Using the SIDES algorithm to the identify patient phenotypes that have the potential to benefit most from switching to Relvar

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Overview of Presentation

- Motivation
  - SLS COPD Study
- SIDES Algorithm (as applied to SLS)
- Results
- Conclusions and Learnings

Motivation

SLS COPD

Salford Lung Study for COPD Overview

- A 12-month, open label, randomised, *effectiveness* study to evaluate the initiation of FF/VI (**Relvar - Breo**) against continuation of existing COPD maintenance therapy (**Usual Care**)
- Study run in pharmacies in Salford area of Gt. Manchester
- **Primary Endpoint:** mean annual **rate of moderate or severe exacerbations**
- 2799 subjects randomised (ITT) with 2269 in the PEA (Primary Efficacy Analysis) population*
- Statistical Analysis Complete May 2016

* - at least one moderate or severe exacerbation in the year prior to Visit 2 (baseline) and was the primary analysis population for the primary endpoint.

SLS COPD Results

PEA Population (similar results for ITT)

Rate of Moderate or Severe On-treatment Exacerbations (PEA Population)	Usual Care N=1134	FF/VI N=1135
Least Squares (LS) Mean Annual Rate	1.90	1.74
Ratio of FF/VI to Usual Care	0.92	
95% CI	(0.85, 0.99)	
Percent Reduction	8.41%	
95% CI	(1.12%, 15.17%)	

Why Run a Subgroup Identification Analysis?

Reasons Discussed by Steering Committee

- Relevance of covariates in primary model had been investigated via subgroups
  - COPD maintenance therapy at BL
  - Number of exacerbations in the previous year (<2, ≥2)
  - Smoking status
- Plus many further pre-specified subgroups:
  - Age
  - Adherence (PDC)
  - CAT score

- **Targeted Medicine**
  - ***Identify patients subgroups****, defined by phenotypes, demographics, substance use and pre-treatment laboratory tests, that* ***are more likely to benefit from a FFVI combined therapy*** *over usual-care and achieve better control in terms of exacerbation rate compared to the primary results*

Maximising Treatment Benefit

Choosing the Algorithm

- Choice of GUIDE[1] vs SIDES[2]
  - **GUIDE** focuses on identifying subgroups, which will provide the **most gain in overall accuracy in exacerbation rate prediction**
  - **SIDES** focuses on identifying subgroups, **either maximise the differential effect between subgroups** or **maximise the benefits of FFVI over usual care in a single subgroup**
- Several other techniques considered
- SIDES chosen due to the team's focus on maximising benefits within specific subgroups

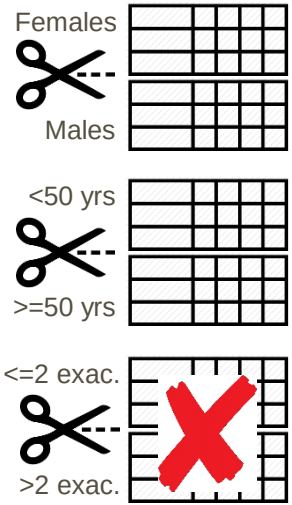
1. Loh, W.-Y., He, X., and Man, M. A regression tree approach to identifying subgroups with differential treatment effects. Stat Med. 2015; 34: 1818-1833
2. Lipkovich I, Dmitrienko A, Denne J, Enas G. Subgroup identification based on differential effect search--a recursive partitioning method for establishing response to treatment in patient subpopulations. Stat Med. 2011 Sep 20; 30(21):2601-21.

The SIDES Algorithm

SIDES

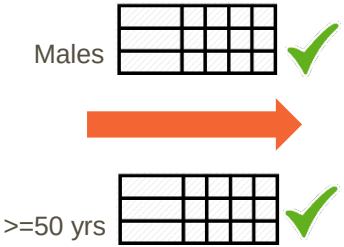
Simplified example

Slice the data
Ignore small subsets



Etc.

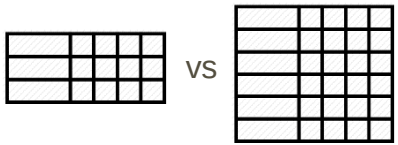
Which subgroups **largest treatment benefit**?



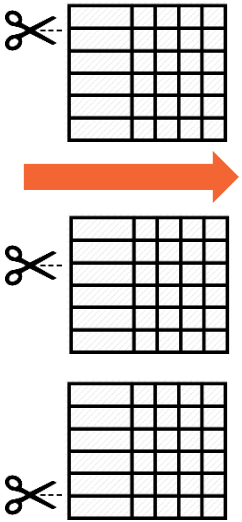
Šidák-based
multiplicity adjustment

Compare each subset with
parent group

$p_{child} \leq \gamma * p_{parent}$



Resample to
'confirm'



Go again…

Glossary: exac. = exacerbations in the previous 12 months

Variables (Features)

Identified by Clinical Team

Classification	Characteristics
Demographics	Age Sex BMI*
Medical history	Current medical conditions: hypercholesterolemia, diabetes mellitus, hypertension, cerebrovascular accident, CAD, arrhythmia, congestive heart failure, myocardial infarction, asthma Pneumococcal vaccination Influenza vaccination
COPD history	Duration of COPD Smoking status Number of pack-years Number of exacerbations during the 12 months prior to randomisation
Baseline disease characteristics	Baseline CAT score COPD maintenance therapy at baseline Post-BD FEV_1*: absolute values
Other	Socioeconomic status Adherence (PDC) Polypharmacy

*BMI and FEV_1 were included in separate sensitivity analyses due to missing data.
BD, bronchodilator; PDC, proportion of days covered.

Algorithm Inputs

Selection of parameters to control

- SIDES lets us choose:
  - **Model and Splitting criterion**
    - Negative binomial model for exacerbations
    - Maximise the treatment effect in at least one of the two child subgroups
  - Relative **improvement factor,** γ
    - Tuned using 10-fold X-validation

Algorithm Inputs

Selection of parameters to control

Area of Control	Parameter Description	Input
Restrict tree width/depth	The number of best promising subgroups selected at each stage	5
	Maximum number of covariates selected to form the subgroup	3
Number of subjects in subgroups	Minimum number of subjects in either half of a split	100
	Minimum number of subjects in one treatment arm for a split	30
Type I Error (weak control)	Type I error compensation (cut-off level of permutation test)	0.1
	Permutations	500
Binning	Maximum number of bins for ordinal/continuous covariates	20

Modification to original algorithm

– As a hypothesis-generating exercise we did not partition our data to create a test set(s)

Configuring the Improvement Factor

Gamma Tuning

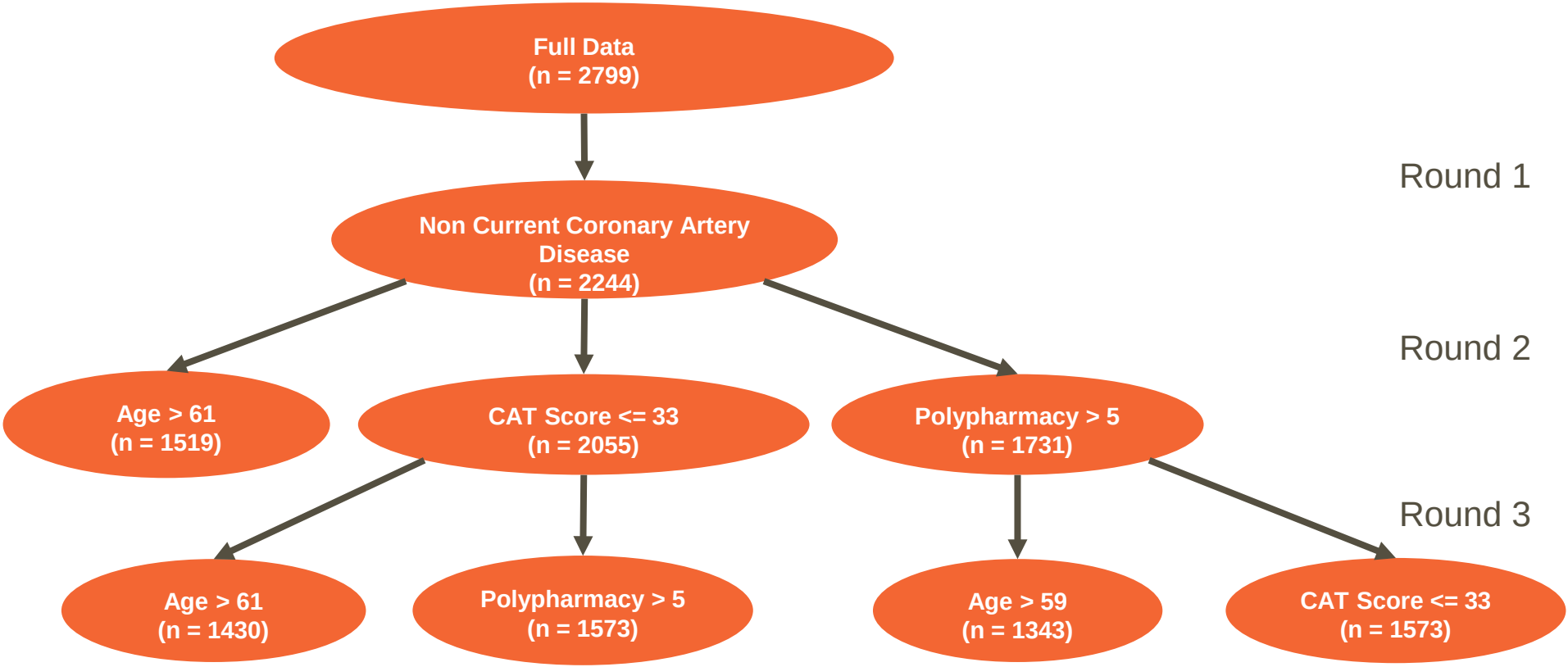
- For subgroup, the comparison $p_{child} \leq \gamma * p_{parent}$ is made
- Defining γ can be a team decision
- Else use cross-validation
  - Extremely computationally intensive
  - Not possible on most laptops!

Our approach

Results

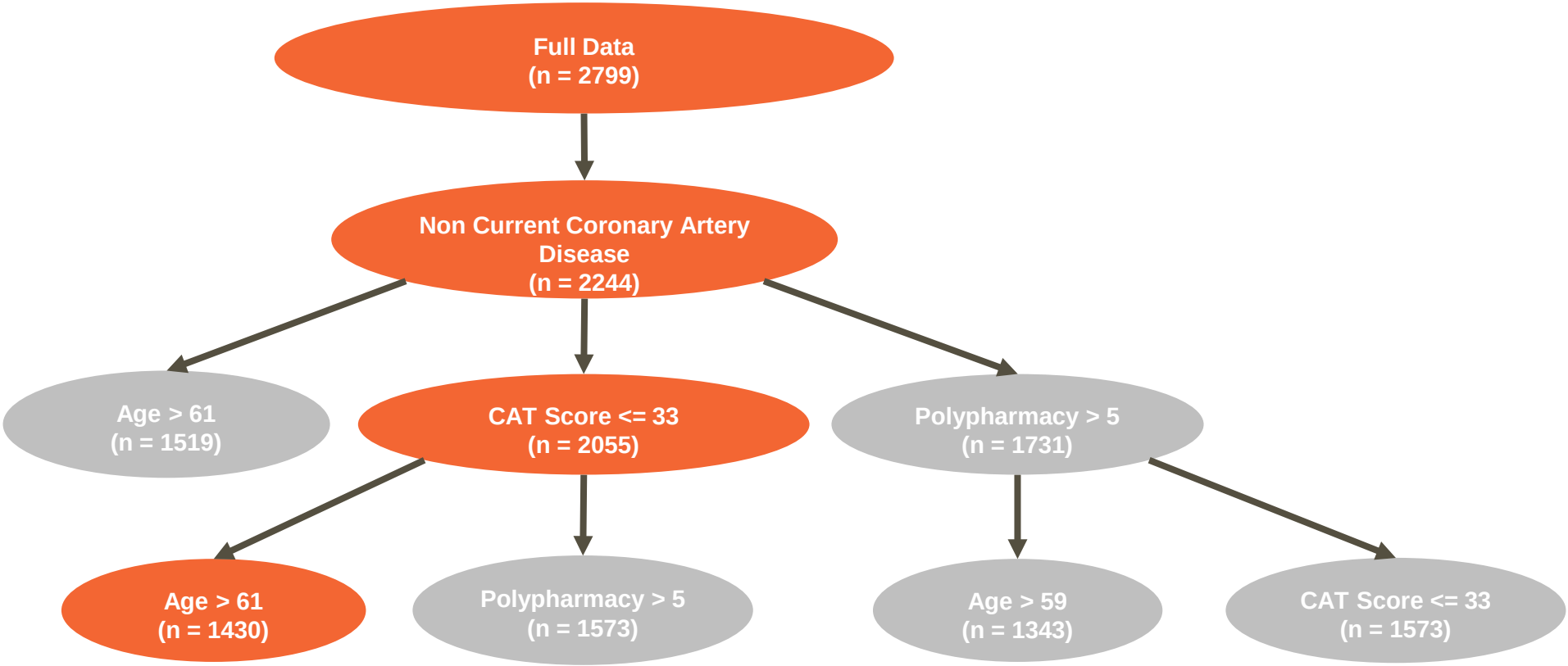
Building the Tree

Using the Full Data



Building the Tree

‘Best’ Group



Performance

"Best" Cluster vs Original Study

- The primary analysis model was re-fitted against the "best" cluster
- An adjusted **21% reduction** in exacerbations could be seen in the best cluster, **compared with 8.4%** in the full ITT population

Cluster		Usual Care	FF/VI	Ratio (95% CI)
Noncurrent coronary artery disease and CAT score at baseline <= 33 and age > 61 years old	N	714	716	
	LS Mean Annual Rate	1.71	1.35	0.79 (0.71, 0.87)
Full ITT Population Results	N	1403	1396	
	LS Mean Annual Rate	1.64	1.50	0.92 (0.85, 0.99)

- So it seemed to 'work'…

Conclusion and Learnings

Conclusion

- Identified a subgroup of patients with **noncurrent CAD**, baseline **CAT score ≤ 33** and **age >61** years who may be more likely to benefit from initiating FF/VI 100/25µg versus continuing UC
- Much larger treatment benefit in this group (**21%** reduction **vs 8%** reduction)
- This was a hypothesis-generating exercise (‘learn’ but no ‘confirm’)
  - No test dataset was defined and results should be interpreted with caution
  - Work is ongoing to validate these findings in an alternative COPD dataset
- ‘Unexpected’ subgroup makes this even more important to test!

Learnings

- Lack of options for validation limited the impact
  - Consider dividing into training and test
- Gamma tuning is computationally intensive
  - Consider pre-specifying γ
- SIDES CRAN package has matured
  - Consider use of open source rather than in-house maintenance

Summary

- SIDES algorithm successful in identifying candidate subgroups with an increased treatment effect
- Hypothesis yet to be formally tested

Acknowledgements

- Harriet Dickinson for doing half the work and providing guidance throughout!
- GSK SLS Governance Team and Scientific Committee for approving this work
- R&D Tech for our grid!

Questions

NEW Data Science SIG

- A new Data Science Special Interest Group is forming
- Targeting both Data Scientists and Statisticians with an interest in Data Science
- Full details to be determined in the New Year
- Please get in contact if you're interested!