OUTCOME OF SURVEY ON CURRENT STANDARDS AND IMPLEMENTATION OF COVARIATE ADJUSTED & STRATIFIED ANALYSES

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BACKGROUND

The FDA's guidance on covariate adjustment encourages the inclusion of baseline covariates to enhance efficiency. However, following covariate adjustment in non-linear models, care must be taken on preserving estimation of the target estimand. This poster summarises key learnings and outcome of a recent survey with focus on oncology trials.
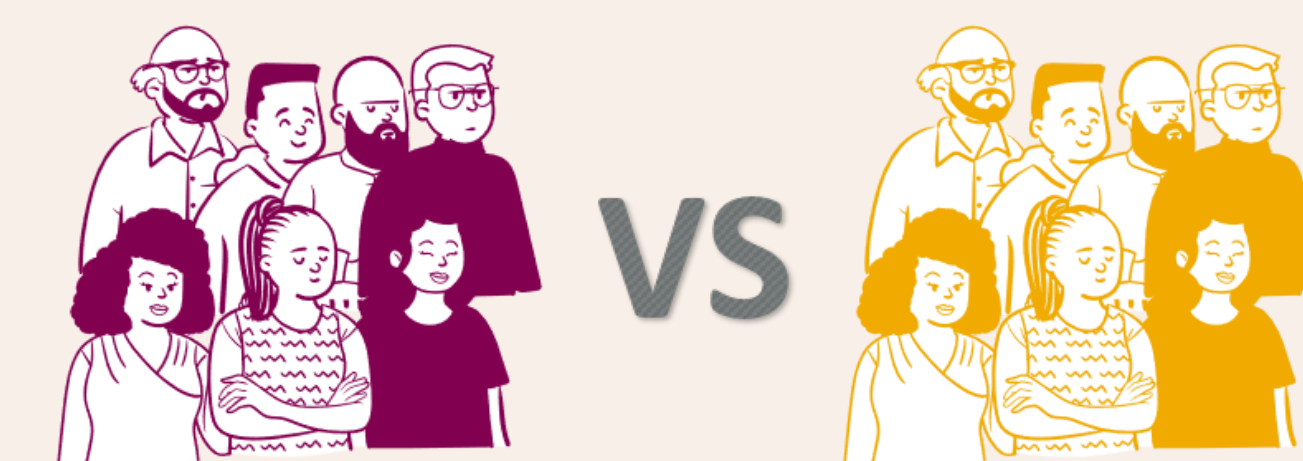
Non-collapsibility of hazard ratio

CONDITIONAL ESTIMAND

VS

Treatment effect had the patients with covariate values X taken test treatment vs. had they taken control.

More relevant interpretation for the individual patient as effect defined by the values X.

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MARGINAL ESTIMAND

VS

Treatment effect had all patients in the population taken test treatment vs. had all patients taken control

Provides an average population treatment effect in the observed trial population.

Must align estimation method with estimand!

WHAT'S THAT ESTIMAND?

Stratified Cox model often specified as primary analysis method in oncology trials:
- Estimates separate baseline hazards for each stratum
- Overall hazard ratio obtained by multiplying each stratum-specific partial log-likelihood

What estimand does this target?

19 QUESTIONS WITH 5 KEY OBJECTIVES (HIGHLIGHTS)

SURVEY DESIGN & OBJECTIVES

Hosted on SurveyPlanet.com from June to July 2023, distributed amongst Oncology Estimand WG networks, posted in the ASA Biopharm section

Aims:
1. Understand current practices of covariate adjustment and analysis methods
2. Identify challenges associated with covariate adjusted and stratified analysis

① PARTICIPANT CHARACTERSITICS

	Respondents (N = 122)
Country	
United States	57 (46.7%)
China (Including HK)	24 (19.7%)
Switzerland	14 (11.5%)
Other or unknown	26 (21.3%)
Affiliates	
Pharmaceutical / Biotech company	97 (79.5%)
Contracting / Consulting company	11 (9.0%)
Academic center	10 (8.2%)
Government agency	3(2.5%)
Non-profit organization	1 (0.8%)
Stage of development	
Confirmatory	100 (81.3%)
Early phase exploratory	22 (17.9%)
Pre-Clinical	1 (0.8%)

② UNDERSTAND HOW INDIVIDUALS THINK ABOUT THE TARGET ESTIMAND AFTER COVARIATE ADJUSTMENT OR STRATIFICATION

Do the following target the same estimand? (N=122)	Yes	No
stratified vs unstratified	61.48%	31.97%
covariate adjusted vs covariate unadjusted	56.56%	38.52%
remove/pool strata post-hoc vs pre-specified	57.38%	38.52%

Note: these three questions are not mandatory, for each question there are non-responders.

- Evidence of gap in the understanding of different statistical analysis models targeting different estimands for non-linear models

- Highlights critical need of further guidance and training on this topic

- Excellent literature in this area (e.g. Daniel et al. 2021), but clearly still a need for clarification/implementation in practice

③ SELECTION OF STRATIFICATION FACTORS / COVARIATES

Response to Q7: 65.6% people have considered adding additional covariates to be adjusted in the analysis model beyond those used for stratified randomization

Response to Q9: How are the covariates for adjustment selected?
In addition to selecting covariates based on literature/previous trials (69.67%) and a mixture of literature and implementation of variable selection procedures (63.11%), the majority also make the selection with the clinical team (81.15%). Presents ppportunity to simultaneously have discussion with clinical about target estimand

Response to Q8: In a trial with stratified randomization, how do you incorporate the stratification factors as well as other prognostic covariates in a Cox model?	% Respondents (N=122)
Stratified analysis using strat factors from stratified randomisation and adjust for additional covariates in Cox Model	59.84
Adjust all factors as covariates in an adjusted Cox Model	23.77
Adjust all factors as strat factors in a stratified Cox Model	20.49
Unanswered	7.38
Other	2.46

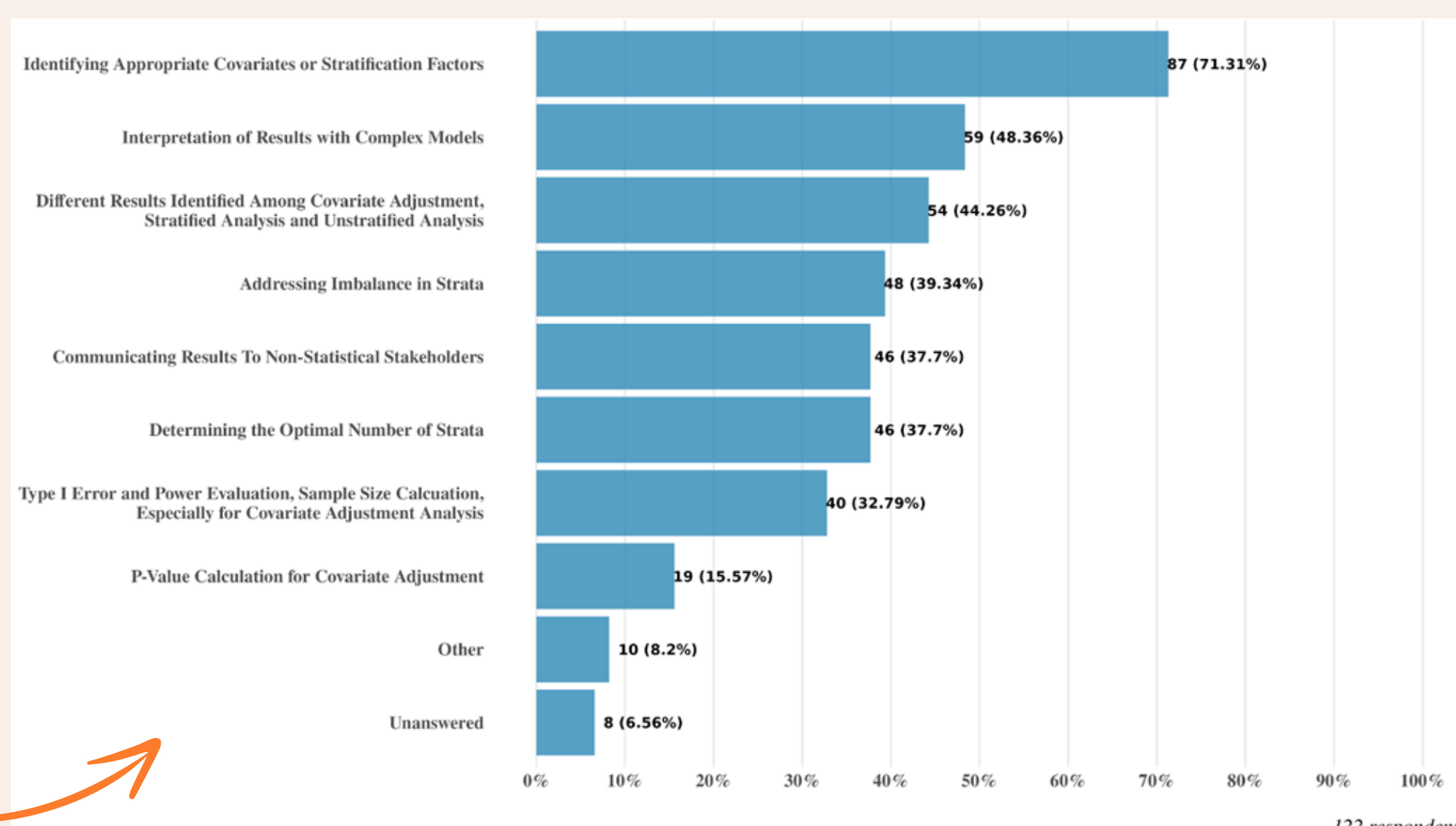### ④ UNDERSTAND THE CHALLENGES OF SMALL STRATA

Response to Q10: 16.4% of participants suggest small strata leads to biased estimates.
On reality, unlikely to be systematic bias due to randomisation (imbalance due to small strata could equally favour either treatment arm)

Response to Q13: Majority either pool strata (81.15%) or drop them from the analysis (55.74%) to address problems with small strata. Caution: this would change interpretation in a conditional estimand as your individual treatment effect has different set of characteristics

⑤ REGULATORY INTERACTIONS & CURRENT CHALLENGES

- Feedback inconsistent from HAs (63% did not receive consistent feedback on covariate adjustment and stratified analysis). Difficult to really make any general recommendations for covariate adjustment
- Important to engage with regulatory bodies and have open discussions – ask questions specifically on the analysis model with regards to the target estimand

Response to Q18: In your experience, what are the most common challenges you have faced when implementing covariate adjustment or stratified analysis in clinical trials?

Identifying Appropriate Covariates or Stratification Factors	87 (71.31%)
Interpretation of Results with Complex Models	59 (48.36%)
Different Results Identified Among Covariate Adjustment, Stratified Analysis and Unstratified Analysis	54 (44.26%)
Addressing Imbalance in Strata	48 (39.34%)
Communicating Results To Non-Statistical Stakeholders	46 (37.7%)
Determining the Optimal Number of Strata	46 (37.7%)
Type I Error and Power Evaluation, Sample Size Calculation, Especially for Covariate Adjustment Analysis	40 (32.79%)
P-Value Calculation for Covariate Adjustment	19 (15.57%)
Other	10 (8.2%)
Unanswered	8 (6.56%)

122 respondents

LIMITATIONS & DISCUSSION

Survey was very much an exploratory and scoping exercise! (not a Delphi, which is based on statistical stability of consensus)
- May have had multiple responses from same company
- Selection bias towards more industry responses
Clearly there is still a need for more training:
- Platform for collaboration and discussion with fellow statisticians;
- Consultation or mentorship from experienced professionals; or
- Access to specialized software or tools for covariate adjustment and stratified analysis

FUTURE DIRECTIONS OF TASK FORCE

Merge into ASA BIOP Covariate Adjustment Working Group
- Working on software development (RobinCar) to provide a validated package for covariate adjusted/stratified analyses
- Standardization and Outreach Sub-team of the ASA BIOP working group can be leveraged to address some of the aspects highlighted in survey

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Useful References on Covariate Adjustment and Estimands
Van Lancker K, Bretz F, Dukes O. Covariate adjustment in randomized controlled trials: General concepts and practical considerations. Clinical Trials. 2024;0(0)
Daniel R, Zhang J, Farewell D. Making apples from oranges: Comparing noncollapsible effect estimators and their standard errors after adjustment for different covariate sets. Biometrical Journal. 2021; 63: 528–557
Morris TP, Walker AS, Williamson EJ, White IR. Planning a method for covariate adjustment in individually randomised trials: a practical guide. Trials. 2022 Apr 18;23(1):328
Wei, J., Xu, J., Bornkamp, B., Lin, R., Tian, H., Xi, D., ... Roychoudhury, S. (2024). Conditional and Unconditional Treatment Effects in Randomized Clinical Trials: Estimands, Estimation, and Interpretation. Statistics in Biopharmaceutical Research, 1–11.