%) | 1.1 (0.32 | 2, 4.15) | 0.52 |



Today's program

Documentary

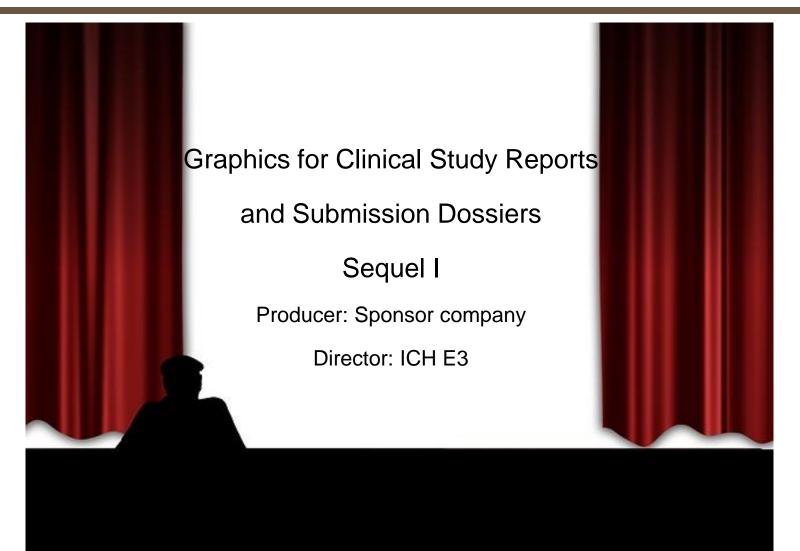
- Graphics for Clinical Study Reports and Submission Dossiers I
- Drama / Comedy
 - Presentations (all sorts of)
- Science
 - Data exploration and other interesting things

Science fiction

- Graphics for Clinical Study Reports and Submission Dossiers II
- Wrap up (not a film)



Today's program Documentary





Documentary How CSRs and dossiers look like





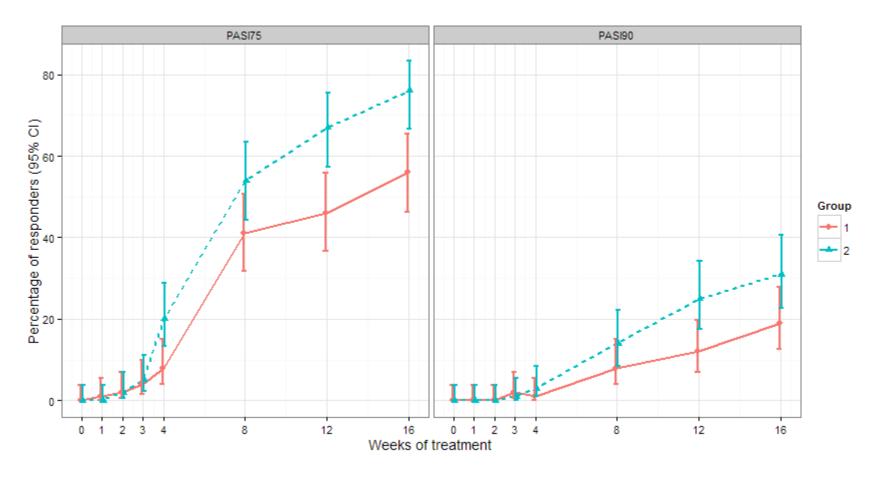
Documentary How CSRs and dossiers look like

- A recent Novartis submission
 - Paper copy for Australia
 - 1485 Folders in 375 boxes for a total weight of 4152 KG
- Thousands of pages of tables, listings and (some) graphs
- How does anyone view pieces of information that belong together but are separated by meters?

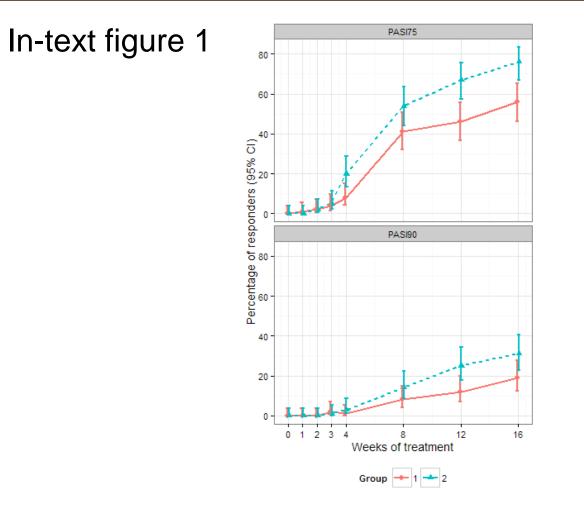
Post-text and in-text figures



Post-text figure 1



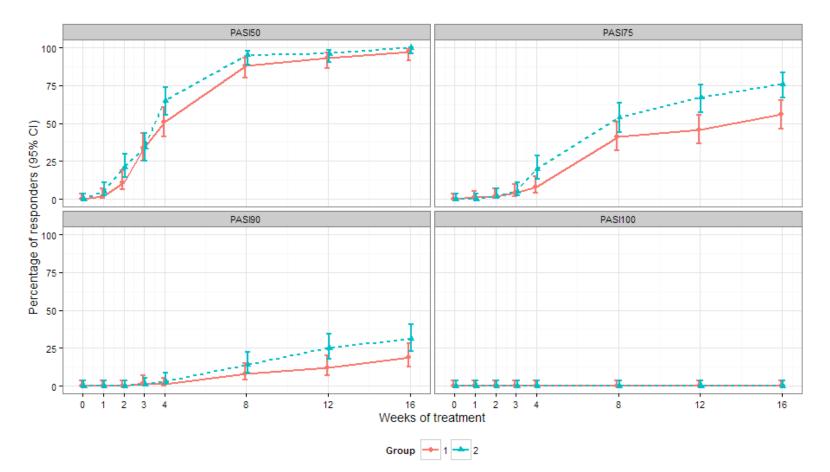
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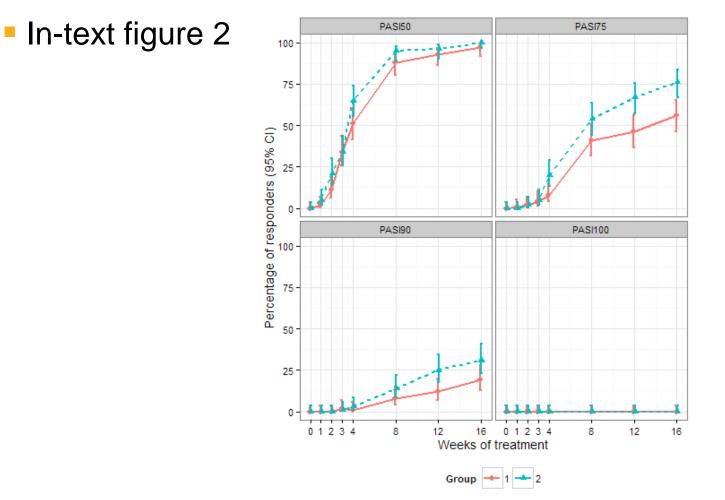


• (at least the aspect ratio in each cell is maintained)

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Post-text figure 2



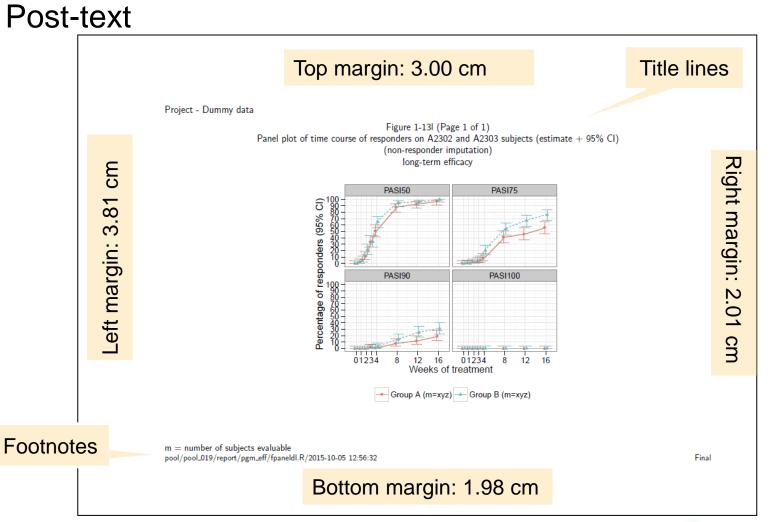


• (aspect ratio now sacrificed due to portrait: different message?)

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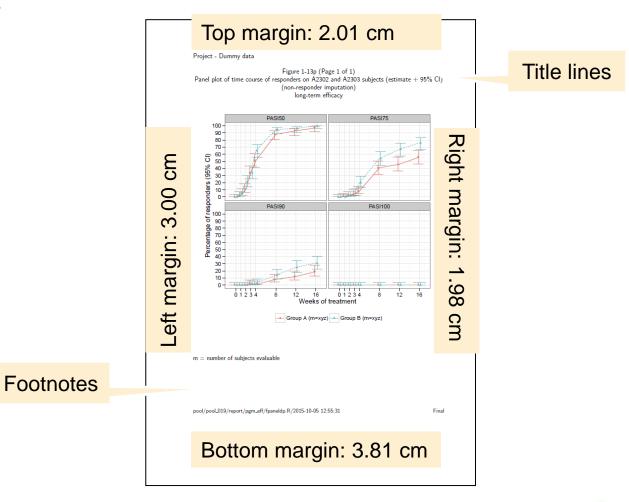
Documentary *Constraints for figures (graphs) in CSRs and dossiers*





Documentary *Constraints for figures (graphs) in CSRs and dossiers*

In-text





Documentary *Limitations and constraints*

- Static
- Limited use of colour (black and white safe)
- Limited size (page margins!)
- Only certain image file formats, no transparency (?)
- Orientation defined by document (not graphical principles)
- Audit trail
- Reproducible
- Validated



NOVARTIS

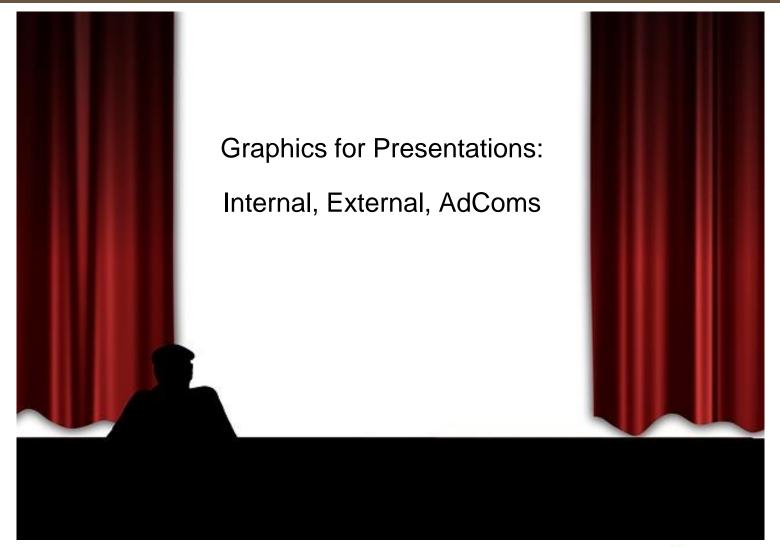
- We produce them as RTF and render to PDF
- The PDF is stored in the document management system (along with the RTF source)
- The medical writer extracts the image (copy or screenshot) and pastes into Word document, resizes as needed (a bitmap file!)
- For convenience, an image file (PNG) may be directly used
 - Produced as a "side product" in SAS (not formally validated, audit trailed, stored)

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Is there a better way?

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Today's program Drama / Comedy





Drama, Comedy Internal or external slide deck

- Static, possibly animations
- Orientation: landscape
- Company colours

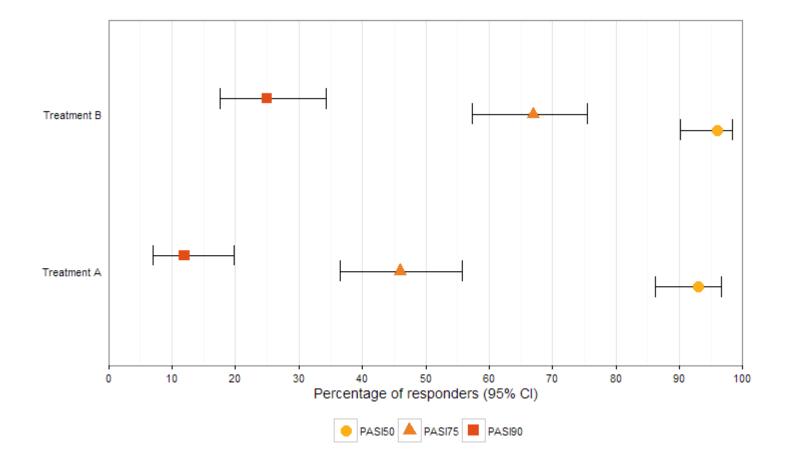
| R | G | В | Hex | Preview |
|-----|-----|----|--------|---------|
| 252 | 175 | 23 | FCAF17 | |
| 236 | 128 | 38 | EC8026 | |
| 228 | 76 | 22 | E44C16 | |
| 146 | 50 | 34 | 923222 | |
| 99 | 67 | 41 | 634329 | |

Simplicity

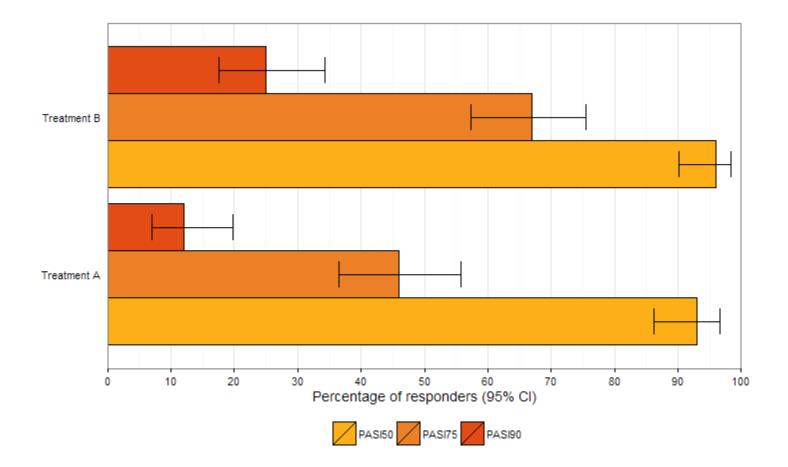
Chart types that audience is used to



Drama, Comedy Statisticians' preference (minimize ink)



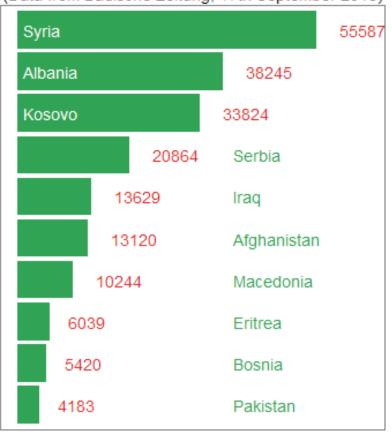
Drama, Comedy Customers' preference (= simplicity or custom?)

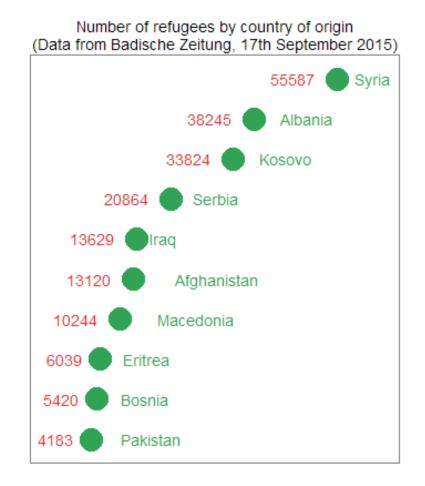




Drama, Comedy My wife's preference?

Number of refugees by country of origin (Data from Badische Zeitung, 17th September 2015)





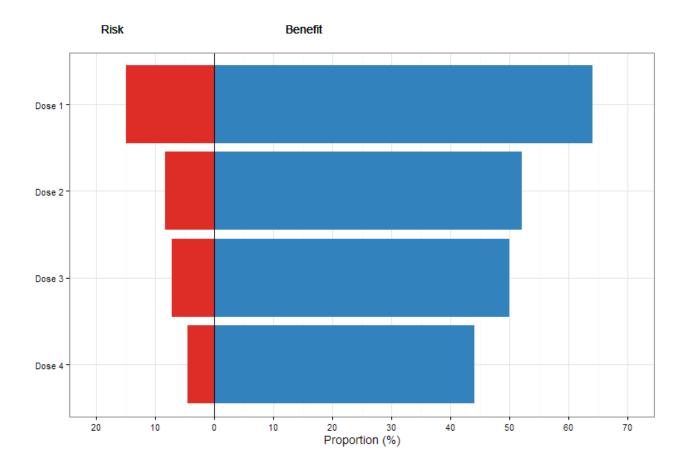
Drama, Comedy AdCom, HA presentation

- Static
- Orientation landscape
- "FDA colours" (not respected here)
- Simplicity
 - Charts that audience is used to: "laypersons"
- Benefit-risk



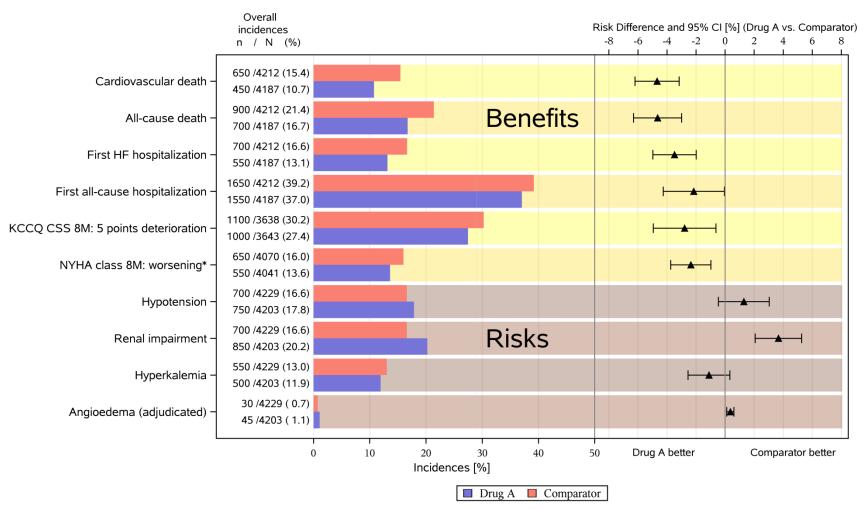
Drama, Comedy Benefit-risk: FDA

FDA presentation at AdCom





Drama, Comedy Benefit-risk: more sophisticated



* death also counted as a worsening

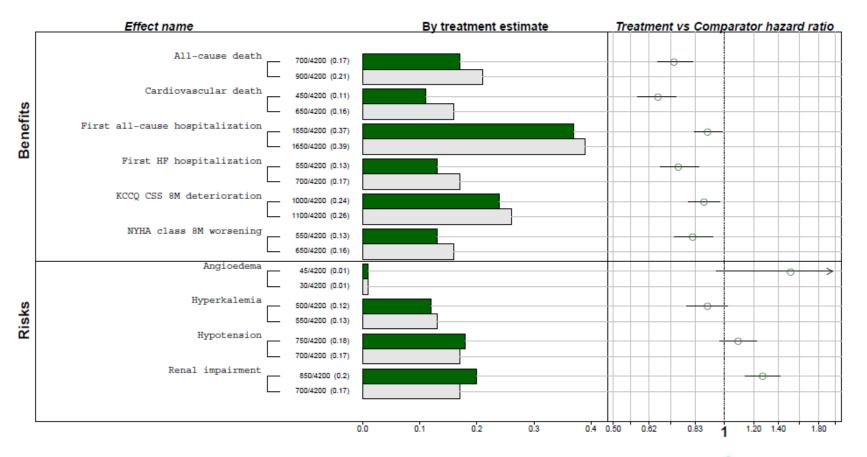
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Drama, Comedy Benefit-risk: more sophisticated (alternative version)

Confidence interval

(arrows if outside plotting range) Point estimate

(Cross if outside plotting range)



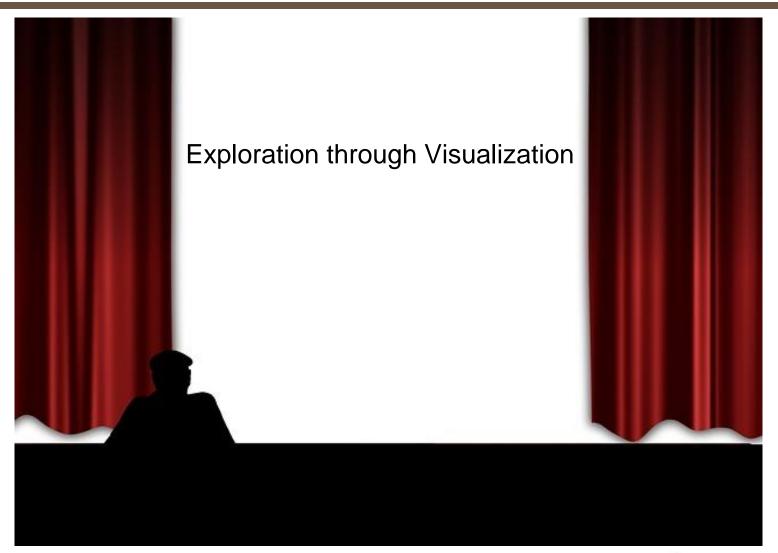


Treatments

Group A

Group B

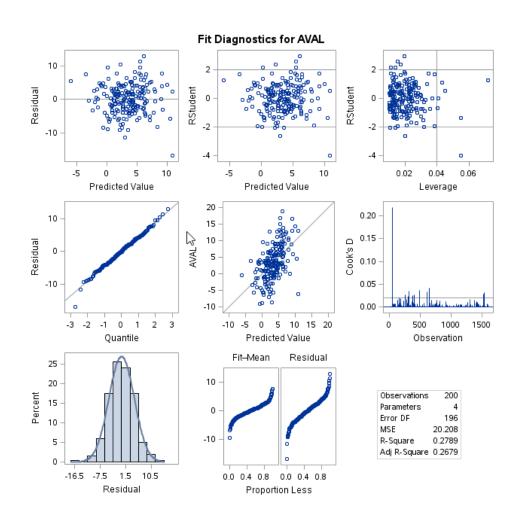
Today's program Science





Science Diagnostic plots

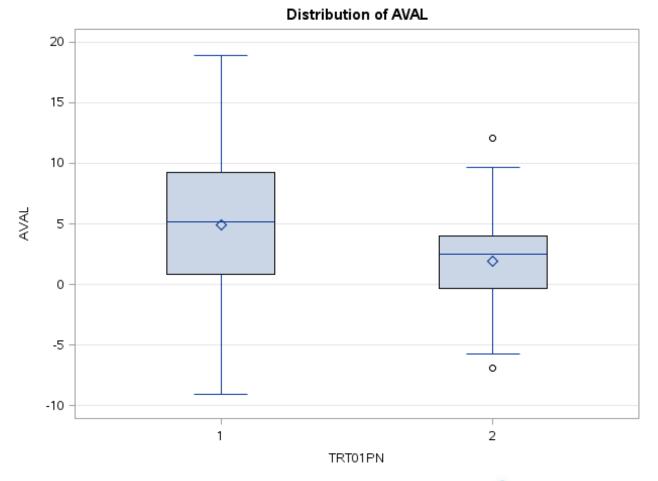
E.g., ANCOVA





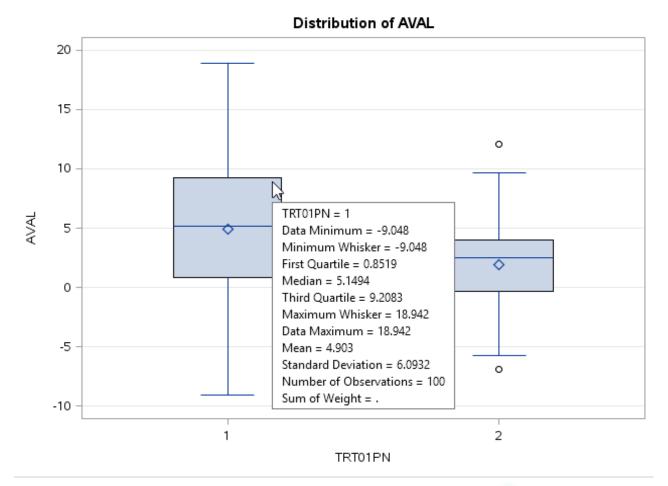
Science Diagnostic plots

E.g., ANCOVA



Science Diagnostic plots

E.g., ANCOVA



- Static
 - Quick, perhaps using "point and click" software
- Interactive
 - Provide pre-made "templates"
 - Let the user decide what to look at (and how)
 - <u>https://loeffju1.shinyapps.io/Histogram</u>
 - <u>https://loeffju1.shinyapps.io/Boxplot</u>



| | I | Instream Clinical Review System |
|--|--|--|
| Clinical Study Data Source : LSH post-conformance Spotfire Instream Release: 2.4 | | Please visit our <u>Share Poi</u> Please mail any question NOTE: Only subjects for v |
| DEMOGRAPHICS Demography ADVERSE EVENTS AE Summary AE Treemap Linked AE & MH | LABS Lab Summary Lab Results by Subject Lab Post Baseline Vs Baseline Std eDISH Plot Bivariate Analysis Lab -> AE Profile AE -> Lab Profile | CONCOMITANT MEDICATIONS Concomitant Medication CM Subcategories PATIENT PROFILE Patient Profile Patient Profile (Details) Patient Profile (Details2) |
| MEASUREMENTS <u>Vital Signs (VS) Summary</u> <u>VS Post baseline vs Baseline</u> <u>ECG Summary</u> <u>ECG</u> <u>Lung Function Test (1)</u> <u>Lung Function Test (2)</u> | MEDICAL HISTORY Medical History MS History | EFFICACY <u>PASI Scores</u> <u>Tender and swollen Joint Count</u> <u>QS (DLQI)</u> <u>ACQ</u> <u>Assessment of Rebound & IGA</u> |



| nmary) | AE (Heatmap/Tre | eemap) / | AE Statistics | MH (Summary) | Linked AE & MH | CM (Treemap) | Listing Builder | Subset Comp | arison V | S (Summary/Histogram) | | 1 | * | Y [| 3 ≡ |
|---|-------------------|--------------|-------------------|-----------------------|----------------------|-------------------|-------------------------------|-----------------|-------------------------|--|---|------------------------------------|--|-----------------------------|--------------------------------------|
| NOTE: S | ections in the tr | reemap are (| colored by the | e worst case, i.e. if | f one subject experi | enced a serious A | AE, the whole recta | ngle will be ma | irked as seri | ous. | | | | | |
| Color by: Did AE Lead to Stud N Y Size by: Unique Count of Su Hierarchy: SOC ->HLGT->HLT | | | INFECTION | IS AND INFESTATIO | INS | GASTR | DINTESTINAL DISOF | DERS | NEOPLAS UNSPECIF | SMS BENIGN, MALIGNA IED (INCL CYSTS AND | NT AND POLYPS) | S SYSTEM DISORDERS | | | |
| | | | | | | | ARDIAC DISORDERS | ; | HEPATOBILIARY DISORDERS | | GENERAL DIS AND ADMINIS SITE COND | TRATION | RATION SUBCUTANEOU | | US TISSUE |
| | | | | | | | | | PSYCHIA | ATRIC DISORDERS | RENAL AND URINARY DISORDERS | | RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | C AND TINAL |
| | | INJURY, I | RY, POISONING AND | ND PROCEDURAL COM | OMPLICATIONS | | | | | | METABOLISM AND NUTRITIC | SYS | IUNE TEM RDERS | EM (Empty) | |
| | | | | | | MUSCULOSKE | LETAL AND CONNEC DISORDERS | TIVE TISSUE | VASOU | ILAR DISORDERS | DISORDERS | BLOOI AND LYMPHA C SYST | | BYRINT H | PREGNAN CY, PUERPERI UM AND |
| | | | | | | | | | VASCO | DAT DISURDERS | EYE DISORDERS | CONGE TAL, FAMILIA AND GE | | IDOCRI NE SORDE RS | REPRODU CTIVE SYSTEM AND BR |

Science Visual data review

Use the heirarchy slided on the left to adjust the visualization. Rectangles are sized by the # of unique subjects reporting that event.

NOTE: Sections in the treemap are colored by the worst case, i.e. if one subject experienced a serious AE, the whole rectangle will be marked as serious.

| Color by: | | | | | | | | |
|--|--|--|--|--|------------------------------|--|----------------|--|
| Did AE Lead to Stud N Y Size by: Unique Count of Su Hierarchy: SOC ->HLGT->HLT | INFECTIONS AND INFESTATIONS | GASTROINTESTINAL DISORDERS | NEOPLASMS BENIGN, MALIGNA UNSPECIFIED (INCL CYSTS AND | | TEM DISORDE | EM DISORDERS | | |
| | | CARDIAC DISORDERS | HEPATOBILIARY DISORDERS | GENERAL DISO AND ADMINISTE SITE CONDIT | RATION SUI | SKIN AND BCUTANEOUS DISORDER | TISSUE | |
| | | | PSYCHIATRIC DISORDERS | RENAL AND UR DISORDEF | | RESPIRATOR THORACIC A MEDIASTINA DISORDER | AND AL | |
| | INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | METABOLISM AND NUTRITION | IMMUNE SYSTEM DISORDEF | (Emp | pty) | |
| | | MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | VASCULAR DISORDERS | DISORDERS | AND LYMPHATI | EAR AND PR LABYRINT H PU DISORD UN | CY, JERPERI | |
| | | | VASUULAR DISORDERS | EYE DISORDERS | CONGENI TAL, | ENDOCRI RE NE (DISORDE S) | | |

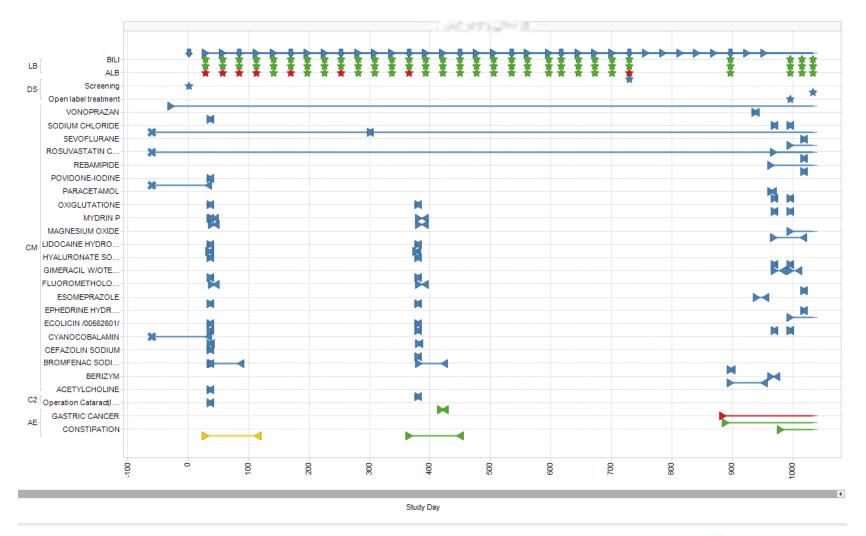


Science Visual data review

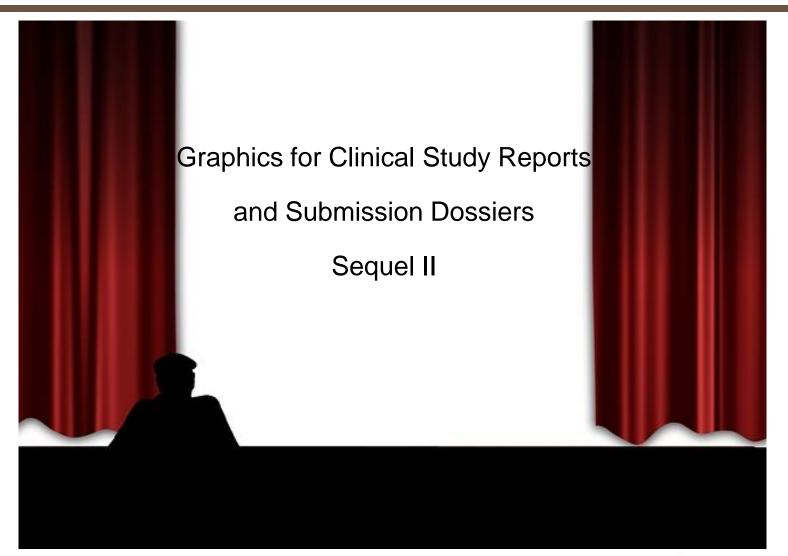
Use the heirarchy slided on the left to adjust the visualization. Rectangles are sized by the # of unique subjects reporting that event.

| by: | INFECTIONS AND INFECT | ATIONS | | 0.40704 | | | | AE Lead to Study | | 17: Y | | | | | | | | | | | | | | |
|----------------------------------|--------------------------------|---|----------------|--------------------------------------|---------------------|--|---|-------------------|--|--|---|---|--|--|--|--|---|----------------------------|--|-----------------|-----------|------------------------------|--------|-------------------------|
| E Lead to Stud | INFECTIONS AND INFEST | GASTRO | DINTESTINAL DI | SORDERS | S Unio | que Count of Subje | ects: 3 | | | | | | | | | | | | | | | | | |
| y: ue Count of Su chy: | | INFECTIO | | BACTERIAL INFECTIOUS DISORDERS | | INFECTIOUS | | INFECTIOUS | | DIVERTICULAR DISORDERS | GASTROINTE AL ULCERATI AND PERFORATI | STIN HEF ION AB ON | DOMINAL RNIAS AND OTHER DOMINAL WALL NDITIONS | GASTROINTE STINAL NEOPLASMS MALIGNANT AND UNSPECIFIED | HEPATOB NE | TIVE NEOPLASM S MALE MALIGNANT AND UNSP ERV REPR US ODUC | | ROLOGICA RDERS NE | DIS AL PARK C CRAN L NERV DISOR | E HEADA CHES | | | | |
| | INFECTIONS - PATHOGEN UNSPECI | INFECTIONS - PATHOGEN UNSPECIFIED | | | | GASTROINTESTI NAL MOTILITY AND | BENIGN NEOPLASMS GASTROINTES NAL | STI EAS | R TINAL CONDI TION | MALIGNANT | MS MAL MISCELL NE ANEOUS AND SITE | STE TIVE M NEOPL :O ASM SKIN :OPLASMS | SYSTE | AL NERVO M VASCUL SORDERS | AR (INCL SUBT | R SPINAL CORD | | | | | | | | |
| | | 1 | | | VIRAL INFECTIOUS | DEFAECATION CONDITIONS IRAL CTIOUS | | GINTE GE TINAL | R GASTR S OINTES L TINAL M VASCU LAR | PSYCHIATRIC | PERSO ALITY DISORE | N IE GALL | | | GENERAL DI | | | | | | | | | |
| | | | DISORDERS | C/ | ARDIAC DISORD | ERS | | DISORDERS AI | | DIS | ORDERS | S | DISORDE | | | | | | | | | | | |
| | | | FUNGAL | | | | | | DISTURBANCE | S SCHIZO HRENI/ AND OTHER SUICID/ | | | DUCI - | BODY TEMPE E | E | | | | | | | | | |
| | INJURY, POISONING AND PROCEDUR | DISORDERS RAL COMPLICATIONS | | IRAL COMPLICATIONS | | RAL COMPLICATIONS | | | | | | | | CORONARY DISORD | | | IDIAC THMIAS | PSYCHIATRIC DISORDERS N | | - | | RDER | CON | JE DISOR DERS NEC |
| | | | | | | | | | | | | DISORD | ERS | ARREIT | THMIAS | VASCULAR DI | SORDERS | RENAL AND U | JRIN | METABOLI | ISM AN E | YE DISO | | |
| | | INJURIES PROCEDUR RELATED INJU AND COMPLICATIC NEC | | | | | | | VASCULAR HYPERTENSIVE | DECREASE D AND NONSPE EMBOLISM AND | NEPHRO PATHIES URETHRAL | | GLUC METAB DISORDEI DIABE MELLI | OLISM E RS (INCL ETES | NTERIOR YE STRU OCULAR TRUCTU | | | | | | | | | |
| | | | ES NEC | MUSCULOSKELET | AL AND CONNE | CTIVE TIS | SUE DIS | DISORDERS | THROMB | DISORDERS (EXCL CAL | UROL | IMMUNE S | BLOOD. | CONG | | | | | | | | | | |
| | BONE AND JOINT INJURIES | | | | | CON | CULOSKEL AL AND INECTIVE ISSUE | | VENOUS VARICES | URINARY TRACT SIGNS AN | ITHIA SES | ALLERGIO | C PLATELE | CARDIA C AND VASC | | | | | | | | | | |
| | | | | | | | | | | | | | | | JOINT DI | DEF | ORMITIES (INCL RVERTEBR ISC DISO | SKIN AND SUBCUTANEOU | | RESPIRATOR | PLE UR | IMMUNE DISORDE (Empty) | HEARIN | ENDO ENDOCR |
| | | | | | | | E MUSC | EPIDERMAL AN | | RESPIRATOR Y DISORDER | R AL | | | DISOR REPRO | | | | | | | | | | |
| | | | USE | | | DISO | R ULOSK S ELETA | CONDIT | IONS | NEC | OR DE RS | (Empty) | ABORTI ONS | VULVOV AGINAL DISOR | | | | | | | | | | |

Science Visual data review



Today's program Science Fiction





Science fiction The eCSR and eDossier

- Recent Novartis submission:
 - US Electronic dossier was about 200 GB of data

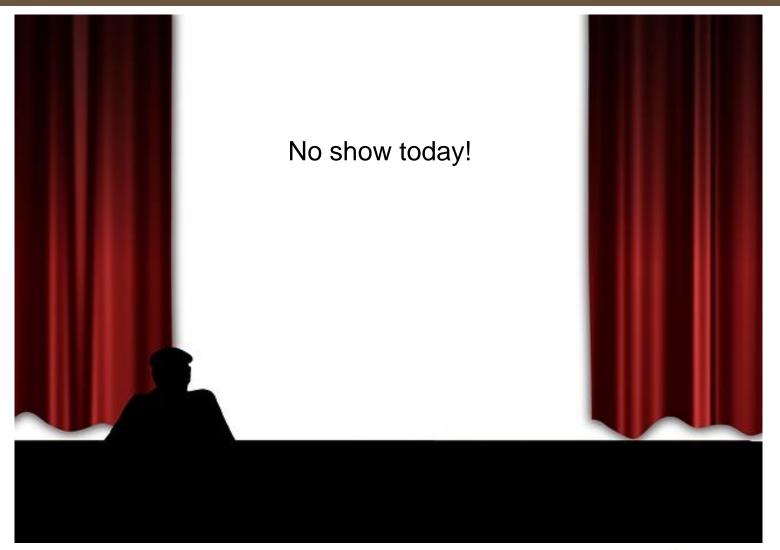




Science fiction A vision: the CSR of the future

- What will the eCSR and eDossier in the (near) future look like?
- Minimum: hyperlinked PDF
- Vision: hyperlinked, dynamic web format
 - The graphical CSR?
- Interactive Report Example

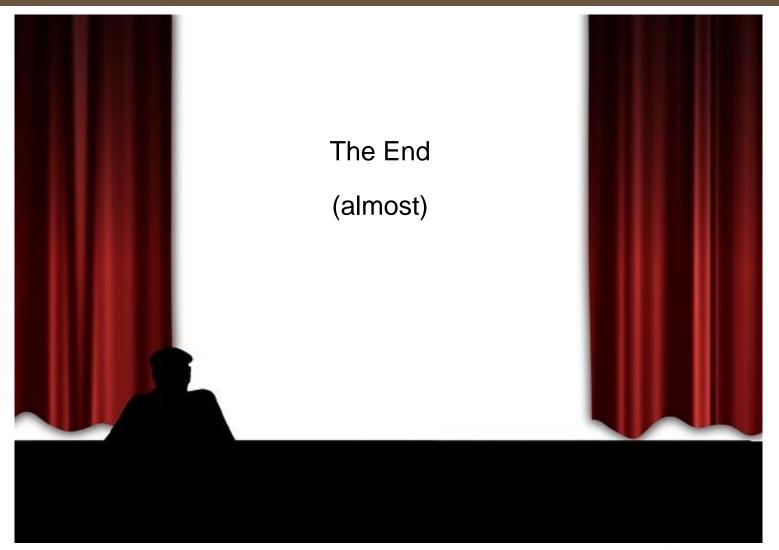
Today's program Advertisement





- But what you might have seen:
- Graphics for commercial material, sometimes publications
 - Paper (brochure), internet or sceenshow, TV
 - Fancy infographics
 - Static, animated, interactive
 - Video?

Today's program



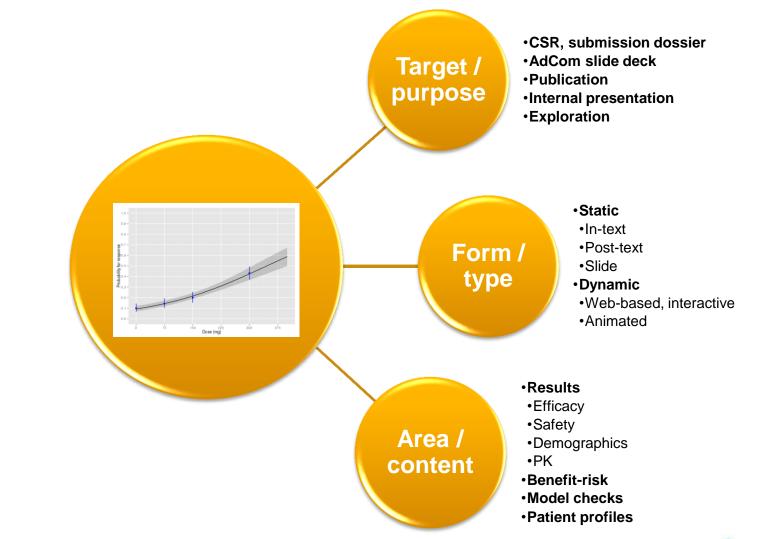


Classification



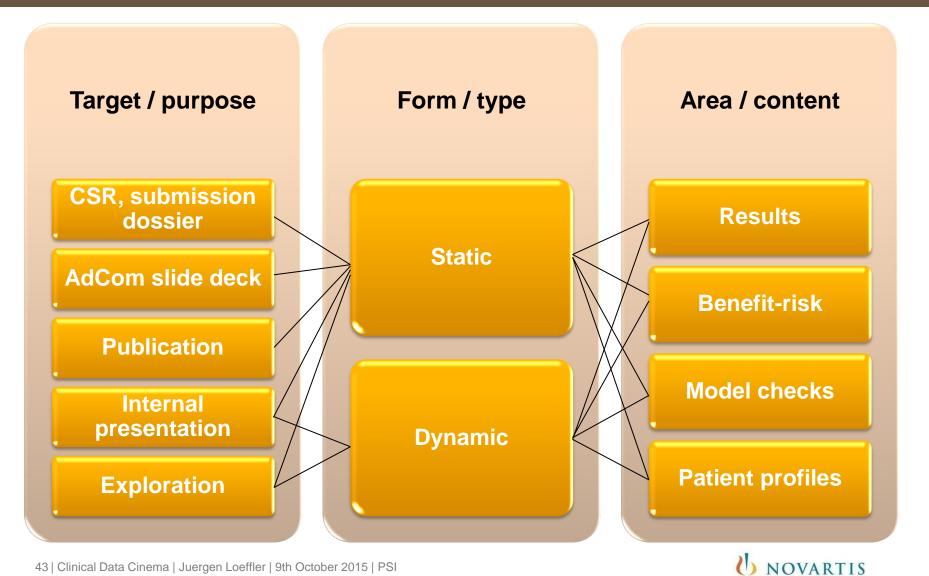


Classification



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Classification



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Structured approach

- How do we best design an individual graph (be it static or dynamic)?
- Follow graphical principles
- A structured approach has recently been published:
 - Duke SP, Bancken F, Crowe B, Soukup M, Botsis T, Forshee R. (2015) Seeing is believing: Good graphic design principles for medical research. Statist. Med., 34: 3040-3059.
 - <u>http://www.ctspedia.org/do/view/CTSpedia/SelectRightGraph</u>



Summary

- Data visualization is used in many areas of clinical development
- The type of visualization depends on the target and the content (but also the audience)
- Most importantly, visualizations can be static or dynamic
- Restrictions and limitations mainly imposed by target
- The future will hopefully be more dynamic
- By the way:
 - All data shown are dummy data (unless noted otherwise)



Acknowledgements

- David Carr
 - For programming the BR plot alternative 1
- Oumaima Fdil, Richard Nixon & Dieter Haering
 - For programming the shiny app creating BR plot alternative 2
- Fabrice Bancken, David Carr & Baldur Magnusson
 - For various discussions and ideas
- Achim Guettner
 - For the photographs of the "submission package"

