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WHAT MEDICAL REVIEWERS CAN DO WITH STANDARDIZED DATA AND METADATA RECEIVED IN MODULE 5

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Disclaimer: *This presentation reflects the views of the author and do not necessarily represent FDA's views or policies.*

Clinical Review Goals

"Purpose of medical review
is not
to replicate all analyses
but independently assess that
-the clinical protocol was implemented as planned
-the data needed was collected and documented
-the analyses were appropriate and
-the results provide information on the drug's efficacy and safety"

BENEFIT > RISK

Substantial evidence purported under labeled conditions of use – KH Amendments 1962

ALL tests reasonably applicable to show drug to be safe under proposed labeling – FDCA 1938

LABEL

adequate directions for use

Content and Format of an Application (21 CFR 314.50), eCTD

Module 5

(1) human pharmacokinetics
(2) microbiology
(3) clinical data
(4) statistical section
(7) pediatric use
(8) CRF and CRT

http://www.fda.gov/cder/regulatory/gov

Clinical Section

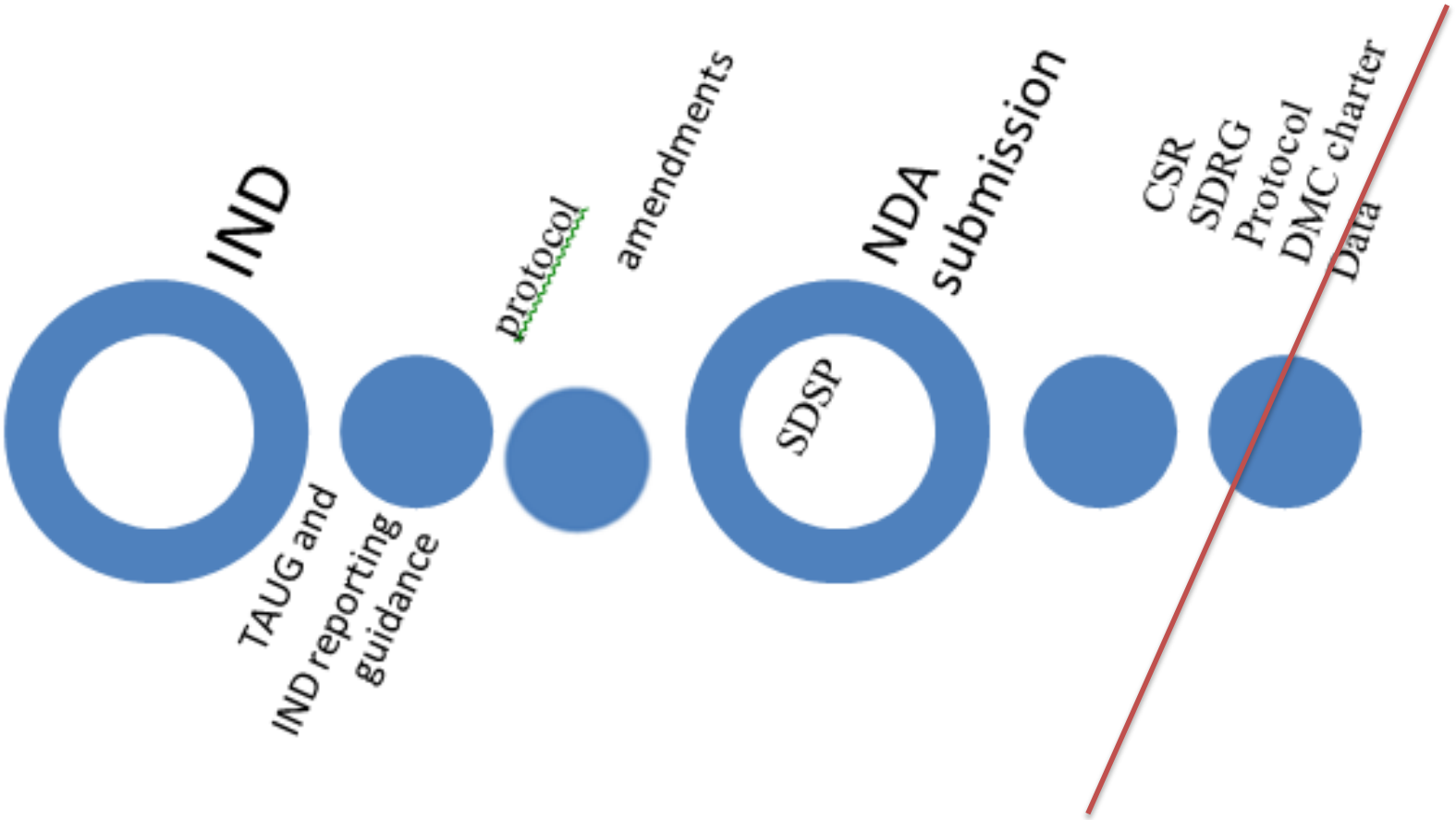
1. STUDY REPORTS – description of every study & the statistical analys used to evaluate it
2. Non NDA information relevant to evaluation of safety and effectiveness – from any source evidence (other investigations, commercial marketing experience, scientific literature, unpublished papers)
3. Integrated summaries

   Efficacy – to assess substantial evidence and support dosage modifications for subgroups

   Summary and updates of safety – all available information (animal data, summaries, abuse potential, subgroups based on biology – rena hepatic, disease severity, 4 month updates)
4. Benefit/Risk assessment
5. Documentation of Human subject protection
6. Trial Audit reports or monitored studies and a list of such studies

21 CFR 314.50, ICH E3

Putting data in perspective



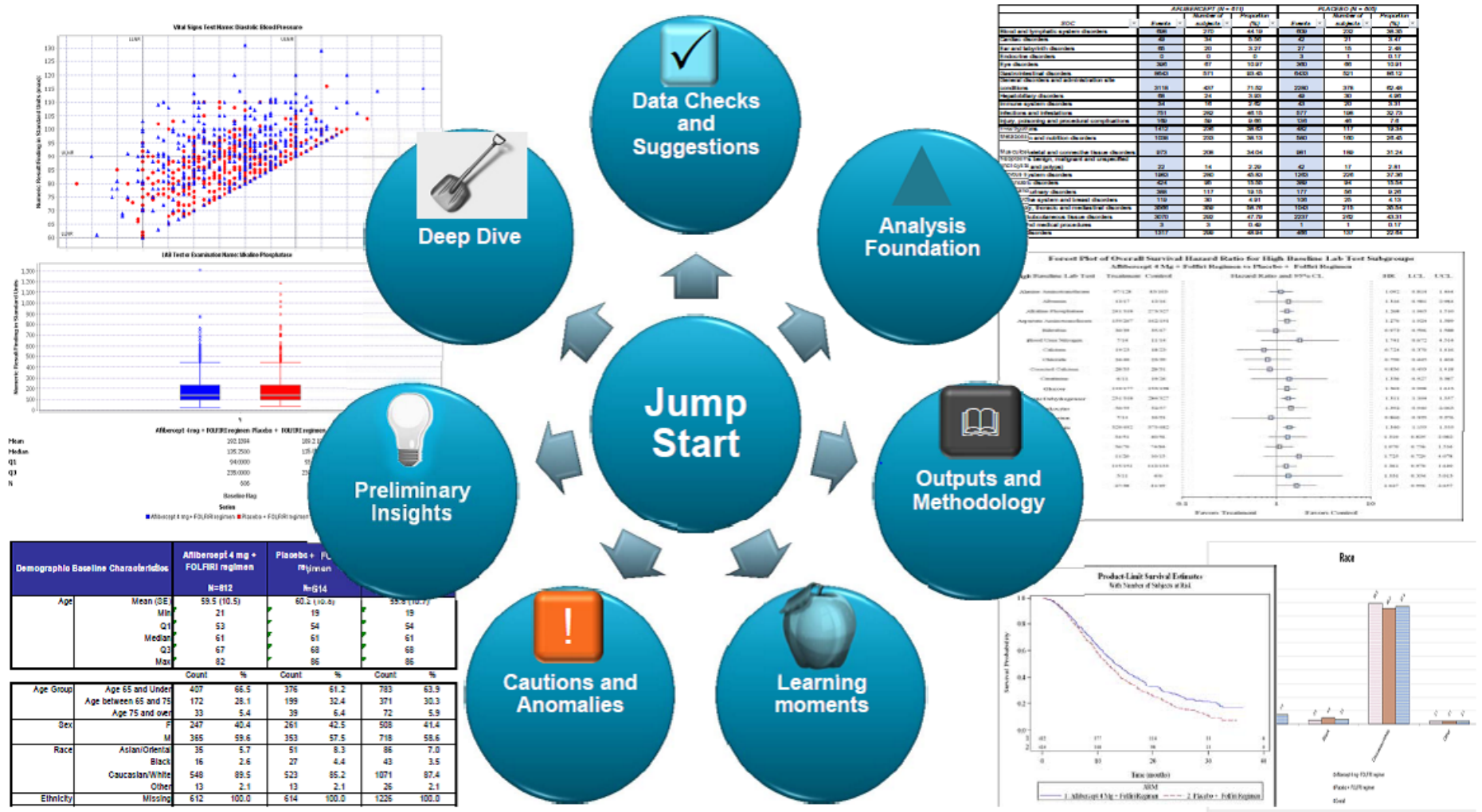
Clinical Filing Checklist (Day 45) :

- Are datasets available for all pivotal trials?
- Are they reliable, transparent, traceable to the CRF?
- Do the datasets reflect the Sponsor's report of dosage, treatment arms, adequate exposure of doses and duration?
- Are the datasets in a format to allow review of patient data? Are endpoints, adverse events evaluable?
- Is the raw data available to derive the composite endpoints? Do the data allow replication of findings?

Source Data Validation

- assess consistency of the data provided (e.g., compare information in CRF, CRT, and narrative summaries)
- for important AEs, assess narrative description, and may ask to see CRF, hospital records and laboratory, radiology, or pathology results

Standards Facilitate the Review Process



https://www.youtube.com/watch?v=UhJaBmmPNxY

M5

Submission Datasets/Documents and Integrated Studies

- The below table shows if a document was provided for the integrated studies and what information about integration methods and analyses it typically contains:

Document	Description	Provided for Integrated Studies (Yes/No)
Summary of Clinical Safety (SCS)	A summary of data relevant to safety in the intended patient population while integrating the results of individual clinical study reports as well as other relevant reports.	Yes
Integrated Summary of Safety (ISS)	The ISS will be more extensive than the SCS and should include not only text and incorporated tables and figures, but additional appendices of tables, figures, and datasets as well.	No
Statistical Analysis Plan (SAP)	The SAP is a technical document which describes the planned statistical analysis of the integrated studies as outlined in the protocol.	No[1]
Define.xml	This file describes the structure and contents of the data collected during the clinical trial process. It may also come in PDF format.	Yes
Analysis Data Reviewers Guide (ADRG)	The ADRG, or SDRG when submitted with tabulation data, provides additional context for datasets and terminology that benefit from additional explanation beyond the define.xml file.	Yes

[1] SAPs were provided for the individual studies.

Summary

Standards / Dictionaries

- SDTM-IG 3.1.2
- SDTM-CT 2016-12-16
- MedDRA 14.0

Subjects

- 763 - Subjects
- 0 - Screen Failures (0.0%)
- 0 - Not Assigned (0.0%)
- 0 - Not Treated (0.0%)
- 0 - Unplanned Treatment (0.0%)

Datasets

- 29 - Total Datasets
- 1 - Custom Datasets
- 9 - Suppqual Datasets

Reports

- Deaths
  - Death Summary
  - Death Details
  - Death Reconciliation
- Adverse Events
  - Adverse Events Coding Quality
- Disposition
  - Disposition Coding Quality
- Supplemental Info
  - Supplemental Contents
- Laboratory
  - Upper Limit Normal Summary

Findings

Adverse Events

- 3,144 (100.0%) of adverse events are missing treatment emergent flag in SUPPAE
- 1 (< 0.1%) of adverse events have neither severity or toxicity grade populated
- 2 (< 0.1%) of events are missing end time-point
- 8 (0.3%) of values for required variable AEDECOD are missing
- 4 (6.0%) of serious adverse events are missing seriousness criteria
- 324 (10.3%) of adverse events have started after the last disposition date
- 48 (1.5%) of adverse events are potential duplicates

Disposition

- 82 (9.6%) of disposition events are missing Start Date/Time of Disposition Event (DSSTDTC) and Study

Supplemental Info

- No significant findings

Terminology

- 1,774 (17.6%) of Body System or Organ Class (MHBODSYS) values not found in MedDRA dictionary

Laboratory

- 9,242 (4.7%) of observations are missing Reference Range Upper Limit in Standard Units (LBSTNRHI)
- 4,651 (2.1%) of laboratory test results are potential duplicates
- 4,638 (2.5%) of Standard Units (LBSTRESU) are missing when Standard Results (LBSTRESC) are prov
- 4,702 (2.6%) of observations use inconsistent values for Standard Units (LBSTRESU)

Vital Signs

- 8 (< 0.1%) of vital sign results are potential duplicates

Demographics

- 61 (8.0%) of randomized subjects are missing Subject Reference End Date/Time (RFENDTC)
- 61 (8.0%) of randomized subjects are missing Subject Reference Start Date/Time (RFSTDTC)
- 6 (0.8%) of RACE values not found in CDISC codelist

Exposure

- 106 (2.4%) of exposure records are missing timing information

Other

- EPOCH variable was not provided
- The Subject Elements (SE) domain is missing
- 343 (8.2%) of ECG test results are potential duplicates

Standardized data and metadata facilitates subject reconciliation

Submission Datasets/Documents and Integrated Studies

- The number of subjects in the ISS datasets are consistent with the individual studies' tabulation datasets:

Study	Total Subjects in Indiv. Study DM	Total Subjects in ISS ADSL	Notes
Study 4	15	14	The ISS datasets do not include the one screen failure subject.
Study 1 Study 2	126	125	The ISS datasets do not include the one randomized but not treated subject from study Study 1 The 113 subjects that participated in the extension are not double counted.

- The number of subjects in Study 2 analysis datasets are consistent with the individual studies' tabulation datasets:

Study	Total Subjects in Indiv. Study DM	Total Subjects in 302 ADSL	Notes
Study 1 Study 2	126	125	St 2 analysis datasets do not include the one randomized but not treated subject from study Study 1 The 113 subjects that participated in the extension are not double counted.

Standard data help characterize the study population – who was excluded, who was enrolled, randomized, treated, analysed?

SCREEN FAILURE DATA AND SUBGROUP REPRESENTATION IN DIABETES CLINICAL TRIALS

Szarfman, A[1], Tesfaldet, B[2], Patel, T[2], Pucino, F[3], Taylor, A[4], Matto, K[4], Li, J[1], Rosario L[2], Navarro E[2]

1 FDA, Center for Drug Evaluation and Research, Office of Translational Sciences , 2 FDA, Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Computational Science,
3 FDA, Center for Drug Evaluation and Research, Office of New Drugs, Division of Metabolism and Endocrine Products, 4 IBM, Strategy and Analytics

EXCLUSION:

Renal and electrolyte criteria were a common reason for exclusion of Asian subjects. Whereas renal, hepatic, CK elevations and anemia were common causes of screen failures in blacks. In addition CK elevations and anemia were disproportionately more frequent in Blacks compared to the other subgroups. Interestingly, renal criteria was the most common cause for exclusion in the rest of the racial subgroups.

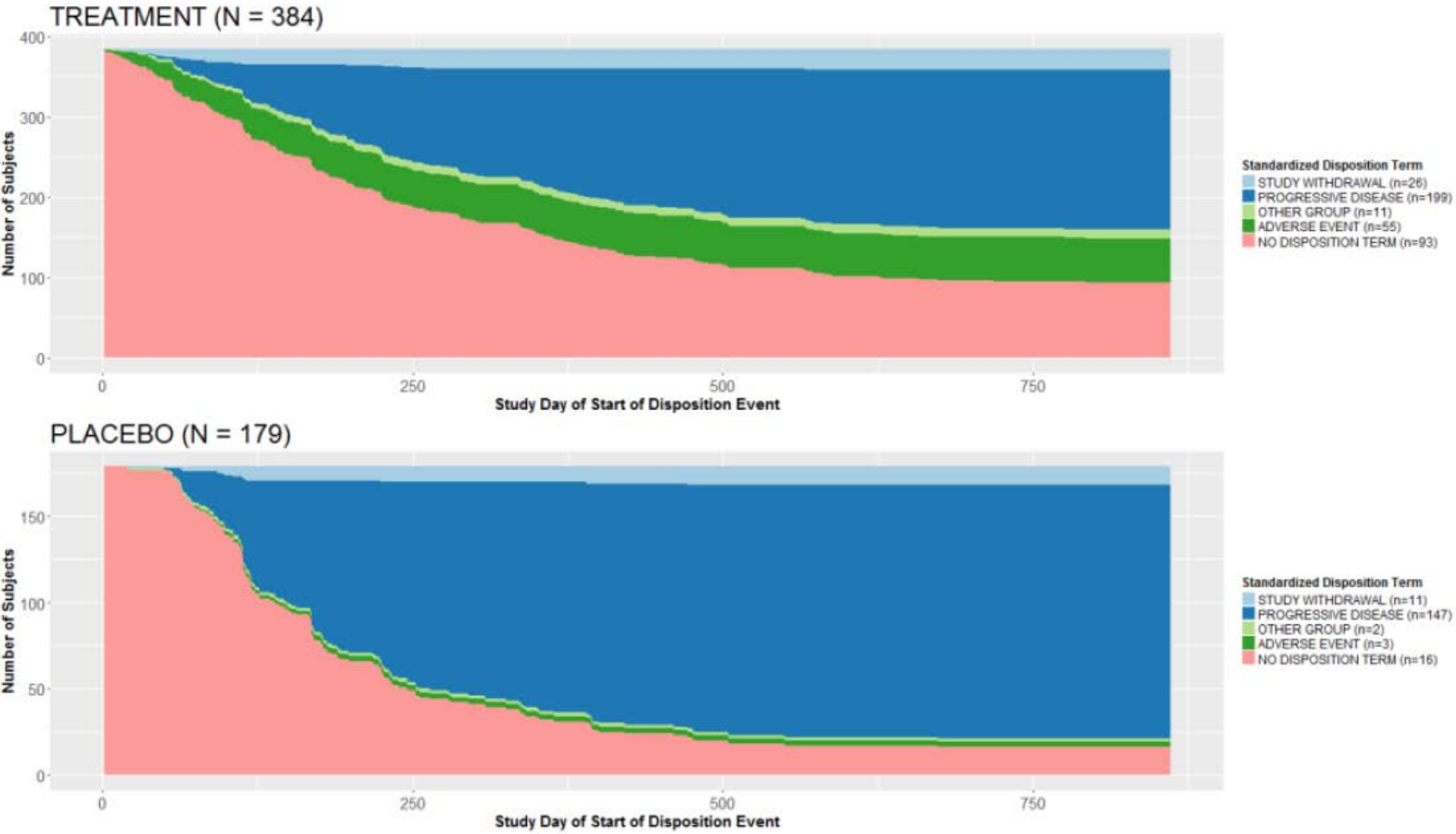
Standard data enables data trace across various domains

- Date of End of Participation (RFPENDTC) in the Demographics (DM) domain was not implemented according to SDTM guidance. Below is the definition for RFPENDTC from the SDTM Implementation Guide and an example of a failure:

Date of End of Participation (RFPENDTC) - Date when subject ended participation or follow-up in a trial… Should correspond to the last known date of contact.

DOMAIN	USUBJID	VSTESTCD	VSDTC	RFPENDTC (DM)
VS	Study4 -001	DIABP	2015-11-24	2015-09-16

Vital Signs Date of Collection (VSDTC) is 2+ months after Date of End of Participation (RFPENDTC)


TREATMENT (N = 384)
Number of Subjects
400
300
200
100
0
0
250
500
750
Study Day of Start of Disposition Event
Standardized Disposition Term
STUDY WITHDRAWAL (n=26)
PROGRESSIVE DISEASE (n=199)
OTHER GROUP (n=11)
ADVERSE EVENT (n=55)
NO DISPOSITION TERM (n=93)
PLACEBO (N = 179)
Number of Subjects
150
100
50
0
0
250
500
750
Study Day of Start of Disposition Event
Standardized Disposition Term
STUDY WITHDRAWAL (n=11)
PROGRESSIVE DISEASE (n=147)
OTHER GROUP (n=2)
ADVERSE EVENT (n=3)
NO DISPOSITION TERM (n=16)

Event Data

Population – quantitative and qualitative comparison by treatment arm, across subgroups

- death
- serious AE (SAE)
- AE leading to discontinuation (AEDC)
- discontinued patients lost to follow-up (LTFU)
- Aes of special interest, grouped by system, special tests

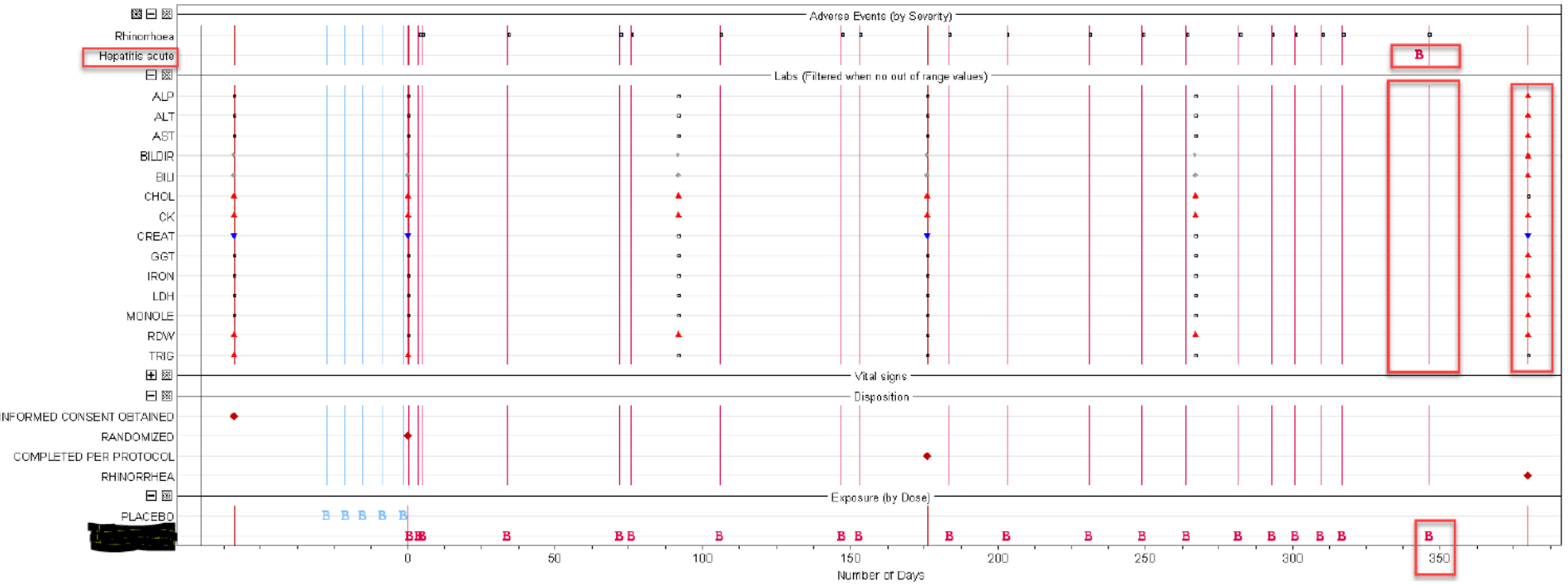
Individual – detailed assessment of individual events

- Assess causality, drug interaction
- Suspected adverse reaction (temporality, re-occurrence)
- Determine whether reported terms refer to the same event (do different codes really refer to the same event)
- Assess in context of other clinical procedures or events (blood transfusion, surgical procedure, etc)

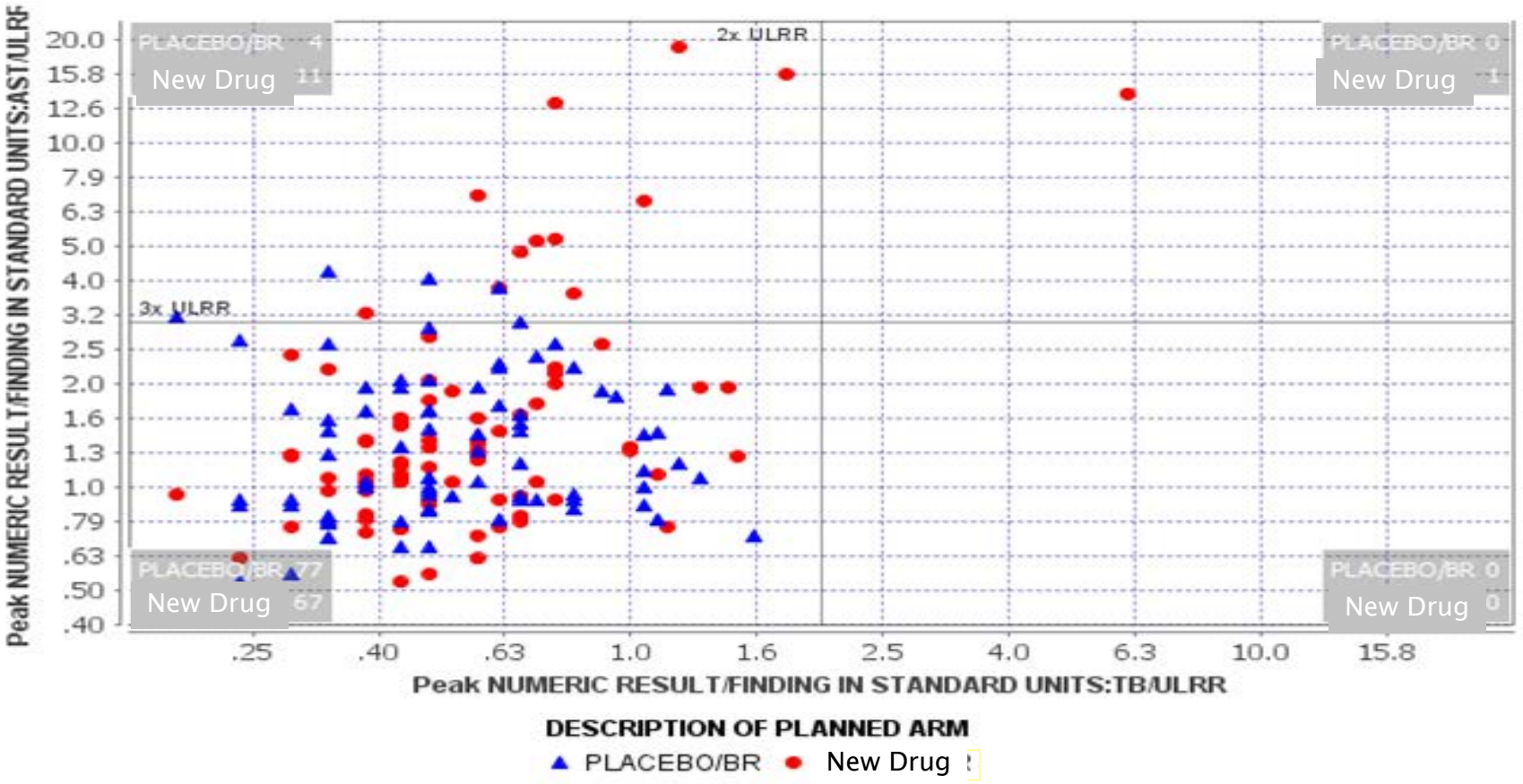
Test Data

- Laboratory: distribution of baseline and change on treatment, central tendency and dispersal, outliers, cumulative rates, time to event, resolution, preclinical/class effects
- Special assessments and other analyses: hepatic, QT, immunogenicity, carcinogenicity, reprotox, effect on growth, population differences, drug-drug interaction, drug-disease interaction

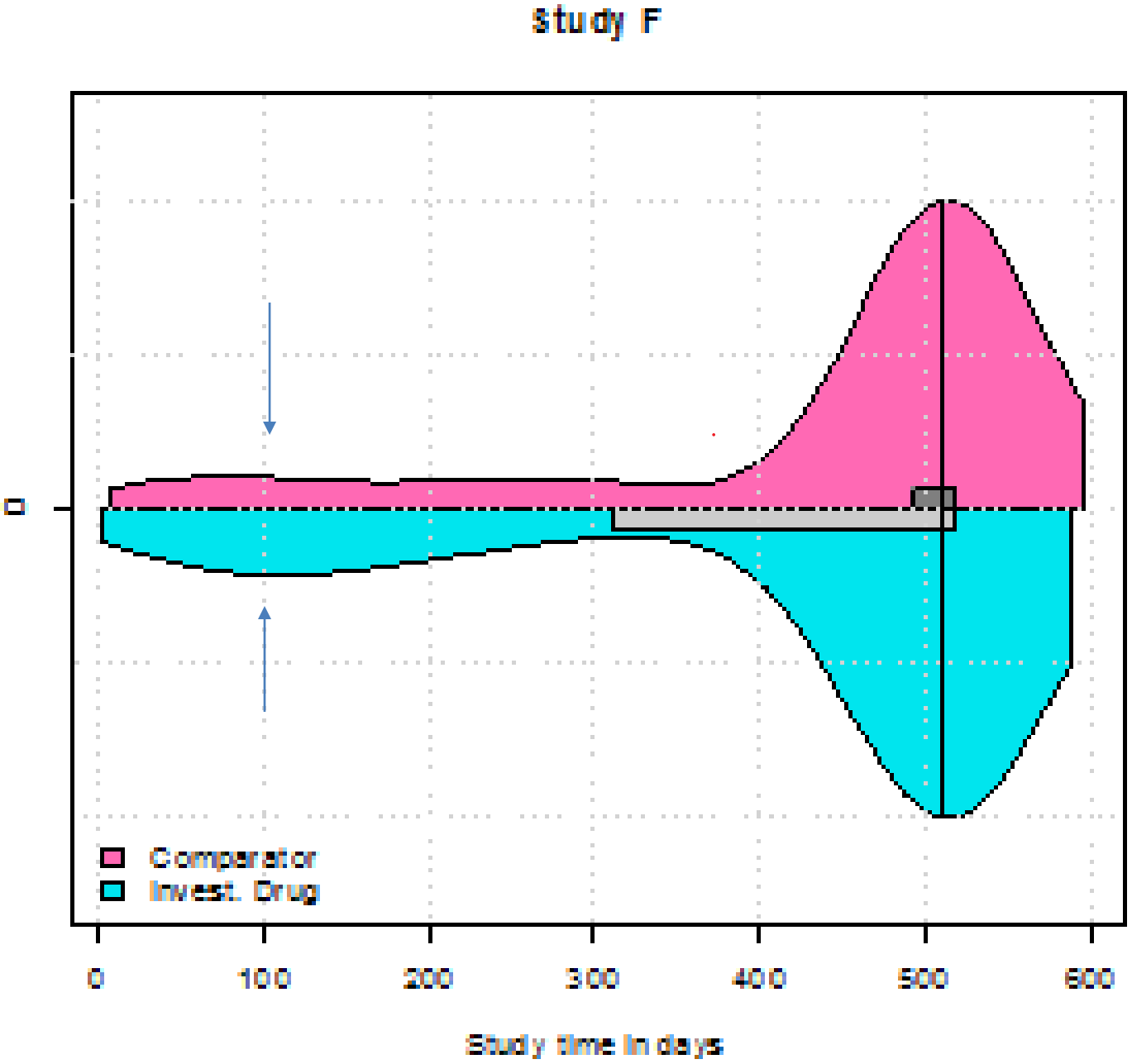
Standard data leads to standard AE definition – integration of clinical AND laboratory data

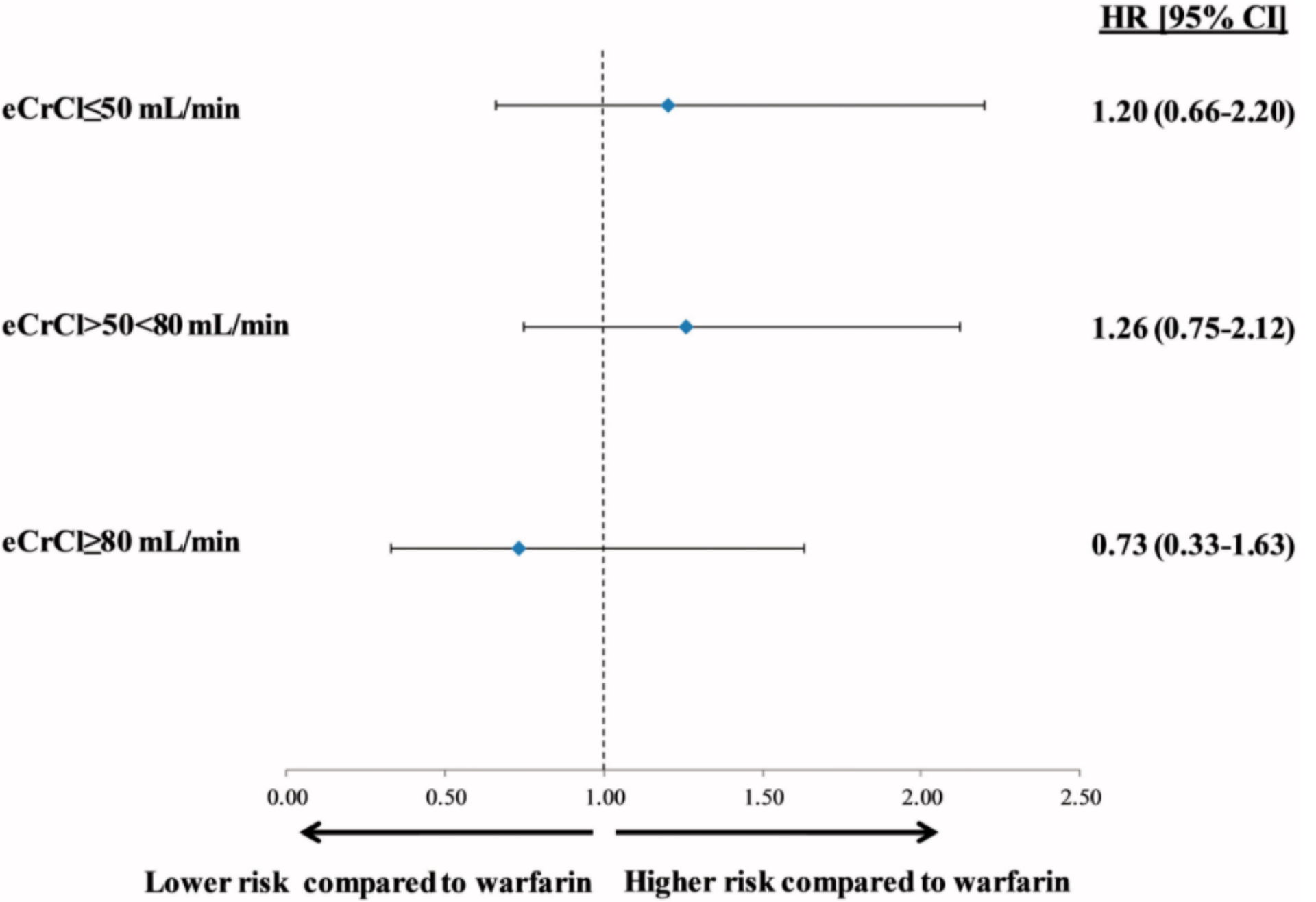


Evaluation for Hepatotoxicity – Hy's Law

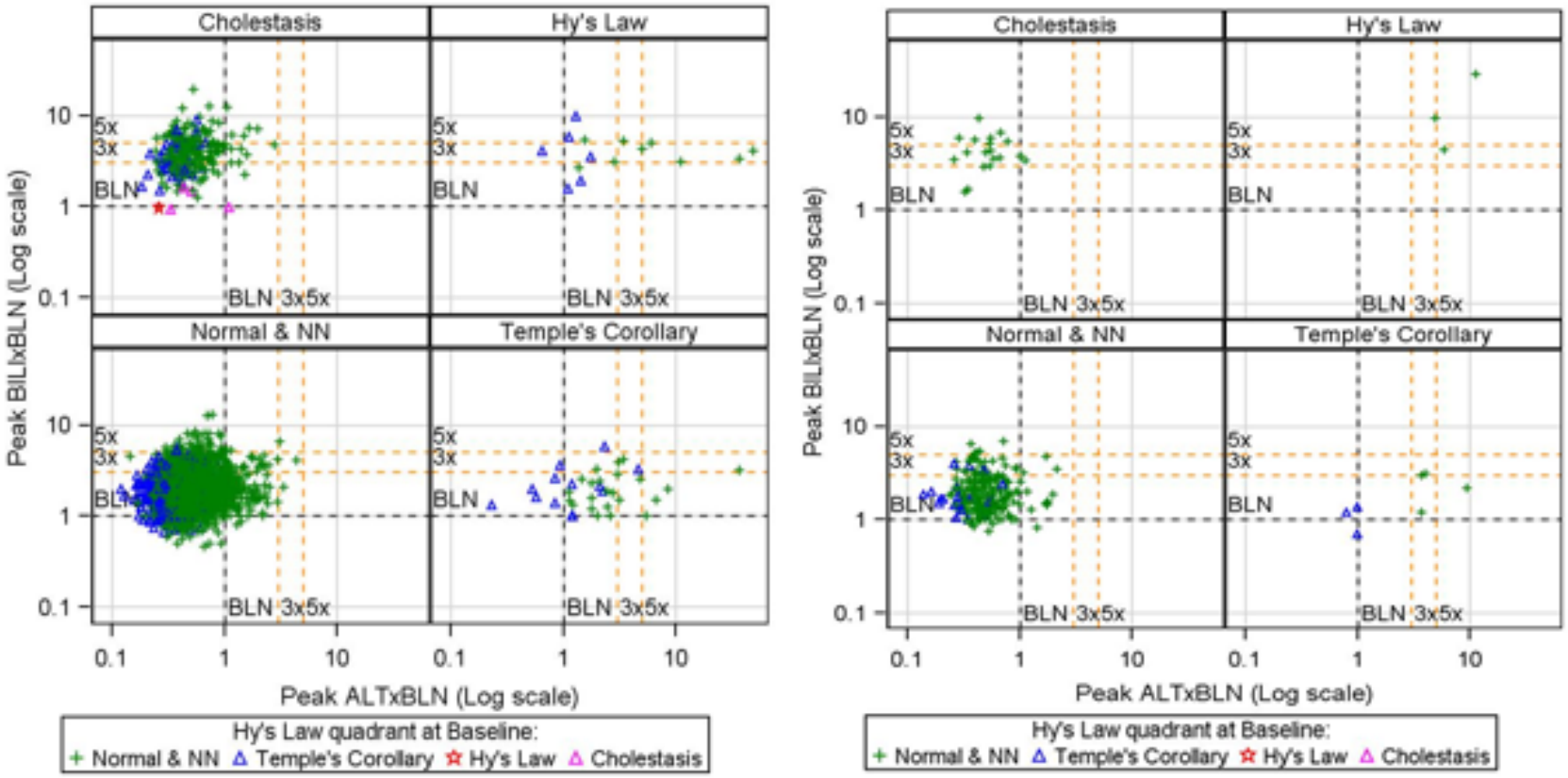


208 Stage ii : T.BILI 2xULN vs AST 3xULN Upper Limit Normal Range Plot

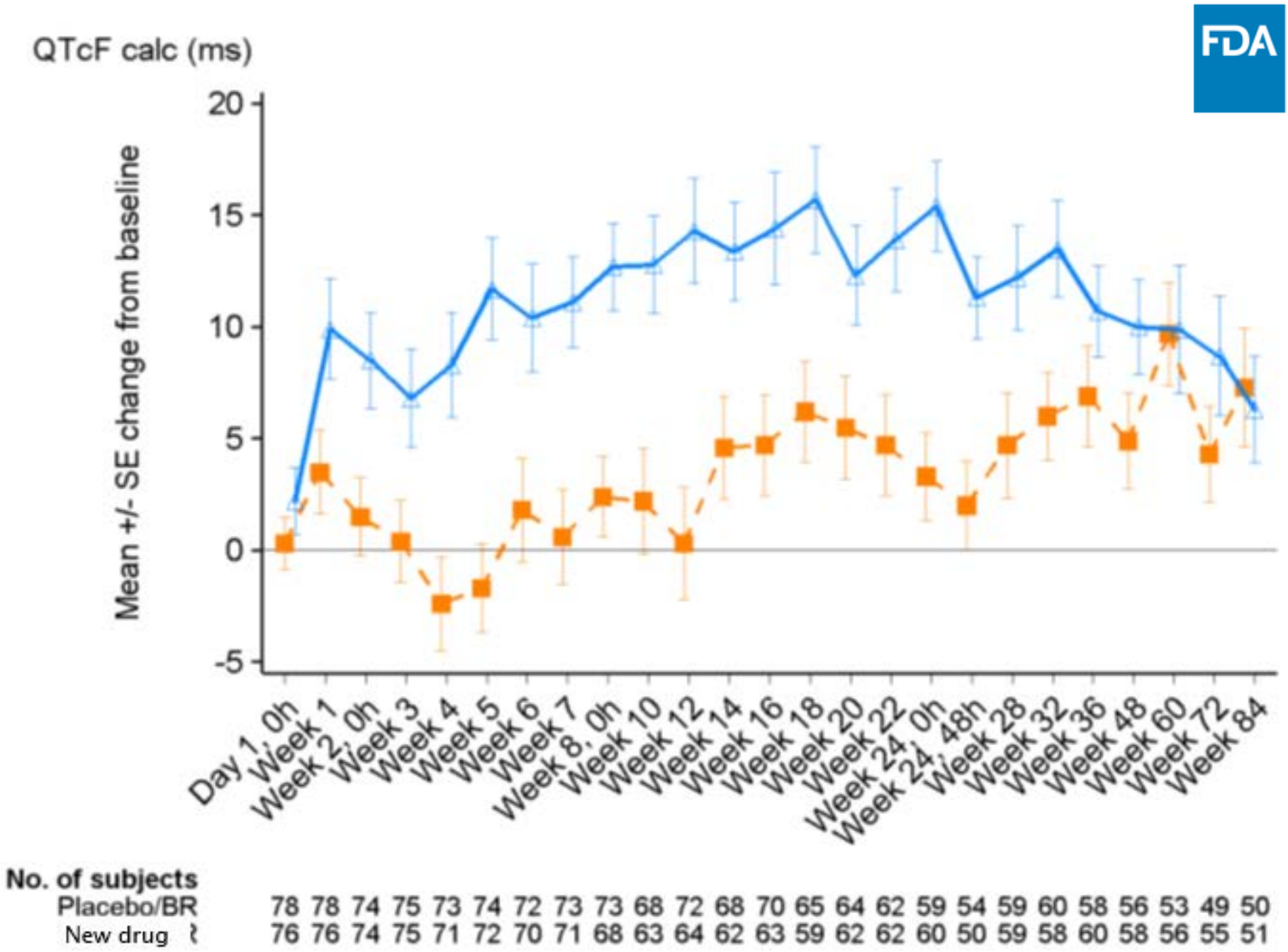

Study F
0
Comparator
Invest. Drug
0
100
200
300
400
500
600
Study time in days

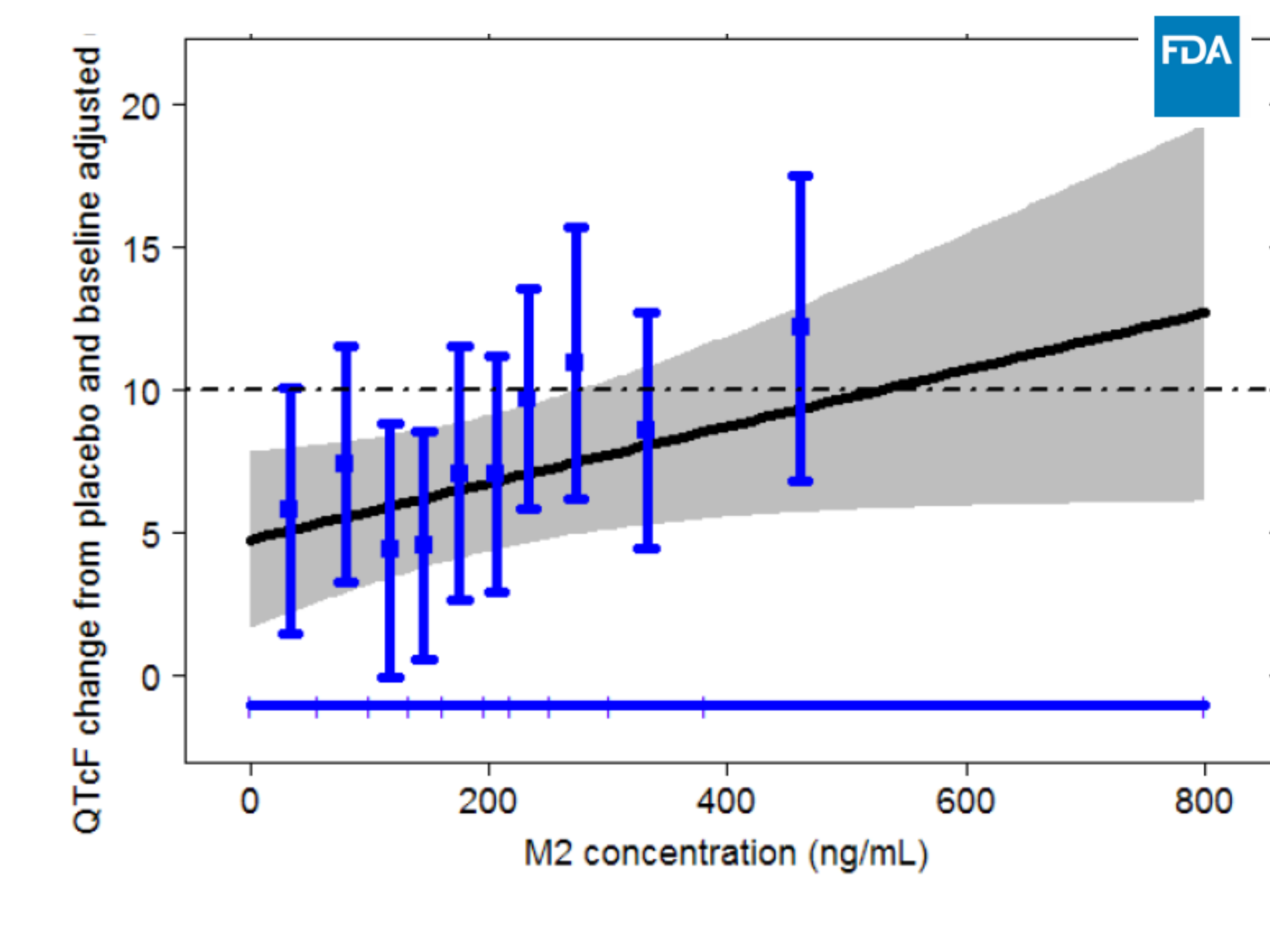

HR [95% CI]
eCrCl≤50 mL/min
1.20 (0.66-2.20)
eCrCl>50<80 mL/min
1.26 (0.75-2.12)
eCrCl≥80 mL/min
0.73 (0.33-1.63)
0.00
0.50
1.00
1.50
2.00
2.50
Lower risk compared to warfarin
Higher risk compared to warfarin

Standard data helps reviewers develop new safety visualizations



Legend: ULN = upper limit of normal, BLN = baseline liver test result, ALT = alanine aminotransferase, BILI = total bilirubin


QTcF calc (ms)
FDA
Mean +/- SE change from baseline
20
15
10
5
0
-5
Day 1, 0h
Week 1
Week 2, 0h
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8, 0h
Week 10
Week 12
Week 14
Week 16
Week 18
Week 20
Week 22
Week 24, 0h
Week 24, 48h
Week 28
Week 32
Week 36
Week 48
Week 60
Week 72
Week 84
No. of subjects
Placebo/BR 78 78 74 75 73 74 72 73 73 68 72 68 70 65 64 62 59 54 59 60 58 56 53 49 50
New drug 76 76 74 75 71 72 70 71 68 63 64 62 63 59 62 62 60 50 59 58 60 58 56 55 51


FDA
QTcF change from placebo and baseline adjusted
20
15
10
5
0
0
200
400
600
800
M2 concentration (ng/mL)

St d
to n

Enter the number of age groups:

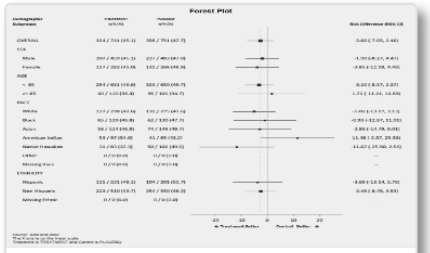
3

Age Group #1

0 18 100

Welcome to the Office of Computational Science Analysis Toolbox.

FDA

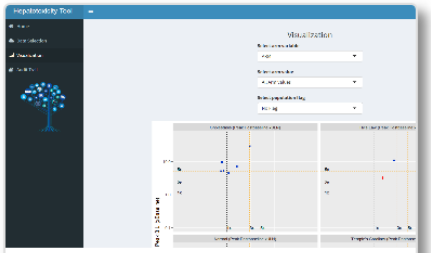


Demographic Tool

Performs demographic subgroup analysis through a web app

User Guide

Start Setup

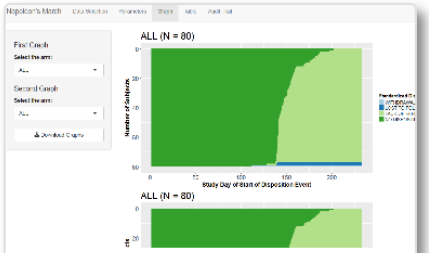


Hepatotoxicity Tool

Examine drug-induced liver injury through composite visualization

User Guide

Start Setup



Napoleon's March

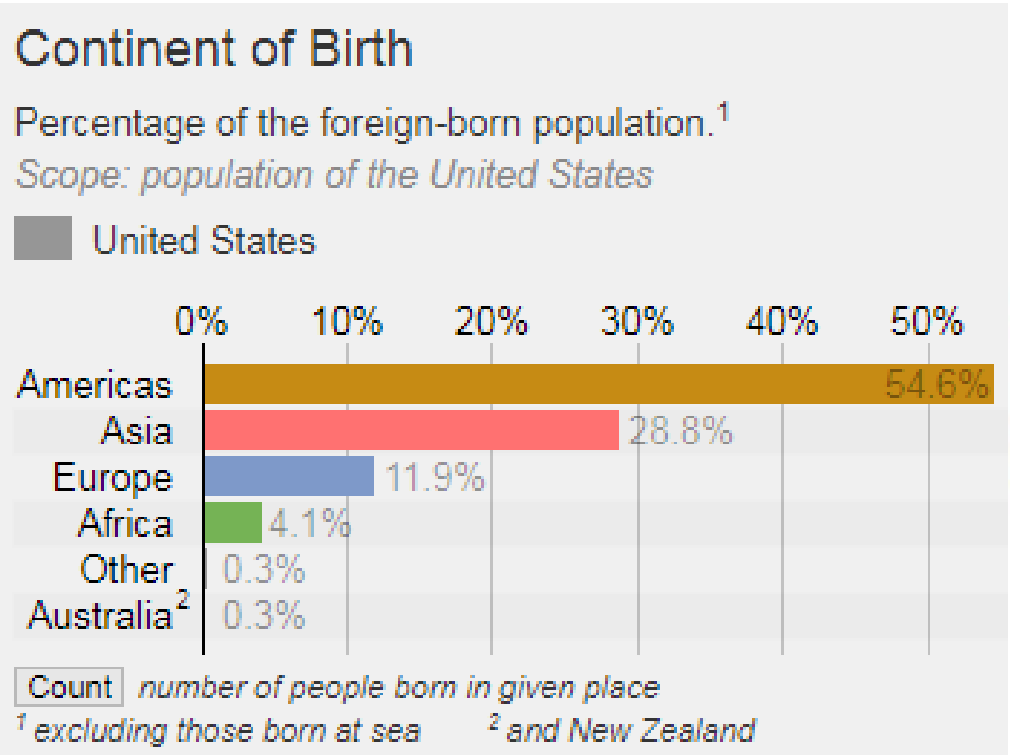
Longtitudinal visualization of disposition categories

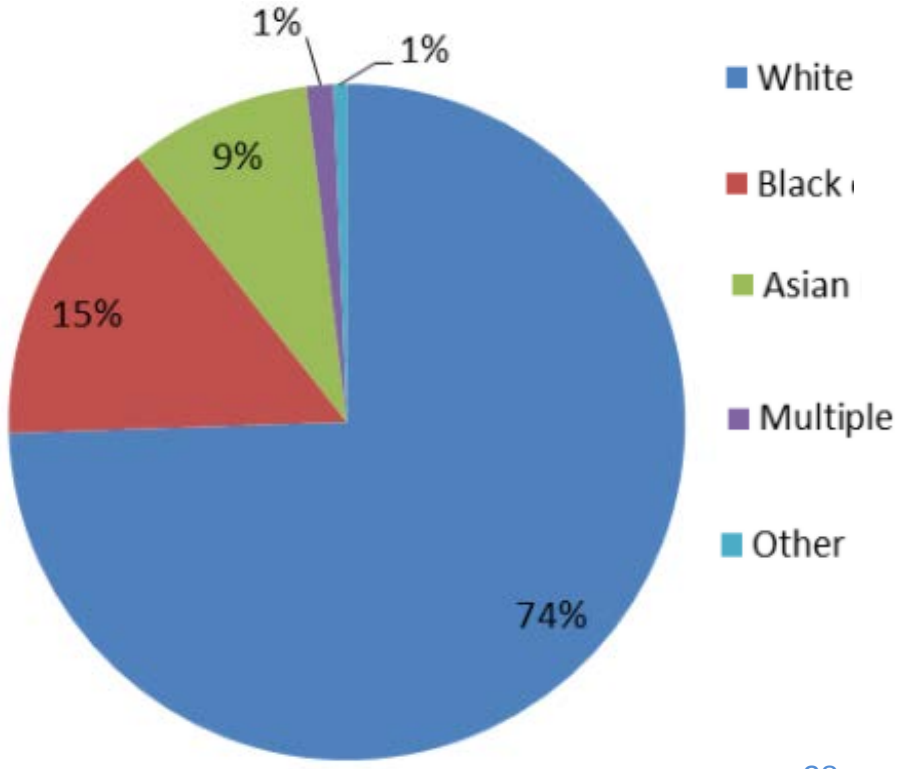
User Guide

Start Setup

Standardized data enables subgroup analyses

"The risk of increased liver-related blood tests were higher in women, Asians and in patients that were older than 65."

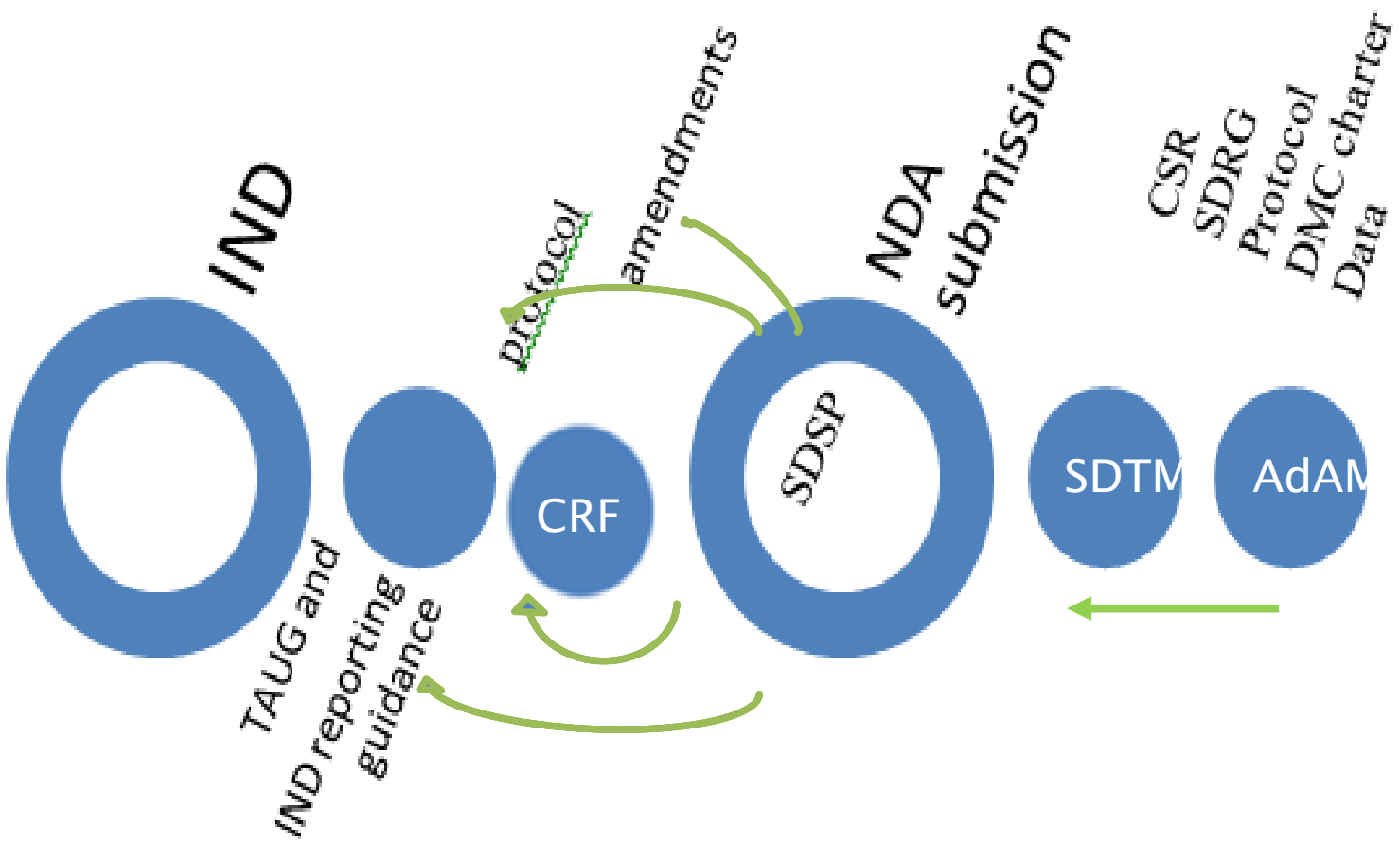




https://statisticalatlas.com/United-States/National-Origin

https://www.fda.gov/Drugs/InformationOnDrugs/ucm484361.htm

End to End Standardization



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