

Statistical Input into Improving Data Quality: the Impact on Respiratory Endpoints in a COPD Trial

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13 November 2015



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Overview

- Data cleaning benefits from involvement from statisticians
- Our experience in SUMMIT
 - COPD Exacerbations
 - FEV1
- Impact on endpoints

What are we trying to do?

- Clinical trials want to answer a set of questions
- Does drug affect:
 - Mortality
 - Rate of decline in FEV1
 - Rate of moderate/severe COPD exacerbations
- Need reliable data for statistical analysis

Data Cleaning

- Process:
 - Identify data issues
 - Clean data via querying sites
- Issues:
 - Vast quantities - can't clean everything
 - Use rules based upon individual data points
 - Might not think longitudinally or of impact on statistical analysis of endpoints

Stats Contribution

- Clean data that will have an effect on statistical analysis of endpoint
- Design novel visual methods to demonstrate effect unusual data was having on analyses
- Build a close relationship with clinical and CRO

SUMMIT

Study to Understand Mortality
and Morbidity in COPD

Placebo

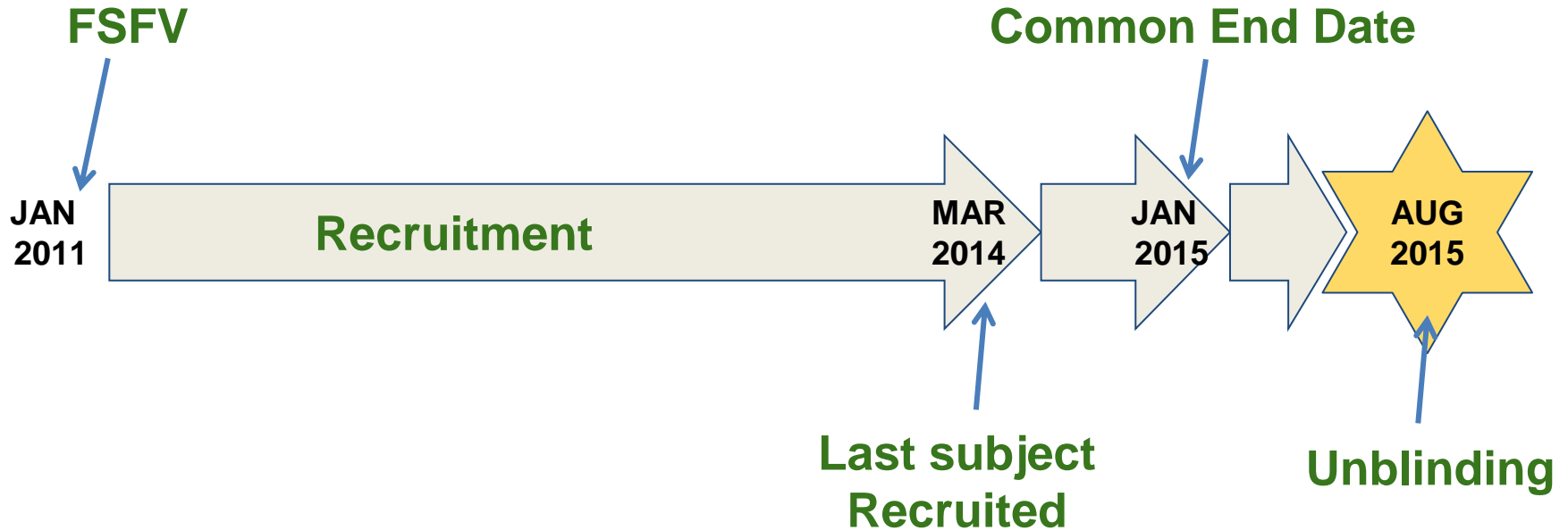
ICS

LABA

ICS/LABA

- **>16,000** subjects with moderate COPD and cardiovascular history or risk
- Primary endpoint: **Survival**
- Other endpoints involved **FEV1** and **COPD exacerbations**

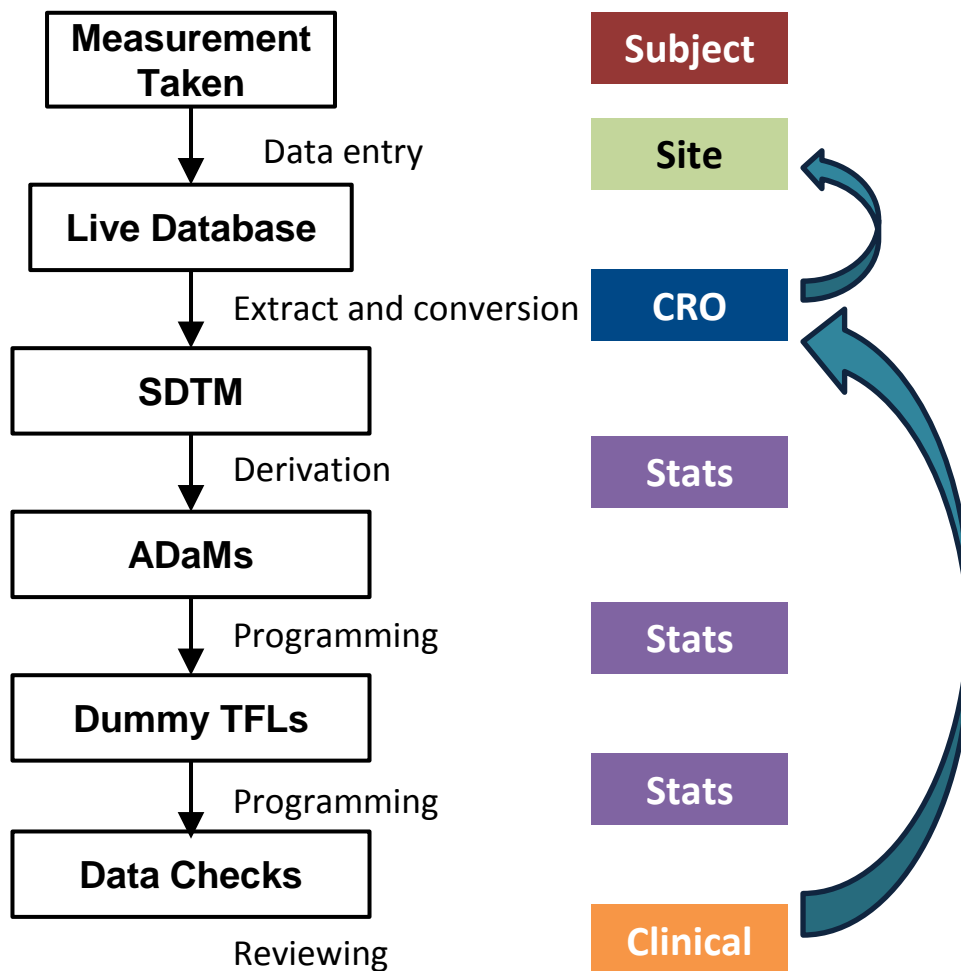
SUMMIT Timelines



Over 4 years of data collection

Study Process during Data Collection

- >16000 subjects
- >1300 Sites
- 43 Countries



COPD Exacerbations

- Protocol defined:

Adverse event of worsening of symptoms of COPD requiring Antibiotics or Systemic Corticosteroids (moderate) or hospitalisation (severe)

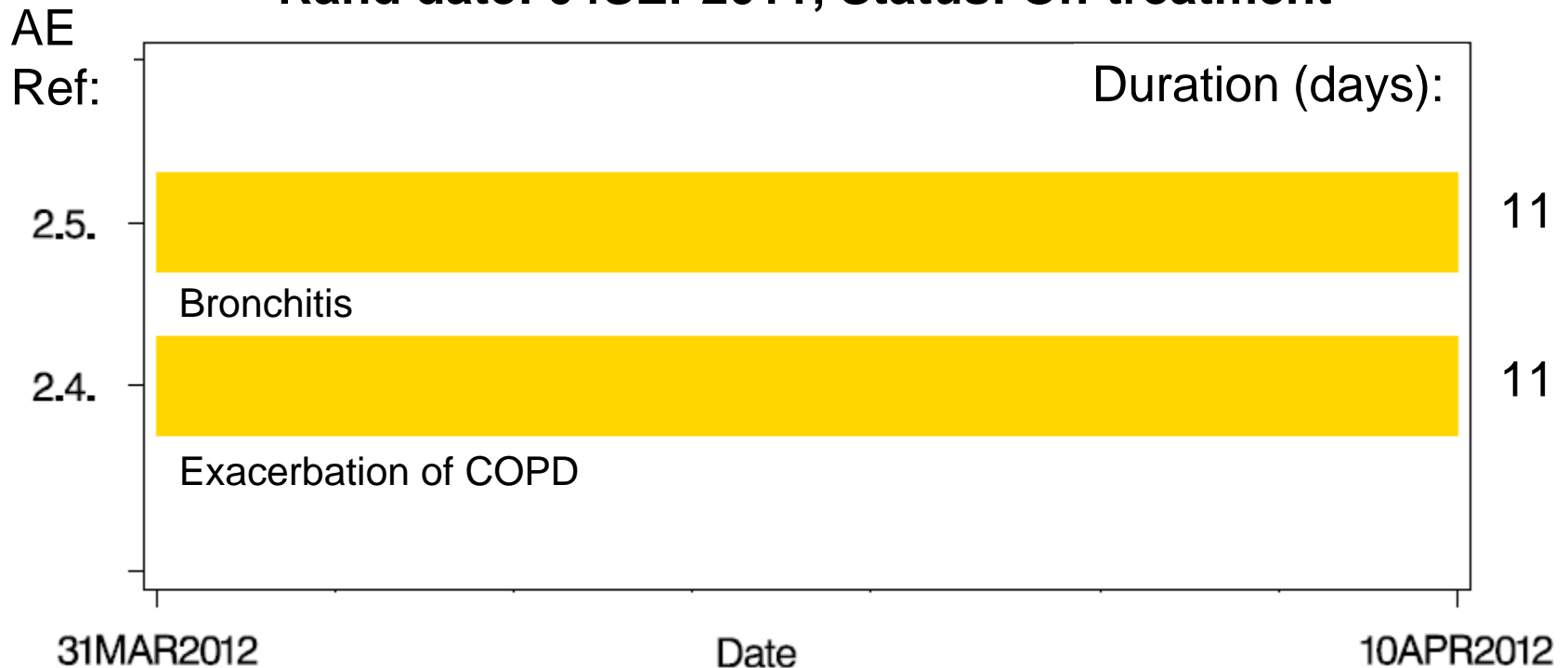
- Endpoints: *Rates and Time to First*
- Collected on adverse event CRF page:
“Did this AE meet the definition of a moderate / severe COPD exacerbation?”

Overlapping Exacerbations

Subject: 123456, Site: 12345

Investigator: J DOE, Country: USA

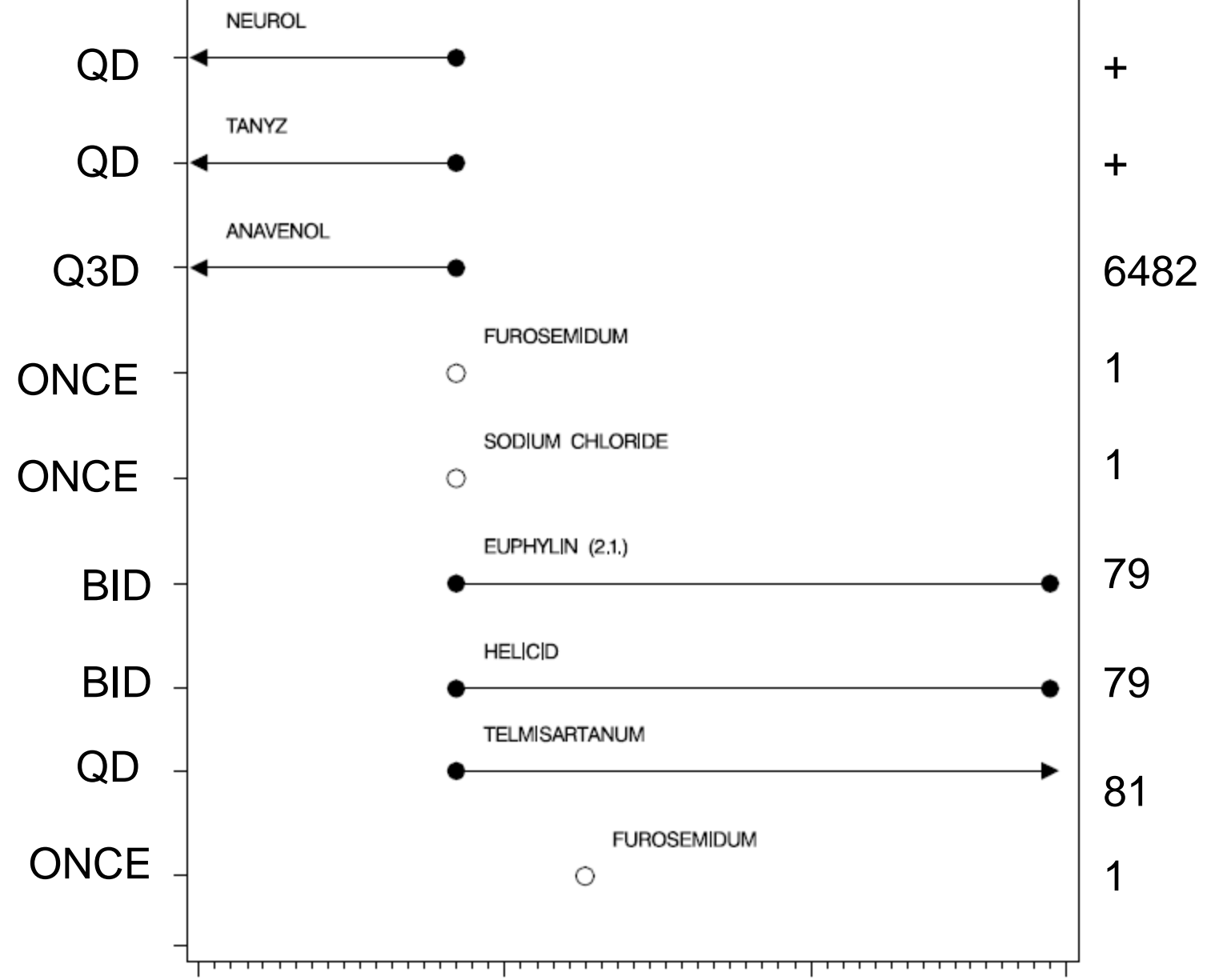
Rand date: 04SEP2011, Status: On-treatment



Dose Freq.:

Duration (days):

CM.:



18FEB2013

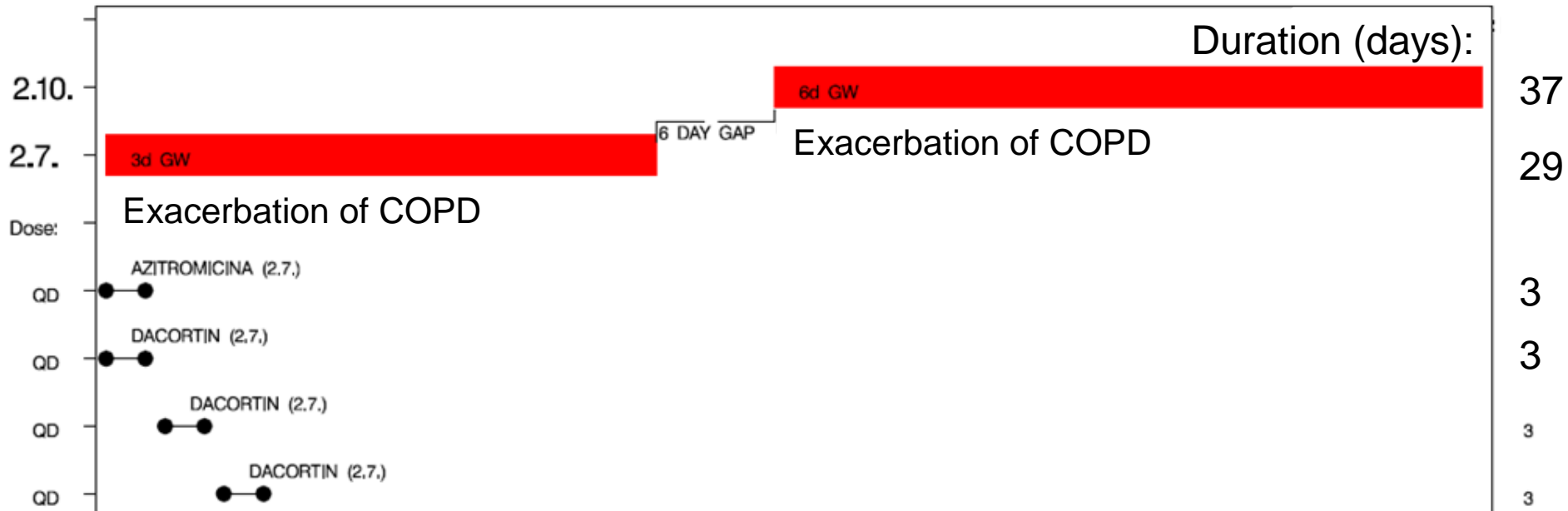
24MAY2013

Close Exacerbations

Subject: 654321, Site: 54321

Investigator: J SMITH, Country: UK

Rand date: 17JAN2012, Status: Withdrawn (03NOV2013)



Missing Adverse Event

- Concomitant Medication page of CRF:
“Was this medication taken for a COPD exacerbation?”
- Answered ‘Yes’ when antibiotic or systemic corticosteroid entered
- ... but no AE marked as a moderate or severe COPD exacerbation

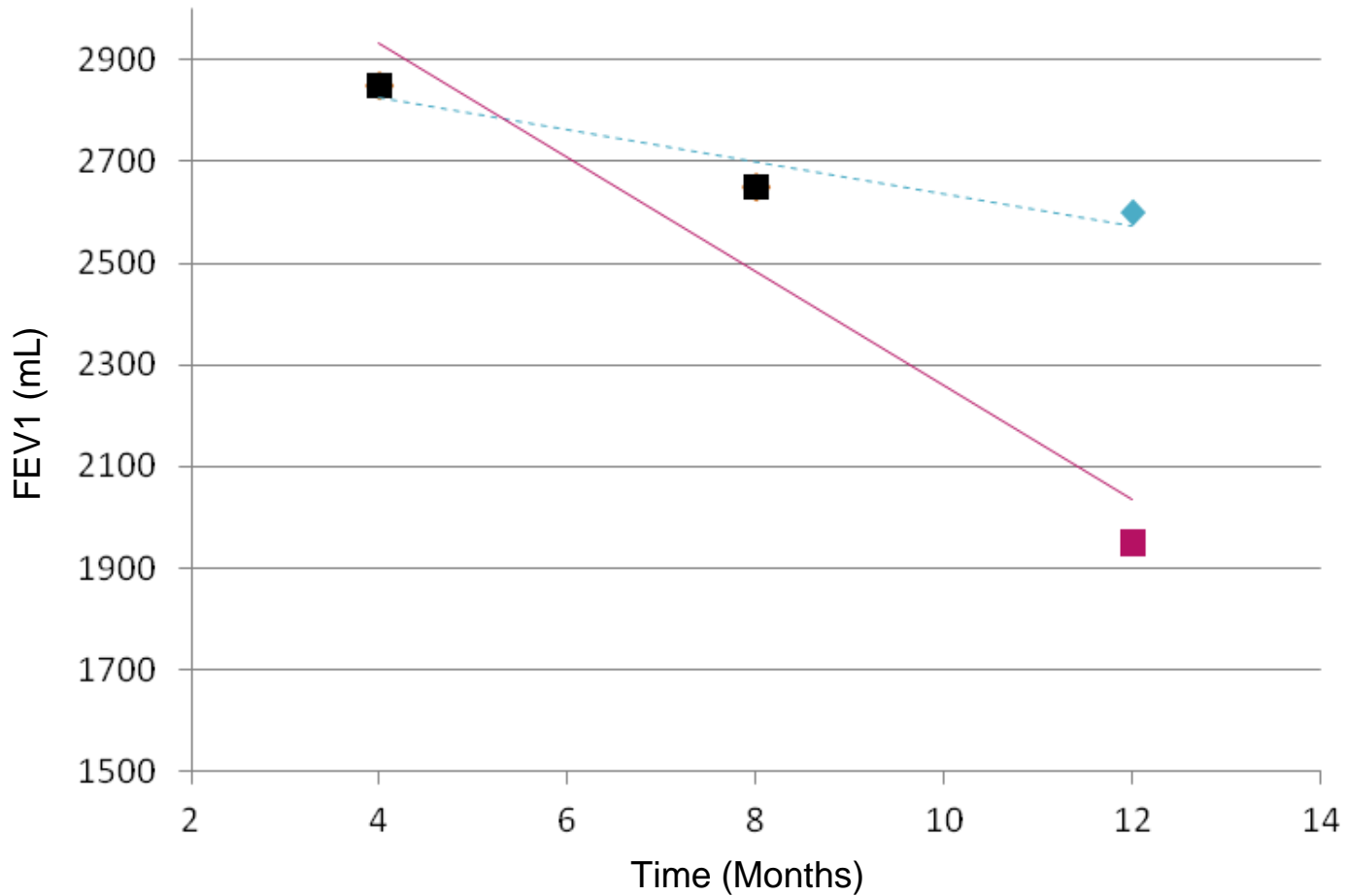
Impact on COPD Exacerbation Endpoints

- Overlapping COPD exacerbations would
 - Falsely **increase** COPD exacerbation rates
- Missing COPD exacerbations would
 - Falsely **decrease** COPD exacerbation rates
 - Could falsely **push back in time** first event in time to first analysis

FEV1

- Endpoint: Forced Expiratory Volume in 1 second
- Measured on-treatment only
- Analyses:
 - **Secondary** Rate of decline in FEV1,
 - **Sensitivity** Differences in rate of Decline using Individual Regression Slopes,
 - **Tertiary** Change from baseline FEV1

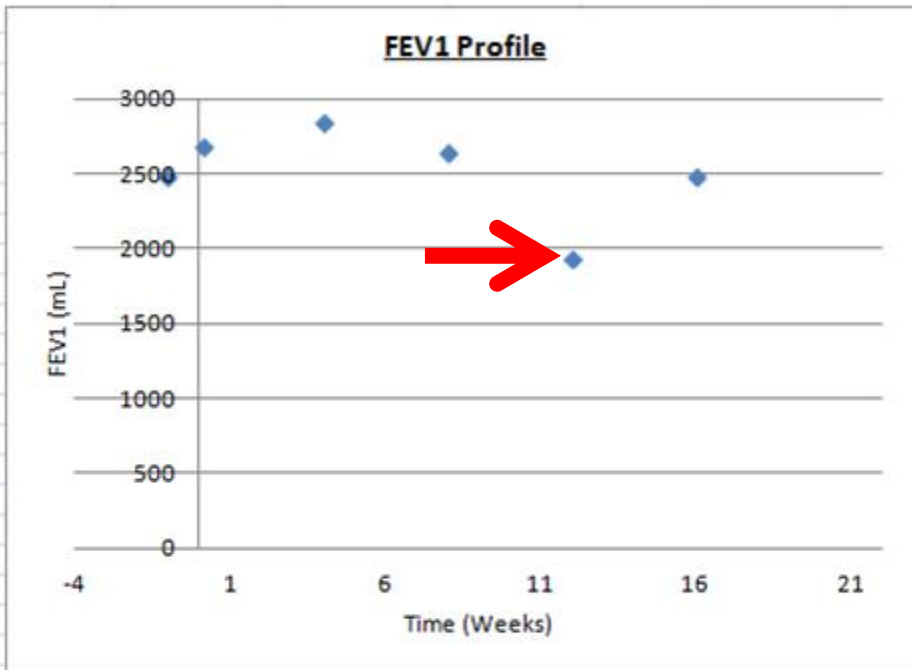
Extreme FEV1 Slopes



FEV1 checks

- Values within specified ranges.
- Difference from Baseline.
- DM checks are limited - more statistical checks required. e.g.:
 - Subjects SD within specified range
 - % change between visits
 - Individual Slopes less than specified value.

FEV1 Profile Review Tool



Subject #
102

Trt Start Date
01-Jan-15
Trt Stop Date
12-May-15

Reviewed
2
Left to review
0

Previous Queries	
Visit	Response
001	Substantial Difference between Baseline and Visit 5. RESPONSE 001: Data is correct

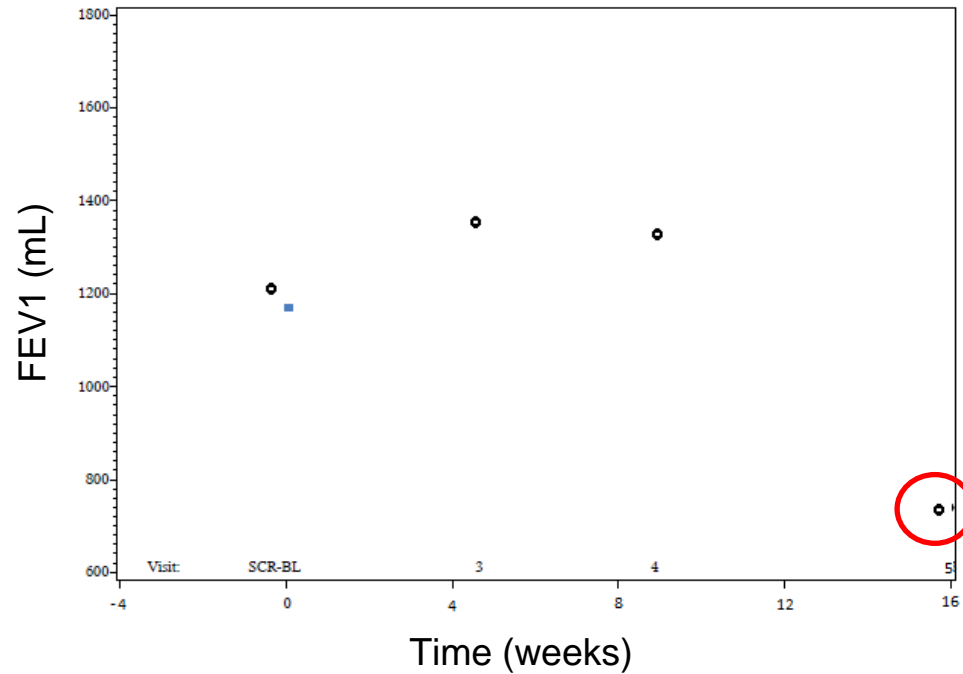
Rules for Review						
Difference between Baseline and Screening >500mL	SD >800mLs	SD >500mLs (on Trt)	Slope >750 mL/yr	>Con. Visits	Change from Baseline >750mLs	Value is out of range <0.5L or >3.5L
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Site	Subject	Status	Comment:
002	102	Withdrawn	Please reivew data at Visit 5. This value represents a substantial decrease in FEV1.

FEV1 Profile Review Tool

FEV1 Profile: Subject 001, Status=Withdrawn
United Kingdom Site=101 (SMITH, JOHN)

Page 1 of 1



NOTE: Blue square represents baseline value

Comments:
Please review data at last visit. Reduction in FEV1 is not consistent with normal rate of decline for subject.

PI Comments & Signature:

Impact on Analysis - An Example Simulation

- Simulate normally distributed FEV1 data $N(1600, 400)$
- Trt A 1000 subjects, each subject decrease of $N(10, 20)$ per 3 months.
- Trt B 1000 subjects, each subject decrease of $N(6, 20)$ per 3 months.
- Constant withdrawal of 4% of remaining subjects per 3 month period.
- Set limits of 300mL lower and 4000mL upper to remove invalid values.

Impact on Analysis - An Example Simulation

Simulation	Normally Distributed data		Normally distributed data with 10% of slopes replaced with extreme slopes < -750mL/yr		Normally distributed data with 5% of slopes replaced with extreme slopes < -1500mL/yr	
Model	Random Coefficients Model	Individual Slopes (equally weighted)	Random Coefficients Model	Individual Slopes (equally weighted)	Random Coefficients Model	Individual Slopes (equally weighted)
Average Slope mL/yr	Trt A -44 mL/yr Trt B -20 mL/yr	Trt A -44 mL/yr Trt B -21 mL/yr	Trt A -101 mL/yr Trt B -74 mL/yr	Trt A -104 mL/yr Trt B -76 mL/yr	Trt A -118 mL/yr Trt B -94 mL/yr	Trt A -117 mL/yr Trt B -89 mL/yr
Difference between slopes Trt B - Trt A	23	23	24	28	24	28
p-value	<0.001	<0.001	0.042	<0.001	0.457	<0.001

Summary

- Data cleaning benefits from involvement from statisticians
- Statisticians benefit from involvement in Data Cleaning
- In respiratory trials, useful to graphically represent:
 - COPD Exacerbations
 - FEV1
- Impact on endpoints:
 - Improved precision of estimates

Thank you!

Questions?